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ABSTRACT

The treatment of patients with chronic kidney disease (CKD) and cancer is a problem for nephrologists and oncologists, because everything is interlaced: kidney disease is often a result of cancer, CKD patients are more often suffering from cancer, and treatment of cancer causes kidney damage. The diagnosis and treatment of tumors in these patients is difficult; and the results of therapy, for many reasons, differ from those obtained in the general population. Oncology is an extremely fast-growing field of medicine, there has been a huge advance in cancer treatment, and, as a result, cancer-related mortality has drastically decreased over the last decade. We want these advances to affect nephrological patients as well.

Generally, nephrooncology focuses on the relationship between cancer and kidney; therefore, it involves many medical specialties taking care of patients afflicted with cancer and kidney disease. There are many areas where the cooperation is crucial for the patient's benefit, such as: 1) diagnosis of cancer in patients with CKD (including end-stage kidney failure treated with hemodialysis, peritoneal dialysis, and kidney transplantation), 2) complexity of cancer treatment in such patients, 3) possibility of the application of novel molecularly targeted agents in CKD patients, 4) acute kidney injury and other side effects of anticancer therapy, 5) paraneoplastic renal manifestations, 6) native and transplanted kidney cancer and its treatment, 7) kidney transplantation in patients with a history of different cancers, and 8) diagnosis and treatment of rare systemic diseases affecting the kidneys, such as tuberous sclerosis complex. The aim of such cooperation is the improvement of patient survival and their quality of life, as well as obtaining, in nephrological patients, the results of treatment similar to those in the general population.

These are only examples, and a multidisciplinary cooperation is needed also in numerous other fields. In this special issue, we present some of the problems related to nephrooncology.

Cancer epidemiology in chronic kidney disease

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Cancer is becoming recognized both as a complication and a cause of morbidity and mortality in patients with chronic kidney disease (CKD). There is a bidirectional relationship between CKD and cancer, as both diseases may be caused by common factors. Cancer incidence in CKD is higher than in the general population. Some cancers may cause kidney impairment. Finally, CKD influences cancer diagnosis and treatment.[1]

Large observational studies have shown a 2- to 3-fold higher risk of cancer in patients after kidney transplantation. This risk increases with time after transplantation, but it also increases with the duration of hemodialysis before transplantation. There is 20% to 50% excess risk for any cancer in patients with early stage CKD and those on dialysis.[2] Moreover, the mortality rate in kidney transplant recipients is 5- to 6-fold higher than in the general population. It is well known that the risk of death from cardiovascular causes increases with decreasing estimated glomerular filtration rate (eGFR). The risk of death from cancer is approximately 2-fold higher in patients with an eGFR of less than 30 ml/min/1.72 m^2 compared with those with an eGFR of more than 60 ml/min/1.72 m^2. CKD is common in patients with cancer and is an independent risk factor for death in cancer patients.

Several factors may cause both CKD and cancer. Analgesics and herbal toxins (eg, aristolochic acid) may induce interstitial nephritis and urothelial cancers. Hepatitis C virus infection causes liver cancer and membranoproliferative glomerulonephritis. Smoking is linked with several cancers and renovascular disease. Even obesity and type 2 diabetes cause kidney damage (diabetic nephropathy) and increase the risk for cancer (liver, pancreatic, and kidney) by up to 2-fold. Some kidney diseases are related to cancer, including membranous nephropathy, minimal change disease, crescentic glomerulonephritis, and thrombotic microangiopathy.

The presence of albuminuria coincides with increased cancer risk. Albuminuria may reflect a paraneoplastic kidney disease, but it may also represent a widespread endothelium dysfunction or smoldering inflammation—both often present in malignancies. In the large Tromsø study,[3] increased albuminuria at baseline correlated with increased cancer risk in the follow-up, and the first cancer diagnosis was on average 10.3 years after the initial assessment. The mechanisms for the association between cancer and albuminuria remain unknown. The renin–angiotensin system may play a role: angiotensin II has been implicated in the development and invasion of several cancers. The risk of dying from cancer is also higher in patients with albuminuria compared with those without.

Renal cell carcinoma (RCC) is not uncommon in patients with CKD. Hofmann et al[4] found that the risk of RCC is 2.8-fold higher in patients with CKD. The relative risk varied from 1.1 in whites to 10.4 in blacks. The risk of RCC is approximately 0.03% in the general population; it is 5 to 35 times higher in patients with end-stage renal disease (ESRD) and 10 to 100 times higher after kidney transplantation.[5] The 5-year survival in RCC is 47%, varying from 84% in stage I to 6% in stage IV. Almost one-fourth of patients with RCC have metastatic disease at diagnosis. Active screening for RCC may improve survival; however, it is difficult. Ultrasound can diagnose from 85% to 100% of renal tumors with a diameter of 3 cm, but only 67% to 82% of those with a diameter of 2 to 3 cm. The rates in patients with ESRD are significantly lower. Contrast computed tomography has higher detection rates, but its use is limited by repeated radiation and the need for nephrotoxic contrast agents. Both the Kidney Disease Improving Global Outcomes and American Society of Transplantation acknowledged that there are no sufficient data to recommend any screening scheme for RCC in patients with CKD. In recent years, new biomarkers for RCC have been described. Aquaporin 1 and perilipin 2 detected in urine have a sensitivity of 85% to 92% and specificity of 87% to 100%, but they require validation before they can be routinely used.

Secondary hyperparathyroidism develops in CKD as a response to impaired phosphate elimination and is present in almost all patients with ESRD. While parathyroid cancer is not very frequent, secondary hyperparathyroidism correlates with a 10- to 14-fold increased risk for thyroid cancer.

The presence of CKD limits therapeutic and diagnostic options for cancer patients. The use of contrast agents in imaging may be limited. Chemotherapy is difficult due to decreased clearance,

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not established dosing, increased toxicity, and multiple drug-drug interactions.

The development of erythropoiesis-stimulating agents (ESAs) lowered the need for transfusions. They are used both in CKD and in cancer patients. Anemia may be either cancer-related or chemotherapy-induced. ESAs are indicated for the latter. Concerns about the safety of ESAs include thromboembolic events, increased disease progression, and increased mortality in cancer patients. Data on CKD patients with cancer and ESAs are scarce. In the TREAT trial,[6] darbepoetin alpha increased the risk for cancer-related death in patients with malignancy present prior to randomization. Several meta-analyses confirmed that treatment with ESAs in patients with cancer increased mortality and worsened survival (mostly due to thromboembolic events). The increased risk of death associated with ESA treatment should be balanced against its benefits.[7]

CKD increases the risk of different cancers mildly at the predialysis stage, moderately in ESRD, and severely after transplantation. Not only is the risk of developing cancer higher, but also mortality from cancer is increased in CKD. Treatment with ESAs increases the risk of death, and they should be used with caution in patients with cancer.

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Treatment of cancer in patients with chronic kidney disease: the nephrologist's point of view

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General issues The principle of good oncological practice could be formulated in the simplest way as follows: the treatment should kill cancer, eradicate all neoplastic cells, and simultaneously maintain the patient alive with the smallest possible organ injuries, including the kidneys. Chronic kidney disease (CKD) is common in malignancies, with the reported prevalence at cancer diagnosis from 12% to 53%. The real occurrence may even exceed this upper range, considering the fact that the evaluation of glomerular filtration rate (GFR) is based on the formulas derived from serum creatinine values, which can be misleadingly reduced due to the decreased muscle mass in the course of cancer. Unfortunately, cancer patients have been excluded from 85% of randomized clinical trials with anticancer drugs, even though a negative impact of CKD on cancer prognosis has been well documented.[1] One of the critical factors limiting the effectiveness of cancer chemotherapy is acute GFR deterioration during tumor treatment. Patients with malignancies are particularly prone to the development of acute kidney injury (AKI). This predisposition is associated, apart from preexisting CKD, with such clinical features of the cancer population as advanced age and comorbidities, including diabetes, hypertension, and heart failure. To prevent severe AKI or to treat it effectively, the management of cancer patients should be based on the following key principles:

1 careful monitoring of the volume status to avoid volume depletion;

2 identification and correction of acid-base and electrolyte derangements, that is, hypercalcemia, hyperkalemia, hyponatremia, hypokalemia, and hypomagnesemia;

3 diagnosis of infective processes;

4 recognition of tumor lysis syndrome;

5 alertness to tumor and tumor treatment–related vascular (microangiopathies), glomerular, and tubular injuries, including a wide array caused by a monoclonal protein;

6 detailed knowledge of the possible nephrotoxicity mechanisms of a particular anticancer drug;

7 careful analysis of nephrotoxicity of all drugs administered to a patient in addition to cancer chemotherapy;

8 consciousness of cancer-related obstructive uropathies.

In summary, if an AKI signs are observed in a cancer patient, it requires a careful differentiation between prerenal, renal, and postrenal causes. Moreover, the physician should be aware that an overlap of AKI and preexisting CKD is also common in this clinical setting. Therefore, it is important to avoid the use of drugs with additional nephrotoxicity, such as nonsteroidal anti-inflammatory drugs, and proton pump inhibitors, and, in volume-depleted patients, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics.[2,3]

The specificity of pharmacokinetics in cancer patients is a noteworthy issue, as the kidneys are the main route of elimination for multiple anticancer drugs. Therefore, the dosing of all these drugs should be adjusted to kidney function. A common abnormality in cancer is that hypoalbuminemia increases the free-drug fraction. This, along with liver impairment, should be considered in drug prescription. Another important factor is the drug removal during blood purification in patients with AKI and end-stage renal disease (ESRD) who are on dialysis. This removal may be different in various techniques, for example, in the course of intermittent hemodialysis versus continuous arteriovenous hemodialysis or hemodiafiltration.[2,3]

Specific issues **Targeted therapies: new drugs, new toxicities** The last decade has witnessed a tremendous advance in the development of so called targeted anticancer therapies, which are defined by the National Cancer Institute as: "drugs or substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression." There are numerous categories of the targeted drugs, for example, antiangiogenic (directed against vascular endothelial growth factor [VEGF]) and immune checkpoint inhibitors. The phrase "so called" is particularly applicable to the targeted therapies, because their action is not limited to the concrete tumor but may be associated with general life-threatening side effects, including severe direct and indirect nephrotoxicity. In a simplistic

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way, the toxicity of these presumably specific therapies can be explained by the 2 main mechanisms: the ubiquitous presence of the targeted molecules not confined to the tumor, and autoimmunity induction due to immune system augmentation produced by immune checkpoint inhibitors. For example, VEGF blockade in the vascular wall by the antiangiogenic treatment distorts vasodilatory pathways and induces hypertension. The appearance of hypertension during this therapy may be a biomarker of a better clinical effect. Therefore, the current practice is to continue treatment and control blood pressure with antihypertensive agents rather than stop it. The opposite approach is recommended in cases of acute interstitial nephritis induced by immune checkpoint inhibitors, which may occur after a few months of treatment. The drug should be withdrawn and a course of corticosteroids applied.[2,4]

Renal cell carcinoma: bidirectional connections with chronic kidney disease Patients with CKD have a significantly higher risk of renal cell carcinoma (RCC) development. The excessive incidence occurred at an GFR of 55 ml/min/1.73 m^2, with an adjusted hazard ratio of 2.28 for an GFR of less than 30 ml/min/1.73 m^2. Patients with ESRD and renal cysts have a 100-fold elevated risk for RCC.[5] At the time of the surgery, more than one-fifth of patients with RCC are in CKD stage 3 or greater, which increases to 40% at the age of 70 years. In patients with RCC and CKD, comorbidities, and advanced age, the nephrologist should cooperate with the urologist in terms of the choice between partial nephrectomy, radical nephrectomy, and palliative care. Percutaneous biopsy should be also considered as a minimally invasive tool for the differentiation between benign and malignant renal masses with tumor pathology grading. Importantly, surgically induced CKD is less progressive than CKD from other causes. The pathologist's report on the changes in nonneoplastic renal parenchyma should be ordered to precisely evaluate the postsurgical risk of GFR deterioration.[5]

Summary Nephrotoxicity is a common side effect of oncological treatment. Its occurrence weakens the chances for effective treatment and, in consequence, worsens patient survival. Therefore, the nephrologist should participate in an oncology team in the process of therapy planning and administration. The nephrologist should be viewed not only as a specialist in various kidney lesions but also as an expert in water-electrolyte disorders, which are common in cancer patients. The severity and complexity of complications that occur during an anticancer treatment require an immediate access to various medical specialists. For that reason, I believe that the oncology ward should be located in the confines of a multidisciplinary hospital instead of a separate cancer center.

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Chemotherapy in patients with chronic kidney disease: the oncologist's point of view

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The kidneys are one of the main organs involved in elimination of antineoplastic drugs from the body. Chronic kidney disease (CKD) can result in delayed drug excretion. This raises numerous questions during cancer treatment as to drug dosing, toxicity, and the final effectiveness. Moreover, patients with CKD are excluded from clinical trials, which usually require the serum creatinine level of lower than 1.5 the upper limit of normal.

According to the retrospective observational IRMA studies (Insuffisance Rénale et Médicaments Anticancéreux – Renal Insufficiency and Anticancer Medications), performed in French oncology centers, kidney insufficiency with a glomerular filtration rate (GFR) lower than 60 ml/min/1.73 m^2 affects about 12% of cancer patients with solid tumors. The final results showed that renal insufficiency (GFR <60 ml/min/1.73 m^2) was a prognostic factor for reducing overall survival (OS) both in early-stage and metastatic groups.[1] The possible explanation for shorter OS could be worse initial performance status, comorbidities, reduced doses of cytotoxic drugs, longer intervals between courses of chemotherapy, and a tendency to premature treatment discontinuation.

It is also known that the excessive toxicity of anticancer drugs in CKD patients is a result of altered pharmacokinetics.[2] This complex process is modified in all phases. Absorption is influenced by the changed gastric pH and the increased permeability of the gastrointestinal wall due to accompanying inflammation. It can finally lead to increased oral drug exposure. Drug distribution is changed by the altered volume of distribution and decreased plasma protein binding, which may result in a higher amount of unbound fraction of the drug that is responsible for treatment toxicity. Metabolism is affected by changes in hepatic enzyme activity, which can lead to reduced nonrenal clearance. Finally, CKD results in modification of renal excretion, causing a delayed elimination of cytotoxic drugs and their metabolites.

Considering the complex medical condition of patients with CKD and the limited knowledge about pharmacokinetics in this group, it is difficult to propose a dose adjustment of cytotoxic drugs that would have both high effectiveness and low toxicity. Available recommendations are usually based on an estimated GFR and potential drug toxicity.[2] The Cockroft–Gault formula is most frequently used to calculate GFR, but the method has some limitations. In obese people GFR can be inflated, and underestimated in elderly and underweight patients. In obese patients with a body mass index (BMI) above 25 kg/m^2, the use of an adjusted body weight is recommended. The maximum calculated GFR should not exceed 125 ml/min.

Patients with a reduced GFR usually require dose modification, especially for drugs eliminated by the kidneys. Caution is also needed with cytotoxic drugs eliminated by the liver, especially in elderly patients.[2]

If possible, nephrotoxic anticancer drugs should be avoided or replaced by a less nephrotoxic treatment, for example, cisplatin for carboplatin. When a nephrotoxic drug cannot be exchanged for a drug with lower nephrotoxicity, methods to prevent further kidney injury should be applied, including appropriate hydration, osmotic diuresis (eg, 20% mannitol), or use of cytoprotective agents (eg, magnesium salts for cisplatin). There are some anticancer drugs contraindicated with a decreased GFR, for example, pemetrexed (GFR <45 ml/min), capecitabine and cisplatin (GFR <30 ml/min), or gemcitabine and oxaliplatin (GFR <20 ml/min).[2]

Use of concomitant nephrotoxic agents in supportive care should be also limited. For example, intravenous bisphosphonates should be avoided or more nephrotoxic zoledronic acid should be exchanged for second-generation bisphosphonates. Nonsteroidal anti-inflammatory drugs should be replaced with other, less nephrotoxic, classes of analgesics.

Data on dose adjustment in patients on dialysis are even more limited than in patients with CKD stages 3 and 4. The CANDY (Cancer and Dialysis) study, conducted retrospectively in 12 institutions in France, showed that 72% of cancer patients on dialysis received at least one cytotoxic drug at a reduced dose or a drug for which there were no data about dose adjustment.[3]

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Based on available recommendations,[4,5] a dose reduction is usually required to prevent excessive drug exposure and subsequent toxicity in patients on dialysis. A proper selection of cancer drugs is also crucial. Not all cytotoxic drugs can be used. Those with contraindications include pemetrexed, methotrexate, and ifosfamide. The carboplatin dose is calculated using the Calvert formula with a target area under the curve (AUC) equal to 0 (AUC×25). Cisplatin is administered without any extra hydration, with a dose reduction of 50% to 75%. To determine the proper time of dialysis session, drug clearance should be considered. Drugs whose significant fraction is eliminated during hemodialysis should be administered after a dialysis session to prevent premature elimination and loss of efficacy. Drugs that are not dialyzable can be administered both before and after hemodialysis. Data on combination regimens are derived from single case reports.

Recommendations for CKD patients are based on limited data. They can only serve as a proposition, that should be adapted for an individual therapeutic decision. Hemodialyzed patients constitute a special group at the highest risk for treatment toxicity, so decisions about chemotherapy should be taken with caution. Medical care for patients with CKD requires the close cooperation of both the oncologist and the nephrologist.

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Targeted therapies and chronic kidney disease

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The National Cancer Institute defines a targeted therapy as "a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells."[1] It has been recognized that targeted therapies offer superior patient survival rates compared with classic intravenous chemotherapy. This is a paradigm shift in oncological treatment.

The most common cancer therapies are targeted at proteasome, vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), dimerizations of HER2, v-Raf murine sarcoma viral oncogene homolog B (BRAF), anaplastic lymphoma kinase (ALK), programmed cell death protein 1 (PD-1) and its ligand, receptor activator of nuclear factor–κB ligand, and mammalian target of rapamycin. Targeted therapies exhibit dose-limiting toxicities that are often markedly different from those of chemotherapy. They also show different relationships between the levels of exposure, particularly exposure over time, and pharmacological effects on the molecular drug target. Lastly, they have a unique mechanism of action and many of them are highly specific for single or multiple key cellular biological pathways implicated in carcinogenesis. Anticancer activity of targeted therapies is significantly enhanced in the presence of the specific cellular and molecular markers in a particular pathology, such as HER2 expression in certain tumors (breast, gastric) to administer trastuzumab and/or pertuzumab or to administer imatinib for cases with chronic myelogenous leukemia harboring an oncogenic *BCR-ABL* translocation.

Targeted drugs are generally not cleared by the kidneys; therefore, its dose does not need to be adjusted according to kidney function.[1] Now, all of the orally active kinase inhibitors (most of which are tyrosine kinase inhibitors [TKIs]), as well as inhibitors of the BRAF serine/threonine protein kinase pathway (such as vemurafenib, dabrafenib, and trametinib) and some therapeutic monoclonal antibodies (such as alemtuzumab, ofatumumab, or pertuzumab), are administered using a fixed dose schedule for all patients regardless of weight or body surface area. On the other hand, other monoclonal antibodies (such as ipilimumab, bevacizumab, trastuzumab, panitumumab, brentuximab, and ramucirumab) are given on a mg/kg basis, while still others (such as rituximab and cetuximab) are administered according to body surface area.[2]

The renal toxicity of a targeted therapy is most probably due to the coexpression of the same target molecules by both normal and malignant cells.[3,4] VEGF pathway inhibitors include: 1) VEGF ligand inhibitors, which bind to and inhibit ligand binding to VEGFR, thus preventing activation of the receptor such as bevacizumab or ramucirumab (targeted at VEGFR2); 2) antiangiogenic small-molecule TKIs (sunitinib, sorafenib, pazopanib, ponatinib, axitinib, cabozantinib, lenvatinib, vandetanib), which block the intracellular domain of the VEGFR; and 3) a soluble recombinant decoy that binds to circulating VEGF (aflibercept [VEGF-Trap]).

The major renal adverse effect of all VEGF--targeted agents is proteinuria, which is rarely within the nephrotic range (>3.5 g/24 h) and, even more rarely, is associated with the nephrotic syndrome, hypertension, as well as acute and chronic interstitial nephritis.[2,3] The implications of this asymptomatic proteinuria caused by VEGF inhibitors is unknown, and it is possible that it has no long-term clinical relevance. TKIs also have additional class effects, including gastrointestinal events, such as diarrhea or nausea, which might contribute to acute kidney injury.[3,4] Kidney biopsy performed in patients with proteinuria who are administered VEGF-targeted agents revealed thrombotic microangiography, collapsing glomerulopathy, proliferative glomerulonephritis, and in some cases cryoglobulinemic and immune complex glomerulonephritis.[3,4]

Proteinuria occurs in 21% to 63% of bevacizumab-treated patients or patients with renal cell carcinoma receiving antiangiogenic TKIs, but grade 3 or 4 proteinuria (defined as 3+ on dipstick, >3.5 g of protein/24 hours, or nephrotic syndrome) affects approximately 2% and 6.5% of patients, respectively. In a meta-analysis, the incidence of all- and high-grade proteinuria with antiangiogenic TKIs was lower, reaching 18.7% and 2.4%, respectively.[5] Factors predisposing to proteinuria are a preexisting renal disease

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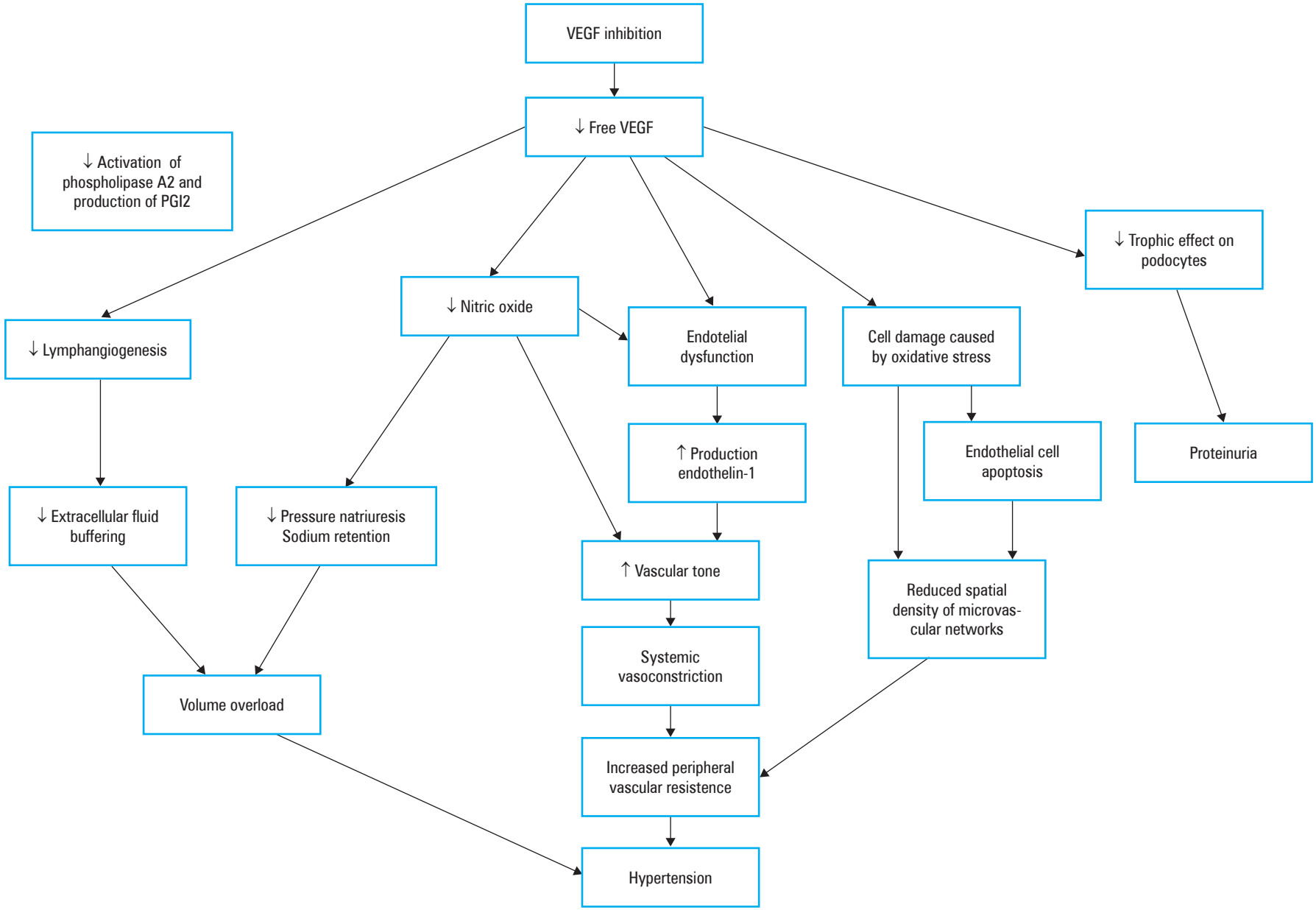

FIGURE 1 Proposed mechanisms of renal adverse events induced by anti–vascular endothelial growth factor (VEGF) therapy (modified from Małyszko et al)[5]

(including higher baseline urinary protein excretion and hypertension) and a diagnosis of renal cell carcinoma. The mechanism of proteinuria as well as kidney damage are not precisely understood (FIGURE 1). Studies on animals revealed the major role of VEGF in the maintenance of a fenestrated endothelium and repair of glomerular endothelial injury. Dose-dependent proteinuria was diagnosed in bevacizumab-treated patients, and the risk was elevated in combination with chemotherapy. The relationship between treatment duration and proteinuria is unclear. It is also unknown whether the development of proteinuria and / or hypertension may serve as a surrogate marker of antitumor efficacy of the therapy.[6] There are no guidelines available for proteinuria management while on antiangiogenic therapy. Bevacizumab is recommended to be temporarily withdrawn if protein levels are higher than 2 g/24 hours and permanently discontinued in nephrotic syndrome. Pazopanib should be discontinued at protein levels of 3 g/24 hours or higher. There are no guidelines for other TKIs. Usually the withdrawal of the offending drug leads to a significant reduction in proteinuria; however, persistence is common. In the latter cases, treatment with drugs affecting the renin–angiotensin–aldosterone system such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers lowers intraglomerular pressure and reduces proteinuria. There are no data available on whether the renin–angiotensin–aldosterone system blockade is beneficial in patients with proteinuria during antiangiogenic therapy. Monoclonal antibodies targeting the EGFR (cetuximab, panitumumab, necitumumab, and matuzumab) are associated with the progressive development of hypomagnesemia due to renal magnesium wasting. Immune checkpoint inhibitors represent major improvements in outcomes of oncological patients. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1 are 2 essential immune checkpoint receptors. Ipilimumab and tremelimumab (anti–CTLA--4-blocking antibodies) and pembrolizumab and nivolumab (antibodies targeting PD-1 receptors) have already been approved in several malignancies. Proteinuria, hypertension, renal failure, and acute interstitial nephritis were reported in patients who were treated with anti–PD-1 antibodies.[3,6] In patients treated with CTLA-4 antibodies, nephrotic syndrome, acute tubular injury / acute tubular necrosis, acute interstitial nephritis, and acute kidney injury have been reported.[3] The observed acute renal damage can be reversed upon drug discontinuation and introduction of a systemic steroid therapy.

