RESEARCH LETTER

Clear cell renal carcinoma metastasis mimicking primary thyroid tumor

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Introduction Secondary tumors of the thyroid gland occur very rarely and constitute an uncommon cause of thyroid enlargement.[1] Usually, they manifest as widespread malignant processes or as a thyroid invasion from other malignancies or affected adjacent organs or tissues.

Metastases of clear cell renal carcinoma (CCRC) to the thyroid gland are also rare, although CCRC is the most common malignant tumor that metastasizes to this organ.[1] It might be connected with epidemiology, which shows that the occurrence of CCRC has been rising steadily, increasing by 2% to 4% per year.[1,2] If thyroid metastases of the CCRC coexist with multinodular goiter, potential diagnostic difficulties may appear. However, in some cases, even a solitary metastatic mass localized unilaterally in the thyroid gland may imitate a primary thyroid lesion. An extremely rare manifestation of thyroid CCRC metastasis might be the active bleeding of the thyroid gland.[3]

Regardless of the high sensitivity and specificity of some diagnostic modalities to detect thyroid nodules, many of them are still insufficient for the diagnosis of thyroid metastatic tumors. The situation might be even more challenging when the thyroid nodule is the initial manifestation of renal disease. Diagnostic and therapeutic difficulties are common in the management of thyroid tumors.[4]

We undertook this study to emphasize that it is important to include a CCRC metastasis to the thyroid gland in a differential diagnosis before referring a patient for surgery. We sought to assess the occurrence of this secondary tumor in comparison with all benign and malignant thyroid lesions, efficacy of diagnostic methods and surgical treatment, and patient survival.

Patients and methods We retrospectively analyzed the medical records of consecutive patients who underwent surgical treatment due to thyroid pathology in a single center between 2008 and 2016. Among the 4327 patients with thyroid tumors, 384 (8.87%) had thyroid malignancy and 10 (0.23%) were diagnosed with secondary tumor. Finally, 9 patients (0.2%) with a CCRC metastasis mimicking a primary thyroid tumor were identified. We analyzed and compared the clinical and pathological characteristics of patients with metastatic CCRC of the thyroid gland. The collected data included demographic characteristics of patients, clinical manifestations, imaging studies, tumor characteristics, treatment modalities, and final outcome. All data were obtained from the medical records and interviews with patients or their relatives. All patients underwent an ultrasound-guided fine-needle aspiration biopsy (FNAB) before surgery. All cytologic and histopathologic specimens were reanalyzed, and final diagnoses were graded according to the 8th TNM staging classification for urologic cancers.

The study was approved by the ethics review board (No. KB-296/2015).

Results Metastatic CCRC occurred in 6 women and 3 men (mean age, 68 years [range, 43–81 years]). Almost all patients (7 of 9) underwent unilateral nephrectomy due to CCRC a minimum of 5 years before thyroid tumor appearance (mean, 9.7 years [range, 5–13 years]). In 2 of the 9 patients, the thyroid mass was the initial manifestation of CCRC. Symptoms of thyroid tumor were present for a mean of 6 months. In 2 of the 9 patients, an unspecified malignancy was suspected on the basis of ultrasound-guided FNAB (category V according to the Bethesda System for Reporting Thyroid Cytopathology). In 7 cases, metastases of CCRC affected the right lobe of the thyroid as a solitary mass (mean diameter, 38 mm [range, 26–60 mm]). In 2 individuals, metastases were localized in the left lobe. Total thyroidectomy was performed in 7 patients; nonradical surgery, in 1 patient; and tracheostomy, in 1 patient. Five patients died due to dissemination of the disease

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TABLE 1 Treatment modalities and outcomes of all patients with clear cell renal carcinoma metastasis to the thyroid gland

No.	Sex	Age at CCRC metastasis diagnosis, y	Treatment modality	Further management	Status	Disease-free survival, mo	OS since CCRC diagnosis, mo	Immunohistochemistry	
								Positive	Negative
1	F	69	Total thyroidectomy	PET scans revealed the presence of micronodules in the lungs.	Deceased	50	144	Vimentin, CD10, CK7	CK19, HBME-1, CgA
2	M	81	Total thyroidectomy	Imaging studies (CT, ultrasound) excluded new disease.	Deceased not due to CCRC metastasis	26	179	CK8/18, CD10, RCCM	–
3	F	72	Hemithyroidectomy	Patient refused further diagnostic workup.	Deceased	36	141	Vimentin, EMA, CD10, RCCM, CK7, S-100	–
4	F	61	Total thyroidectomy	PET/CT scans revealed the presence of a renal nodule; patients underwent right nephrectomy. Histopathology confirmed CCRC.	Alive, no evidence of disease	71	72	Tg, TTF, vimentin	EMA, Syn, CgA, CD10, RCCM
5	F	77	Total thyroidectomy	PET/CT revealed lung and brain metastasis.	Deceased	12	137	CK8/18, CD10, RCCM	–
6	F	67	Total thyroidectomy	Without new signs on imaging studies, systematic follow-up	Alive, no evidence of disease	48	156	Vimentin, EMA, CD10, RCCM, CK7, S-100	–
7	M	43	Tracheostomy/ surgical biopsy	–	Deceased	0	0	Vimentin, CK7, CK1/3, CK19, CD10	p63, desmin, calcitonin, CgA, RCCM,
8	F	78	Total thyroidectomy	PET scans revealed lung metastasis.	Deceased	6	145	CK8/18, vimentin, CD10	CK19, HBME-1, cyclin D1, S-100, CD34
9	F	64	Total thyroidectomy	Without new signs on imaging studies, systematic follow-up	Alive, no evidence of disease	24	168	CK8/18, CD10, RCCM	–

Abbreviations: CCRC, clear cell renal carcinoma; CT, computed tomography; EMA, epithelial membrane antigen; F, female; HBME-1, Hector Battifora mesothelial-1; M, male; OS, overall survival; PET, positron emission tomography; RCCM, renal cell carcinoma marker; TTF, thyroid transcription factor

(mean, 4.1 years); 1 individual died due to disease other then CCRC metastases; and 3 patients are still alive without symptoms of CCRC. The median survival was estimated at 2.5 years with a 5-year survival rate of approximately 11%. Demographic data, immunohistochemistry results, treatment modalities, and outcomes are presented in TABLE 1.

