CLINICAL IMAGE

Antineutrophil cytoplasmic autoantibody–associated vasculitis with rapid progressive glomerulonephritis following SARS-CoV-2 infection: a cause or coincidence?

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Acute kidney injury has been reported in numerous studies as one of the most common complications of COVID-19.[1] Acute tubular injury secondary to hemodynamic instability and localized immune cell infiltration are postulated as mechanisms associated with kidney damage.[1] Promotion of the loss of immune tolerance by SARS-CoV-2 infection, which may trigger autoimmune disease, should be also considered.[2] Here we present a case of a fulminant antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) and rapid progressive glomerulonephritis after SARS-CoV-2 infection.

A 59-year-old male patient with a history of arterial hypertension, without any documented kidney or lung disease, was admitted to the Department of Infectious Diseases due to atypical pneumonia. The polymerase chain reaction (PCR) test for SARS-CoV-2 performed on nasal swab specimens was negative, as were the antigen tests for viral proteins presence and for immunoglobulin G antibody levels. Ground-glass opacities in the left lung were visualized on chest X-ray (FIGURE 1A). Laboratory tests performed on admission showed the following: a serum creatinine level of 2.2 mg/dl (reference range, 0.7–1.3 mg/dl), estimated glomerular filtration rate (eGFR) of 31.61 ml/min/1.73 m^2, a urea level of 66.1 mg/dl (reference range, 19.26–49.22 mg/dl), and an albumin level of 2.9 g/dl (reference range, 3.2–4.8 g/dl). In the urine test, proteinuria and erythrocyturia were found. Moreover, anemia was diagnosed, with a normal platelet count and an elevated white blood cell count; however, the level of ferritin was high (606.3 ng/ml; reference range, 22–322 ng/ml). Initial treatment comprised administration of azithromycin, ceftriaxone, methylprednisolone, and enoxaparin. Despite an improvement in the general condition and lowering of serum levels of inflammatory parameters, a progression of ground-glass opacities in both lungs was observed 10 days after admission (FIGURE 1B), together with deterioration of the kidney function (urea, 83.7 mg/dl; creatinine, 3.14 mg/dl; eGFR, 20.56 ml/min/1.73 m^2). The repeated PCR test for SARS-CoV-2 was positive. The patient received oxygen therapy, methylprednisolone, ceftriaxone, and azithromycin, which did not improve the kidney function—the serum creatinine level reached 6.03 mg/dl (eGFR, 9.3 ml/min/1.73 m^2). Immunological tests were positive for myeloperoxidase ANCAs (MPO-ANCAs) (127.44 RU/ml; normal level <20 RU/ml), whereas the results for antinuclear antibodies and proteinase-3 ANCAs were negative. After 10 days, the SARS-CoV-2 test was negative and the patient was transferred to the Department of Nephrology, where intermittent hemodialysis procedures were started. On a follow-up chest X-ray, an increased parenchymal lung density dominated, and ground-glass opacities were not observed (FIGURE 1C). Abdominal ultrasound showed enlarged kidneys, without structural abnormalities (FIGURE 1D). A kidney biopsy was performed, leading to a diagnosis of pauci-immune rapidly progressive crescentic glomerulonephritis (FIGURE 1E and 1F). Five procedures of therapeutic plasma exchange were performed. As part of immunosuppressive treatment, the patient received 3 infusions of methylprednisolone, followed by cyclophosphamide infusions. Despite targeted treatment, his condition worsened, and new lesions in the lungs were observed (FIGURE 1G and 1H). Moreover, symptoms of brain ischemia