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Radiation therapy in patients with chronic kidney disease

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Advances in renal replacement therapy (RRT) that have occurred during the last 20 years have resulted in longer survival of patients with end-stage renal disease (ESRD), especially among the older population. Another consequence is an increase in the incidence of malignancies in a rapidly growing group of patients on RRT. Among them, kidney transplant recipients have the highest risk of cancer, which is associated with the original kidney disease, dialysis therapy, and long-lasting immunosuppressive treatment, all promoting oncogenesis.

Radiation therapy (RT) is frequently a part of cancer treatment to remove a primary malignant tumor or to prevent tumor recurrence after surgery. Furthermore, a synergistic effect of RT and chemotherapy is used in susceptible cancers (head and neck tumors, lung, stomach, rectal, and cervical cancers). Literature data concerning RT in patients receiving RRT are scarce and derived mostly from single case reports and small case series.

In general, the specific aspects of RT in patients receiving RRT in comparison with nonrenal patients include the risk of peritoneal membrane injury in patients on peritoneal dialysis and kidney graft irradiation toxicity in transplant recipients. Peritoneal membrane injury caused by radiation appears to increase the membrane's permeability and to predispose patients on peritoneal dialysis to develop a catheter-related trauma with intraperitoneal hemorrhage. Hutchison et al[1] described complications of RT in a 25-year-old man on continuous ambulatory peritoneal dialysis (CAPD). Abdominal RT (40 Gy in 20 daily fractions) was applied for lymphadenopathy in the course of testicular teratoma. A month after therapy completion, a dramatic increase in peritoneal permeability was observed, confirmed by a peritoneal equilibrium test. It resulted in a loss of ultrafiltration, and consequently discontinuation of CAPD 2 months later.[1] Hassel et al[2] reported intraperitoneal hemorrhage (hemoperitoneum) in a CAPD patient after previous RT for transitional cell urinary bladder carcinoma without peritoneal infiltration. It seems that the bleeding was caused by a mechanical injury of the peritoneal membrane after its irradiation, related to an indwelling peritoneal catheter.

Kidney transplant recipients are a specific group of oncological patients. As with the native kidney, the transplanted kidney is the dose-limiting organ for RT in gynecological and prostate cancers, lymphomas, and sarcomas of the lower abdomen and pelvis, as well as during total body irradiation (TBI). Radiation-induced kidney injury is usually classified based on the criteria developed in TBI studies in nonrenal patients. Acute injury (observed within 3 months after irradiation) is generally subclinical. The signs and symptoms of radiation-induced kidney injury usually develop with long latency within 3 to 18 months and are defined as a decrease in an estimated glomerular filtration rate or an increase in serum creatinine, urea, renin, or β_2-microglobulin levels, proteinuria, hematuria, increased urinary β_2-microglobulin excretion, and kidney atrophy, which differs from the definition recommended by the Kidney Disease Outcomes Quality Initiative. Chronic kidney disease (<20 months after irradiation) is characterized by hypertension, anemia, and glomerular filtration rate decline, leading in some cases to ESRD. Past this period, development of chronic kidney disease related to previous irradiation is unlikely.[3] The dose associated with a 5% risk of radiation-induced kidney injury during TBI without the use of nephrotoxic drugs was 9.8 Gy (median, 12 Gy [range, 7.5–14 Gy]), regardless of the fractionation scheme used. The risk in non-TBI procedures increases from 5% to 50%, with a dose escalation from 18 to 28 Gy for the whole kidney. Therefore, it is generally accepted that the mean dose for the whole kidney irradiation should not exceed 10 Gy for TBI and 18 Gy for non-TBI procedures.[3] Contrary to the native kidneys, data on radiation-induced toxicity in a transplanted kidney are not sufficient for risk estimation.

The use of novel techniques of external beam RT, such as intensity-modulated RT without elective pelvic irradiation or low-dose rate brachytherapy was shown to be a minimally invasive treatment in kidney transplant recipients with localized prostate cancer.[4,5] Intensity-modulated RT should be performed with a full bladder to reduce the risk of late side effects, such as ureteral

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stenosis, and to avoid irradiation of the femoral heads due to the potentially high risk of avascular necrosis of the hips related to long-term corticosteroid use.

The literature concerning RT outcomes in patients on RRT is also very limited. One of the exceptions is a recently published analysis of prostate cancer treatment based on a Korean national database.[6] This study showed that RT is performed almost as frequently in ESRD patients as in non-ESRD patients (19.6% vs 17.1%, respectively), and that 5-year cancer-specific survival rates are worse in patients on dialysis (55.5%) compared with transplant recipients (75.6%) and non-ESRD patients (78.8%). However, the analyses were performed without stratification for specific methods of oncological treatment or the stage of cancer.

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Glomerulonephritis and tumors: the nephrologist's point of view

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Paraneoplastic glomerulonephritides (PGs) are recognized in the presence of malignancy and are induced by molecules (antigens) released by tumor cells. They often undergo remission after the tumors have been eradicated, and, inversely, they relapse with the recurrence of malignancy. The pathogenesis and morphological picture of these glomerulopathies vary depending on the nature of solid tumors or hematologic disorders.[1]

Membranous nephropathy (MN) is the most common presentation of PG in patients with solid tumors. The prevalence for biopsy-proven MN is 10%, whereas in cases of anti–PLA2R- and THSD7A-negative MN, it increases to about 20%. MN mostly involves men aged above 50 years and manifests as nephrotic syndrome, sometimes preceding cancer symptoms (most commonly lung and prostate cancer). The pathogenesis involves not only the subepithelial deposition of immune complexes as in primary MN, but also mesangial or subendothelial deposition. Furthermore, glomerular immunoglobulin IgG1 and IgG2 subtypes were identified, in contrast to IgG4-predominant deposition in primary MN. It suggests that in paraneoplastic MN, both T-helper 1 (Th1) and Th2 pathways of immune activation are involved, which results in an increased number of inflammatory cells in glomeruli as compared with the idiopathic form of MN.[2]

Minimal change disease occurs mainly in association with lung, renal, and colon cancers.[1] Nephrotic syndrome is a typical manifestation of glomerulopathy that can undergo remission after tumor ablation. There are some data suggesting the role of the vascular endothelial growth factor in the pathogenesis of the disease, because this molecule can increase glomerular permeability.[3]

Membranoproliferative glomerulonephritis has been reported in association with lung, renal, breast, and gastric cancers.[1] In these cases, tests for the presence of hepatitis C virus infection and cryoglobulins are negative, but the deposition of immune complexes containing tumor antigens was observed. Removal of the tumor can induce remission of glomerulopathy. Interestingly, prednisone proved effective in some patients with metastatic prostate cancer.[4]

Rapidly progressive glomerulonephritis can develop in association with renal, gastric, and lung cancers.[1] On the other hand, patients with systemic vasculitis and rapidly progressive glomerulonephritis are at higher risk of malignancy, especially when they are treated with immunosuppressive agents. However, this type of therapy can be introduced after tumor removal.

IgA nephropathy can develop in patients with solid tumors of the respiratory tract, buccal mucosa, and nasopharynx,[1] and also in elderly patients with renal carcinoma. In these cases, IgA deposits were found within renal tumor tissue.[5]

Thrombotic microangiopathy (TM) is associated mainly with disseminated gastric, lung, and breast cancers, but also in patients with hematologic malignancies. Microvascular tumor emboli are the main cause of tumor metastases. The prognosis and response to plasma exchange therapy are rather poor.[1]

Paraneoplastic glomerulonephritis can occur also in association with lymphoid and myeloid malignancies. Minimal change disease, focal/segmental glomerulosclerosis, and membranoproliferative glomerulonephritis are the main histological types of PG in these cases.[1]

Early recognition of malignancy-associated glomerulonephritis remains the major problem in the management of PG. Delayed diagnosis and the introduction of immunosuppressive therapy as in the case of primary glomerulonephritis may be harmful to the patient and may induce rapid growth of the tumor. Routine screening for malignancy should be performed in all patients with glomerulonephritis, especially in elderly ones and those with MN. Early diagnosis and tumor removal are the best way to obtain remission.

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Renal manifestations of lymphoproliferative disorders

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Lymphoproliferative disorders (LPDs) are a heterogeneous group of malignancies derived from lymphoid cells at different stages of maturation or differentiation. The current World Health Organization classification defines the following major groups of these diseases: B- or T-lymphoblastic leukemia or lymphoma (included in the "myeloid neoplasms and acute leukemias" category), mature B neoplasms, mature T neoplasms, Hodgkin lymphoma, posttransplant lymphoproliferative disorders, as well as histiocytic and dendritic cell neoplasms.[1]

A lymphoid cell that has undergone malignant transformation is the source of LPDs. As lymphoid cells are scattered over virtually all organs, such transformation may occur not only in bone marrow and lymph nodes but also in any extranodal organ. Although lymph nodes are usually the primary site, it is not infrequent that the tumor is restricted to an extranodal tissue or organ, especially those rich in lymphoid cells. More frequently, extranodal organs are secondarily involved as a sign of disease dissemination.

Symptoms of renal function impairment, the severity of which vary from a slight increase of serum creatinine levels to life-threatening signs of acute renal injury, are quite common in LPDs. Renal symptoms may result either from the infiltration of the kidney, kidneys, or surrounding tissues by malignant cells, or may be an indirect effect of malignancy, or a side effect of chemotherapy. These factors may lead to acute kidney injury (AKI), the etiology of which may be complex. The classification of AKI is as follows: prerenal AKI, intrarenal AKI, and postrenal AKI.

Prerenal AKI in LPDs is the most frequent and is due to volume depletion as a result of insufficient fluid intake, emesis, diarrhea, or polyuria. It may also be a complication of some drugs affecting kidney afferent and efferent tone, like diuretics.[2]

Intrarenal kidney injury in LPDs encompasses a spectrum of pathologies concerning different renal structures and resulting from different causes: acute tubular necrosis, tubulointerstitial disorders, glomerulopathies, or renovascular disorders. Acute tubular necrosis is the most common intrarenal mechanism of AKI during LPDs. It may result from excessive urinary secretion of lysozyme (lysozyme-induced tubular necrosis), may be a manifestation of tumor lysis syndrome as a complication of cytostatic treatment, or may be caused by nephrotoxic antibiotics or cytostatic drugs.[2]

Tubulointerstitial disorders are caused mainly by renal infiltration by tumor cells either as a primary lymphoma of the kidney or as its secondary involvement during disease dissemination. Primary lymphoma of the kidney is very rare, probably due to the absence of lymphoid cells in renal parenchyma. It accounts for less than 1% of all extranodal lymphomas. It is asymptomatic or causes flank pain, hematuria, or hypertension. The diagnosis is based on renal biopsy.[3] In contrast, secondary infiltration of the kidneys frequently occurs during lymphoma progression. In a series of 700 autopsies of patients with Hodgkin and non–Hodgkin lymphoma, the presence of malignant infiltration in the kidneys was detected in 34% of cases. Again, the diagnosis is made on the basis of renal biopsy.[4] The detection of renal involvement is crucial for the proper staging of Hodgkin and non-Hodgkin lymphoma, and thus for therapeutic decision making.

Glomerulopathies of different types have been reported in a number of lymphoid malignancies. Their mechanism is supposed to be related to an aberrant cytokine production, resulting in immune complex deposition, and cellular proliferation. In patients with lymphoma and concomitant nephrotic syndrome and renal insufficiency, it is necessary to test for amyloid light-chain (AL) amyloidosis, caused by glomerular deposits of amyloid, a protein derived from immunoglobulin light chains or their fragments.[2]

Finally, renovascular disorders include renal venous or arterial thrombosis and thrombotic microangiopathies. The principal underlying conditions are nephrotic syndrome, antiphospholipid syndrome, chemotherapy, and leukostasis when bone marrow infiltration leads to hyperleukocytosis. It must be noted that leukostasis is exceptional in indolent non-Hodgkin lymphomas or chronic lymphocytic leukemia, even if the peripheral lymphocyte count is very high, but patients with acute or chronic myeloid leukemias are

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at risk when the white blood cell count is higher than 100 000 /μl.

Postrenal AKI in the lymphoma setting is usually caused by the compression of the urinary tract by enlarged lymph nodes. Occasionally, it may result from intrarenal obstruction or retroperitoneal fibrosis.[2]

Renal function impairment is particularly frequent in multiple myeloma (MM), a disease characterized by clonal proliferation of plasma cells or their precursors with subsequent bone destruction and impairment of medullar hematopoiesis. It is found in 20% to 50% of patients at diagnosis and even in more patients during disease progression. The laboratory hallmark of MM is the presence of serum monoclonal immunoglobulin produced by the malignant clone. The light chains, when produced in excess as compared with heavy ones, are secreted by the kidneys and detected in urine. The principal cause of renal function impairment in MM is the formation of tubular casts in the distal nephron by the binding of the light chains and Tamm–Horsfall protein (myeloma kidney). Other causes of renal insufficiency include hypercalcemia related to bone lysis, AL amyloidosis, hyperviscosity syndrome, and gout. The investigation of renal function in MM is all the more important considering that the elevated creatinine level is one of the indications for cytostatic treatment.

AL amyloidosis is another form of clonal plasma cell proliferation, which often leads to renal function impairment. It can occur along with MM, other B-cell malignancies, or alone. As mentioned above, the most typical syndromes are nephrotic syndrome and renal insufficiency, often moderate.[5]

In conclusion, the assessment of renal function is extremely important for hematologists who treat patients with LPDs. In particular, detection of renal lymphomatous infiltration, as well as of other nonlymphoid organs, is crucial for the proper staging of lymphomas and for the choice of therapeutic strategy. Renal function must also be considered when choosing the cytostatic drugs, especially those which are nephrotoxic or are eliminated by the kidneys. This is why a close collaboration between the hematologist and nephrologist is necessary for successful management of those malignancies.

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Monoclonal gammopathy of renal significance: a nephrologist's perspective

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Introduction The current diagnostic criteria define monoclonal gammopathy of undetermined significance (MGUS), which is considered a benign plasma cell dyscrasia, include serum M protein levels of less than 3 g/dl and bone marrow infiltration of clonal plasma cells of less than 10%, with no disease-related end-organ damage. Monoclonal gammopathy of renal significance (MGRS) fulfills the hematologic criteria for monoclonal gammopathy defined as a heterogenic group of disorders pathogenetically characterized by proliferation of a B-cell or plasma cell clone. This small clone synthesizes and secretes a monoclonal immunoglobulin (Ig) or its components (light or heavy chains), which may be directly deposited in the kidneys or indirectly cause alternative complement pathway dysregulation and cause glomerular, tubular, interstitial, or vascular damage. The term MGRS does not encompass kidney disorders associated with large clone lymphoproliferative disorders, such as multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, and malignant lymphoma. The prognosis for survival is more severe when compared with MGUS, because if untreated, MGRS leads to progression of kidney damage. Moreover, in MGUS treatment is not necessary, while in MGRS therapy is fundamental and has been shown to improve long-term outcomes.[1,2]

Diagnosis of monoclonal gammopathy of renal significance The diagnosis of a suspected MGRS is based on the presence of kidney damage (progressive kidney failure, nephrotic syndrome and nonnephrotic proteinuria, Fanconi syndrome, or tubulointerstitial dysfunction) in association with monoclonal peak in serum electrophoresis. In most cases, the diagnosis is established using serum and urine electrophoresis, and according to recommendations, a 24-hour urine collection for electrophoresis is required. However, in cases where the concentration of monoclonal protein in plasma or urine is undetectable in conventional electrophoresis, plasma and urine immunofixation must be additionally performed. Immunofixation will identify the type of monoclonal protein and determine whether free light chains are present in blood and urine. Interestingly, most cases of kidney damage in MGRS are diagnosed mainly on the basis of findings in kidney biopsy. Kidney biopsy is required for the diagnosis of MGRS, and must include immunohistochemistry, immunofluorescence, and electron microscopy. Monoclonal Ig deposition is involved in many types of MGRS.[3,4]

Pathological studies may require electron microscopy because it allows a proper characterization of the ultrastructural organization of Ig deposits. Importantly, the diagnosis of amyloid light-chain (AL) amyloidosis requires not only Congo red staining of the biopsied tissue but also immunohistochemistry and immunoelectron microscopy or mass spectrometry. These methods are also used to exclude a late-onset hereditary form of amyloidosis or the wild-type transthyretin. Laser microdissection and mass spectrometry proteomics are recommended to confirm not only AL amyloidosis but also cases of monoclonal Ig deposition disease with truncated monoclonal Ig or types where the specific monoclonal Ig region is of interest. To identify a pathological clone, diagnostic workup should begin with a bone marrow biopsy, which in most cases is sufficient for clonal identification. Flow cytometry is important for identification of smaller clones, which may be often missed by a histologic examination. It is important especially in the presence of clonal plasma cells or B cells, even when marrow cellularity is below 5% of pathological marrow cells. When the bone marrow specimen is negative for atypical plasma cells or B-cells, a lymph node biopsy may be necessary. Positron emission tomography, computed tomography, or magnetic resonance imaging may be helpful in locating adenopathy.[1,5]

Pathogenesis of renal damage in monoclonal gammopathy of renal significance Two major pathophysiological mechanisms have been involved in MGRS: direct and indirect, which mainly depend on physicochemical properties of monoclonal Ig. The direct mechanism is the most common. Here kidney damage is induced by direct monoclonal Ig deposition. It is preceded by receptor-mediated endocytosis into glomerular or tubular cells after monoclonal Ig has been filtered into

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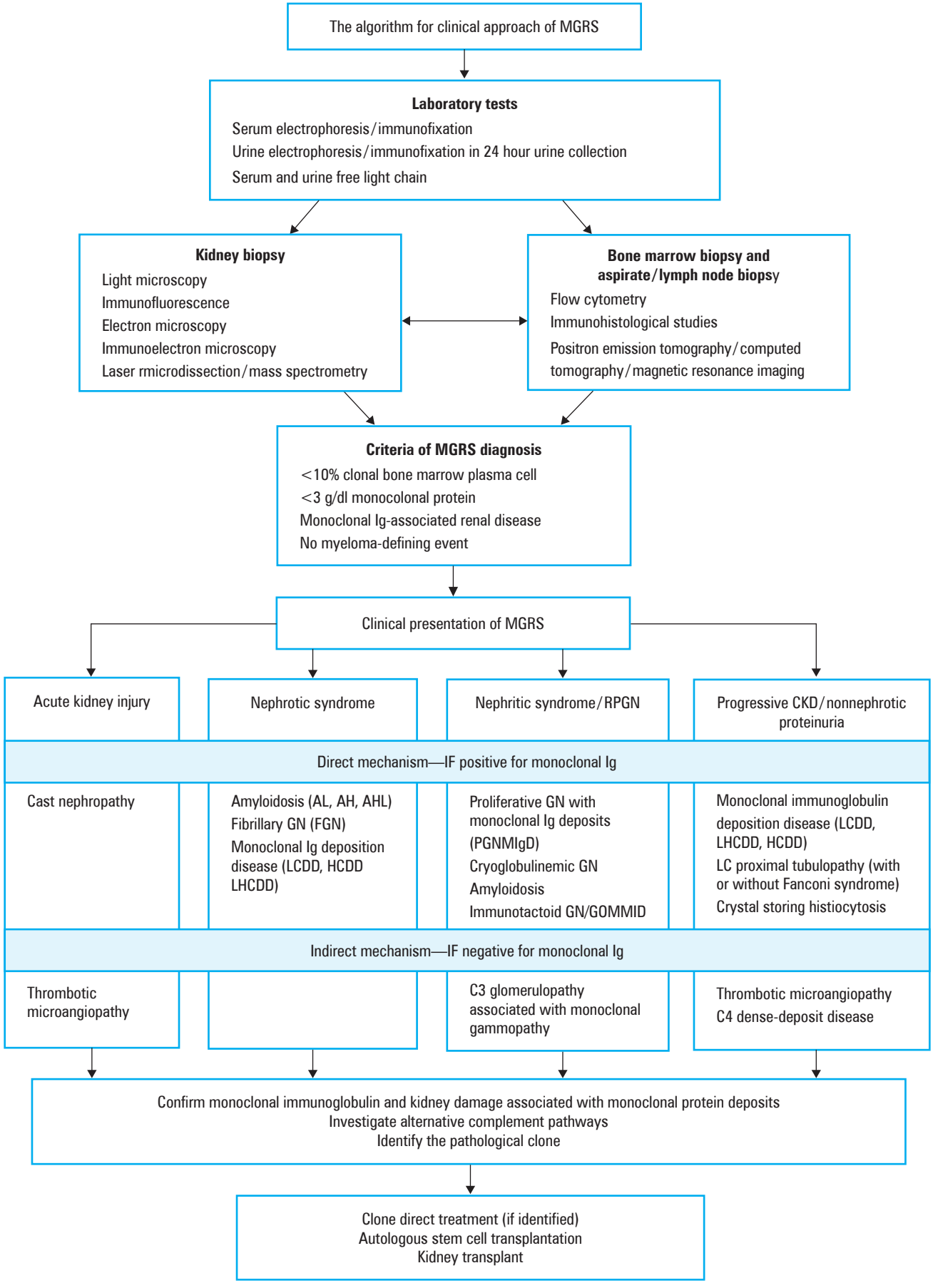

FIGURE 1 Proposed algorithm for nephrologic workup in patients with monoclonal gammopathy of renal significance
Abbreviations: AH amyloidosis, heavy-chain amyloidosis; AHL amyloidosis, heavy- and light-chain amyloidosis; AL amyloidosis, light-chain amyloidosis; GN, glomerulopathy; GOMMID, glomerulopathy with organized microtubular monoclonal deposits; HCDD, heavy-chain deposition disease; LC, light chain; LCDD, light-chain deposition disease; LHCDD, light- and heavy-chain deposition disease; MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease; PGNMIgD, proliferative glomerulopathy with monoclonal immunoglobulin deposits

the urinary space. The indirect mechanism depends on monoclonal Ig acting as an autoantibody, as in the case of C3 glomerulopathy and atypical hemolytic uremic syndrome. Here antibodies influence dysregulation of the liquid or solid phase of the alternative complement pathway; for example, anti–factor H is the main antibody involved in C3. A similar mechanism was also found in C4 dense deposit disease with dysregulation of the mannose-binding lectin pathway of the complement.[2]

The algorithm for the clinical approach to MGRS is presented in FIGURE 1.

Histologic findings The diagnosis of MGRS requires an analysis of morphologic alterations seen on light microscopy, electron microscopy, and immunofluorescence, in correlation with clinical parameters. Immunofluorescence should be performed using panel antibodies specific for different light chains and monoclonal Ig isotypes.

Among the histologic lesions observed in MGRS, we distinguish organized and nonorganized Ig deposits. Examples of organized deposits are fibrillar Ig deposits, amyloidosis, fibrillary glomerulonephritis, microtubular Ig deposits, immunotactoid glomerulopathy, type I cryoglobulinemic glomerulonephritis, and types with crystal inclusion (such as proximal tubulopathy, with or without Fanconi syndrome, and histiocytosis, in which the crystal deposits are not found in tubular epithelial cells but inside the histiocytes). On the other hand, histomorphological lesions include also nonorganized Ig deposits such as proliferative glomerulonephritis with monoclonal IgG deposits, C3 glomerulopathy with monoclonal gammopathy, and monoclonal immunoglobulin deposition disease.[5] Clinical manifestations of the heterogeneous group of diseases occurring in MGRS are presented FIGURE 1.

Treatment of monoclonal gammopathy of renal significance Every case of MGRS should be consulted by a hematologist for eradication of the clonal disease. The most common multidrug treatment regimen that would be appropriate for the clones detected in MGRS disorders includes cyclophosphamide, proteasome inhibitors (bortezomib or carfilzomib), dexamethasone, bendamustine, and rituximab. Immunomodulatory agents (thalidomide, lenalidomide, or pomalidomide combined with dexamethasone) are also prescribed. In the future, anti-D38 monoclonal antibody (daratumumab) can be used for the treatment of newly diagnosed MGRS, as in patients with multiple myeloma. In MGRS caused by the indirect mechanism (such as C3 glomerulonephritis and dense deposit disease), the use of eculizumab may result in the reduction of proteinuria and serum creatinine levels. After hematologic remission in patients with MGRS and end-stage renal disease, autologous stem cell transplantation and kidney transplantation should be considered.[3,4]

MGRS is a disease of the kidney, secondary to a B-cell or plasma cell clonal proliferation or the alternative pathway of complement dysregulation and immune dysfunction. It requires a therapeutic intervention to eradicate the offending clone. Untreated MGRS leads to kidney damage and renal replacement therapy, worsening prognosis and decreasing survival in this patient group.

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Thrombotic microangiopathy as a manifestation of cancer or a complication of chemotherapy

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Introduction Thrombotic microangiopathy (TMA) related to malignancy is a complex disease syndrome characterized by small vessel thrombosis with subsequent ischemia and failure of target organs, predominantly the central nervous system (CNS) and kidneys. The 2 main disease entities are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).[1]

TMA can be a manifestation of cancer or a complication of chemotherapy. The complexity of TMA may range from autoantibody-related TTP or HUS to different forms of secondary TMA (eg, drug-induced TMA, TMA after bone marrow transplantation, malignancy-associated TMA) and TMA associated with infections (eg, sepsis, HUS caused by Shiga toxin–producing *Escherichia coli*, or HIV-associated TMA) (**FIGURE 1**).

Clinical manifestation Thrombotic microangiopathy may present as a generalized condition or may be limited only to the target organ. The pentad of symptoms characterize TTP: 1) thrombocytopenia, 2) microangiopathic hemolytic anemia (MAHA), 3) neurological disturbances, 4) kidney injury, and 5) fever.

Most of the cases of TTP are acquired (97.5%). The main mechanism of TMA is caused by ADAMTS13 deficiency (either due to thrombotic exhaustion or autoantibodies), which leads to impaired clearance of ultralarge von Willebrand factor, promotion of platelet aggregation, and thrombus formation, with subsequent occlusion of small vessels. Hemolytic uremic syndrome is clinically characterized by MAHA, thrombocytopenia, and microvascular thrombosis with subsequent endothelial damage and predominantly kidney injury. Two main forms of HUS are characterized by altered complement activation, promoted either by factors inhibiting complement regulation (atypical HUS) or HUS triggered by endothelial damage caused by bacterial (Shiga or pneumococcal) or viral infection.

