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Case Report: Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody (MPO-ANCA) Associated Vasculitis Following Coronavirus Disease (COVID-19)

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Abstract

Anti-Neutrophil Cytoplasmic Autoantibody (ANCA) -Associated Vasculitis (AAV) is an autoimmune disorder characterized by inflammation and damage to small blood vessels. It's a systemic disease affecting several organs. Rare cases of AAV following SARS-CoV-2 infections were published. We report in this article a Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody (MPO-ANCA) associated vasculitis following COVID-19 infection. It is about A-54-year-old women, with a history of type 2 diabetes and hypertension. She was vaccinated against COVID-19 with an RNA vaccine, a single dose on June 2021. On July 2021, she had COVID-19 pneumonia with 97 µmol/l serum creatinine level. Afterwards the patient presented with deterioration in her general condition with prolonged fever. The biological analyzes showed a severe acute renal injury with 606 µmol/l serum creatinine level, anemia (hemoglobin = 6 g/dl), absence of leukocyte or red blood cells on Cytobacteriological Examination of Urine (CBEU), 24 h proteinuria was 0.7 g/24 h with a diuresis of 1500 ml/24 h. She was thus admitted to the nephrology department. Ten days later, the patient's renal function worsened even more with creatinine reaching 1011 µmol/l but still without hematuria on CBEU. Immunological investigations and renal biopsy was performed. MPO ANCA was positive and the renal biopsy showed severe glomerular and tubulointerstitial damages. The glomeruli contained extracapillary proliferation. Necrotic cells were observed within tubes lumen. Edematous changes associated with an abundant and acute inflammatory infiltrate within the interstitium were found. The patient had an intra-alveolar hemorrhage confirmed by the chest CT scan with respiratory distress and recourse to mechanical ventilation. She had IV methylprednisolone followed by prednisone 1 mg/kg/d, 6 boli of cyclophosphamide and 7 plasmapheresis sessions as induction therapy. The evolution was marked by clinical and biological improvement with a creatinine at 120 µmol/l. To conclude, diagnosis and management of ANCA related vasculitis is a big challenge for medical practitioners. VAA can be associated to COVID-19. In fact, SARS-CoV-2 can be a trigger factor for the VAA.

Keywords: Acute kidney injury; Glomerulonephritis; Anti-neutrophil cytoplasmic antibody associated vasculitis; COVID-19

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Introduction

Anti-Neutrophil Cytoplasmic Antibody (ANCA) -Associated Vasculitis (AAV) are a group of small vessel vasculitides characterized by granulomatous and neutrophilic tissue inflammation, often associated with the production of antibodies that target neutrophil antigens. The two major antigens targeted by ANCAs are leukocyte Proteinase 3 (PR3) and Myeloperoxidase (MPO) [1].

It is a disorder that affects predominantly small- and medium-sized arteries and has similar features on kidney histology [e.g., a focal necrotizing, often crescentic, pauci-immune Glomerulonephritis (GN) [2].

The biological mechanisms underpinning this autoimmune disease are not entirely known, but research points to a combination of genetics and environmental factors, such as exposure to pollutants, drugs, and microbial infections [3].

In some instances, the diagnosis is difficult, and if the degree of organ disorder is severe, the disease becomes refractory and is associated with a poor prognosis.

Only a few cases of AAV after Coronavirus Disease 2019 (COVID-19) have been reported. We herein report a case of Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody (MPO-ANCA) associated vasculitis following COVID-19 infection.

Case Presentation

A-54-year-old women, with a history of type 2 diabetes and hypertension. She was vaccinated against COVID-19 with an RNA vaccine, a single dose on June 2021.

On July 2021, she had COVID-19 pneumonia with 97 µmol/l serum creatinine level. She had several antibiotics (initially cefotaxime and levofloxacin then amoxicillin and clavulanic acid then ciprofloxacin); she had CT scan of the chest with contrast.