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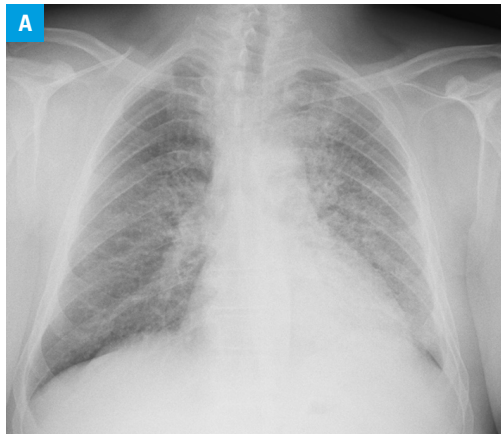
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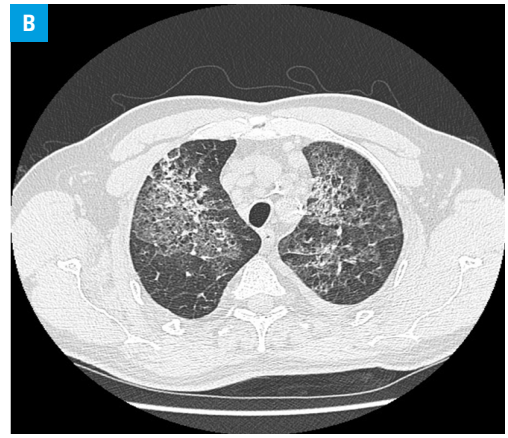
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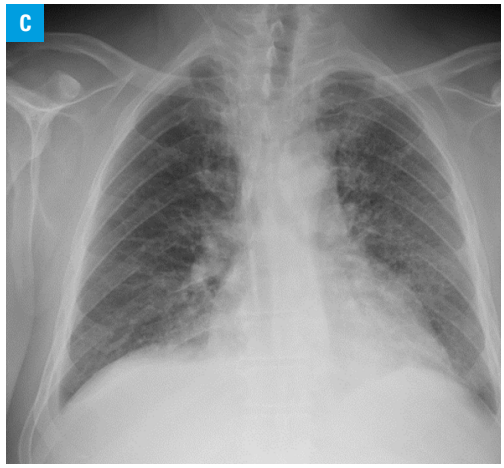
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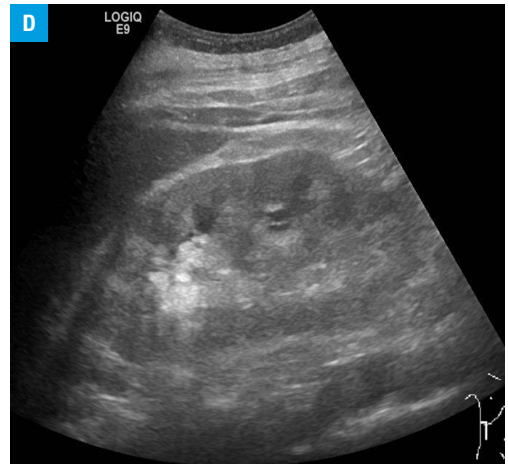
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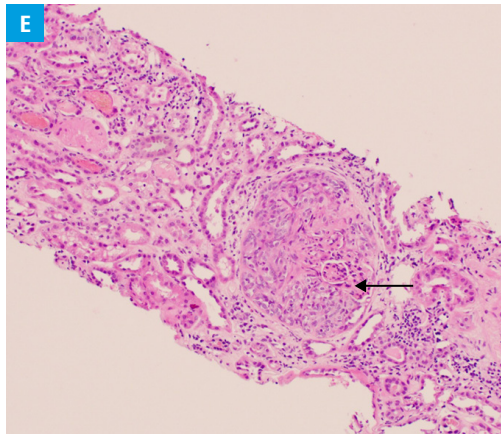
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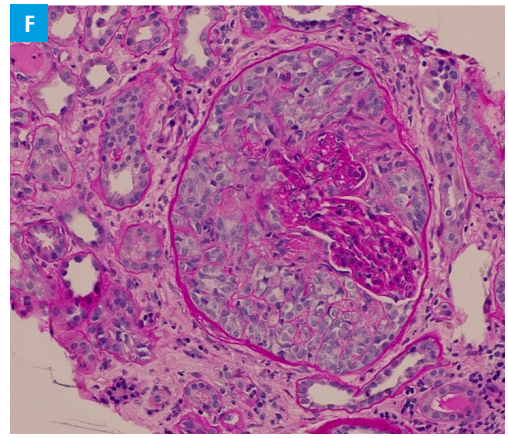
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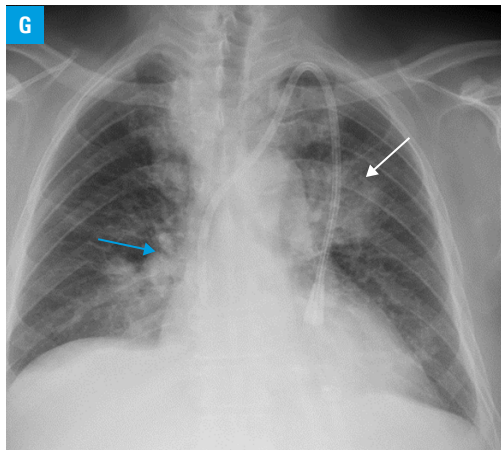
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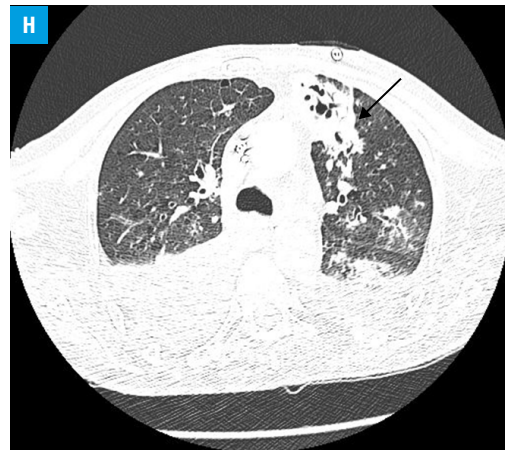
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FIGURE 1 **A** – chest X-ray showing ground-glass opacities in the medial and lower areas of the left lung and a bronchial pattern in the right lower perihilar area; **B** – computed tomography of the chest showing multiple dispersed parenchymal ground-glass opacities bilaterally, mainly in both lobes of the left lung and the upper lobe of the right lung; **C** – follow-up chest X-ray showing increased parenchymal lung density and bronchiectasis in the right lower lobe and the left perihilar area; **D** – abdominal ultrasound showing enlarged kidneys: right, 141 × 66 mm (shown in the figure), left, 141 × 72 mm, with normal corticomedullary differentiation and mild dilatation of the renal pelvis bilaterally; **E** – histological examination; glomerulus with proliferation of Bowman's capsule epithelial cells, with segmental necrosis (arrow) and a complete collapse of the capillary tufts. Tubules of the cortex show focal signs of segmental necrosis of epithelial cells with erythrocytes within their lumen as well as segmental signs of regeneration (hematoxylin and eosin staining; magnification × 200). **F** – histological examination; glomerulus showing massive proliferation of epithelial cells forming a crescent, which fully obliterate Bowman's space, with a complete collapse of the capillary tufts (periodic acid–Schiff staining; magnification × 400); **G** – chest X-ray showing a 6-cm lesion in the upper and medial left lung areas, connecting with the left hilus (white arrow); a 2-cm lesion in the right lower lobe (blue arrow); increased parenchymal lung density; mediastinal widening on the right; and bilateral pleural effusion; **H** – computed tomography of the chest showing fluid in the pleural cavities, especially on the right side; cavitary lesions in the upper and medial left lung areas (arrow); increased parenchymal lung density; and irregular perivascular consolidations with a spiculated contour localized in the left lung