In cancer patients, TMA may be a manifestation of malignancy itself, a complication of chemotherapy, may occur after bone marrow transplantation, may be caused by treatment with antibodies and immunotoxins or evoked by infectious complications.[2] Most cases of cancer-related TMA were attributed to mucin-producing adenocarcinoma with stomach cancer as the most common, but also breast, prostate, lung, pancreatic cancer, and lymphoma. As a rare disease, TMA accounts for 0.25 to 0.45 cases per million, but exceeds 5% in patients with metastatic disease.[3] In cancer, TMA is caused by neoangiogenesis in bone marrow, with formation of abnormal vessels and liberation of ultralarge von Willebrand factor. Decreased ADAMTS13 activity is caused by autoantibodies.

Clinically, TMA may manifest as an acute event with full-blown symptoms (MAHA, acute kidney injury [AKI], and CNS involvement) or a subacute event with mild thrombocytopenia and slow progression of kidney failure. Chemotherapeutic agents may induce TMA due to direct toxicity (drug-induced TMA) or autoimmunity with anti-ADAMTS13 antibodies or anticomplement antibodies. The most prominent dose-dependent toxic effects are displayed by gemcitabine and mitomycin C, whereas autoimmunity may be triggered by oxaliplatin treatment. Immunotoxins stimulate proinflammatory cytokines, which promotes TMA. Antiangiogenic drugs exert their prothrombotic activity by inhibiting vascular endothelial growth factor and subsequently disarranging podocytes and the filtration membrane. Thrombotic microangiopathy after hematopoietic stem cell transplantation (HSCT; transplant-associated TMA) develops in 15% to 20% of patients and clinically presents as slowly deteriorating kidney function, hypertension, and disproportionately severe anemia. Infrequently, AKI and seizures may be a manifestation of TMA caused by graft versus host disease. Other transplant-associated TMA–related factors include radiation damage of

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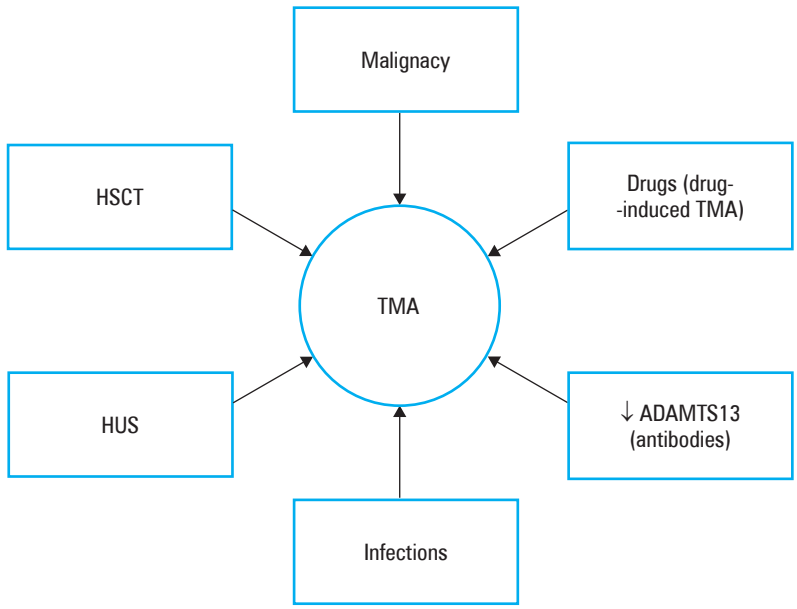

FIGURE 1 Causes of malignancy-related thrombotic microangiopathy. Abbreviations: HUS, hemolytic uremic syndrome; HSCT, hematopoietic stem cell transplantation; TMA, thrombotic microangiopathy

kidney vasculature and mTOR inhibitors (sirolimus) effects. Bone marrow transplantation also increases the risk of sepsis and thrombotic events.

Diagnosis The presence of MAHA and thrombocytopenia with target organ involvement is usually sufficient to diagnose TMA. Kidney biopsy is typically not indicated unless there is poor treatment response or massive kidney injury. In such a case, mesangiolysis with intraluminal thrombi is typical for TMA. Bone marrow biopsy can be sometimes diagnostic, especially in recurrent cases with new-onset TMA, where marrow infiltration may be present.

Complications There may be several complications of TMA: 1) acute respiratory distress syndrome with high mortality, 2) AKI, 3) seizures with CNS involvement, 4) pancreatic insufficiency with transient diabetes mellitus, 5) cardiomyopathy and myositis, and 6) chronic TMA with progression of CKD.

Diagnostic criteria At present, there are no diagnostic guidelines for TMA. The diagnosis is based on recognizing MAHA, thrombocytopenia, AKI, CNS involvement, and acute onset of hypertension.

Differential diagnosis Both disseminated intravascular coagulation (DIC) and TMA may cause microvascular thrombosis associated with thrombocytopenia, bleeding tendency, and organ failure. DIC is a more common coagulation abnormality (300 cases per million) than TTP (2 cases per million). Most patients with TMA share DIC criteria, whereas only 10% to 15% of patients with DIC share TMA features.[4] DIC is characterized by lung and kidney involvement, shock, low blood pressure, erythrocyturia (rare), anemia (frequent), low platelet count, high levels of products of fibrin degradation, prolonged prothrombin time, and low albumin levels. ADAMTS13 activity of less than 10% defines TTP and differentiates it from other thrombotic microangiopathies.[5]

Treatment Treatment consists in lowering the increased blood pressure, protecting the kidney during pre-HSCT radiation, removal of immune complexes (plasmapheresis, plasma exchange, immunoadsorption). In the case of drug-induced TMA, discontinuation of the drug is recommended, and reintroduction is possible beginning at a lower dose to avoid recurrent TMA. Eculizumab, an antibody that blocks cleavage of complement C5 protein and thus prevents the generation of the terminal complement attack complex C5b-9, may also be useful in TMA induced by HUS.

A detailed differential diagnosis is necessary to confirm malignancy-related TMA. The type of cancer, history of treatment, and type of used drugs are important to establish the diagnosis. Development of TMA may be a direct consequence of cancer, its treatment, or it may occur after HSCT.

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Kidney lesions secondary to malignancy: a pathologist's perspective

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The currently known mechanisms of kidney injury in the course of malignancy are complex and include direct renal tissue infiltration by malignant cells; an injury caused by a paraprotein released by neoplastic cells; glomerulonephritis (GN) related to the glomerular deposition of immune complexes containing neoplastic antigens; glomerulonephritis related to the malignancy-associated complement activation; and thrombotic microangiopathies.[1]

The concept of paraneoplastic glomerulopathy refers to glomerular injury that is indirectly caused by malignant tissue via hormones, cytokines, antigens, and other substances released or stimulated by neoplastic cells. The true incidence of paraneoplastic glomerulopathies is unknown owing to diagnostic difficulties.

The diagnostic criteria for paraneoplastic glomerulopathy or nephropathy include the resolution of renal lesions following the remission of malignancy, correlation between reoccurrence of malignancy and kidney lesions, as well as detection of neoplastic antigens and specific antibodies within glomerular deposits.[1]

Membranous nephropathy (MN) is one of the most common types of GN associated with the presence of immune complexes in glomeruli. This is a chronic glomerulopathy defined by the presence of immunoglobulin G (IgG)–containing immune deposits in the subepithelial region of the glomerular basement membrane (GBM). Membranous nephropathy may arise as a manifestation of an idiopathic autoimmune process, most commonly associated with the PLA2R antigen, or develop secondary to systemic conditions, such as infections, autoimmune disorders, drug toxicities, and malignancies.

The concept of its potentially paraneoplastic character is based on several observations. First, 69% of patients with malignancy and nephrotic syndrome are found to have MN.[2,3] Second, in comparison with the general population, individuals with MN are at higher risk of malignancy, and this risk is age dependent (1% among patients younger than 60 years, 10% among those older than 60 years).[3]

There are 3 proposed pathomechanisms of paraneoplastic MN: 1) immune-complex formation in situ, in which antineoplastic antibodies bind to neoplastic antigens that are deposited in the subepithelial region of the GBM, or antineoplastic antibodies bind to podocytic antigens, which are similar or identical to the neoplastic ones; 2) immune-complex formation by neoplastic antigens and their specific antibodies originate in circulation and are then deposited in the subepithelial region of the GBM; 3) both MN and malignancy are evoked by the same extrinsic factors (eg, oncogenic viruses).[1,2]

Apart from clinical investigation, the paraneoplastic character of MN may be suspected on the basis of the domination of IgG1 and IgG2 within the subepithelial glomerular deposits, together with the absence of IgG4 and PLA2R antigen in the same localization. Another factor that has been recently suggested to be involved in the diagnosis of paraneoplastic MN is thrombospondin type-1 domain-containing protein 7A (THSD7A).[4]

IgA nephropathy is the most common type of chronic glomerulonephritis in the world and is defined by the dominance or codominance of IgA within the glomerular immune complex deposits. IgA nephropathy may be primary or secondary. Among the various potential etiologies, secondary IgA nephropathy has been linked to renal cell carcinoma but also malignant tumors of the respiratory tract, nasopharynx, and oral cavity.[1-3]

Adult patients with Henoch–Schönlein purpura (HSP) have been reported to have a significantly higher risk of malignancy, as compared with the general population. The risk factors are male sex, older age, joint involvement, and the presence of cutaneous necrosis.

It has been reported that crescentic glomerulonephritis, both related and unrelated to antineutrophil cytoplasmic antibodies, is associated with an increased risk of kidney, stomach, and lung cancers.[1-3]

Although mostly related to chronic inflammatory processes, amyloid A amyloidosis has been shown to occur also in the course of renal cell carcinoma, with the frequency of 3%. It has been proposed that renal cell carcinoma stimulates the development of amyloid A amyloidosis via interleukin 6 released by tumor cells.[2,3]

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TABLE 1 Renal lesions evolving secondary to monoclonal gammopathies or malignant lymphoproliferation

Lesions associated with organized deposits
Amyloidosis: • Light-chain amyloidosis (λ chain in 75% of cases, κ chain in 25% of cases) • Heavy-chain amyloidosis • Light- and heavy-chain amyloidosis
Paraprotein-associated fibrillary glomerulonephritis
Immunotactoid glomerulonephritis
Glomerulonephritis associated with cryoglobulinemia type 1
Lesions associated with nonorganized deposits
Monoclonal immunoglobulin deposition disease (MIDD): • Light-chain deposition disease (about 75% of MIDD cases, in most cases associated with monoclonal κ light chain) • Heavy-chain deposition disease (about 15% of MIDD cases) • Light- and heavy-chain deposition disease (about 10% of MIDD cases)
Proliferative glomerulonephritis with monoclonal IgG deposits
Paraprotein-associated C3 glomerulopathy with monoclonal gammopathy

TABLE 2 Tubular lesions related to monoclonal gammopathies and malignant lymphoproliferation

Proximal tubulopathy associated with the presence of monoclonal light chain: • Proximal tubulopathy with crystals and clinical manifestation of the Fanconi syndrome • Proximal tubulopathy without crystals and without manifestation of the Fanconi syndrome
Cast nephropathy

Minimal change disease (MCD) is one of the patterns of glomerular injury, a podocytopathy, that may be idiopathic or develop secondary to infections, drug toxicities, and malignancies.

Among the various forms of neoplasia thymoma, Hodgkin lymphoma and renal cell carcinoma were shown to have the strongest association with MCD. Malignancy-related factors most probably involved in the development of MCD are vascular endothelial growth factor and interleukin 13.[2,3]

Membranoproliferative glomerulonephritis is one of the chronic forms of glomerulonephritides, defined by the presence of immune deposits in the subendothelial region of the GBM and double contouring of glomerular capillaries. Among the various forms of malignancy, chronic lymphocytic leukemia, monoclonal gammopathy, and B-cell lymphomas were shown to have the strongest association with membranoproliferative glomerulonephritis.[2,3,5]

Thrombotic microangiopathy most commonly complicates the course of mucus-producing tumors, such as stomach, lung, and breast cancers.[2,3] Some types of nephropathies develop as a renal manifestation of monoclonal gammopathy of unknown significance, in such case being recognized as monoclonal gammopathy of renal significance (MGRS) or as a complication of malignant lymphoproliferation (multiple myeloma or lymphoma) (TABLES 1 and 2).[5]

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Tumor lysis syndrome

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The risk of acute kidney injury (AKI) is 2-fold higher in patients with malignancies than in those with conventional risk factors, such as infection or heart failure. In patients with hematologic malignancies, dehydration and tumor lysis syndrome (TLS) are the 2 most common causes of AKI (48% and 42%, respectively).

Tumor lysis syndrome is an oncologic emergency resulting from rapid cell death that may occur spontaneously or as a consequence of tumor-targeted chemotherapy.[1,2] It is most often reported in patients with hematologic malignancies and only sporadically in those with solid tumors. The highest incidence of TLS has been reported in B-cell acute lymphoblastic leukemia (26%), acute lymphoblastic leukemia (23%), acute myeloid leukemia (19%), and Burkitt lymphoma (15%).[3] The first description of TLS was made in 1929 in patients with chronic leukemia, and its current definition was introduced in 1992 (**TABLE 1**). Although several risk factors for TLS have been established, including the type of malignancy, advanced age, bulky lymphatic disease, elevated lactic dehydrogenase, and white blood cell count exceeding 25 000 cells/mm^3 and baseline creatinine exceeding 1.4 mg/dl or uric acid exceeding 7.5 mg/dl, the baseline risk assessment equations have not yet been implemented in clinical practice.

The pathogenesis of TLS includes the chain of events starting from rapid and massive breakdown of tumor cells.[1,3,4] It leads to a release of large amounts of potassium, phosphate, and nucleic acids, which may cause injury to the kidneys and heart. Acute arrhythmias and heart failure caused by TLS increase the risk of sudden death. The mortality in established TLS is around 21% but rises to 66% after the development of AKI. Therefore, the prevention of AKI is the most important target in the management of TLS. Early laboratory diagnostic workup includes a basic metabolic panel with additional assessment of blood lactic acid and electrocardiography. The current algorithm for the management of TLS includes the initial risk stratification based on the type of tumor. Low-risk patients are hydrated orally or with intravenous crystalloids to maintain diuresis of >2 to 3 l/24 h or higher than 2 ml/kg/min. Allopurinol may be considered for those patients, but it is recommended routinely only in intermediate- and high-risk patients. Allopurinol is given orally at doses adjusted to baseline kidney function for 7 days before chemotherapy. The same prophylaxis is recommended for patients at high risk of TLS. All patients need to be monitored for TLS during and after chemotherapy. The laboratory parameters including serum creatinine, phosphate, uric acid, and calcium are measured every 12 to 24 hours. In case of TLS, the possible complications (AKI, arrhythmia, heart failure) must be intensively managed and urease supplementation (rasburicase) should be considered.[3]

Several specific problems related to TLS management, including hyperuricemia, hyperphosphatemia, hypocalcemia, urine alkalization, and dialysis, may require a modification of the basic algorithm. Hyperuricemia is due to a massive release of nucleic acids from avidly metabolizing tumor cells. Nucleic acids are purine precursors and are metabolized to hypoxanthine and xanthine, which are eventually converted by xanthine oxidase to uric acid with poor water solubility. Humans lack the enzyme urate oxidase (uricase), which converts uric acid to water-soluble allantoin. This defect makes them prone to the development of uric acid urinary stones and obstructive AKI caused by uric acid crystal formation inside renal tubules. The prevention of TLS-induced AKI is the cornerstone of the management of TLS.[1,3] The treatment focuses on the decrease of uric acid formation by an inhibition of xanthine oxidase by either allopurinol or a more specific inhibitor, febuxostat, together with promotion of uric acid excretion. Since both these drugs do not decrease serum uric acid levels if they are already elevated, their use is limited to the prophylaxis of TLS-associated AKI. The inhibition of xanthine oxidase also increases the concentration of xanthine and hypoxanthine, which may lead to the formation of xanthine-containing stones that may cause AKI. The only method to effectively remove excess uric acid is to convert it to a more soluble allantoin by supplementation of recombinant uricase. Rasburicase has been available for the treatment of TLS-associated hyperuricemia in adults since 2009. The drug effectively lowers serum uric acid levels in all treated patients, is administered intravenously for 5 to 7 days, and is not cumulated in renal disease. Rasburicase is contraindicated in patients with a deficiency of

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TABLE 1 Cairo–Bishop criteria for the classification of tumor lysis syndrome in adults (modified from Wilson and Berns)[3]

Laboratory TLS	Clinical TLS
• Serum uric acid ≥8.0 mg/dl (≥476 µmol/l) • Serum potassium ≥6.0 mEq/l (≥6.0 mmol/l) • Serum phosphorus ≥4.6 mg/dl (≥2.1 mmol/l) • Serum calcium ≤7.0 mg/dl (≤1.75 mmol/l)	• AKI (defined as creatinine >1.5-fold the upper limit of normal for patient age and sex) • Cardiac arrhythmia • Seizure, tetany, or other symptomatic hypocalcemia
• Patients must meet more than 2 of the 4 laboratory criteria in the same 24-hour period within 3 days before to 7 days after chemotherapy initiation. • A 25% increase from baseline laboratory values is also acceptable. • Other causes of AKI (eg, exposure to nephrotoxin, urinary tract obstruction) should be excluded.	

Abbreviations: AKI, acute kidney injury; TLS, tumor lysis syndrome

glucose-6-phosphate dehydrogenase owing to the risk of hemolysis.

The risk of hyperphosphatemia is very high in TLS due to the release of large amounts of phosphate after the rupture of tumor cells, which have an accelerated metabolism and cumulate 4 to 5 times more phosphate than normally dividing cells. In spontaneous TLS, hyperuricemia is mild owing to an uptake of phosphate by other tumor cells. Hyperphosphatemia increases extraskeletal calcification and calcium phosphate urinary stone formation and may lead to secondary hypocalcemia. In TLS caused by chemotherapy, the prevention of hyperphosphatemia includes intensive hydration and administration of oral calcium-containing phosphate binders that also protect against hypocalcemia.

Hyperkalemia is one of the most clinically relevant complications of TLS because of an increased risk of cardiac arrest and arrhythmia. It is aggravated by coexisting metabolic acidosis. The treatment includes the administration of intravenous calcium preparations, β_2-mimetics, insulin with glucose, and potassium-binding resins.

Alkalization of urine by the administration of sodium bicarbonate had been recommended as an essential part of TLS treatment until the recognition of the risks related to possible formation of calcium phosphate crystals inside renal tubules and a decrease of serum ionized calcium levels possibly leading to life-threatening cardiac arrhythmia. Alkalization is now not routinely recommended. Hemodialysis is not routinely recommended and is currently required only in 5% of adults and 1.5% of children that developed TLS-related AKI.

In summary, TLS is a frequent complication of hematologic malignancies treated by chemotherapy. The risk of TLS is determined mostly by the type of malignancy and tumor size but is modified by several factors, including the baseline kidney function. Furthermore, AKI is the most important complication of TLS, and simple hydration and inhibition of uric acid formation are the cornerstone of its prevention.

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Malignancy-related electrolyte and acid–base disorders

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Electrolyte and acid–base derangements are among the most common health problems. In patients with malignancies, they increase mortality, decrease quality of life, affect frequency and length of hospitalization, delay antineoplastic therapy, or may even lead to treatment discontinuation. In some cases, the presence of electrolyte disorders may reduce the effectiveness of treatment.

Increased nonosmotic secretion of antidiuretic hormone (ADH) is the most common cause of hyponatremia in patients with cancer (so called syndrome of inappropriate ADH secretion). Possible sources of ADH include cancer cells (usually small cell lung cancer), increased activity of posterior pituitary lobe induced by vomiting, chemotherapy agents (vincristine, vinblastine, cyclophosphamide), or symptomatic treatment (analgesics, nonsteroidal anti-inflammatory drugs, antidepressants). Potentiation of ADH release leads to a reduction in free water clearance and an increase in intravascular volume, causing serum sodium dilution. Elevated atrial natriuretic peptide levels caused by volume expansion or paraneoplastic synthesis may increase natriuresis, exacerbating electrolyte disorders. Unfortunately, an inappropriate high-volume hydration often used for prophylaxis before chemotherapy may contribute to adverse water and electrolyte shifts.[1]

Cancer treatment may cause electrolyte disorders but may also prove effective in their resolution. However, the specific regimen often cannot be introduced until hyponatremia is at least partially resolved. Therefore, symptomatic treatment should be directed at the underlying disorder. When deciding on a treatment strategy, intravascular volume should be considered. In patients with euvolemia or hypervolemia (ie, with syndrome of inappropriate antidiuretic hormone secretion), fluid restriction is the mainstay of treatment. A hypertonic (in most cases 3%) NaCl solution is suggested in severe hyponatremia. Recently V_2 receptor antagonists (so called vaptans) have been successfully used in the management of euvolemic or hypervolemic hyponatremia. They increase water diuresis leading to quick resolution of hyponatremia. However, it is advised to use them as a short-term therapy, mainly to enable an antineoplastic therapy, or as a palliative treatment.[2]

Vomiting, diarrhea, or chemotherapy-induced tubular damage (ie, after cisplatin use) may lead to severe hyponatremia and hypovolemia. In those patients, euvolemia should be the primary goal of treatment. The choice of an appropriate solution should also improve electrolyte balance.

Regardless of the cause, the sodium level should always be raised in a controlled manner to avoid osmotic demyelination.[1] The longer the duration of hyponatremia, the longer the resolution.

Hypokalemia is the second leading electrolyte disorder related to malignancy. A confluence of pathological processes leads to excessive potassium loss via the gastrointestinal tract (diarrhea after chemotherapy) or urine (lysozymuria in some leukemias, increased renin activity, or Fanconi syndrome after chemotherapy) and transmineralization (certain leukemias, treatment with myelopoietic growth factors). Some rare cases of hypokalemia caused by malnutrition or paraneoplastic adrenocorticotropic hormone secretion (small cell lung cancer) should be considered. The treatment in the oncologic population does not differ from the management in the general population. Resolving other electrolyte disorders (magnesium, phosphates) is important, particularly in the case of Fanconi syndrome.[2]

Hypercalcemia and hypophosphatemia are the main calcium and phosphate homeostasis disorders in oncologic patients. The former is most commonly the result of neoplasm potential of osteolysis activation, while the latter is frequently a consequence of oncologic treatment. Osteoclast activation by parathyroid hormone-related protein (urinary tract, ovarian, breast cancers) or cytokine-mediated bone resorption (metastases of breast cancer, lymphoma, myeloma) results in osteolysis. Increased calcium and phosphate absorption may be the result of 1,25-dihydroxycholecalciferol (1,25-OH-D)–secreting lymphomas.[3]

Refeeding syndrome after an intensive course of chemotherapy, excessive phosphate loss as a result of tubular damage, or increased phosphatonin release (parathormone, fibroblast growth

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factor 23) are the main causes of hypophosphatemia in patients with cancer.[2]

The primary aim of hypercalcemia treatment is to reverse the renal consequences of high calcium level (ADH resistance, intravascular volume depletion, afferent arteriole constriction), which requires isotonic fluid infusion. Currently, there is no evidence to confirm the efficacy of loop diuretics in hypercalcemia. Inhibition of osteolysis is the second target of treatment. Bisphosphonate or denosumab regimens directly inhibiting osteoclast activity seem to be effective.[2,3]

In hypophosphatemia the main effort should be aimed at a proper protein-rich diet and phosphate supplementation.[2]

Type B lactic acidosis is a quite interesting complication of neoplastic disease. It is assumed that cancer cells present a specific pattern of lactate metabolism. They switch their metabolic pathways to a glycolytic state even at normal oxygen concentrations (Warburg effect). Although increased lactate dehydrogenase activity is found in many tumors, in most cases there are no symptoms of acidosis because most of the lactate is recycled back to glucose in the liver (Cori cycle) and kidneys. Interestingly the majority of patients with malignancy-related lactic acidosis have no signs of liver or kidney function deterioration. Some authors suggested gluconeogenic pathway impairment as a possible reason of lactic acidosis in this population.[4]

Recently, some specific tumor lactate transport pathways have been found. Monocarboxylate transporters facilitate shuttling of lactate between the neighboring cells, which is probably necessary for angiogenesis, neoplasm growth, and metastases formation. Therefore, the transporters seem to be critical elements in maintaining intracellular lactate concentrations. Targeting those transporters as well as inhibiting lactate dehydrogenase may prove effective in cancer therapy.[4] Neutralization of tumor acidity was found to potentiate the effects of immunotherapy.[5]

Prediction, early diagnosis, and proper treatment are crucial in electrolyte and acid–base balance disorders. In cancer patients, it is even more important because untreated metabolic derangements increase mortality, hinder the implementation of cancer-specific treatment, and lead to further complications. Some acid–base disorders and their role in tumor cell biology may be a target for new antitumor agents, enriching the anticancer armamentarium.

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Dialysis in a patient with acute renal failure and malignancy

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Patients with malignancies are at high risk of acute kidney injury (AKI). In its most advanced form, namely, acute renal failure (ARF), renal replacement therapy (RRT) is required. Both, AKI and ARF are associated with high mortality rates. Renal cell carcinoma (RCC), hematologic malignancies (multiple myeloma [MM] and other paraproteinemias, leukemias, and lymphomas), and hepatocellular cancer are most frequently complicated by AKI, which is also common after bone marrow stem cell transplantation.

Among patients with AKI undergoing RRT (usually continuous RRT [CRRT]) in the intensive care unit (ICU), hematologic malignancies have significantly higher incidence and mortality rates than solid malignancies. Outside the ICU, intermittent techniques are typically used. An uncuffed non-tunneled central venous catheter allows a blood access for hemofiltration, hemodiafiltration, and hemodialysis. The preferred location for the catheter is the right jugular vein, followed by femoral veins and left jugular vein. The subclavian access is associated with a high risk of post-implantation venous stenosis.[1]

At the ICU, the blood flow for CRRT is usually set at 150 ml/min, and citrates are used as an anticoagulant. Regular monitoring of serum calcium levels allows a detection and prevention of hypocalcemia. If unfractionated heparin is used as an anticoagulant, a 50 IU/kg bolus is followed by a continuous infusion of 1000 IU/h (alternatively, 2500 IU bolus and 5–10 IU/kg/h infusion). The effectiveness of heparin should be checked every 4 hours. Fractionated heparins can also be used in CRRT.