Afterwards the patient presented with deterioration in her general condition with prolonged fever. The biological analyzes showed a severe acute renal injury with 606 µmol/l serum creatinine level, anemia (hemoglobin = 6 g/dl), absence of leukocyte or red blood cells on Cytobacteriological Examination of Urine (CBEU), 24-h proteinuria was 0.7 g/24 h with a diuresis of 1500 ml/24 h. She was thus admitted to the nephrology department.

Acute Tubular Necrosis (ATN) with conserved diuresis was suspected given the context and the renal presentation. Ten days later, the patient's renal function worsened even more with creatinine reaching 1011 µmol/l but still without hematuria on CBEU. So an immunological investigations and renal biopsy was performed. MPO ANCA was positive and the renal biopsy showed showing severe glomerular and tubulointerstitial damages (Figure 1). The glomeruli contained extracapillary proliferation (Figure 2). Necrotic cells were observed within tubes lumen (Figure 3). Edematous changes associated with an abundant and acute inflammatory infiltrate within the interstitium were found (Figure 4A, 4B).

The patient had an intra alveolar hemorrhage confirmed by the chest CT scan with respiratory distress and recourse to mechanical ventilation and the need for several hemodialysis sessions. A transthoracic echocardiogram showed septal hypokinesia with left ventricular outflow function =35% and myocarditis signs.

She had 3 boli of 1 g of methylprednisolone followed by prednisone 1 mg/kg/d, 6 boli of cyclophosphamide and 7 plasmapheresis sessions as induction treatment and 10 mg of prednisone with azathioprine as maintenance treatment.

The evolution was marked by clinical and biological improvement with a creatinine at 120 µmol/l, improvement in transthoracic echocardiogram signs.

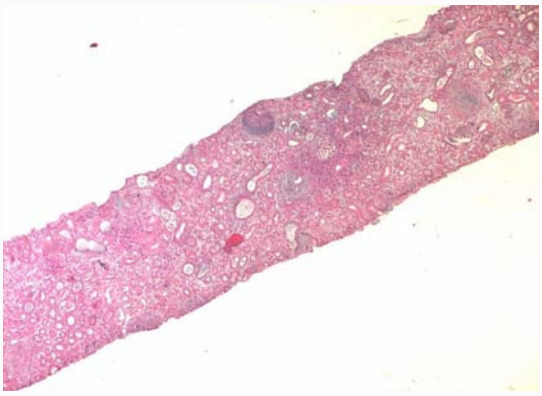

Figure 1: Low magnification showing severe glomerular and tubulo-interstitial damage (TM x50).

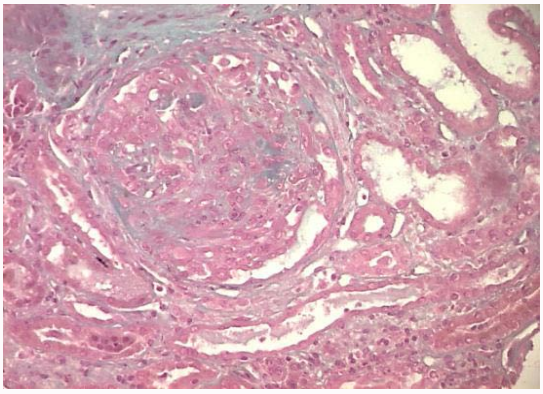

Figure 2: High magnification showing extracapillary glomerulonephritis characterized by cell proliferation within the urinary space (TM x400).

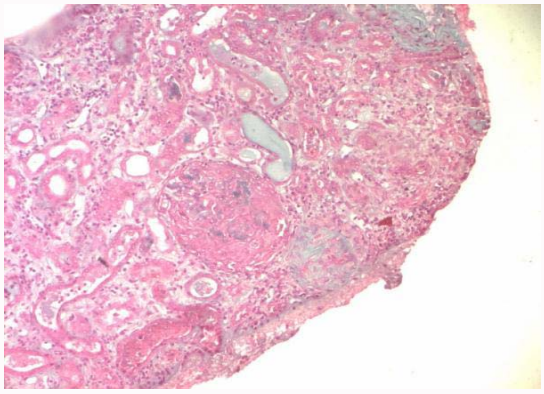

Figure 3: Necrotic cells within tubes lumen (TM x100).