occurred, followed by a subarachnoid hemorrhage. Unfortunately, despite intensification of immunosuppressive and antimicrobial treatment, severe multiorgan failure led to the patient's death.

Cases of COVID-19–related pauci-immune glomerulonephritis are extremely rare.[3,4] To our best knowledge, this is the first report of a very severe form of pANCA-associated vasculitis after SARS-CoV-2 infection. Due to similar clinical and radiological features of AAV and COVID-19, proper diagnosis can be challenging. In most cases it is difficult to clearly state whether AAV was present before SARS-CoV-2 infection, coexisted with COVID-19, or was triggered by the disease; however, findings such as irregular cavities on radiological imaging, presence of ANCAs in the serum, and proteinuria were shown to be useful in the differential diagnosis of AAV and COVID-19.[5] Despite the fact that a transient increase in ANCA levels had been previously reported in asymptomatic patients with COVID-19, our patient had atypical radiological features, such as cavities with irregular walls and proteinuria with active urinary sediment, suggesting de novo vasculitis with organ involvement after the viral infection. The release of antigens leading to ANCA production, formation of neutrophil extracellular traps, epitope spreading, autoantigen complementarity, and molecular mimicry are considered as possible mechanisms associated with the occurrence of ANCAs after SARS-CoV-2 infection.[5]

Moreover, the decision to start immunosuppressive treatment should be made with great caution, particularly in patients with an inconclusive result of the PCR test for SARS-CoV-2. Interestingly, false negative results have been recently reported in patients with cardiological and neurological diseases, cancer, and diabetes, as well as in individuals receiving immunosuppression and those with an elevated leukocyte count and a decreased lymphocyte count, as in the presented case. This should increase physicians' awareness while making therapeutic decisions in the case of suspected AAV.

In conclusion, our case indicates that it is possible to develop de novo AAV secondary to SARS-CoV-2 infection. In every patient with a severe kidney function impairment during or after COVID-19, especially with radiological findings that are not typical for SARS-CoV-2 infection, AAV should be taken into consideration in the differential diagnosis. Immunosuppression should be carefully considered in the selected group of patients with AAV due to false negative results of the SARS-CoV-2 tests in some cases.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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