In patients with normal catabolism and ARF and in those with nonhematologic malignancies, the ultrafiltration in hemodiafiltration is typically set to 25 ml/kg/h in the postdilution mode and 35 ml/kg/h or higher in the predilution mode. The latter is preferred in hypercatabolic patients and in those with paraproteinemias. The filtration fraction should always be less than 15% during postdilution and less than 25% during predilution. To convert hemofiltration into hemodiafiltration during CRRT, the dialysis fluid flow of 1000 to 2000 ml/h is added. Both hemofiltration and hemodiafiltration efficiently remove middle molecules (0.5–20 kD): β_2-microglobulin (11.8 kD), myoglobin, and hemoglobin. Some high-flux dialyzers (high cutoff) can remove even the tumor necrosis factor α (30 kD), immunoglobulin free light chains (25–50 kD), pentraxin 3 (40 kD), visfatin (52 kD), and some advanced glycation end products (1–70 kD).

If intermittent RRT is used, the blood flow is set at 250 to 400 ml/min, and the dialysis fluid flow, at 500 to 800 ml/min. In the case of online hemodiafiltration, the substitution volume ought to exceed 40 l. Intermittent hemodialysis is used in patients on maintenance RRT. Hemodialysis is preferred to CRRT in tumor lysis syndrome because of its efficiency in removing small molecules (<0.5 kD), mainly urea, uric acid, calcium, and potassium.

In paraproteinemias, the most common cause of AKI in hematologic malignancies, hemofiltration, hemodiafiltration, or hemodialysis using high-flux dialyzers are preferred because a rapid decrease in plasma light chain concentrations improves prognosis (EuLITE study).[2] The median survival of patients with MM undergoing maintenance hemodialysis is 2 years, and in 30% of cases, it exceeds 3 years despite death in 15% to 30% of patients during the first months from diagnosis. In patients with MM, the concomitant use of high-cutoff hemodialysis and bortezomib seems highly effective in recovering renal function.[3]

Hydration (3 l/24 h) to achieve euhydration and euvolemia, followed by strict fluid balance control, is obligatory (Kidney Disease Improving Global Outcomes guidelines). In patients with MM, furosemide increases the probability of cast forming.

Alkalization does not improve renal outcomes in MM and is contraindicated in tumor lysis syndrome.

It is recommended to avoid the use of nephrotoxic medications, and the dose of drugs in hemodialysis patients with MM should be adjusted: the oral dose of melphalan should be reduced by 50% (high dose, 140 mg/m^2), and of lenalidomide, by 5 mg/24 h. No dose modification is needed for dexamethasone, bortezomib, thalidomide, doxorubicin, and cyclophosphamide.

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In dialysis patients with malignancy, daily hemodialysis is not superior to hemodialysis 3 times/wk. The efficacy of therapy for ARF is determined solely on the basis of achieving independence from dialysis, but the renal effects of chemotherapy in MM can be seen long after 3 months of treatment (MYRE study).[4]

In dialysis patients with ARF, the prognosis, either in terms of survival or renal function recovery, does not depend on the presence of hematologic or nonhematologic malignancy.[5,6] In ARF patients with malignancy who did not recover their renal function, another malignancy should be suspected because 10% of patients on maintenance hemodialysis have been shown to have 2 malignancies.[7]

In dialysis patients with electrolyte imbalance (eg, hypercalcemia or hyperkaliemia) and hyperuricemia, the standard dialysis fluid and concomitant pharmacotherapy should be used. In the case of hypercalcemia, high doses of corticosteroids, short treatment with calcitonin (for tachyphylaxis), and inhibitors of the receptor activator of nuclear factor κB ligand (eg, denosumab) are safe, but bisphosphonates should be prescribed with extreme caution.

In conclusion, malignancy in patients with AKI does not influence prognosis, either in terms of survival or renal function recovery. Thus, the malignancy itself is not a reason why RRT should not be used in patients with AKI; rather, depending on the type of malignancy, the standard RRT protocols should be adjusted as necessary.

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Acute kidney injury in patients with cancer: the role of palliative care

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Acute kidney injury (AKI) is the most common form of kidney disease that occurs in patients with cancer.[1] The causes of AKI in the setting of malignancy are similar to those in other clinical settings and include prerenal, renal, and postrenal entities. Prerenal AKI can be due to fluid depletion (poor intake, vomiting, diarrhea), hypercalcemia, and medications, for example, nonsteroidal anti-inflammatory drugs and anticancer drugs. Renal causes comprise glomerular nephropathies, tubulointerstitial pathology (acute tubular necrosis, contrast nephropathy, cast and uric acid nephropathy [eg, tumor lysis syndrome]), and thrombotic microangiopathy. Extrarenal obstruction causing postrenal AKI may be due to primary disease, retroperitoneal lymphadenopathy, or fibrosis.

The incidence and severity of AKI depends on the type and stage of cancer, functional status, and comorbidities. Morbidity and mortality rates increase in the presence of critical illness and the need for renal replacement therapy. While dialysis may be perceived as a life-saving therapy, in many cancer patients, especially with end-stage disease, it may present as a futile, life-sustaining treatment associated with functional and psychological burdens.

Palliative care is specialized medical care that focuses on improving the quality of life of both the patient and the family. It should be provided in the early stages of chronic disease with the goal of relieving physical, psychological, social, and spiritual symptoms. It may help patients cope with emotional distress, as well as increase their understanding of the prognosis. In addition, it may facilitate choosing appropriate therapeutic pathways in accordance with the patient's priorities and goals of care. Instead of providing treatments that answer the question of "What interventions are available?," the patient-centered vision of care should address the issue of treatment goals that are attainable and desired for that particular patient, and how they can be translated into medical care.

Unfortunately, palliative care consultation is underused and rarely offered to patients and families with AKI, especially those hospitalized in the intensive care unit.[2]

A patient-physician relationship that promotes shared decision making is recommended for all patients with AKI. This is one of the recommendations that has been introduced in the form of clinical guidelines in the United States and in many other countries afterwards.[3] When the outcome is uncertain, patients may be offered time-limited trials of dialysis, with the goal to withdraw dialysis if it does not provide benefit in the specified time.[4]

Advance care planning has been defined as a process of formal decision making that aims to help patients make decisions about future care that may take effect when patients lose capacity. Advance care planning facilitates the delivery of care that is more in keeping with patient wishes, takes patient's preferences and values into account, and increases patient and family satisfaction with care.

Symptom management is crucial for cancer patients experiencing AKI.[5] Pain and nonpain symptoms are frequent and affect the quality of life. For mild pain, acetaminophen can be used safely without any dose adjustment, whereas nonsteroidal anti-inflammatory drugs should generally be avoided. Gabapentin or pregabalin at reduced doses with or without antidepressants may be added as an adjuvant therapy. For moderate to severe pain, tramadol can be used cautiously (≤200 mg/d). Fentanyl and methadone are the preferred opioids for use in patients with end-stage renal disease, while morphine, because of the accumulation of active metabolites, should be given when death is imminent. The dose of opioids should be adjusted: in the case of stage 5 of kidney failure, the dose of fentanyl should be reduced to 50%; methadone, to 50% to 75%; and morphine, to 25% of the usual dose. For agitation, a short-acting benzodiazepine like midazolam is safe to use, but the risk of exacerbating delirium should be considered. Haloperidol is recommended for hallucinations, delirium, and nausea with the dose reduced by 50%. Pruritus can be managed with phosphate binders, emollients, antihistamines, gabapentin, pregabalin, antidepressants, or naltrexone. For dyspnea, ensure optimal fluid balance, and for refractory shortness of breath, fentanyl (12.5 μg) every 2 hours

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subcutaneously or intravenously is recommended, with morphine being left for the end-of-life care. Fatigue should be screened for reversible causes and can be relieved by individualized physiotherapy. Psychological symptoms like depression and anxiety should be diagnosed appropriately and treated with cognitive behavioral therapy or integrative psychotherapy. Selective serotonin reuptake inhibitors such as fluoxetine, sertraline, and citalopram have been proved to be useful and are recommended in chronic kidney disease. Restless leg syndrome and sleep disturbances may be successfully controlled with gabapentin (100–300 mg/d) or pregabalin (25–75 mg/d) at reduced doses and benzodiazepine and nonbenzodiazepine receptor agonists such as lorazepam, temazepam, zolpidem, zoleplon, and zopiclone.

Social and spiritual symptoms should be addressed by strengthening personal relations and bonds, open communication on existential domains (eg, purpose, meaning in life, and capacity for personal growth and self-transcendence), as well as social and financial support.

Good collaboration and open and honest communication among oncologists, nephrologists, palliative care teams, and often intensivists, is necessary to guarantee that in the case of sophisticated modes of treatment for AKI, the degree of advanced life support therapy remains proportional to the expected long-term prognosis and quality of life. In addition, provision of palliative care for patients with end-stage cancer is of utmost importance in relieving burdensome symptoms in patients and families.

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Progressive kidney failure in a patient with a neuroendocrine neoplasm treated with a somatostatin analogue

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Neuroendocrine neoplasms (NENs) are rare tumors characterized by their ability to secrete peptides, resulting sometimes in distinctive hormonal syndromes, which facilitates the diagnosis. The majority of NENs arise sporadically, and the most frequent primary sites are the gastrointestinal tract and lungs. However, up to 22% of patients are not diagnosed until liver metastases have developed.

Surgery and somatostatin analogue therapy are the cornerstone of treatment, while classic chemotherapy and radiotherapy play a minor role. Somatostatin analogues result in temporary stabilization of the disease and improvement of symptoms. Peptide receptor radionuclide therapy (PRRT) utilizes somatostatin receptor overexpression on NEN to deliver targeted radiotherapy. PRRT is given to patients with NENs. The radiopeptide is reabsorbed in the proximal tubule and retained in the interstitium, leading to kidney irradiation. Renal failure may become clinically evident years after radionuclide therapy, especially following the use of ^{90}Y-labelled analogues, so kidney toxicity remains an issue for this therapy. The mechanism of kidney damage during PRRT is not clear. Renal manifestation in a patient diagnosed with NEN can result also from primary renal localization but it is very rare.

A 65-year-old man with NEN of unknown origin and liver metastases diagnosed in 2009 and treated with long-term somatostatin analogue therapy for 7 years was admitted to the Nephrology Department for deterioration of kidney function, with no other markers of kidney damage. Except for type 2 diabetes of 1-year duration, controlled only with diet, the prior history was unremarkable. Four cycles of ^{90}Y-HYNIC TATE were administered due to the progression of NEN (from September 2014 to May 2015; cumulative dose, 14.8 GBq) 8 months before admission. Kidney function was normal before radionuclide therapy.

Five months after cessation of PRRT, an increase in serum creatinine (sCr) levels was noted. When the levels increased to 2.6 mg/dl (estimated glomerular filtration rate [eGFR], 26 ml/min/1.73 m^2), the patient was referred to the nephrologist. On admission to the Nephrology Department, he was in good general condition, had no edema, and his vital signs were stable with normal blood pressure (113/60 mm Hg). Initial laboratory tests showed an elevated sCr concentration (4.1 mg/dl; reference range, 0.72–1.18 mg/dl; eGFR, 16 ml/min/1.73 m^2; reference range, >16 ml/min/1.73 m^2), slightly reduced white blood cell count (3.9×10^3/μl; reference range, 4.0–10.0 $\times 10^3$/μl), and hemoglobin concentrations of 9.0 g/dl (reference range, 13.5–18.0 g/dl). Urinalysis showed no proteinuria with normal urinary sediment. Urine culture test was negative. The patient had hyperlipidemia: total cholesterol, 243 mg/dl; low-density lipoprotein cholesterol, 173 mg/dl; triglycerides, 153 mg/dl. Other routine biochemical blood tests were within normal ranges. He tested negative for hepatitis B virus, hepatitis C virus, and HIV as well as for antineutrophil cytoplasmic, antinuclear, and antiglomerular basement membrane antibodies. Abdominal ultrasound and computed tomography showed an enlarged lymph node (69 × 35 × 50 mm) in the extraperitoneal space and 2 metastatic lesions in the liver: 12 mm and 32 mm, and a slightly reduced kidney size (right kidney, 98 × 42 mm, with a core of 14 mm; left kidney, 90 × 40 mm, with a core up to 14 mm) with no signs of urinary obstruction or kidney stones. Renal artery stenosis was excluded. A kidney biopsy revealed membranous nephropathy (MN). Anti-PLA2R1 antibody titers were negative. Renin–angiotensin system blockers were not tolerated by the patient because of symptomatic hypotension. Systemic steroids were introduced. Three pulses of intravenous methylprednisolone (500 mg), followed by

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oral prednisone (0.5 mg/kg) with dose reduction over 6 months to 10 mg/d, were administered. The treatment resulted in improvement and stabilization of kidney function. In a 2-year follow-up, the patient was treated with maintenance steroid therapy and somatostatin analogues. His kidney function was stable (sCr, 2.9–3.1 mg/dl; eGFR, 25–30 ml/min/1.73 m^2) with small proteinuria (up to 0.4 mg/dl, with negative urinary sediment). There was also no evidence of NEN progression.

This case demonstrates the rapid deterioration of kidney function caused by MN developed shortly after administration of ^{90}Y-labelled analogue in a patient with NEN and liver metastases treated long-term with somatostatin analogues. The diagnosis of MN was surprising owing to atypical clinical presentation with no proteinuria, rapid progression of kidney failure, and late appearance after cancer diagnosis. We do not know if nephropathy may reflect primary or secondary glomerulonephritis or is a manifestation of nephrotoxicity.

The time relationship with PRRT may indicate nephrotoxicity as a cause of MN. Our hypothesis is supported by the lack of anti-PLA2R1 antibodies. The progression of kidney failure is one of the adverse events in the course of PRRT. A decline in creatinine clearance of 7.3% per year in patients treated with ^{90}Y-labelled analogues and 3.8% per year with ^{177}Lu-labelled analogies, which are less nephrotoxic, may be expected. However, rapid kidney function deterioration, as observed in our case (decrease in eGFR over 50% during 6 months after the last cycle of PRRT), with annual eGFR losses of 40% to even 60% was also described. The coadministration of positively charged amino acids, such as L-lysine or L-arginine, which competitively inhibit proximal tubular reabsorption of radiopeptide by binding to the megalin receptor (which has renoprotective effects), is used during PRRT. Our patient received it along with the administration of the ^{90}Y-labelled analogue, but he was exposed to a high dose of radiopeptide (14.8 GBq [400 mCi]), higher than the recommended cumulative dose. Pathophysiological conditions leading to the development of radiation nephritis are incompletely understood, and a kidney biopsy is very rarely performed. In patients in whom histopathology was available (single cases), radiation-induced thrombotic microangiopathy was most frequently reported, with marked tubular atrophy and compensatory interstitial fibrosis.

In our case, the most important factor considered in the choice of treatment method was the absence of proteinuria accompanied by an aggravating oncologic history and a rapid progression of kidney failure. Administration of drugs recommended in MN, namely, cyclophosphamide, chlorambucil, cyclosporine A, or tacrolimus, was not advised due to the history of NEN. Thus, although steroid therapy alone is not recommended for remission induction in MN, it was chosen as a treatment option for our patient. It resulted in a decrease of sCr levels and stabilization of kidney function in the 2-year follow-up.

The unusual clinical manifestation of MN probably due to radiopeptide nephrotoxicity emphasizes the necessity of a kidney biopsy in every patient with kidney injury of unknown origin.

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Membranous nephropathy: anti-PLA_2R–guided diagnosis versus clinical reality

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Membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome (NS) in adults. Most cases are of autoimmune origin (so called primary or idiopathic MN), while some cases (so called secondary MN) are associated with malignancy (it is often the primary or prodromal presentation of neoplastic disease, usually of common solid cancers, or can be regarded as paraneoplastic syndrome), infections, autoimmune systemic diseases, or drugs. The natural course of primary MN is variable and unpredictable. In approximately one third of patients, the symptoms completely disappear (remission) after 5 years without any treatment; about 25% to 40% of patients show partial remission, whereas most patients with persisting severe NS will progress to end-stage renal disease within 10 years.[1] Proteinuria was previously the only marker of disease activity, and immunosuppressive treatment indications and adjustments were essentially empirical, after intensive clinical workup and exclusion of secondary MN.[1,2]

A major progress in the understanding of the pathophysiological mechanisms of primary MN was made in 2009, when the first target autoantigen was identified, namely, the M-type phospholipase A_2 receptor (PLA_2R), a podocyte membrane glycoprotein. Anti-PLA_2R antibodies can be nowadays detected in serum and measured by immunoassays in up to 80% of patients with primary MN. There also seems to be a relationship (in most but not all patients) between the titer of circulating anti-PLA_2R antibodies and clinical disease activity as defined by proteinuria.[2,3]

The discovery has dramatically changed and improved the approach to treatment. It allowed the patients with clinically occult and unidentified causes of secondary MN to avoid aggressive and unnecessary immunosuppressive therapy, often employing steroids and cytotoxic alkylating agents.

We report here a case of a 65-year-old man positive for anti-PLA_2R antibodies, who was initially aggressively and successfully treated for primary MN. He later developed localized chondrosarcoma, and his MN recurred and became progressive.

The patient was a practicing obstetrician-gynecologist. He developed an ankle edema in September 2009. This led to the diagnosis of severe nephrotic syndrome with normal estimated glomerular filtration rate. A percutaneous renal biopsy was then performed and revealed MN stage II. On immunofluorescence, the parietal deposits were granular and stained for immunoglobulins IgG and IgM, complement C3, and fibrinogen. Immune deposits were positive for the PLA_2R antigen, and serum was positive for anti-PLA_2R antibodies. A complex antiproteinuric treatment with telmisartan, atorvastatin, furosemide, and low-dose spironolactone was administered, along with acenocoumarol for deep vein thrombosis prophylaxis. The patient was started on immunosuppressive therapy (a modified Ponticelli regimen) consisting of 3 intravenous infusions of methylprednisone (1.0 g) at the beginning of months 1, 3, and 5, followed by oral prednisone (0.5 mg/kg body weight) (along with a proton pump inhibitor) for the remaining 27 days, tapered at the end of the month to 10 mg/d. In months 2, 4, and 6, he was given 150 mg/d of oral cyclophosphamide. Then, in line with the Ponticelli protocol, the treatment was terminated (it may not be prolonged and must not be administered more than once in a lifetime). The patient achieved full remission (actual daily proteinuria below 0.5 g) and was negative for serum anti-PLA_2R antibodies.

He was readmitted 7 years later with full-blown NS, slightly impaired kidney function (serum creatinine of 1.2 mg/dl, estimated glomerular filtration rate of 57 ml/min/1.73 m^2), and again with a high titer of serum anti-PLA_2R antibodies. Kidney biopsy was not repeated, and he was administered 15 mg of prednisone and 150 mg/d of cyclosporine A for the next 6 months. Partial proteinuria remission was achieved (about 1.5 g/d) and kidney function was stabilized.

Importantly, on repeated diagnostic tests, a small nodule (about 1 cm in diameter) was found in the 5th right costa in the anterior axillary line (opacity with dense margin on X-ray). The patient palpated the nodule several months before while sunbathing, deemed it to be a benign fibroma (in which he was also reassured by his son, an orthopedic surgeon), and did not consent to a nodule biopsy or excision. In the following months,

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the mass was gradually growing, and 13 months after the previous hospitalization, the lesion together with the costal fragment was surgically removed. It showed up to be grade G1 chondrosarcoma, a malignant tumor of a relatively low-grade invasiveness and slow growth potential.[4] The patient also underwent aggressive radiotherapy of the chest (cancer cells in the cutting line). During a 6-month follow-up, no tumor recurrence was noted, while proteinuria increased to 10 g/24 h and serum creatinine, to 2.5 mg/dl. Further immunosuppressive therapy was contraindicated and presumably useless due to the cirrhotic appearance of the kidneys on ultrasound.

In summary, our case raises several important clinical questions: 1) Was chondrosarcoma already present but occult on initial NS presentation? 2) Was the tumor the actual cause of secondary MN while the anti-PLA_2R antibodies suggestive of primary MN were only a false positive finding or not causative of MN? 3) Did chondrosarcoma develop as a result of long-term immunosuppressive therapy for MN? In other words: was chondrosarcoma the cause of MN or an effect of its treatment?

The take home message could be as follows: be aware of the neoplastic disease during the diagnostic workup for glomerular disease (occult cancer) and administration of immunosuppressive therapy, which may enhance the growth or development of malignant tumors.

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Cancer in patients with end-stage renal disease and kidney transplant recipients

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Organ transplantation is the current treatment of choice for end-stage organ failure. The number of organ transplantations and life expectancy of organ transplant recipients have increased worldwide, thus the community of recipients is growing. Organ replacement therapy compensates for organ function loss; however, it does not imply complete health normalization. In many cases, the primary disease persists, and also other diseases may occur. Lifelong immunosuppressive treatment implemented in these patients has many side effects, including cancer and infections.

The incidence of cancer among patients with end-stage renal disease (ESRD) and kidney transplant recipients is higher compared with the general population, and these neoplasms are more aggressive. There are also some other discrepancies in epidemiology and risk factors for cancer between these patients and the general population. It could result from the complex etiology and pathogenesis of posttransplant malignancy, including impaired immunosurveillance, increased DNA damage, or an increased rate of infections. For example, numerous arising tumors have features different from those seen in the general population. Genomic damage manifested by the number of micronuclei in lymphocytes from dialysis patients was more severe compared with healthy individuals, which could result from the increased concentration of uremic toxins: angiotensin II, hydroquinone, indoxyl sulfate, and others. DNA damage also correlates with serum creatinine concentrations.[1,2] Increased serum levels of metabolic toxins in patients with ESRD could also be involved in mitochondrial dysfunction as well as tricarboxylic acid cycle or fatty acid β-oxidation disorders, which are present in renal cancers.[3] The role of viruses, especially the Epstein–Barr virus, human herpes virus 8, human papillomavirus, and hepatitis C and B viruses in the pathogenesis of cancer has been confirmed. Currently, also parasites are recognized as cancer risk factors. It is estimated that prevention of viral and parasite infection would decrease cancer incidence by 23% in less developed countries and by 7% in well-developed countries.[4]

A recent study of cancer incidence in hemodialysis patients, conducted between 1996 and 2009 in the United States, found a standardized incidence ratio (SIR) of 1.42, as compared with the general population.[5] Kidney transplantation increases the risk of cancer. In renal transplant recipients, the cumulative cancer incidence was 49.3% for all cancers and 39.7% for tumors (excluding nonmelanoma skin cancers), as compared with 21% for the general population.[6] However, when epidemiology and cancer incidence are considered in patients with ESRD or kidney transplant recipients, the primary disease should also be considered because it could be a risk factor for cancer itself. For example, type 2 diabetes is associated with higher incidence of cancer, and the SIR is 1.16 compared with the general population.[7] On the other hand, cancer incidence among renal transplant recipients due to polycystic kidney disease (PKD) is lower compared with the incidence among kidney transplant recipients without PKD. A study conducted in the United States revealed that the overall cancer risk was increased by 48% in recipients with PKD compared with the general population, while the overall cancer risk in non–PKD recipients was increased by 86%.[8]

Patients with ESRD and kidney transplant recipients develop similar types of cancer, but different from those observed in the general population. These patients are more likely to have kidney, bladder, and liver cancer, and in the case of women, breast cancer. On the other hand, the incidence of colon, lung, stomach, mouth and tongue, cervical, uterine, and other cancers is the same as in the general population.[5,9]

The milieu of risk factors in patients with ESRD or kidney transplant recipients is wider than in the general population, and there are some discrepancies in their significance. In the general population, the average number of newly diagnosed cancers and the rates of cancer increase with age, in both sexes, but only until the age of 70 years. After this age, the average number of newly diagnosed cancers decreases, while the rate still increases. Similarly, in patients with ESRD and kidney transplant recipients, the risk

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of newly diagnosed cancers increases with age, and the SIR is 4.93 at the age of 65 years compared with the age of 18 to 34 years. There are no data regarding older patients.[10] The age at transplantation also affects the risk of cancers: it increases by 78% in patients who underwent transplantation at the age above 50 years, as compared with those below 50 years of age.[6] Other independent risk factors for cancer in patients with ESRD and kidney transplant recipients are male sex and the presence of reactive antibodies before transplantation. Interestingly, the history of cancer in the pretransplant period does not increase the risk of cancer after transplantation.[6]

In patients with ESRD and kidney transplant recipients, the body mass index does not influence the risk of cancer. On the other hand, in the general population, it is one of the most important risk factors for cancer development and also influences the outcome (eg, the relative risk of death), especially in the case of kidney cancer, which is among the most common cancers in patients with ESRD.[10,11]

The role of the primary disease in cancer development was mentioned above. Another problem is therapy, both before and after transplantation, including immunosuppression. Epidemiological studies confirmed that the incidence of cancer has increased with the introduction of immunosuppressive regimens (azathioprine, cyclosporine, cyclosporine / azathioprine, tacrolimus, tacrolimus / mycophenolate mofetil (MMF), cyclosporine / MMF); however, it does not differ significantly between particular regimens. A tendency for lower cancer incidence was observed among patients receiving sirolimus-based therapies. On the other hand, the addition of MMF was shown to increase tumor development.[6] Interestingly, the risk of cancer is not increased in patients with multiple transplantations despite a long immunosuppression therapy, which is burdened with increased cancer risk.[12] The use of interleukin 2–receptor antagonists in the pretransplant period had a slight protective effect against cancer development.[6] Many patients with ESRD receive erythropoietin. It is beneficial in anemia, but it also has serious adverse effects, especially when administered to patients with cancer. Erythropoietin could increase the risk for local-regional progression and shorten 12-month and overall survival rates in patients with cancer.[13] Currently, hypoxia-inducible factor prolyl hydroxylase inhibitors are under investigation and show promising results in anemia treatment in dialysis patients. However, possible adverse effects in patients with cancer, similar to those of erythropoietin, should be considered.[14]

The mortality rate from malignancy in patients with ESRD was shown to be 2.9-fold higher, and in transplant recipients, 1.7-fold higher than in the general population. However, when patients with malignancies as primary disease were excluded, the mortality rates from malignancies were accordingly 2.2- and 1.5-fold higher.[15] Other diseases, such as diabetes, hypertension, cardiovascular diseases, chronic lung disease, and chronic liver disease, increased the mortality rate in dialysis patients with cancer by 69%, 30%, 54%, 47%, and 34%, respectively.[9] Therefore, the above mortality rates could be further reduced by the exclusion of these diseases.

In summary, despite the progress in medicine and transplantation, further research is needed to clarify the problem of cancer pathogenesis in patients on dialysis and kidney transplant recipients and to guide the development of effective prevention and treatment methods.

In the above considerations, the problem of skin cancers and posttransplantation lymphoproliferative diseases was not considered.