Discussion

Antineutrophil Cytoplasmic Autoantibody (ANCA) -Associated Vasculitis (AAV) is an autoimmune disorder characterized by inflammation and damage to small blood vessels. It's a systemic disease affecting several organs. Renal damage is frequent and can lead to permanent loss of kidney function. It is most often a rapidly progressive Glomerulonephritis (GN). Histologically, there is a crescentic extra capillary GN without immune deposits in immunofluorescence study (Pauci Immune GN).

The search for ANCA is useful as additional diagnostic criteria for these diseases and has a predictive value since clinical relapses are almost always associated with persistence or associated with the persistence or reappearance of ANCA.

Concerning the COVID-19, as its epidemic continues to expand; many features of this disease are being defined and described in detail. Among these aspects, we define Acute Kidney Injuries (AKI). It has been reported in 36.6% of patients hospitalized with COVID-19 [4]. Several Causes of SARS-CoV-2-induced AKI have been reported. It may be a functional AKI, an acute tubular injury requiring renal replacement therapy, thrombotic microangiopathy, vasculitis, or a collapsing glomerulopathy [5-7].

Although cases of kidney damage due to COVID- 19 have been reported, an association between COVID-19 and crescentic GN has

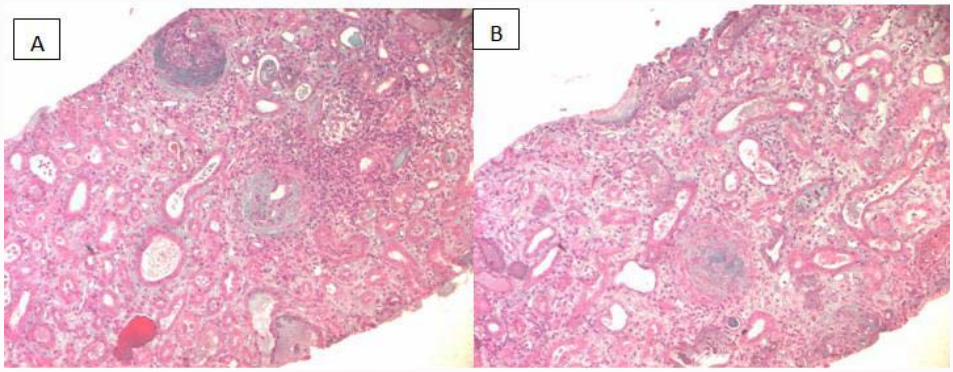

Figure 4: A and B) Edematous changes associated with an abundant and acute inflammatory infiltrate within the interstitium (A: TM x100, B: TM x200)).

been rarely identified. Only few cases of AAV with COVID-19 have been reported [8]. In our case, the lesions were essentially glomerular with extracapillary proliferations but with the presence of tubular necrosis lesions and interstitial infiltrates. The tubular necrosis lesions may also be related to the nephrotoxicity of the antibiotics which the patient had.

It has been shown in the pathophysiology of COVID-19 that it may lead to the emergence or exacerbation of autoimmune diseases in genetically susceptible patients [9,10].

Indeed, in a series of 33 patients hospitalized with coronavirus pneumonia, 15 patients (45%) tested positive for at least one autoantibody, including 11 for ANA (33%), 8 for anti-cardiolipin antibodies (Immunoglobulin (Ig) G and/or IgM; 24%) and 3 for anti-β2-glycoprotein antibodies (IgG and/or IgM; 9%) [11].

Further, vasculitis such as VVA can be induced by bacterial, fungul, parasitic and mainly viral infections (83). SARS-CoV-2, such as other virus may constitute a trigger factor for vasculitis and autoimmune diseases. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection can potentially lead to an array of autoimmune disorders by molecular mimicry (cross-reacting epitope between the virus and the host), bystander killing (virus-specific CD8+ T cells migrating to the target tissues and exerting cytotoxicity), epitope spreading, viral persistence (polyclonal activation due to the constant presence of viral antigens driving immune-mediated injury) and formation of neutrophil extracellular traps NET [12].