Discussion Clear cell renal carcinoma accounts for 3% of all malignant tumors in the general population and is the third most frequent urologic cancer.[5] It is also the most common subtype of renal malignancy and accounts for approximately 70% to 80% of all cases.[6] Moreover, CCRC is associated with approximately 13 000 deaths per year.[7] Metastases in patients with CCRC are not very rare. The prevalence of solitary CCRC metastases is approximately 4%.[3] The most common metastatic sites are the lungs, adrenal glands, gastrointestinal tract, brain, lymph nodes, bone,

and liver, while the thyroid gland is the most common site of CCRC metastasis within the head and neck region.[8] Approximately 25% to 48.1% of all secondary thyroid tumors are attributed to CCRC.[1,3] Nevertheless, the thyroid gland is considered an atypical localization of CCRC metastases, along the orbits, parathyroid glands, nasal and paranasal cavities, tongue, tonsils, heart, skin, muscles, and joints.[3,9]

The majority of patients present a metastatic thyroid tumor many years after an initial CCRC diagnosis and effective treatment. There have been several reports of late metastasis from CCRC, which may occur even many years after nephrectomy. Prolonged disease-free intervals might be observed, with an average period of 7.5 years.[9]

Heffess et al[10] emphasized the high vascularity of the thyroid gland and stressed the fact that metastases to this gland are rarely observed in clinical practice. Usually, the thyroid is the most common metastatic site for lung, kidney, breast, skin, and stomach cancers.[4-6] However, even malignant melanoma metastasis to the thyroid might be isolated.[11] There are some hypotheses explaining why CCRC metastasis to the thyroid gland is rare. According to the most recent theory, high oxygen and low carbohydrate thyroid tissue concentrations, large amounts of iodine, and high vascularity are the reasons for low incidence.[12] All of these factors protect thyroid vessels from malignant cell embolization. Thus, it may be concluded that pathological changes in thyroid tissue are a risk factor for the proliferation of metastatic cells. It might be the reason why we observed metastatic tumors in the multinodular goiter of 4 patients. Astl et al[12] emphasized that in such a situation, the thyroid metastasis of CCRC may be mimicking a primary thyroid tumor. A thorough diagnostic workup with biochemical tests, imaging studies, and ultrasound-guided FNAB is recommended in these patients.

Clear cell renal carcinoma is curable with surgery; however, metastasis from the kidney may develop in many organs, such as the lungs, liver, bone, and thyroid. Thyroidectomy due to metastasis is a common treatment option for oligometastatic disease and is often considered in patients who develop a metastasis after renal resection or as an alternative treatment when systemic therapy fails.[1] In our study, 7 patients underwent radical thyroidectomy due to CCRC metastasis. In 1 patient, we resected a single lobe of the thyroid gland, and in another patient, only a tracheostomy was performed owing to an advanced malignant process. Of the 7 patient who underwent radical surgery, 3 are still alive. The prognosis for metastatic CCRC is rather poor, with a median survival of only approximately 2 years and a 5-year survival rate of less than 10%. There are several factors associated with favorable prognosis when radical surgery is performed: a long interval between the occurrence of CCRC and manifestation of thyroid metastases, a solitary metastatic tumor, absence of disease dissemination, the presence of necrotic tissue in metastatic tumors, and a slow development of the metastases. In our study, the longest interval between CCRC development and metastasis manifestation was 13 years. Thyroid metastases of CCRC presented as a solitary tumor in 5 patients. Dissemination of the disease was observed in 3 patients, and 1 patient refused further diagnostic workup. We did not observe necrotic tissue in metastatic tumors in any of the patients.

Histopathologic features that may indicate the metastatic nature of a thyroid tumor include the histologic similarity to the primary tumor, different architecture than in primary thyroid tumors, the presence of small deposits within the lymphatic spaces, or a solitary mass. A cytologic evaluation revealed the characteristic features of CCRC, such as clear cytoplasm, distinct cell membranes, and small nuclei. Moreover, in histologic examinations, a rich network of blood vessels, as well as spaces filled with extravascular erythrocytes, could be observed. The histopathologic examination of the presented cases showed a clear cell carcinoma immunoreactivity for vimentin and CD10, occasional immunoreactivity for renal cell carcinoma marker (RCCM), and negative immunoreactivity for cytokeratin 19, Hector Battifora mesothelial-1, and chromogranin, confirming the renal origin of the tumor. The characteristic immunohistochemical profile for CCRC is positive for vimentin, cytokeratin antibodies AE1/AE3, CD10, RCCM, PAX2 and PAX8 proteins, and CAIX enzyme, and negative for high-molecular-weight cytokeratin, CK7, CK20, CD117, kidney-specific cadherin, and parvalbumin.

In all patients with multinodular goiter or with a single mass localized in the thyroid gland and previously treated due to CCRC, metastasis to the thyroid gland should be considered in a differential diagnosis. However, a thyroid tumor might also be a primary manifestation of CCRC. Ultrasound-guided FNAB is still an insufficient diagnostic method in secondary thyroid tumors. Radical surgery is the main therapeutic option for CCRC metastasis to the thyroid gland; nevertheless, in some cases, only a palliative procedure may be performed.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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