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The risk of cancer associated with immunosuppression in kidney transplant recipients

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In kidney transplant recipients (KTRs), the incidence of cancer is 2- to 3-fold higher compared with the general population. The increased risk of cancer following kidney transplantation, in addition to the well-known environmental and genetic risk factors, is associated with immunosuppressive therapy. Immunosuppression is considered to be the most important risk because it decreases cancer immunosurveillance and can increase the incidence of oncogenic viral infections, as well as potentially provoke direct carcinogenic effects. The risk is especially high for cancers associated with oncogenic viruses, such as post-transplant lymphoproliferative disease (PTLD) caused by Epstein–Barr virus (EBV), Kaposi sarcoma (KS) caused by human herpesvirus 8, and nonmelanoma skin cancer (NMSC) caused by human papillomavirus. It is widely recognized that it is the overall immunosuppressive dose rather than the contribution of individual immunosuppressive drugs that is associated with the increased cancer risk in KTRs.[1]

Maintenance immunosuppression Maintenance immunosuppression is fundamental after kidney transplantation. It usually consists of a calcineurin inhibitor (CNI), an antiproliferative drug, and glucocorticoids.

The CNIs cyclosporine and tacrolimus are the pillars of immunosuppression in KTRs. They are both associated with an increased risk of malignancy. By inactivating calcineurin, CNIs inhibit interleukin (IL) 2 production, thus inhibiting T-cell activation and proliferation. As a result these drugs impair natural immunosurveillance. Cyclosporine and tacrolimus have also been found to increase the expression of transforming growth factor $ß_1$ and to upregulate vascular endothelial growth factor (VEGF). Both growth factors are involved in the development of cancer cell growth. In addition, CNIs can increase viral replication of EBV, human herpesvirus 8, and human papillomavirus as well as increase production of viral-inducing IL-1 and IL-6. Uncontrolled infection with these viruses can result in PTLD, KS, and skin cancers.[2]

The antimetabolites commonly used in patients after kidney transplantation include azathioprine and mycophenolic acid (MPA). The latter is available as mycophenolate mofetil (MMF) and mycophenolate sodium (MPS), prodrugs of MPA. The incorporation of azathioprine metabolite, 6-thioguanine, into DNA and RNA disrupts cell division of lymphocytes. Azathioprine is also photochemically reactive and can sensitize KTRs to the DNA-damaging effects of ultraviolet radiation, so it can contribute to an increased risk of NMSC in KTRs. It was shown that KTRs exposed to azathioprine had a 56% higher risk of NMSC compared with those who were not receiving azathioprine.[3]

Both MMF and MPS inhibit the enzyme inosine monophosphate dehydrogenase, resulting in the inhibition of T- and B-cell proliferation. Mycophenolate mofetil was first developed as an antineoplastic drug. However, further studies determined that it does not inhibit the growth of tumors at doses used to prevent transplant rejection. A systematic review of randomized controlled trials comparing MMF with azathioprine in KTRs found no significant differences in the incidence of NMSC between patients receiving these 2 immunosuppressants. Mass data revealed that the risk of malignancy associated with mycophenolates was not increased.[4]

Mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, inhibit the mTOR pathway resulting in inhibition of T-cell proliferation. They also have an anticancer activity. The mTOR pathway is upregulated in many cancers, and mTOR inhibitors can upregulate the transcription factor, T-bet. T-bet seems to be essential for tumor-suppressive activities. It has been also suggested that the anticancer properties of mTOR inhibitors are due to inhibition of VEGF, which is required for angiogenesis. Clinical data suggest a lower incidence of malignancies in KTRs who receive an mTOR inhibitor.[5]

Data on the oncogenic properties of glucocorticoids are heterogeneous. Glucocorticoids are used to treat certain types of cancer, including

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lymphomas, but they have also been associated with the occurrence of malignancies. It has been suggested that glucocorticoids may have pro-oncogenic properties by modulating the immunosurveillance mechanism. Glucocorticoids are also known to induce the growth of KS through activation of transforming growth factor ß$_1$.[6]

Monoclonal and polyclonal antibodies can be used during induction therapy and can serve as a treatment of acute rejection. They are divided into T and B cell–depleting and T and B cell–nondepleting antibodies.

Basiliximab, an IL-2Rα antagonist and a nondepleting anti-CD25 antibody, has not been associated with an increased risk of cancer after transplantation.[7]

T cell–depleting antibodies such as anti-CD52 (alemtuzumab) or antithymocyte globulin have been shown to be associated with a higher risk of PTLD in patients who had received these drugs for acute rejection treatment. It has been shown that both CD4$^+$ and CD8$^+$ T cells are essential in antiviral immunity. Also, direct antitumor effects have been attributed to CD4$^+$ T helper 1 cells, CD8$^+$ cytotoxic T cells, and natural killer cells. Polyclonal T cell–depleting antibodies target a variety of T cell and natural killer cell–derived antigens, including CD2, CD3, CD4, CD8, and CD16. It has been demonstrated that higher doses of antithymocyte globulin were associated with a higher risk of PTLD. When antithymocyte globulin was administered at lower doses (6 mg/kg of body weight), the risk of PTLD was not increased.[7]

B cell–depleting anti-CD20 antibody (rituximab) can be used as a prophylaxis or treatment in patients with antibody-mediated rejection. Rituximab is also the drug of choice in the treatment of non–Hodgkin PTLD and other lymphomas.[8]

A novel biologic agent, belatacept, is a selective T-cell costimulatory blockade drug. Initially, a few cases of PTLD of the central nervous system were reported in patients treated with belatacept. Therefore, the US Food and Drug Administration placed a warning for the risk of PTLD, especially in EBV-negative recipients. Follow-up data of belatacept showed only a small increase in the incidence of PTLD.[9]

Modifications of immunosuppression in kidney transplant recipients with cancer Specific recommendations for modification of immunosuppression after malignancy diagnosis in KTRs have not been established. The most common approach is reduction or withdrawal of maintenance immunosuppression. Following the diagnosis of PTLD, for example, MPA may be disrupted, with a 25% to 50% reduction of CNI therapy. Modifications can vary based on the extent of the disease, with just a 25% reduction for limited disease or discontinuation of antimetabolites and CNI in patients with disseminated cancer disease. Reduction of immunosuppression is often implemented with standard treatment for cancers, such as surgery, radiation, and chemotherapy. Also the risk of potential rejection has to be weighed against the benefits of reduction of immunosuppression. The clinical implications following reduction or withdrawal of immunosuppression differ based on the transplanted organ. The risk of rejection in KTRs may be perceived differently compared with heart and lung transplant recipients. Another problem is the risk of allograft rejection associated with newly developed cancer immunotherapies, such as interferon therapy and the use of checkpoint inhibitors in KTRs. Interferons and checkpoint inhibitors, cytotoxic T-lymphocyte antigen 4 and programmed cell death 1 inhibitors, are part of immunotherapy. Blockade of cytotoxic T-lymphocyte antigen 4 and programmed cell death 1 allows activation and proliferation of T cells and produces strong antitumor responses.[10] However, the use of these medications is also associated with graft rejection as they can activate alloreactive T cells.

Another option is conversion to an mTOR inhibitor. In KTRs with KS, a conversion from cyclosporine to sirolimus resulted in complete clearance of KS lesions. Also the use of an mTOR inhibitor with low doses of CNIs may result in a lower incidence of cancers. However, in a study by Ying et al,[5] everolimus was not associated with a reduction in the incidence of cancer, NMSC, or cancer-related death compared with controls. Based on these studies, universal use of mTOR inhibitors in KTRs with neoplasms cannot be recommended at present.

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Treatment of skin tumors in organ transplant recipients

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Introduction Patients after organ transplantations are particularly prone to developing skin tumors. The most common de novo tumors in organ transplant recipients (OTRs) are skin tumors; in 95% of cases, it is nonmelanoma skin cancer (NMSC), mostly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[1] Other, less frequent tumors are melanoma, Kaposi sarcoma, Merkel cell carcinoma, sebaceous carcinoma, and anogenital cancer.

In the general population, BCC is more prevalent than SCC. In patients after transplantation, however, this ratio is reversed and SCC is more frequent: the risk of developing BCC and SCC in OTRs is 10- and 65-fold greater, respectively. SCC in OTRs usually develops much faster, is often multifocal, has a tendency to invasive growth, and in 8% of cases metastasizes to regional lymph nodes.[1] Approximately 70% of SCC cases develop from actinic keratosis (AK). AK is a premalignant condition, characterized by the presence of red-yellow hyperkeratotic lesions, stemming from areas of the skin that were damaged by UV radiation. It usually occurs in 40% of OTRs within 5 years after the transplantation.

The most important risk factors of skin cancer in OTRs are Fitzpatrick skin type, cumulated sun exposure, certain types of immunosuppression, as well as longer duration and intensity of immunosuppression. Other risk factors involve age at transplantation, history of skin cancer prior to transplantation, biological treatment, type of transplanted organ (with the highest risk in heart transplant recipients, followed by lung, kidney, and liver transplant recipients). Some additional risk factors are human papillomavirus (HPV) infection, history of leukemia or lymphoma before or after transplantation, and voriconazole treatment. Patients with AK, warts, and papillomas have a higher incidence of SCC compared with those who do not present with the above conditions.[1]

Treatment Destructive therapy of skin cancers involves, for example, cryotherapy, laser ablation, electrocoagulation, curettage, radiotherapy, and surgical treatment. The most common method is cryotherapy because of its wide accessibility, low cost, and effectiveness. It also does not require local anesthesia. It is commonly used in the therapy of AK, superficial NMSC, and flat, sebaceous, and viral warts. It should only be used to remove solitary lesions. There is no evidence that curettage, electrocoagulation, or laser ablation is a more effective method than cryotherapy.[2]

In OTRs, considering the recurrent and multifocal character of skin lesions in this population, it is recommended to treat the field cancerization, which is basically the removal of visible and subclinical lesions within the field of UV-damaged skin. This method allows not only a removal of the existing lesions but also a prevention of new ones. The most common therapeutic methods in skin tumors include the use of 5-fluorouracil (5-FU), imiquimod, diclofenac sodium, ingenol mebutate, and photodynamic therapy (PDT) (**TABLE 1**).[2]

Photodynamic therapy is based on a phototoxic reaction, which is achieved by a mutual influence of photosensitive substance and light with appropriate wavelength. The most common photosensitive compounds are 5-aminolevulinic acid and methyl aminolevulinate. It is proved to be an effective and safe method of AK and NMSC treatment in OTRs. Cyclic PDT may be beneficial in the prophylaxis of AK and SCC in patients with a high risk of developing NMSC; however, further randomized studies with a broader spectrum are necessary.[3] However, the use of PDT is limited due to its being a painful and expensive method.

The cytotoxic agent 5-FU acts by disrupting DNA replication and RNA synthesis, leading to cellular death. It is used topically as a 5% cream. Indications include AK, solitary or multiple forms of BBC that are hard to access surgically, and Bowen disease. The most common adverse effects are pain, itching, erythema, burning sensation, exfoliation, depigmentation, and secondary infections. There are multiple treatment regimens, but 5-FU is frequently administered twice a day over the course of 4 weeks. Less frequent doses may reduce the

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TABLE 1 Treatment and prophylaxis of skin tumors in organ transplant recipients

Destructive therapy	Surgical removal (Mohs method)
	Radiotherapy
	Cryotherapy
	Curettage, electrodestruction
	Laser ablation
	Resurfacing
Local chemotherapy	5-fluorouracil
	Imiquimod
	Diclofenac sodium
	Ingenol mebutate
	Photodynamic therapy
Systemic immunomodulating therapy	Reduction of immunosuppression
	Conversion to mammalian target of rapamycin
	Vaccinations
Primary and secondary prophylaxis	Solar protection
	Systemic (acitretin) and local retinoids

adverse effects and increase drug tolerance. Better treatment outcomes are achieved with a combination of 5-FU and tretinoin.[3]

Imiquimod is used in the form of a 5% cream. Its clinical effectiveness was proved in treating genital warts, AK, and superficial BCC. Its action is due to stimulation of immune response, enabling antiviral, antiproliferative, and anticancer response. The safety and efficacy of topical imiquimod were observed while treating AK in OTRs. The overall clearance ratio in patients treated with imiquimod was calculated at 62% compared with 0% in the placebo group.[3] Adverse effects were most commonly itching, burning sensation, severe erythema, exfoliation, and scab formation.

Diclofenac is a nonsteroidal anti-inflammatory drug, applied as 3% gel dispersed in hyaluronic acid. The mechanism of action in AK treatment is unknown but may be linked to cyclooxygenase-2 inhibition, which inhibits prostaglandin E_2 synthesis. Local reactions to diclofenac gel formulation are smaller and appear later than after 5-FU or imiquimod administration.

Urlich et al[4] investigated the safety and effectiveness of 3% diclofenac gel in OTRs. Thirty-two patients who underwent organ transplantation were administered 3% diclofenac gel (n = 24) or placebo (n = 8). It was distributed on the skin area of 50 cm^2 with ≥3 AK lesions twice a day over the course of 16 weeks. In the group treated with diclofenac, complete regression of AK was obtained in 41% of patients compared with 0% in the placebo group. Adverse reactions in most patients involved a mild erythema and mild-to-moderate swelling of treated areas. Neither a tendency to a deterioration of transplanted organ function nor organ rejection was observed. In 55% of patients with prior regression of AK, 9.3 months was the average time after which a secondary lesion occurred. No patient developed invasive SCC within 24 months of follow-up. This study suggests that 3% diclofenac gel is not only an efficient and well-tolerated drug in OTRs, but it may also prevent an invasive SCC in high-risk patients.[4]

Ingenol mebutate is a relatively new drug with a double mechanism of action. It directly contributes to cellular death by its destructive action on the mitochondrial membrane, and also via inducing an infiltration of inflammatory cells (lymphocytes, neutrophils, and inflammatory cytokines). Ingenol mebutate is available in 2 concentrations, 0.015% (face and scalp) and 0.05% (limbs and trunk). Its advantage is the short period of treatment, which is usually 2 to 3 days.[2] Research on its safety and effectiveness in OTRs is currently ongoing.

Systemic immunomodulating therapy Discontinuation of immunosuppression might be a reasonable approach in patients who are at high risk of SCC metastases or develop more than 5 to 10 high-risk SCCs per year. It might be achieved via reducing the dose or changing the treatment regimen. Many factors, such as age, serum drug concentrations, HLA matching, history of graft rejection, allograft source, prior transplantation and time after transplantation, should be considered when tapering immunosuppressive treatment.[3]

Sirolimus is a nonnephrotoxic immunosuppressive agent with anticancer and antiangiogenic properties. Similarly to everolimus, it is a mammalian target of rapamycin inhibitor. In a 2014 systematic review and meta-analysis, sirolimus was linked to a 40% reduction in malignancy risk and 56% lower risk of NMSC. It was the most beneficial in patients who switched to sirolimus from immunosuppression based on calcineurin. However, it was also connected with an increased risk of death in comparison with the control group, so it seems reasonable to consider whether it should be administered to the majority of patients after kidney transplantation. The authors stressed that further research is necessary to determine whether switching to sirolimus could be beneficial for OTRs at high risk for cancer.[5]

In a study on rodents (*Mastomys coucha*), Vinzón et al[6] aimed to determine the effectiveness of HPV vaccination (HPV caused skin infections) and whether it would reduce the number of skin tumor cases. One group of rodents were supplemented with cyclosporine A. The vaccine prevented the development of both benign and malignant skin tumors. The study provided the first evidence that this vaccine induces an effective cutaneous immunologic response in both competent and suppressed immune systems in the animal model, regardless of prior infection status. The research could serve as the basis for developing an appropriate clinical approach both to HPV skin infections and HPV-induced tumors. This applies in particular to patients who are waiting for an organ transplant.

Prophylaxis Effective solar protection is a condition necessary to limit the prevalence of AK and NMSC in OTRs. Ulrich et al[7] studied 120 patients after transplantation, of whom 60 individuals used a broad-spectrum UVA/UVB SPF 50+ cream every day over 24 months. None of the patients who used sun protection developed SCC (8 cases of SCC in the no-protection group). Moreover, patients presented with much fewer AK lesions, and BCC was diagnosed in 2 patients (9 in the second group). These results show that sun protection plays a key role in AK and SCC prophylaxis.[2]

Systemic retinoid therapy (acitretin) reduces the number of skin cancer lesions, dysplastic lesions, and AK. It should be used as chemoprevention only in patients who develop 5 to 10 SCC per year or with a high risk of aggressive SCC. It may be used in patients with metastases or in those with contraindications to surgical treatment as a means to lower morbidity and mortality rates. In order to reduce adverse effects, it is recommended to start with a lower dose of 10 mg/d. A dose of 20 to 25 mg/d is considered optimal. Potential contraindications to acitretin must be considered (eg, pregnancy).[3]

Melanoma In OTRs, melanoma is 3- to 5-fold more frequent than in the general population. In the case of detecting melanoma, the surgical treatment is the same as the one performed in the immunocompetent group of patients. Its assessment is based on its depth and the Breslow scale. Sentinel node excision may indicate the necessity to reduce or discontinue immunosuppression. In metastatic melanoma, there are a few options of systemic treatment. Primary treatment with interferon alfa increases the 5-year survival rate only by 3% and significantly increases the risk of organ rejection.[3] The cytotoxic T-lymphocyte antigen-4 inhibitor, ipilimumab, can be used safely in OTRs. There are scarce data on dabrafenib and trametinib treatment (median survival, 15 months). PD1-inhibitors (nivolumab, pembrolizumab) have a good therapeutic effect but increase the risk of acute organ rejection. There are no data on patients after life-saving organ transplantations. Reducing the dose of calcineurin inhibitors is recommended. The mammalian target of rapamycin inhibitors combined with prednisone reduce the risk of rejection when cytotoxic T-lymphocyte antigen-4, BRAF, and MEK inhibitors are administered.

Follow-up Frequency of total-body skin examinations in OTRs depends on risk factors for skin tumors. Patients with no skin diseases should be examined once a year. Patients with some skin conditions or a single NMSC should undergo an examination every 3 to 6 months, and OTRs with multiple NMSCs or high risk of SCC or melanoma, every 3 months. Patients with SCC metastases should be controlled every 1 to 3 months.[3]

Conclusion Dermatological care is of the utmost importance for OTRs. Furthermore, it is a good opportunity to educate patients on sun protection. It mostly includes prophylaxis, diagnosis, and treatment of skin tumors in early stages. Patients after transplantation should apply sun protection (UVA/UVB SPF 50+ cream) all year round. It is also necessary to inform patients about potential risk factors and prophylaxis.

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Cancer in a transplanted kidney

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This paper presents the differences between renal cell carcinoma (RCC) in native and transplanted kidneys in patients with end-stage renal disease (ESRD). In patients with ESRD, cancer can be diagnosed before and after kidney transplantation, and RCC can be found in functioning and failing grafts as well as in the native kidney.

There are 3 classic histologic types of RCC: conventional clear cell RCC, papillary RCC, and chromophobe RCC. The 2016 World Health Organization classification distinguishes 2 other RCC types: acquired cystic disease (ACD)–associated RCC and clear cell papillary RCC.[1] They are new entities of RCCs found exclusively in individuals with ESRD, with ACD-associated RCC being now considered the most common subtype of RCC in patients with ESRD (previously it was thought to be papillary RCC). The incidence of ACD-associated RCC is estimated at 36% of renal neoplasms arising from ESRD and increases with longer duration of dialysis. Histologically, it has a distinct cribriform and microcystic growth pattern (sieve-like), which differentiates it from papillary RCC. The presence of intratumoral oxalate crystals is unique to ACD-associated RCC.[2] These newly established morphotypes are likely to behave in a less aggressive way. In clear cell papillary RCC, no instances of metastatic disease have been reported.

The original sense of the Bosniak classification, that is, to preserve renal tissue by exact preoperative diagnosis, has lost its importance in patients with ESRD and ACD. In patients with ACD, there is a generous indication for nephrectomy even in the lower Bosniak categories; this is true especially for cystic lesions of category IIF (F stands for follow-up).[3] To sum up, RCC in native kidneys in patients with ESRD has the following characteristics: 1) it is usually of papillary subtype (new classification: ACD-associated RCC, clear cell papillary RCC); 2) it is often asymptomatic; 3) it is often low stage and low grade at diagnosis, which results in good outcomes; 4) it is multifocal, bilateral; and 5) it has indications for nephrectomy.

Cancer in the graft can be of donor origin (donor-transmitted or donor-derived cancer) or, in exceptional situations, of host origin. A donor-transmitted tumor is present in the donor before transplantation and transmitted with the transplanted organ. A donor-derived tumor can develop de novo from donor cells at any time after transplantation, but it is not present in the donor at the time of organ procurement.[4,5] Cancer can also originate from the recipient tissue. Determination of cancer origin is important for the staging and management of RCC in the graft: localized, small (stage I, T1N0M0 according to the TNM staging system) cancer originating from the allograft kidney carries a favorable prognosis, and partial nephrectomy may preserve adequate function of the allograft. Localized, small cancer originating from the host tissue may be considered metastatic (stage IV) and requires total nephrectomy and other oncological treatment. The TNM staging of RCC in the graft should be also adapted to new circumstances. Since grafts are freed of all surrounding fatty tissue before transplantation, the usual T3 and T4 stages relative to Gerota fascia cannot be applied. Instead, other surrounding anatomical structures that are invaded are included in T3 (renal sinus fat or peritoneum, external or primitive iliac vein, inferior vena cava) and T4 (psoas muscle, iliac vessel wall, bladder, small intestine or colon).[3] To sum up, tumors in renal grafts usually: 1) are diagnosed at the asymptomatic low stage; 2) are of a low grade of malignancy; and 3) are mainly of papillary RCC subtype. Nephron sparing treatment should be preferred in patients with good graft function, cortical localization of tumors, and a tumor size of <4 cm.

A short period of time between the transplantation and the diagnosis suggests that RCC is transmitted from the donor. Methods for discrimination are as follow: fluorescence in situ hybridization, microsatellite allelic analysis, and comparative genomic hybridization. Routinely processed paraffin-embedded tissue can be used to perform one of the methods. In case of a positive test match between donor and tumor material, a second method should be performed to definitively confirm the donor origin of the tumor.[5]

Renal cell carcinoma can be also diagnosed in a potential donor, and it is one of the most frequently transmitted neoplasms. The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) classifies the risk of disease transmission in donors with a history of treated non-CNS malignancy (≥5 years prior) on the basis of probability that

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the tumor was cured (low, intermediate, high risk).[5] Depending on staging/grading, RCC can be of any risk. It can be diagnosed during donor procurement or be present in the donor medical history. The information on staging/grading at the time of diagnosis and also complete tumor resection (R0) is required for the decision. The tumor of less than 1 cm in diameter and with nucleolar grade I/II (Fuhrman grade I/II) has a minimal risk for transmission. In a donor with a history of cancer, risk categories correspond to the type of RCC and its staging/grading at diagnosis and to the recurrence-free follow-up. Clear cell RCC is usually diagnosed in donors, as it is most frequent in the general population. Three key aspects should be underlined: 1) the risk of RCC transmission is small but it exists; 2) clear cell RCC is the most common type of RCC; and 3) if there is a minimal risk according to recommendations, the decision on acceptance of the organs from such donors is at the discretion of the center and potential recipients.[5]

Renal cell carcinoma can be present in a potential candidate for kidney transplantation. There are some rules to follow. The time between radical treatment and inclusion on the transplant waiting list depends on the type of cancer, staging/grading of the cancer, histological prognostic features typical for the cancer, and the 80% probability of 5-year survival. In RCC, time between radical treatment and inclusion on the waiting list can vary from none (asymptomatic, T1N0M0, Fuhrman I/II) to above 5 years (≥T2 or symptomatic, any stage/grade).

To sum up, RCC is not a contraindication for transplantation and appropriate period of time between radical treatment without recurrence and referral should be established on an individual basis.[6]

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New perspectives in the treatment of renal cell carcinoma

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Renal cell carcinoma (RCC) is currently the sixth most common type of cancer in men and the tenth in women in Poland and Western countries. It comprises 3% to 4% of all carcinomas, meaning that many medical specialists such as general practitioners, radiologists, oncologists, radiotherapists, andm, of course, urologists see RCC quite often.

Changes in the RCC incidence are very interesting. In the 1980s and early 1990s, we observed a sharp increase in the incidence caused by the introduction of ultrasound and computed tomography (CT). From then on, the old triad of symptoms—hematuria, pain, and palpable mass—has started to lose its importance. The development of good diagnostic tools has resulted in an increase in the discovery rates of less advanced cases. Subsequently, since the late 1990s, a decrease in the age-standardized mortality ratio has been visible. However, because of population aging, the raw incidence and mortality rates have not declined, meaning that much has to be done in the future.

Further progress may be possible by defining risk factors. This in turn will enable education of society and reduction of the population to be screened. Unfortunately, there are no strong data that would indicate a clear relation between any factor and RCC incidence apart from male sex and age. Some studies pointed to obesity, hypertension, smoking, or using nonaspirin analgesics, but it would be difficult to develop any cost-effective screening program based on that. However, numerous studies indicated a link between inherited gene mutations and RCC development, with the mesenchymal–epithelial transition and Von Hippel–Lindau genes being the ones most extensively studied.[1] We expect that familial genetic screening will play a bigger role in the future.[2]

The diagnostic methods like ultrasound, CT, or magnetic resonance imaging have proved to be very effective in discovering and staging of the RCC. Thus, new methods such as positron emission tomography are useful only for the detection of small metastases or early recurrences. Because the current imaging techniques are so effective in discovering solid renal masses and because almost all of them are malignant tumors, biopsy before surgery is not used in most of the cases. What is more, there have been many studies trying to explore if the histologic type or even the malignancy potential of the tumor can be defined by radiologic tools only.[3,4] So far these studies were concerned with rare benign tumors (such as angiomyolipomas) that require active treatment only if they pose a high risk of bleeding, are big, or if patients take anticoagulants or are pregnant.[4]

Nowadays, the biopsy in RCC is done only if the tumor is not to be removed. It happens in very advanced cases when the lesion is to be observed only or treated with minimally invasive ablative methods. The latter type is getting more and more popular, so the importance of the biopsy will grow.

Histology is still crucial for the prognosis. It recognizes clear cell RCC to be the most frequent type and defines other types: chromophobe and papillary as less aggressive or medullary, and collecting duct carcinomas as more dangerous. The grading system was introduced by Susan Furham in 1982 and is still used. However, in the future, more attention will be paid to gene signatures, which will enable subdividing the tumors of similar histologic characteristics into many different subgroups according to the mutations. This in turn will help define the mode of treatment and prognosis.