In fact, patients with AAV also have high levels of NETs in the circulation. ANCAs are capable of inducing NETos is in neutrophils, and their ability to do so has been shown to be affinity-dependent and correlated with disease activity. NETs contain proinflammatory proteins and are thought to contribute to vessel inflammation directly by damaging endothelial cells and by activating the complement system and indirectly by acting as a link between the innate and adaptive immune system through the generation of PR3- and MPO-ANCA [13].

The presence of NETs has been observed on kidney biopsy samples of patients with AAV, and is postulated to be involved in COVID-19 pathogenesis [14,15].

It is also possible that the cytokine storm, with the dysregulation of the immune system in a uremic state, led to an altered response to infection, resulting in AAV [7].

According to the literature, 6 cases of AVV after SARS-CoV-2 infection were published [8,16-18]. Three patients had positive p-ANCA MPO, 3 patients had c-ANCA PR3. Two patients were presented with severe AKI requiring hemodialysis. Imaging lung involvement showed patchy ground-glass opacities in five cases, bilateral pleural effusion in two cases and, alveolar hemorrhage in one case, and bilateral cavitary lesions in one case. All patients had a kidney biopsy. It showed in all cases crescentic glomerulonephritis. Our patient had positive p-ANCA MPO with severe AKI requiring hemodialysis and alveolar hemorrhage.

The current therapeutic means, particularly the immunosuppressive therapies, have improved both the vital and renal prognosis especially when they are rapidly administered. In our case, the diagnosis was difficult given the absence of hematuria and the context suggestive of acute tubular necrosis at the beginning, hence the delay in diagnosis and management of vasculitis. According to the literature all patients received glucocorticoids; cyclophosphamide was administered in three patients; rituximab in two patients; plasmapheresis in one patient and plasma exchange in one patient [8,16-18].

Our patient had glucocorticoids, cyclophosphamide and plasmapheresis. She presented a favorable response to treatment. Her kidney function started to improve 2 weeks after starting therapy. These outcomes join the literature data about the management of VAA associated to kidney failure. In fact, the use of cyclophosphamide is an independent predictor for renal and patient survival presented with ANCA-Associated Vasculitis and Severe Kidney Failure [19]. The effect of cyclophosphamide on patient survival emphasizes the importance of assertive immunosuppression in the setting of severe kidney failure even on dialysis.

Concerning the cases reported for VAA after COVID-19, patients presented also improvement for their kidney function after immunosuppression. Serum ANCA levels have been decreased also during the follow-up [8,18].

Conclusion

Diagnosis and management of ANCA related vasculitis is a big challenge for medical practitioners. The specific treatment of this systematic disease, mainly the immunosuppressive therapy has to be urgently administered so that it does not lead to permanent organ impairments such us the chronic kidney failure. A quick diagnosis raises the chance of better recovery with a minimum of somatic damages.

VAA can be associated to COVID-19. In fact, SARS-CoV-2 can be a trigger factor for the VAA. We should keep in mind that patients who develop an acute kidney injury after COVID-19 can have a crescentic glomerulonephritis in particular ANCA related vasculitis.

In front of any unusual clinical presentation or ulterior evolution, a kidney biopsy has to be performed after an immunological workup. Concerning the management of VAA, the existing literature revealed favorable outcomes after immunosuppressive therapy.

Patient Perspective

After starting etiopathogenic treatment consisting on corticotherapy, cyclophosphamide and plasma exchange, the patient noted a clear improvement in his clinical condition, particularly the respiratory performance and she was so satisfied for the improvement of her renal function and the cessation of hemodialysis sessions.

Authors' Contribution

All authors gave Substantial contributions to conception and design of this article. They participated in drafting the article, revising it, and gave final approval of the final version to be published.

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