One more RCC subtype that needs to be mentioned arises in patient with acquired cystic kidney disease and end-stage renal disease. This population grows as the nephrological care improves. The entity is associated with several problems. Firstly, it is not easy to detect the tumor among the multitude of cysts. Secondly, operating on these huge kidneys can be challenging. Fortunately, acquired cystic kidney–related RCC is not very aggressive, although when the patient is referred for transplantation with immunosuppression, it has to be diagnosed and removed.[5]

As far as the RCC treatment is concerned, the surgical removal of the cancer is still the only cure. Nowadays, with better diagnosis and smaller tumors, the surgery very often means nephron-sparing partial nephrectomy securing preservation of good kidney function during a long

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expected survival. Surgical tumor removal can be done openly, laparoscopically, or with robotic assistance. Oncologic results are equal for all the methods, but the open technique is slowly losing its importance. What is more, it is interesting that the growing number of small cancers that are visible on imaging studies are more and more often subjected to ablation. It consist in the insertion of a needle probe into the tumor under ultrasound or CT control and destruction of the neoplastic tissue with some form of energy. It may be heat generated by a high-frequency electric current or microwaves in thermoablation. Also low temperature can be used in cryoablation or an electric current of special parameters that breaks cell walls in electroporation. The results of these treatments are getting better. It is very probable that in the future the majority of small renal tumors will be treated this way.[6]

Considering that only cancer resection cures patients with RCC, we have to face the reality, where about 20% of patients still come to urologists with disseminated disease, and another 20% develop metastases after surgery. A lot of hope is put in the so-called targeted therapy. In contrast to the classic empirical chemotherapy or immunotherapy that have proved not to be very effective, the new concept is based on the evaluation of the gene mutation that had occurred in the cancer cells and are important for its survival (drive mutations). It requires the examination of the tissue obtained from biopsy or tumor resection. If the specific targets, that is, proteins produced or affected by the drive gene mutation, are defined, then their function can be blocked by targeted drugs. They can be molecules or monoclonal antibodies. The main advantage is that by knowing the targets we can spare the patients toxic and expensive drugs, without false presumptions that they are going to help them.

The above therapy is expensive, but it will undoubtedly dominate the future treatment of disseminated cancer and not only RCC. It is important to distinguish it from the targeted therapy in RCC, where a special class of drugs, usually tyrosine kinase inhibitors, is given based on the assumption that RCC depends on the neoangiogenesis that they block. It is likely to be true, but we do not assign a specific drug to a specific known gene signature yet, and this is probably the reason why the outcomes of tyrosine kinase inhibitors are not so impressive. The results of the "true" targeted therapy are sure to be improved, but it will be a form of palliative therapy as there will always be some amount of neoplastic cells driven by some other new mutations arising in the course of cancer. The only thing that we can count on is that we will be able to change a fatal disease into a chronic one, and this is of course a very promising option.[7]

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Colorectal cancer secondary to kidney transplantation: a need for prophylaxis

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According to the Polish National Cancer Registry, colorectal cancer (CRC) and rectal cancer are the third most common cancer types diagnosed in men, and the second ones in women worldwide, accounting for approximately 8% of cancer mortality.[1] Colorectal cancer is one of the most frequent cancers of the gastrointestinal tract, its incidence is increasing, and it mostly develops after the age of 50 years (94%).[1,2] Cancers are the second most common cause of death in kidney transplant (KTx) recipients (KTRs), with CRC occurring twice as often as in the general population.[3] It usually develops slowly, potentially allowing for its early detection; however, its course is quicker and more aggressive (phenotype B) in KTRs. **TABLE 1** presents CRC risk factors after KTx, with immunosuppression, both before and after surgery, being a significant factor.[1-3] Prevention of CRC is particularly important after KTx, although paradoxically no uniform standards have been established for all transplant centers.[1-3]

A man born in 1961, who had chronic kidney disease (CKD) due to chronic glomerulonephritis diagnosed based on kidney biopsy in 1986, presented with end-stage CKD in 2000. Peritoneal dialysis was introduced and the patient was referred for KTx. Owing to the absence of gastrointestinal symptoms, only abdominal ultrasound and gastroscopy were performed. In June 2001, a KTx using a kidney from a deceased donor was conducted in Provincial Specialist Hospital in Poznań. Immunosuppressive drugs: cyclosporine A (CsA), azathioprine (AZA) (100 mg/d), and steroids were administered (doses according to the protocol). The patient was discharged with a creatinine level of 2.4 mg/dl. Graft function was stable (creatinine, 1.7–2.2 mg/dl; CsA level 12 hours after the last dose, 68–128 ng/ml; AZA, 75 mg/d). In July 2009, AZA was switched to mycophenolate sodium (720 mg administered in 2 equal doses). Prednisone dosage was retained (7.5 mg/d). Abdominal ultrasound with graft assessment was done regularly (every 2–3 years), not showing any significant pathology. Progressive anemia and weight loss have been observed since April 2017. The patient performed fecal occult blood tests (FOBTs) at his own expense. The result was positive.

In December 2017, the patient was referred for gastroscopy and colonoscopy. Gastroscopy revealed aphthous gastropathy, and colonoscopy showed a semicircular ulcer (4 × 2 cm) near the hepatic flexure, with a rigid base and heaped-up edges. A specimen for histopathological examination was obtained. Abdominal ultrasound revealed a liver of normal echogenicity with heterogeneous lesions up to 90 mm, and the halo sign consistent with metastasis. The immunosuppressive protocol was modified: CsA was discontinued, everolimus was introduced (1.5 mg administered in 2 equal doses; everolimus level, 3.1–4.7 ng/ml), and prednisone dosage was retained. Abdominal and chest computed tomography (CT) revealed bowel wall thickening in the pericecal region, with patchy densities in the fatty stroma and a cluster of roundish lymph nodes of 5 to 12 mm. Numerous metastatic lesions were found in the liver parenchyma, and single nodules, 3 to 4 mm in diameter (newly developed lesions, possibly postinflammatory) in the lungs. After obtaining a histopathology report (tubular adenoma), in February 2018 a multidisciplinary therapeutic consultation was held at the Oncology Centre in Olsztyn. Due to the general condition, disease stage 4, and comorbidities, the patient was referred for palliative chemotherapy. Serum laboratory tests revealed anemia (**TABLE 2**). Immunogenetic analysis showed that cancer cells were sensitive to antiepidermal growth factor receptor monoclonal antibodies. The patient was referred for 6 cycles of FOLFIRI chemotherapy (irinotecan, 5-fluorouracil, leucovorin). Control CT showed partial regression of the lesions. Tumor mass was reduced by about 33% and chemotherapy was continued. Kidney parameters during chemotherapy remained stable: creatinine was 1.6 to 2.03 mg% and estimated glomerular filtration rate ranged from 30 to 44 ml/min/1.73 m^2.

Colorectal cancer is a significant cause of mortality after KTx. Its risk increases after 10 years

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TABLE 1 Risk factors for colorectal cancer in kidney transplant recipients (based on Dobies et al[1] and Renke et al,[2] with our modification)

Risk factors	Notes on conditions, mechanisms
Nonmodifiable	
Age	–
Genetic predisposition: family history of colorectal cancer	5%–10% of cases
Type 2 diabetes	Hyperinsulinemia increases the risk of cancer development and its recurrence (caused by high glycemic index food: white bread, sweet desserts)
Colon polyps	Risk of growth and dysplasia: precancerous condition
Inflammatory bowel disease	Particularly ulcerative colitis, potential risk of colonic diverticulitis
Race and ethnicity	The highest incidence rate: Afro-Americans
Previous radiation therapy of the pelvis minor	–
Familial colorectal cancer type X	–
Familial adenomatous polyposis	–
Modifiable	
Diet	Red meat (fried, grilled), animal-based high saturated fat content, shortage of fresh vegetables and fruit
Excessive alcohol consumption	Documented least toxic activity of red wine
Insufficient physical activity	–
Obesity and being overweight	–
Constipation	Longer exposure of bowel wall to carcinogens
Tobacco smoking	–
Chronic stress	Shift and night work
After kidney transplantation	
Duration of dialysis therapy	–
Time span after transplantation	–
Younger age (<50 years)	–
Immunosuppressive therapy before and after kidney transplantation	Treatment of the primary kidney disease and autoimmune comorbidities Immunosuppressive effects and types of medication
Aggressive phenotype b	Overexpression of specific oncogenic proteins

following the transplantation.[2] In KTx recipients, it more often occurs in younger patients (58 years vs 70 years in the general population) and its prognosis is worse (5-year survival, 43.5% vs 62.3% in the general population).[2] Increased immunosuppression may be an independent risk factor for CRC after KTx (TABLE 1).[1-3] In our case, the patient was 67 years old, 17 years after KTx, and CRC was detected in its advanced stage with metastases to the liver and probably to the lungs. Anemia and weight loss are late alarm symptoms that appear in the advanced stage, often when only palliative treatment is possible, as in our case. Our patient had not been screened for CRC for 32 years (FOBT or colonoscopy) in a presymptomatic stage, either during referral for KTx or after surgery. He did FOBT on his own initiative, worried by his symptoms.

European guidelines for the general population list FOBT as a screening method for CRC.[1,2] This test should be performed in individuals 50 to 74 years of age, every 1 to 2 years. It reduces CRC mortality by 20% to 30%; however, in about 60% of patients negative results do not exclude CRC. A lot of data indicate that the method of choice should be colonoscopy, which detects CRC in about 98% of cases and reduces mortality by 60% to 70%.[1,2] Colonoscopy allows a diagnosis of cancer in early stages, prompt introduction of treatment, and monitoring and removal of polyps. Effectiveness of ultrasound in detecting CRC is debatable, as shown by our case. After KTx, therapy is difficult because of reduced glomerular filtration in the graft and comorbidities. Surgical treatment, as in the general population, is the basic procedure. Several studies reported good tolerance to basic chemotherapy protocols, that is, FOLFIRI and epidermal growth factor receptor inhibitors. Radiation therapy is not contraindicated after KTx. In immunosuppressive treatment of CRC after KTx, better results are obtained with immunosuppressant dose reduction and administration of mTOR kinase inhibitors than with calcineurin inhibitors.[4,5] Patients taking CsA develop cancer more often than those on everolimus.[4,5] In the case of our patient, CsA was switched to everolimus only after CRC diagnosis. Cancer prophylaxis consists mostly of a healthy and balanced diet (TABLE 1). The National Cancer Control Program in Poland recommends

TABLE 2 Results of serum laboratory tests of the patient

Serum laboratory tests	Results	Refernce ranges
Hemoglobin, g/dl	8.5	M, 13.5–18; W, 11.5–15.7
AST, U/l	50	2–32
ALT, U/l	58	2–33
Creatinine, mg/dl	1.87	0.5–0.9
CEA, ng/ml	1477	0–3.8
LDH, U/l	1533	240–480
Bilirubin, mg/dl	0.18	0–1.2
CRP, mg/dl	24.64	<5
Alkaline phosphatase, U/l	279	40–129
Potassium, mmol/l	3.8	3.5–5.1
Iron, µg/dl	255	59–158

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CEA, carcinoembryonic antigen; CRP, C-reactive protein; LDH, lactate dehydrogenase; M, men; W, women

colonoscopy for individuals at the age of 50 to 65 years without alarming symptoms or for individuals at the age of 40 to 49 years with a family history of CRC. For patients referred for KTx, abdominal ultrasound, gastroscopy with urease test, FOBT, and colonoscopy are recommended. Colonoscopy should be performed when the FOBT result is positive and in all patients older than 45 to 50 years.[1,2] In patients after KT, FOBT is optionally recommended every 2 years and colonoscopy every 1 to 2 years.[1,2]

Our case and literature data indicate an urgent need to modify guidelines concerning CRC prophylaxis before and after KTx, mainly unifying protocols and lowering the age threshold of examined patients.[1,2] The authors of this report are active in this field, conducting own research.

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Kidney transplantation from a family donor to a recipient with Lynch syndrome: 6 years of follow-up

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Rare cancers with a genetic basis, tendency to occur in various organs, and high risk of recurrence are the challenge for teams that refer patients with end-stage renal disease for a kidney transplantation (KTx). It is difficult to properly estimate the disease-free waiting period for these cancers. The precise period should be determined on an individual basis depending on the type of tumor, its staging, and response to therapy.

Lynch syndrome (LS), or hereditary nonpolyposis colorectal cancer (HNPCC), is characterized by a predisposition to colorectal cancers (CRCs), but also tumors affecting other organs among people under 50 years of age. In the general population, HNPCC accounts for about 1% to 3% of all CRCs. The syndrome is caused by a mutation of 1 of the 6 genes that are responsible for DNA repair: *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, *hMSH6*, *hMSH3*. The mutation of the *hMSH2* and *hMLH1* genes is most common.[1] In approximately 70% of cases, cancer occurs on the right side of the colon. It is characterized by a low degree of differentiation, production of mucus, rapid local growth, and a small tendency to create distant metastasis. There is a high risk of metachronous and synchronous lesions (within 10 years, a new cancer appears in the large intestine in about 40% of patients). The risk of cancer associated with HNPCC applies not only to the large intestine (80%–82%), but also to the endometrium (5%–60%), stomach (13%), ovary (12%), bladder (4%), kidney (3%), small intestine (1%–4%), brain (4%), and bile ducts (2%).

To facilitate the diagnosis of HNPCC, the Amsterdam I (1990) and Amsterdam II (1999) Clinical Criteria, and the most sensitive ones, the Revised Bethesda Guidelines, were developed. The criteria are as follows: 1) CRC diagnosed at an age younger than 50 years, 2) presence of synchronous or metachronous CRC or other tumors associated with LS, 3) CRC with high levels of microsatellite instability (Crohn-like lymphocytic reaction, mucinous / signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old, 4) CRC and a tumor associated with CRC or LS diagnosed in at least 1 first-degree relative younger than 50 years old, 5) CRC and a tumor associated with CRC or LS at any age in 2 first-degree or second-degree relatives. To confirm the diagnosis, it is recommended to conduct genetic tests to recognize mutations of mismatch repair (MMR) genes (immunohistochemical assessment of 4 MMR system proteins) and microsatellite instability.[2]

A case of a 30-year-old man with a CRC diagnosed at the age of 16 years reflects the difficulties during the referral for KTx, selection of safe immunosuppressive therapy, and proper oncological supervision. Due to the young age of the patient and the family history of CRC (father diagnosed at the age of 44 years), genetic testing was performed and LS was recognized (mutations in the *MLH1* gene). In 2004, a subtotal colectomy was performed. Due to hepatic metastases in 2004 to 2005, chemotherapy (5-fluorouracil, cisplatin, leucovorin, followed by interferon with doxorubicin) was introduced to achieve complete remission. In 2008, due to end-stage renal failure (biopsy presented the features of tubulointerstitial nephritis), hemodialysis was started. In 2012 (7 years after the end of chemotherapy), pretransplant evaluation was started. The patient met the criterion of time that should elapse from the time of being cured for CRC (disease-free waiting period at least 5 years according to the European Renal Association–European Dialysis and Transplant Association).

The decision to refer the patient for KTx was made difficult by the fact that LS predisposes to the development of tumors in other organs throughout the patient's entire life. This risk could be additionally increased by immunosuppressive drugs, which are used after KTx. As part of extended diagnostic workup, rectoscopy, gastroscopy, abdominal computed tomography, positron emission tomography and computed tomography, and testing for tumor markers were performed. The examinations did not show any new tumor

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foci. The patient was referred for KTx from a living donor (the mother). The procedure took place on October 16, 2012. Despite the low immunological risk of the recipient (first transplantation, panel reactive antibody level of 0%, 3 mismatches: 1A, 1B, 1 DR), a 4-drug immunosuppressive therapy (baziliximab, steroids, tacrolimus, mycophenolate mofetil) was applied. After 3 months, tacrolimus was switched to everolimus. Due to the high oncological risk, an individual supervision was planned, including screening tests (once a year: abdominal ultrasound, rectoscopy, chest x-ray, and tumor markers; every 2 years: abdominal magnetic resonance imaging, gastroscopy; every 3 years: positron emission tomography and computed tomography). During the 6 years of follow-up, no new focus of cancer was found. The kidney function remained stable, the last creatinine concentration was 1.31 mg/dl, and an estimated glomerular filtration rate (assessed using the Modification of Diet in Renal Disease formula) was 64.7 ml/min.

In patients after KTx, the risk of developing the majority of malignant tumors, measured by the standardized incidence ratio (SIR) method, is more than tripled. According to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), in stage 5 of chronic kidney disease, the SIR is 1.16, during the treatment with dialysis, it is 1.35, and after transplantation, it reaches 3.27.

The described case shows various problems in the process of referral for transplantation and in long-term care. The first step was to balance off benefits and disadvantages in this young patient with cured cancer of the large intestine, metastases in the liver, and a high risk of new cancers, who poorly tolerated dialysis treatment. If the patient was not considered eligible for KTx, the current treatment would be continued at the expense of the quality of life and the risk of other complications associated with hemodialysis. An alternative was to carry out a KTx, which prolongs life and improves its quality but increases the risk of cancer due to the use of immunosuppressive drugs.[3] The patient had a family donor. KTx from a related donor increases the probability of successful surgery, with a lower risk of rejection (lower HLA mismatch) and allows an individualization of immunosuppressive therapy. Three months after KTx, tacrolimus, a drug that increases the risk of cancer, was switched to everolimus with a possible anticancer effect.

Calcineurin inhibitors have an indirect effect on the growth of tumors by inhibiting the T lymphocytes–dependent immune response. They increase the expression of transforming growth factor β, which promotes tumor invasion and metastasis, and support angiogenesis through the increased expression of vascular endothelial growth factor.

The mechanism of activity of proliferation signal inhibitors is based on binding to the immunophilin-binding protein, FKBP12, which inhibits the mammalian target of rapamycin (mTOR), a protein that plays an important role in regulating the growth and proliferation of many cells, including cancer cells. The anticancer effect of proliferation signal inhibitors includes the reduction of protein synthesis, stimulation of apoptosis, inhibition of T-lymphocyte activity, reduction of cell migration and invasion, and reduction of the expression of growth factors. Data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) registry indicate a 60% reduction of cancer risk in patients treated with mTOR inhibitors.[4]

Oncological supervision in patients with LS should be tailored to the patient's sex and disease severity. If no CRC develops in people with a confirmed mutation, it is recommended to perform a full colonoscopy every 1 to 2 years. In the case of patients with CRC, the advantages and disadvantages of a subtotal colectomy should be assessed. This procedure is especially recommended for younger patients.

Women who carry mutations should undergo an annual gynecological examination, transvaginal ultrasound, and endometrial biopsies from 30 years of age onward. In women over 40 years of age and without reproductive plans, the excision of the uterus and ovaries should be considered.

Endoscopy of the upper gastrointestinal tract with mucosal biopsy is recommended in patients with the MMR mutation from 30 years of age onward and should be repeated every 2 to 3 years, based on individual risk. In addition, all carriers of the mutation above 25 years of age should be tested for the presence of *Helicobacter pylori* infection.

Patients with LS should be examined for the development of urinary tract urothelial carcinoma. Diagnostic tests include urinalysis for the assessment of erythrocyturia, cytological examination of urinary sediment, test that measures the nuclear matrix protein 22, ultrasound, computed tomography, and magnetic resonance imaging.

In order to reduce the risk of cancer development, persons who carry mutations are advised to maintain normal body weight and not to smoke cigarettes. The regular use of small doses of acetylsalicylic acid (aspirin) reduces the risk of CRC. For carriers of mutations who are at reproductive age, genetic counseling should be provided on the possible burden of their offspring with this disease. Attention should also be paid to the psychological burden associated with the diagnosis, and, if necessary, the patient should be provided with adequate assistance.[5]

In conclusion, every patient with a high risk of cancer or after oncological treatment who is referred for KTx requires an individual strategy of treatment in the field of immunosuppressive therapy and oncological supervision.

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Malignant sarcoma after kidney transplantation: dangerous but curable

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The beneficial effect of kidney transplantation (KTx) in patients requiring continuous renal replacement therapy (RRT) due to chronic kidney disease (CKD) is commonly accepted. KTx protects patients against numerous severe complications that could develop during chronic dialysis. At the same time, different studies demonstrated that the risk of cancer development is increased in CKD patients.[1] CKD and cancer are mutually linked and both may share common risk factors such as analgesic and aristolochic acid. Abundant evidence indicates also that organ transplant recipients are at higher risk of cancer incidence than the general population.[2] Among those changes, skin cancers other than melanoma occur most frequently. Also, the risk of solid tumors is 2- to 4-fold higher than in the general population.

To the best of our knowledge, we are reporting the first case of myxofibrosarcoma, an aggressive soft tissue neoplasm, in a patient after KTx. Myxofibrosarcoma is a relatively rare histologic subtype of soft tissue sarcomas, which are rather uncommon/rare cancers. They account for less than 1% of all new cancers each year and for approximately 5% of all adult soft-tissue sarcomas.[3] Myxofibrosarcoma is defined as gelatinous nodules with noncohesive spindle or stellar tumor cells within a myxoid matrix. The myxoid part of the tumor usually represents at least 50% of the total surface. Most cases occur in middle-to-late adulthood, with a peak incidence in the seventh decade. They are predominantly encountered in the lower extremities (52%–77%), upper extremities (24%), and trunk (12%–19%).

Because of their extensive spread, myxofibrosarcomas require large resections with frequent reconstructive surgery. The aim is to resect the tumor with healthy tissue margins. In some patients, radiotherapy is given as an adjuvant therapy, mainly in cases where the resected tumor was larger than 5 cm. It is recommended to use fractionated doses of 1.8 to 2 Gy/dose to a total dose of 50 to 66 Gy.[4] When the disease is advanced (metastases to other parts of the body are present), chemotherapy is the primary treatment method, but tumor and metastasis resection should also be considered. Nowadays, limb amputations due to sarcoma are very rare, and are only performed in about 5% to 10% of patients. In cases of local myxofibrosarcoma recurrence, which might occur in 30% of patients, the implemented treatment should be the same as in primary tumors. On the other hand, if the disease recurs in the form of distant metastases (up to 20% of cases), then chemotherapy is used. However, the resection of a single metastasis may be considered. It is worth noting that, in comparison with other soft-tissue sarcomas, high-grade myxofibrosarcoma shows a greater frequency of local recurrences, more often with the character of multiple outbreaks, and the need to perform limb amputation is more frequently reported.[5]

A 57-year-old man with significant tobacco history presented with a fast-growing mass in his leg. His medical history began at the age of 18 when he was diagnosed with autosomal polycystic kidney disease. At 47 years of age, the patient was diagnosed with chronic renal failure, and 4 years later, in 2006, chronic RRT with hemodialysis was started. In 2007, he underwent KTx from a deceased donor. On the day of discharge from the hospital, the creatinine level was 1.69 mg/dl and the estimated glomerular filtration rate was 42 ml/min. He was then treated with triple immunosuppression containing steroids, cyclosporine, and mycophenolate mofetil. In the early posttransplant period, the patient had several infections of the urinary tract and kidney cyst infections were diagnosed. This was the reason for the right-sided nephrectomy surgery in 2008.

Four years later, during the follow-up visit at the transplantation clinic, the patient complained of left leg pain. A large mass, which was noticed by the patient in the last days before the visit, was found. The mass hindered him from walking and squatting. The patient was directed to the emergency room of the hospital where ultrasonography was performed, and the tumor was confirmed. Due to the tumor size, a biopsy was first performed at the outpatient oncological surgery clinic and the myxofibrosarcoma was diagnosed in histopathological examination.

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Then, surgery was performed under general anesthesia, during which a tissue block measuring 22 × 9 × 10 cm was removed. The block contained a tumor measuring 9.5 × 6.5 × 5.5 cm. The perioperative period was without complications. The tumor was inhomogeneous, made of gray, yellow-orange tissue and fibrous baffles, and had a capsule. It had reached the skin, but did not infiltrate it. During pathomorphological examination, high-grade myxofibrosarcoma was diagnosed. Two months later, during a follow-up visit, a healing wound was observed and cyclosporine was switched to sirolimus. The creatinine level was 2 mg/dl at that time. Four months after surgery, the patient started radiotherapy, which was carried out for 16 weeks until December 2012. During 5 years of follow-up, no local recurrence and metastases were found, and the patient remained under the care of an oncologist and a nephrologist. From April 2017, the patient needs RRT with hemodialysis due to symptoms of chronic renal failure and noncompliance.

Cancer plays a major role in mortality and morbidity in CKD patients, especially after KTx. The presented case of a rare malignant myxofibrosarcoma tumor, which occurred in a patient after KTx, has ended up well thanks to complex diagnostic workup and treatment carried out by an interdisciplinary team of a nephrologist, surgeon, and oncologist.

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Renal lesions in tuberous sclerosis complex including renal cell carcinoma

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Tuberous sclerosis complex (TSC) is classified as an autosomal dominant disease, although it is the result of a new mutation in more than half of patients. The disease process affects embryonic development as well as subsequent tissue maintenance and is best thought of as a failure of homeostatic control of tissue development, morphogenesis, and/or maintenance. TSC affects all organ systems and that is the reason why the clinical diagnosis of TSC is made on the basis of major and minor criteria that are agreed on by an international body.[1]

Although neurologic manifestations of TSC are often the first to be recognized, the renal complications can be quite serious, particularly if they are not recognized and treated. Premature decline of glomerular filtration rate occurs in ~40% of patients with TSC,[2] and associated renal disease is the leading cause of death in TSC populations.[3] The most common renal lesions in TSC are angiomyolipomas, detected with age-related progressing frequency in up to 80% of patients. Cystic disease is found in about half of patients with TSC, while renal cell carcinomas have been rarely reported (1.1%–2%).[4]

Proper imaging is critical for detecting, monitoring, and following therapeutic responses, and international guidelines recommend the use of abdominal magnetic resonance imaging (MRI). This is an important point because about one third of patients with TSC and angiomyolipomas have fat-poor lesions that are isoechoic to the kidney and often cannot be detected by ultrasound. Serial MRI assessments of growth characteristics are relevant to distinguish a fat-poor angiomyolipoma from malignancy.

There is an interesting clinical association between TSC and vascular abnormalities. The best known vascular abnormalities are the arterial aneurysms found in larger angiomyolipomas, but certainly cerebral and aortic aneurysms are also well documented. The frequency of aneurysms found in angiomyolipomas is far in excess than for other tumors and may point to a mechanism. Interestingly, angiomyolipomas express cell surface markers that are shared with vascular pericyte, a cell that essentially choreographs formation and maintenance of vessels. If such a cell lost the functional copy of the affected TSC locus, it follows that the cell function could be compromised and the vascular structure could be altered, promoting aneurysm formation. Likewise, this cell may help explain, in part, the homing of lymphangioleiomyomatosis cells to their histological location in the lung. The angiomyolipoma burden can be variable, and nomenclature has been developed to better describe this disease burden. The ability to describe the disease process using this scoring system (**TABLE 1**) is useful for following the course of the disease and therapeutic response.[4] Hemorrhage is a major life-threatening complication of angiomyolipomas. The risk is associated with the tumors greater than 3 cm in diameter and still enlarging and the size of aneurysms greater than 5 mm.

Renal cystic disease is also an important and common factor contributing to chronic kidney disease in the population of patients with TSC. There are 5 basic patterns of renal cystic disease in TSC. The disease, likewise, can be scored so that progression and response to therapy can be followed (**TABLE 2**).[4] While renal cystic disease is often thought to be related to the primary cilium, renal cystic disease in TSC appears to have an entirely different pathomechanism that involves tissue induction–like mechanisms such that genetically normal, type A intercalated endothelial cells of the cortical collecting duct make up the bulk of the cystic lining.[5]

Renal cell carcinomas have been reported in patients with TSC and constitute a significant cause of death in this population.[3] The frequency seems to be much lower than for other inherited syndromes that predispose to renal cancer. Therefore, a noninvasive approach such as serial MRI evaluation is recommended to assess suspicious fat-poor lesions.[4] Furthermore, the diagnosis of renal cells is based on the histologic and immunohistologic characteristics, but these similarities in appearance to von Hippel–Lindau disease and other gene-associated diseases do not guarantee the same clinical outcomes. Further research on

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TABLE 1 Stages of renal angiomyolipomata based on the number and size

Stage	Lesions, n	Lesion size, cm	Morphology
0	None	–	–
1	0 – 5	<3.0	Normal
2	>5	<3.0	Normal
3	<5	1 lesion >3.0	Intact
4	>5	1–4 lesions > 3.0	Intact
5	>5	>5 lesions >3.0	Recognizable
6	>5	1 lesion >5.0	Not recognizable

TABLE 2 Types and stages of renal cystic disease based on the number of cysts

Stage	0	1	2	3	4	5	6
Polycystic disease	0	0–2	3–6	7–10	11–20	21–30	>31
Cortical cystic disease	0	1–10	11–20	21–30	31–40	41–50	>51
Multicystic disease	0	1–10	11–20	21–30	31–40	41–50	>51
Focal cystic disease[a]	0	1	2	3	4	5	>5
Microcystic disease[b]	0	10%	20%	30%	40%	50%	>50%

a Number of cysts in medullary rays

b Percentage of cortex involved

the outcomes of TSC-associated renal cell carcinoma is desperately needed.

The consequence of renal manifestations in TSC is the premature loss of kidney function. This chronic kidney disease can be caused by a disease-related phenomenon, such as acute kidney injury from renal bleeding or replacement of renal parenchyma with angiomyolipomas or cysts, or can result from therapeutic approaches, such as embolization or surgery. There also may be a role for the overactivation of mammalian target of rapamycin complex 1 (mTORC1) as a result of haploinsufficiency leading to early loss of nephrocytes. Moreover, modifiable risk factors such as hypertension, proteinuria, and hyperfiltration—features that occur frequently and early in patients with TSC—should be emphasized and aggressively treated.[4]

The current guidelines for surveillance and treatment of angiomyolipomas in patients with TSC are straightforward. Monitoring growth of lesions using abdominal MRI and mTORC1 inhibitors as the recommended first-line preemptive therapy for angiomyolipomas greater than 3 cm is clearly documented. The short-term results that are reducing or stabilizing angiomyolipomas are accompanied by long-term effects, such as preventing bleeding and preserving renal function.[4] The clinical system of angiomyolipoma scoring is useful to monitor the regression induced by therapy with mTORC1 inhibitors.

Recent evidence has revealed that smaller cysts are also responsive to mTORC1 inhibitors, while larger ones that have likely lost their communication with the renal tubule, are independent and do not respond as well, if at all.[5] These features would suggest that early therapy may be more useful in preventing significant renal cystic disease than treating already advanced disease. Nephrological care of the patient with renal disease in TSC has dramatically changed in the last decade. The standard recommendations for chronic kidney disease care are still important in slowing disease progression. Patients should avoid nonsteroidal anti-inflammatory drugs, maintain an appropriate body mass index, exercise, and pay attention to proper diet and hydration. Blood pressure control and now the consideration of mTORC1 inhibitors for angiomyolipomas and other manifestations of TSC such as seizures and subependymal giant cell astrocytomas may significantly reduce the renal cystic burden and further slow the loss of renal function in these patients.

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Diagnostic difficulties in patients with tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is a progressive, inherited autosomal dominant disease, caused by mutations of the *TSC1* or *TSC2* gene and affecting many organs, especially the skin, central nervous system (CNS), kidneys, lungs, heart, and eyes.[1] Its symptoms are diverse, even among members of one family, and diagnosis is difficult due to clinical variability. Imaging studies are necessary to detect changes in the brain, lungs, and kidneys typical for TSC. Knowledge of radiologic features facilitates diagnosis as well as planning and monitoring of the patient's management.

Brain Among the 11 major pathognomonic criteria for TSC, 3 relate to cerebral lesions recognizable on magnetic resonance imaging (MRI); they are cortical dysplasias, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs). Cortical tubers (cortical dysplasias) occur in 90% of patients and SENs are observed in approximately 80%; SEGAs are less frequent and affect 5% to 15% of patients with TSC.[1]

Cortical tubers are the cause of seizures in more than 80% of cases. They are visible as hyperintense thickening of the cerebral cortex on T2-weighted MRI (FIGURE 1A) with associated radial lines of neuron migration defects in the white matter.

Both cortical tubers and neuron migration disorders are usually easily interpreted radiologic symptoms. Rare cases of cortical nodules with calcification or atypical cystic changes may cause diagnostic problems.

Another major criterion is the presence of SENs, most often located in the lateral ventricles (FIGURE 1B). About 10% of SENs undergo a malignant transformation to SEGAs.[1] Due to their periventricular or intraventricular location, there is a risk of blocking the flow of cerebrospinal fluid and hydrocephalus, which increases intracranial pressure, manifested by severe headaches, vomiting, behavioral disorders, or the appearance of epileptic seizures. These symptoms are an indication for urgent neurologic and radiologic control. A radiologic symptom indicating the malignant transformation from SEN to SEGA is the enlargement of the lesion during the follow-up to a size greater than 13 mm, as well as the presence of contrast enhancement after administration of a contrast medium (CM) (FIGURE 1C). Some of the calcified SENs may have a hyperintense signal in native T1-weighted images. Therefore, it is necessary to compare the signal intensity before and after administration of CM to gain an objective evaluation of the contrast enhancement, to differentiate between SEN and SEGA. The latter is

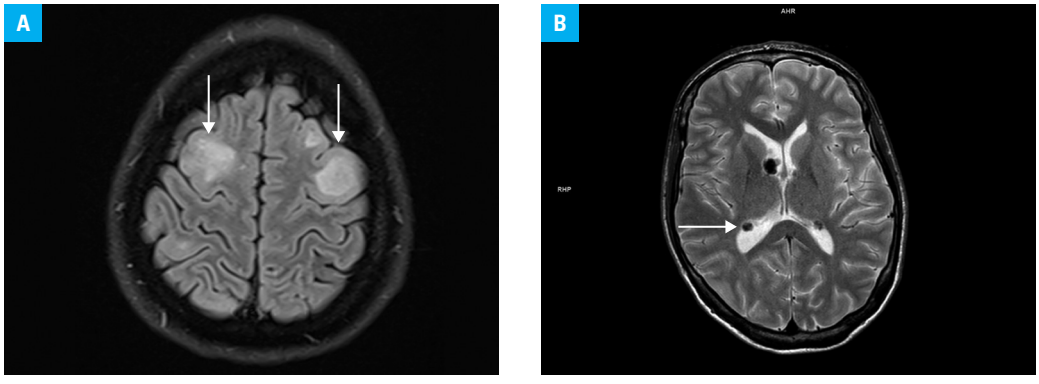

FIGURE 1 Lesions in different organs (brain, lung, and kidney) in patients with tuberous sclerosis complex; **A** – fluid attenuation inversion recovery magnetic resonance image (MRI) showing multiple cortical tubers in the brain (arrows); **B** – T2-weighted MRI showing calcified subependymal nodules located in the lateral ventricles (arrow)

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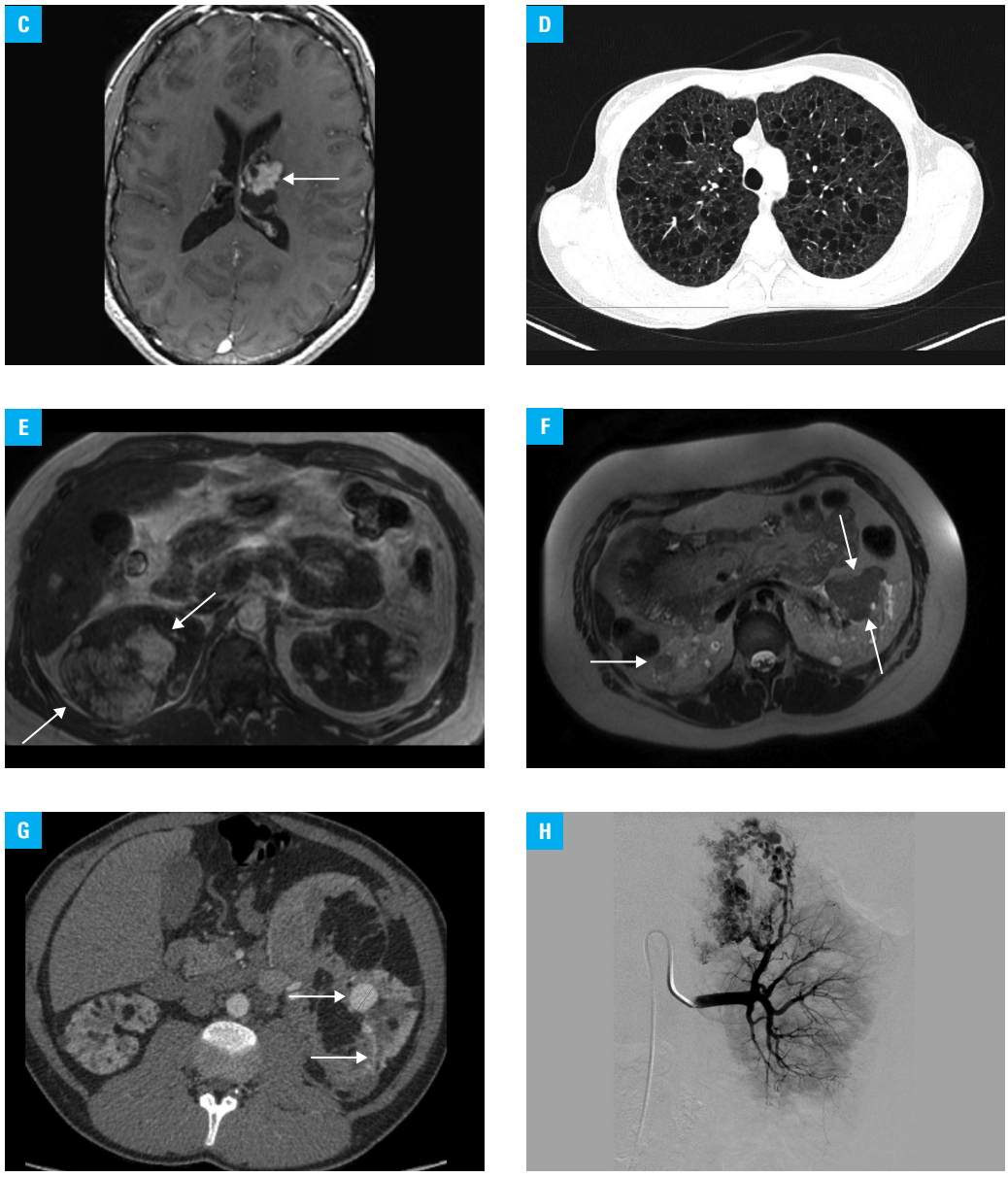

FIGURE 1
C – enhanced T1--weighted magnetic resonance imaging (MRI) showing subependymal giant cell astrocytoma in the left foramen of Monro (arrow); **D** – chest computed tomography scan showing well-limited numerous cysts without accompanying interstitial lesions typical for lymphangioleiomyomatosis; **E** – noncontrast T1-weighted MRI showing the high signal of fat in the fat-rich angiomyolipoma (arrows); **F** – T2--weighted MRI showing low signal of fat-invisible angiomyolipoma (arrows); **G** – arterial--phase computed tomography scan showing multiple aneurysms in triphasic angiomyolipoma (arrows); **H** – digital subtraction angiography showing multiple aneurysms in triphasic angiomyolipoma

classified as a low-grade tumor (grade II according to the World Health Organization). Mostly, it is located in the region of the foramen of Monro. In intraventricular localizations, SEGA should be differentiated from other tumors in this location (eg, meningioma, papilloma), and the extraventricular SEGA, from high-grade gliomas.

The method of choice for brain lesion screening in patients with TSC is MRI with CM administration. Imaging should be performed every 1 to 3 years for patients with TSC until the age of 25 to monitor for SEGA.[1]

Lungs Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease characterized by an uncontrolled proliferation of abnormal cells, similar to smooth muscles around the bronchi, blood vessels, and lymphatic vessels of the lung.[2] It may occur as a separate disease (sporadic LAM) only in women, and LAM in the course of TSC occurs in both sexes (less frequently in men). Changes in LAM are mainly well-limited numerous cysts, measuring 2 to 20 mm, usually without accompanying interstitial changes (FIGURE 1D). Cyst walls are mostly thin and do not exceed 2 mm in width. Cysts do not show a predilection for specific lobes or zones. In the majority of cases, the progression of TSC and LAM is slow or none.

Another pulmonary manifestation of TSC is multifocal micronodular pneumocyte hyperplasia, which creates major diagnostic difficulties because small nodules and ground glass opacity are present and can be misdiagnosed as Langerhans cell histiocytosis, amyloidosis, or lymphocytic interstitial pneumonia.[2] Complications such as edema or bleeding into the alveoli, as well as pneumothorax or chylothorax, and lymphadenopathy can lead to incorrect cancer diagnosis.

Definite diagnosis of LAM can be made based on tissue biopsy, serum vascular endothelial growth factor-D levels, or a combination of history and high-resolution computed tomography (CT) scanning. When the number of cysts exceeds 10 in patients with TSC, LAM can be diagnosed based on high-resolution CT (probable diagnosis of LAM, 2–10 cysts). Centrilobular emphysema and multifocal cystic lung cancer can mimic LAM.

High-resolution CT is recommended every 5 to 10 years in asymptomatic adult women at risk of LAM. It is suggested every 2 to 3 years for patients with lung cysts.

Kidneys The most common renal manifestation of TSC is angiomyolipomas (AMLs), found in up to 80% of patients. The presence of 2 or more renal AMLs is a major diagnostic criterion for the diagnosis of TSC.[3] The histopathologic classification of AML includes typical forms (triphasic AML comprises abnormal blood vessels, sheets of smooth muscle, and mature adipose tissue) and atypical forms (monophasic or epithelioid). The monophasic variant of AML almost always consists of one dominant component, such as an epithelioid type which comprises epithelioid muscle cells and has a tendency toward malignant transformation. Patients with TSC have a greater risk of developing renal cell carcinoma (RCC) than the rest of the population, but TSC-associated RCCs have a unique clinical and pathologic presentation and are usually more benign than the sporadic RCC. Differentiation of epithelioid AMLs and RCCs is difficult using imaging methods but is easier, albeit invasive, by biopsy and immunohistochemistry markers. Due to the relatively slow increase in size of RCCs, imaging follow-up can be used to set the diagnosis.

According to quantitative findings from CT and MRI, AMLs can be classified as fat-rich, fat-poor, or fat-invisible.[4] A typical AML is fat-rich and contains macroscopic adipose tissue visible on CT as areas with negative densities (maximum –10 Hounsfield units), while on MRI it is shown as high signal areas (**FIGURE 1E**) suppressed in sequences with fat saturation. A total of 33% of AMLs associated with TSC are atypical and can be divided into 4 subtypes: hyperattenuating (higher density than renal parenchyma on noncontrast CT), isoattenuating (very rare cases of similar tumor density as compared with renal parenchyma on noncontrast CT), AML with epithelial cyst, and epithelioid AML (usually a large tumor, greater than 7 cm). Hyper- and isoattenuating subtypes of AMLs are also hypointense on T2-weighted MRI and can consist of a very small amount of fat, which can be visible on fat saturation sequences as foci of signal loss or as signal drop on the dual out-of-phase sequence. In the case of fat-invisible AMLs (**FIGURE 1F**), there are no changes in the signal intensity, and RCC should be included in the differential diagnosis.[4]

Magnetic resonance imaging is more sensitive than CT in detecting fat and hemorrhage. The risk of AML bleeding increases in tumors larger than 4 cm and where the intratumoral aneurysm is greater than 5 mm.[5] Aneurysms can be easily recognized and monitored during the arterial phase of multiphase CT and MRI studies as well as in digital subtraction angiography (**FIGURE 1G** and **1H**). Acute tumor bleeding is well visible on CT and MRI, while subacute and chronic bleeding may be detected only by MRI.

Magnetic resonance imaging should be performed every 1 to 3 years throughout the lifetime of a patient with TSC to assess the presence of AMLs and their progression, as well as to differentiate them from RCC. This avoids unnecessary nephrectomies and preserves renal function. Radiologic imaging plays a crucial role in the management of patients with TSC.

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Pulmonary manifestations of tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is an autosomal dominant disease with an incidence of about 1 per 5000 to 10 000 births and high clinical variability. Widespread hamartomas and benign or rarely malignant neoplasms affecting various organs, most commonly the brain, kidney, skin, lungs, retinas, and heart, are in the spectrum of the disease. The main molecular mechanism leading to the development and progression of TSC lesions is the loss of *TSC1* or *TSC2* gene function. It results in the activation of mammalian target of rapamycin (mTOR) signaling pathway and dysregulation of cell growth, survival, as well as upregulation of motility.[1,2]

The pulmonary manifestations of TSC are quite distinctive and include lymphangioleiomyomatosis (LAM), mediastinal lymph angioleiomyoma, chylothorax, multifocal micronodular pneumocyte hyperplasia (MMPH), multiple osteosclerotic lesions in the vertebrae, ribs, and sternum, and fatty deposits in the heart. LAM is caused by the proliferation of smooth muscle-like cells, which carry a mutation in the TSC genes, and can result in polycystic destruction of the lungs, lymphadenopathy, cystic lymphangiomas, and chylothorax. The disease affects mainly women at childbearing age; however, a few cases in men with TSC were also diagnosed. Approximately 300 000 to 400 000 of women with TSC have LAM. The number of cases increases with age, and about 80% of women with TSC older than 40 years have LAM.[1,2]

The prevalence of MMPH, another rare pulmonary manifestation of TSC, is estimated to be around 40% to 60%. It may be associated with LAM or, less frequently, it occurs as an isolated pulmonary manifestation among men and women with TSC. It develops locally as self-limited benign lesions.[3]

Dyspnea on exertion, cough, hemoptysis or chyloptysis, chest pain caused by pneumothorax or chylothorax, and loss of weight are common clinical presentations of LAM, whereas MMPH is usually asymptomatic. High-resolution computed tomography plays a key role in the diagnosis of chest lesions. LAM is characterized by numerous thin-wall cysts (more than 10), no larger than 3 cm, and equally distributed in both lungs. Radiologically, MMPH presents as small, sometimes confluent, ground glass opacities or well-circumscribed nodules with a diameter of 4 to 15 mm with no particular predilection.[1,2]

Histologically, LAM lesions are composed of abnormal, neoplastic, smooth muscle–derived, spindle-shaped cells, reacting with antibodies against smooth muscle markers (α–smooth muscle actin, desmin, and vimentin) and polygonal epithelioid cells, reacting with HMB45 antibody. Estrogen and progesterone, angiotensin II, insulin like growth factor II, and CD44 receptors all occur in LAM cells. MMPH consists of multifocal nodular lesions caused by the proliferation of type II pneumocytes, with usually mild thickening of the alveolar septa, particularly when extensive. The hyperplastic cells display no signs of nuclear atypia, no immunoreactivity for carcinoembryonic antigen or p53. MMPH does not show invasion into blood or lymphatic vessels. These findings differentiate MMPH from the preinvasive lesion of pneumocytes that characterize atypical adenomatous hyperplasia or lepidic form of lung adenocarcinoma.[1-3]

The discovery of the genetic and molecular mechanisms of LAM lead to the introduction of the treatment with mTOR inhibitors. The efficacy of treatment with sirolimus in LAM and with everolimus in renal angiomyolipomas and subependymal tumors has been proved. Elucidation of the disease pathogenesis has resulted in implementation of other therapeutic agents such as vascular endothelial growth factor D inhibitors, statins, interferon, chloroquine analogues, cyclin-dependent kinase inhibitors, matrix metalloproteinase inhibitors, aromatase inhibitors, check-point inhibitors, and their combinations. MMPH and osteosclerotic lesions are not an indication for treatment.[3-5]

The case presented below illustrates some very important aspects of pulmonary lesions in patients with TSC.

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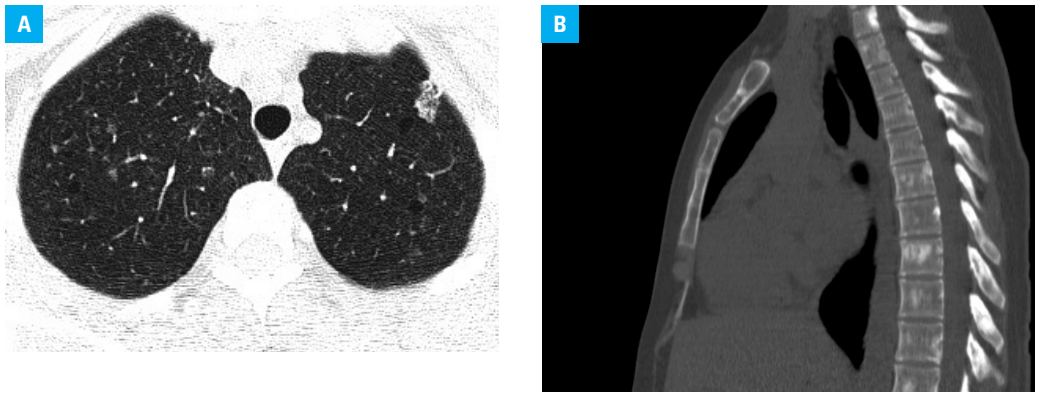

FIGURE 1 **A** – thin-section axial computed tomography image (lung window) showing numerous bilateral small ground-glass nodules and smaller diffuse, rounded, thin-walled lung cysts; **B** – sagittal computed tomography image showing multiple sclerotic bone lesions of the thoracic and cervical spine vertebral bodies and sternum

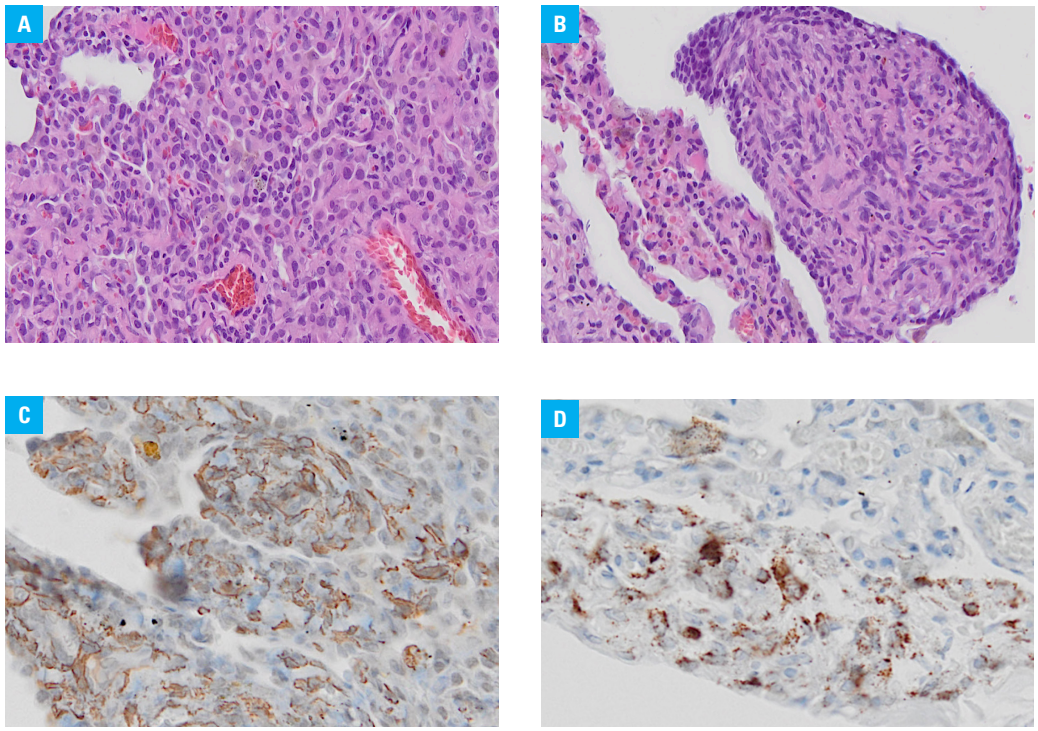

FIGURE 2 **A** – multiple areas of thick alveolar septa filled with hyperplastic type II pneumocytes with slight atypia. The histologic picture was compatible with multifocal micronodular pneumocyte hyperplasia (hematoxylin and eosin staining; magnification × 200). **B** – small cystic lesions with a multifocal nodular proliferation of immature smooth muscle cells. The histologic picture is compatible with lymphangioleiomyomatosis (LAM; hematoxylin and eosin staining; magnification × 200). **C** – nodular proliferation of immature smooth muscle cells with strong immunoreactivity for smooth muscle actin. The histologic picture is compatible with LAM (smooth muscle actin immunohistochemistry, magnification × 200); **D** – proliferation of immature smooth muscle cells with strong immunoreactivity for HMB45 antigen. The histologic picture is compatible with LAM (HMB45 immunohistochemistry, magnification × 200).

Case report A 32-year-old woman, nonsmoker, was admitted to our department with a diagnosis of disseminated adenocarcinoma of the lung with bone metastases. The diagnosis was established in a district hospital on the basis of radiological examinations and histological assessment of lung samples obtained by video-assisted thoracoscopy. During childhood she had epilepsy, and subsequently TSC was diagnosed. Facial angiofibroma, hypomelanotic macules, ungual and periungual fibromas, confetti lesions, gingival fibromas, pits of dental enamel, renal angiomyolipomas, cortical tubers, and subependymal nodules have been present for many years.

On admission, she was in good condition, and complained of a cough for the last 2 years. Laboratory examinations of the blood and urine were normal. Pulmonary function tests and 6-minute walk test were within normal limits (forced expiratory volume in the first second, 94% predicted; forced vital capacity, 104% predicted; total lung capacity, 106% predicted; transfer factor for

carbon monoxide, 79% predicted). Chest computed tomography showed numerous bilateral small ground-glass nodules, the largest being a subpleural nodule located in the apex of the left lung (size, 1.8 × 1.0 cm); the other were smaller, up to 5 mm in diameter, diffuse, rounded, thin-walled cysts. These cysts and nodules were distributed randomly throughout the lung (**FIGURE 1A**). The skeletal images showed multiple sclerotic lesions in the cervical and thoracic spine vertebral bodies, sternum, and single foci in the ribs (**FIGURE 1B**). Abdominal computed tomography showed multiple angiomyolipomas in both kidneys, and a large fatty lesion (9 × 16 cm) expanding from the right kidney to the liver. Brain MRI demonstrated multiple cortical tubers, multiple subependymal nodules, SEGA tumor (1.2 × 1.3 cm), and white matter migration lines.

The histologic reassessment of lung samples revealed multiple areas of thick alveolar septa filled with hyperplastic pneumocytes type II with slight atypia. There were no mitotic figures and signs of infiltration (**FIGURE 2A**). In addition, we observed the small cystic lesions with a multifocal nodular proliferation of immature smooth muscle cells (**FIGURE 2B**) positive in immunohistochemistry for smooth muscle actin (**FIGURE 2C**) and desmin, and perivascular epithelioid cells (LAM cells) positive in immunochemistry for HMB45 antigen (**FIGURE 2D**).

The histologic picture was compatible with LAM and MMPH. Treatment with an mTOR inhibitor was introduced with slight improvement.

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Management of subependymal giant cell astrocytoma in tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is a genetic, autosomal dominant neurocutaneous disorder characterized by the presence of histologically benign hamartomas in different organs, mainly in the brain, kidney, liver, heart, and lungs.[1] The condition appears with an incidence of 1 in 10 000 people in the general population, or 1 in 6800 in the pediatric age group.[1] It is a heterogeneous disease with a highly variable clinical presentation. TSC manifestations are produced by a mutation in the *TSC1* or *TSC2* gene, which is responsible for an overactivation of the mammalian target of rapamycin (mTOR) pathway and dysregulation of cell growth and proliferation.[1]

Subependymal giant cell astrocytoma (SEGA) is one of the 3 principal intracranial manifestations of TSC. The remaining manifestations are cortical tubers and subependymal nodules (SENs). SEGAs are diagnosed in 11% to 14% of patients with TSC, particularly in the first 2 decades of life.[1] Some tumors may be seen on prenatal ultrasound or prenatal brain magnetic resonance imaging (MRI).[2] Usually, they appear in the vicinity of the foramen of Monro, and, due to their location, the growing tumors may cause an obstruction and lead to hydrocephalus and its consequences.

According to the Knudson 2-hit hypothesis, first proposed for retinoblastoma development, SEGA occurs due to inactivation of both copies of the *TSC1* or *TSC2* genes. In clinical practice, loss of heterozygosity is frequently found in patients with TSC in renal angiomyolipomas, but less frequently in SEGA tumors.[1]

Definition Because it is difficult to differentiate SEGAs from SENs, there is no clear definition of SEGA. Both lesions appear in a similar location and are histopathologically identical.[1] In recent years, 2 consensus conferences proposed definitions of SEGA. The TSC Consensus Meeting in Rome in 2012 defined SEGA as "a tumor in TSC patient that is usually characterized by a location near the foramen Monro with >0.5 cm in diameter, with any documented growth, and gadolinium enhancement on neuroimaging."[1] During the Consensus Conference in Washington in 2012, SEGA was defined as "a lesion at the caudothalamic groove with either a size of more than 1 cm or a SEN at any location that has shown serial growth on consecutive imaging regardless of size."[1,3]

Surveillance According to the current recommendations, brain MRI should be performed every 1 to 3 years until 25 years of age in patients in whom SEGA was not previously revealed.[1,3] For uncertain reasons, the probability of developing SEGA significantly decreases after 20 years of age.[1,3] Patients with developmental delay or already diagnosed asymptomatic SEGA may require more frequent follow-up depending on the tumor size, location, and growth rate as well as general clinical status.[1,3] Also, patients with a residual tumor after SEGA surgery require prolonged follow-up due to the risk of tumor regrowth.[1,4]

Treatment For many years, only surgical treatment was available. Currently, with the discovery of mTOR inhibitors, there are 2 treatment options, surgical or pharmacological with mTOR inhibitors (everolimus, approved for SEGA therapy in TSC; sirolimus, not registered for SEGA therapy).[1,3] **TABLE 1** summarizes indications for both pharmacological and surgical treatment. In the case of surgical treatment, there is a risk of regrowth after subtotal tumor removal.[2-4] Surgery in symptomatic patients of younger age, bilateral SEGAs, and greater size of the tumor (especially >3 cm) are correlated with a higher risk of surgical complications.[1-4] Therefore, some patients with asymptomatic but large lesions may benefit from combined treatment of mTOR inhibitors to reduce the size of the tumor, and then surgical resection.[1-4]

Mammalian target of rapamycin inhibitors are immunosuppressive drugs inhibiting an overactivated mTOR pathway. Some reports indicated that SEGA regrowth may occur after therapy discontinuation, and optimal treatment duration has not yet been determined.[1,5] However, interestingly, therapy with everolimus in patients with TSC has not only induced regression of SEGA, but also improved other TSC manifestations, for

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TABLE 1 Therapeutic options for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex

Asymptomatic patients with SEGA	
Both mTOR inhibitors and surgery may be considered, especially if a large size or rapid growth of SEGA is observed; consider the clinical status, the risk of complications, potential impact on TSC comorbidities, and patient's preference.	
Small asymptomatic and nongrowing lesions may be followed by close and frequent imaging (watch and wait); educate patients and parents of early symptoms of hydrocephalus.	
For large asymptomatic lesions, consider combined treatment with mTOR inhibitors to reduce tumor size with subsequent surgery.	
mTOR inhibitors as an option	Multisystem manifestations
	Multiple or infiltrating SEGA lesions that are not amenable to total resection
	Contraindications to surgery
Surgery as an option	Unilateral, single, total resectable SEGA
	No surgical risk factors
	No other TSC comorbidities
	Contraindications to mTOR inhibitors
Patients with symptoms of hydrocephalus	
Only surgical treatment	Transcortical or transcallosal resection of the tumor
	In acute life-threatening hydrocephalus an external ventricular drainage until tumor resection may be required
	After surgery, a ventriculoperitoneal shunt may be required in some patients

Abbreviations: mTOR, mammalian target of rapamycin; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex

example, reduced size of renal angiomyolipomas, facial angiofibromas, and improved seizure control.[1,5] Therefore, mTOR inhibitors should be considered as a therapeutic option especially in patients with other coexisting TSC manifestations. Despite the benefits, mTOR inhibitors may also cause some adverse effects: these include stomatitis, mouth ulceration, dyslipidemia, upper respiratory tract infections or infections of other organs / systems, diarrhea, and bone marrow suppression.[5] The occurrence of some of these effects is an indication for, at least temporary, interruption of the treatment. Therefore, therapy with mTOR inhibitors requires regular blood tests (ie, morphology, liver and renal function assessment, glucose levels, lipid profile) and monitoring of the blood drug concentration because of a narrow therapeutic index. Caution should be executed also with a simultaneous implementation of medications influencing the activity of cytochrome CYP3A4 that metabolizes mTOR inhibitors.

Conclusions SEGA is one of the 3 principal intracranial manifestations of TSC requiring regular monitoring because of the risk of hydrocephalus. In symptomatic patients, surgery is the standard treatment. For asymptomatic lesions, both surgical and pharmacological interventions may be implemented, and a careful assessment of potential benefits and adverse effects should be conducted to choose the best therapeutic option.

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Tuberous sclerosis complex or cancer? The nephrologist's point of view

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Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in one of the tumor-suppressor genes, *TSC1* or *TSC2*. The loss-of-function mutations lead to overactivation of the mammalian target of the rapamycin (mTOR) pathway and result in acceleration of cell growth and inhibition of autophagy. In consequence, hamartomatous lesions are formed in the brain, skin, heart, kidneys, lungs, and other organs.[1] The clinical manifestations of TSC are variable. The expression of the disease is related to age and differs even between members of the same family.[2] Typical, most frequent lesions in TSC are included as major clinical diagnostic features and comprise angiofibromas, hypomelanotic macules, cortical tubers, subependymal nodules, renal angiomyolipomas (AMLs), cardiac rhabdomyomas, and lymphangioleiomyomatosis. However, there are less common manifestations not detailed as diagnostic criteria, including lymphatic involvement, sclerotic bone lesions, multifocal micronodular pneumocyte hyperplasia, or gynecological, endocrine, and gastrointestinal findings. In relation to the multifocal involvement of various organs in TSC, and also the reported increased incidence of malignant tumors, as for example renal cell carcinoma (RCC), it is important to consider all patient's features in the TSC spectrum to avoid misdiagnosis.[3] mTOR inhibitors approved for use in selected TSC manifestations (eg, AMLs, lymphangioleiomyomatosis) and in advanced RCC seem also to be effective in TSC-related RCC.[4]

A 24-year-old male patient, after resection of cardiac tumors (rhabdomyoma) at the age of 7 months, with type 1 diabetes mellitus, and a family history of TSC (older brother and father), was admitted to the reference center for TSC for further evaluation. Two weeks earlier he was hospitalized in a cardiology unit due to a respiratory tract infection and was diagnosed with chronic heart failure, permanent atrial fibrillation, severe mitral regurgitation, and arterial hypertension. Computed tomography (CT) scans revealed multifocal bilateral renal masses suggestive of a malignant process and AMLs, as well as pulmonary nodules consistent with metastatic and osteosclerotic lesions in the bones. An increase in CA-125 level (430 U/ml [reference range, 0–35 U/ml]) was found. Considering the whole clinical presentation, disseminated neoplastic disease was suspected.

When admitted to our department, the patient was in a stable condition. Physical examination revealed skin lesions typical for TSC (facial angiofibroma, forehead fibromas, hypomelanotic macules, confetti lesions, periungual fibromas, shagreen patch), murmur of mitral regurgitation, pleural effusion, enlarged liver, ascites, filled jugular veins, edema of the lower limbs, and palpable enlarged left kidney. Laboratory tests revealed increased creatinine levels (1.1–1.27 mg/dl), proteinuria (urine protein to creatinine ratio, 220 mg/1g), anemia (hemoglobin, 11.1 g/dl), hyperbilirubinemia (2.06 mg/dl) with increased cholestatic parameters (alkaline phosphatase, 238U/l; γ-glutamyltransferase, 262U/l). Magnetic resonance imaging scans showed subependymal nodules and cortical tubers in the brain, multiple bilateral renal AMLs (the largest tumor was 102×127 mm in the left kidney with the presence of large aneurysms, 13 mm and 18.5 mm in diameter), renal cysts, and osteosclerotic lesions in the vertebra. Chest CT showed bilateral pleural effusion, thin-walled cysts, and numerous solid nodules, consistent with multifocal micronodular pneumocyte hyperplasia or metastasis (**FIGURE 1A** and **1B**). Moreover, chest and abdominal lymphadenopathy was found.

The patient met 8 major and 2 minor clinical features of TSC (definite diagnosis). Although the clinical manifestation could correspond to TSC and heart failure, malignancy could not be definitely excluded without further evaluation because of the indistinct character of some lesions. However, the patient refused needle biopsy of the lung nodule, lymph node procurement, or partial left nephrectomy. As he met the criteria for the use of mTOR inhibitors in TSC (AMLs >3 cm), and considering the antiproliferative effect of mTOR

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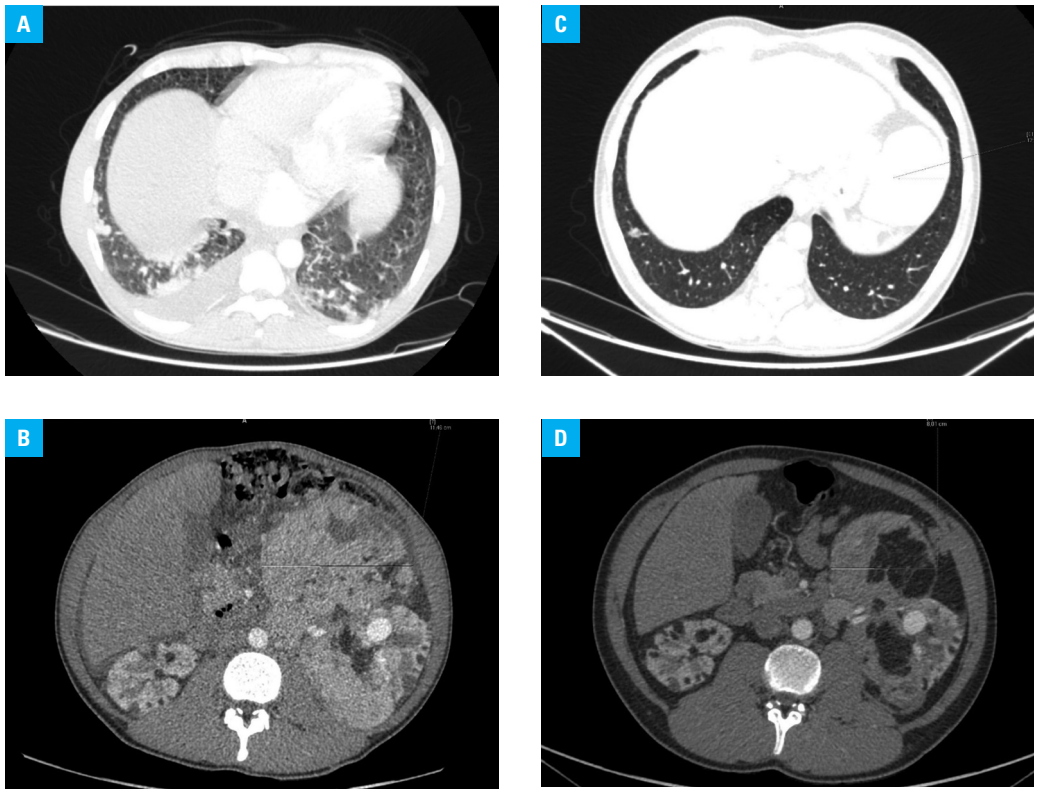

FIGURE 1 Computed tomography (CT) scans of a 24-year-old patient; **A** – chest CT showing pleural effusion, thin--walled cysts, and numerous solid nodules, consistent with multifocal micronodular pneumocyte hyperplasia or metastasis; **B** – abdominal computed tomography presenting multiple bilateral renal angiomyolipomas; **C** – regression of pulmonary lesions after 6 months of sirolimus therapy; **D** – regression of renal lesions after 6 months of treatment with mammalian target of the rapamycin

inhibitors, sirolimus was introduced. Diuretic therapy was intensified and a reduction of body weight, ascites, hepatomegaly, and edema was achieved. Follow-up that lasted 6 months showed a gradual improvement in clinical condition and amelioration of heart condition. Chest and abdominal CT scans revealed regression of pleural effusion and ascites, as well as a response in pulmonary and renal lesions (FIGURE 1C and 1D). CA-125 levels decreased to 43.4 U/ml. Renal function remained stable. Hyperlipidemia and proteinuria were observed as side effects of mTOR inhibitor therapy. The mean sirolimus trough level was 6.1 µg/l and the dose ranged from 1.5 to 2 mg.

Discussion Tuberous sclerosis complex usually manifests in childhood, and is most often associated with the classic triad of symptoms: facial angiofibromas, seizures, and intellectual disability. Patients mildly affected in early life may present in adulthood with life-threatening pulmonary or renal complications. The initial manifestation with tumorous lesions in various organs might be incorrectly regarded as a disseminated malignant disorder; on the other hand, RCC develops in 1% to 4% of TSC patients, and the metastatic course has been reported.[4,5] Patients with diagnosed TSC should be regularly monitored for new lesions or worsening organ involvement to reduce morbidity and mortality by early therapeutic intervention.[1,2] In renal lesions a reasonable approach between the surgical or ablative therapy and active monitoring should be balanced, taking into account the risk of end-stage renal disease and also the progression of suspicious lesions.[5] The systemic treatment with mTOR inhibitors approved for treatment in AMLs was also proved to be beneficial in TSC-related RCC.[4] It can be assumed that mTOR inhibitors may constitute a new management option in indeterminate TSC organ manifestations.

The presented case of the patient with TSC outlines the advantage of referring patients to experienced TSC centers. In such centers clinical and radiological assessment of the disease, as well as therapy effectiveness and safety control, can be provided regularly. Eventually, the patient was fully evaluated and diagnosed, and appropriate management was introduced. The clinical course and response to mTOR inhibitors seem to confirm that organ manifestations initially suspected to be malignant (lymphadenopathy, pulmonary and bone lesions) are in fact TSC manifestations. Nevertheless, due to the current recommendations in TSC, lifelong monitoring and therapy with mTOR inhibitors appear to be unavoidable.

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Tuberous sclerosis complex or cancer? The radiologist's point of view

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Tuberous sclerosis complex (TSC) is a genetic disease caused by mutations in the *TSC1* or *TSC2* gene, leading to dysregulation of the mammalian target of rapamycin (mTOR) kinase pathway and formation of benign or rarely malignant tumors affecting various organs. The most common renal manifestations are multiple bilateral angiomyolipomas (AMLs), occurring in 80% of patients with TSC. Cystic lesions are less frequent and occur in 50% of patients, and renal cell carcinoma (RCC) is very rare (1% to 2% of patients).[1] TSC-related RCC is uncommon, but develops in younger patients and appears multifocally and bilaterally. A considerable proportion of renal masses (complex cysts, fat-poor AMLs) are diagnostically indeterminate and difficult to distinguish from RCC.[2] Limited experience with patients with TSC may result in unnecessary surgeries.

Here we present a patient with TSC and simultaneous manifestation of AMLs, RCC, and cystic lesions. A 32-year-old woman, diagnosed with TSC in childhood, with skin, lung, and brain involvement, was admitted to the hospital due to multiple bilateral kidney tumors. Magnetic resonance imaging (MRI) revealed multiple bilateral fat-containing AMLs, fat-poor lesions stable in size, cysts, and a progressive solid-cystic lesion in the left kidney (86 mm in diameter). The solid part of the cystic lesion displayed contrast enhancement and continuous growth (**FIGURE 1A–1E**).

Due to the indistinctive character of the lesion, the patient was first referred for therapy with mTOR inhibitors, with a plan of early MRI control and surgery in case of progression. Sirolimus at a dose of 3 mg (mean trough level, 3.1 μg/l) was started. Two weeks later the patient presented with fever and pain in the left kidney. Antibiotic therapy was introduced, mTOR inhibitors were stopped, and the patient was referred for renal-sparing surgery. The solid cystic lesion was excised. Pathological analysis revealed clear cell papillary RCC and AML. Six weeks after the surgery, sirolimus was restarted. No local recurrence was found on MRI scans performed 3 and 12 months later. Moreover, significant regression of fat-poor lesions was revealed (**FIGURE 1F** and **1G**). Renal function remained stable, with a creatinine level of 0.66 mg/dl. Sirolimus doses ranged from 1.5 to 3 mg (mean trough level, 4.46 μg/l).

Discussion Renal complications are the leading cause of morbidity and mortality in adult patients with TSC, which makes radiological monitoring crucial. MRI or computed tomography (CT) is recommended every 1 to 3 years to detect and monitor the growth of renal lesions.[1,3] Classic AMLs are hyperechogenic on ultrasound, show fat attenuation on unenhanced CT, and are characterized by loss of signal in frequency-selective fat suppression and chemical shift imaging methods of MRI. However, 30% of AMLs may be fat-poor, which makes the diagnosis challenging. Fat-poor AMLs may be hyper- or isoattenuating with renal parenchyma on CT, T2-hypointense on MRI, with a variable signal in fat suppression and chemical shift depending on fat content, and appear with increased homogeneous contrast enhancement.

Typically, RCC has a heterogeneous appearance with strong enhancement and rapid washout, as well as T2-high signal intensity on MRI. However, the imaging differs depending on the RCC subtype, and may be similar to a benign lesion. In indistinct cases, biopsy or serial follow-up is recommended. AMLs with epithelial cysts typically present as a complex enhancing cystic mass with a solid renal tumor similar to fat-poor AMLs. Considering that cystic disease occurs in 50% of patients with TSC, the presence of a solid mass that is associated with cystic components is common. In the general population, this raises suspicion of RCC, but it is presumed that due to RCC rarity in TSC patients, complex cysts should be serially measured and assessed for growth.[1-4] Nevertheless, slow, indolent growth may be present in small RCC masses as well. For the syndromes with an intermediate and low risk of RCC, like

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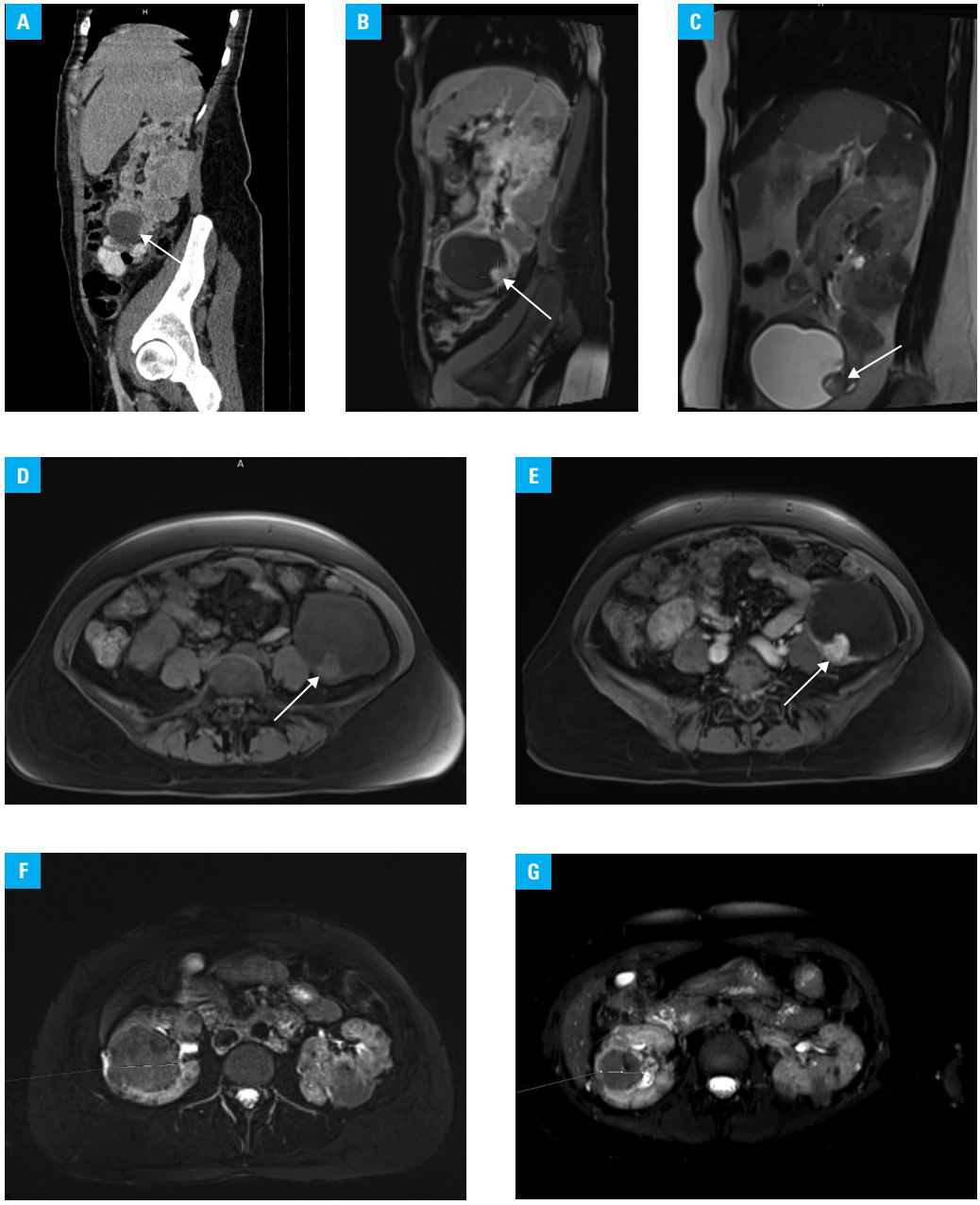

FIGURE 1 Renal manifestations in a patient with tuberous sclerosis complex; **A** – abdominal computed tomography showing a cystic lesion in 2014; **B** – T1--weighted, contrast--enhanced magnetic resonance imaging (MRI) of the abdomen in 2017, showing progression of the size and presence of solid component; **C** – T2--weighted MRI in 2017; MRI in 2017 before (**D**) and after contrast enhancement (**E**); MRI in 2017 (**F**) and in 2018 (**G**), showing regression of renal masses

TSC, and the threshold of 3 cm in diameter of solid tumor, the surveillance strategy has been proved successful in avoiding metastatic disease and delaying loss of renal function. It should be emphasized that overaggressive surgical procedures, especially nephrectomy, must be avoided. Nephron-sparing surgery and focal ablations are recommended to control the tumors and preserve renal function.[3]

Due to the common coexistence of different renal manifestations of TSC, another option can be considered. The presence of AMLs larger than 3 cm is an approved indication for therapy with mTOR inhibitors; moreover, benefits of mTOR inhibitors in the cases of TSC--related RCC have been described. Recently, the off-label use of everolimus in the frontline setting in the case of a patient with TSC with biopsy-proven RCC has been described. Alsidawi and Kasi[5] showed an exceptional and durable response of renal masses to mTOR inhibition. However, pulmonary lesions presumed by the authors to be metastases, in fact seem to be a manifestation of TSC, multiple micronodular pneumocytes hyperplasia, which undermines the diagnosis of metastatic RCC.[5] These findings indicate another management option in indeterminate renal masses in TSC, that is, the use of mTOR inhibitors.

The initial decision for our patient was therapy with mTOR inhibitors and careful radiological monitoring, but because of infectious complications, sirolimus was stopped and nephron--sparing surgery was performed, resulting in the diagnosis of RCC. Reintroduction of mTOR inhibitors was beneficial in the remaining lesions, and no local recurrence was shown.

In conclusion, the coexistence of different, ambiguous renal manifestations of TSC is a diagnostic and therapeutic challenge. Careful radiological monitoring is required, and renal-sparing surgery should be applied with caution. It can be

also assumed that mTOR inhibitors may constitute a new management option in the case of indeterminate renal manifestations of TSC.

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