CASE REPORT

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Cerebral vasculitis – a rare presentation of antineutrophil cytoplasmic antibody associated vasculitis relapse

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis commonly involves kidney, lung, upper respiratory tract, skin, gastrointestinal and occasionally peripheral nervous system. Central nervous system is less commonly affected and is generally part of a multi-organ scenario. We present a case of a 21-year-old female with chronic kidney disease secondary to myeloperoxidase ANCA associated vasculitis, diagnosed at age 19. She then presented with pulmonary-renal syndrome with stage 5 CKD. Three months' cyclophosphamide and prednisone were instituted, followed by azathioprine, but she remained dialysis dependent. After 2 years, while on maintenance treatment, she was admitted to the emergency department with tonic-clonic seizures. She had started oral ciprofloxacin 2 days before for acute gastroenteritis. No illicit drugs were noticed. Blood tests showed an increased myoglobin but were otherwise unremarkable. No anomalies were reported on cerebral computed tomography or cerebrospinal fluid analysis. Magnetic resonance imaging showed diffuse cortico-subcortical lesions with T2 and proton density hypersignal suggesting recent ischemia, and segmental irregularities of various cerebral and vertebral arteries, consistent with small and medium size vessel vasculitis. Intravenous methylprednisolone and oral cyclophosphamide were started. Anti-myeloperoxidase ANCA levels were increased (>200 RU/mL), reinforcing our diagnostic hypothesis of central nervous system (CNS) recurrence of ANCA vasculitis. The patient had a favorable clinical course, with no neurological sequelae.

Conclusions: This is a case of ANCA associated vasculitis that presented with kidney and lung but no CNS involvement and recurred with primarily cerebral disease. Favorable outcome was seen with standard immunosuppression. Awareness of this rare but severe complication is critical for timely recognition and prompt treatment.

Key words: ANCA, antineutrophil cytoplasmic antibody, Central Nervous System Vasculitis, relapse, vasculitis.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing necrosis of small vessels, with few or no immune deposits[1-3]. Serologically, it is associated with a specific ANCA for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). Clinical presentation comprises a wide spectrum of manifestations from the common nephrological, respiratory, dermatological, gastrointestinal symptoms to infrequent neurological and cardiac complications[1-3]. The serotype should be accompanied by the clinicopathologic variant if this can be determined: microscopic polyangiitis, granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg–Strauss), or renal-limited vasculitis. AAV have a peak incidence at 65-75 years old, but may occur at any age, with a slight male predominance[2]. Approximately one fourth to one half of patients with AAV will experience a relapse within several years[2]. Recurrence rate has been reported as 0.16-0.20/patient/year in non-end stage renal disease (ESRD) patients, and lower values in ESRD – 0.08/patient/year[4]. Relapses are diagnosed on the basis of clinical and pathologic evidence of recurrent disease. Some factors have been associated with higher recurrence risk, as PR3-ANCA (*versus* MPO), pulmonary or superior respiratory tract involvement, previous relapses and elevated ANCA titres, mainly when renal involvement is present[5,6].

CNS involvement is an uncommon but serious complication and it often arises when vasculitis is active elsewhere[7,8]. It is thought to be caused by 3 distinct pathogenic mechanisms. First, granulomatous tissue may spread from the nasal or paranasal cavities and contiguously invade the adjacent structures, for example, orbit, optic nerve, meninges or pituitary gland. The second refers to remote granulomatous intracerebral lesions of the brain, meninges, cranial nerves, or parietal bone. Third, vasculitis may affect the cerebral or spinal cord vessels[7]. Clinical presentation may be characterized by headache, focal neurologic deficits, seizures, ischemic stroke or subarachnoid hemorrhage[8]. Diagnosis is usually based on clinical CNS manifestations and multiple ischemic (sometimes hemorrhagic) MR lesions mainly affecting the white matter. Treatment with glucocorticoids and cyclophosphamide usually improves clinical features and MRI lesions[2,3,8-10].

CASE REPORT

We present a case of a 21-year-old female with chronic kidney disease (CKD) secondary to MPO-ANCA associated vasculitis. Past medical history was relevant for cigarette smoking (3 cigarettes/day). Vasculitis had been diagnosed at age 19. She then presented with severe kidney dysfunction, requiring dialysis, and mild bloody sputum, although no massive hemoptysis or severe respiratory impairment

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were present. ANCA titers were elevated (1/640), with MPO specificity (MPO-ANCA >200.0 RU/mL) and anti-glomerular basement membrane (GBM) autoantibodies were negative. Chest computed tomography (CT) showed patchy ground-glass opacities, without pleural effusion. Pauci-immune crescentic glomerulonephritis, with 90% of the glomeruli being sclerosed and 50% of interstitial fibrosis, was seen in the kidney biopsy (end stage kidney). Initial immunosuppressive therapy with pulse methylprednisolone 1g/day for 3 days and oral cyclophosphamide 2 mg/kg per day was started. Considering the severe renal dysfunction and the pulmonary involvement, plasma exchange was also started, with 6 sessions performed in total. Her hemoglobin stabilized and she presented no more evidence of pulmonary hemorrhage. However, she remained dialysis dependent. After 3 months, a switch to maintenance immunosuppression with azathioprine was made. After 17 months, a surveillance chest CT showed comparatively subtle lung opacities in peribroncovascular areas. At this point, she had no recurrence of symptoms, although MPO-ANCA remained elevated (185 RU/mL). No further intercurrences have been observed since then.

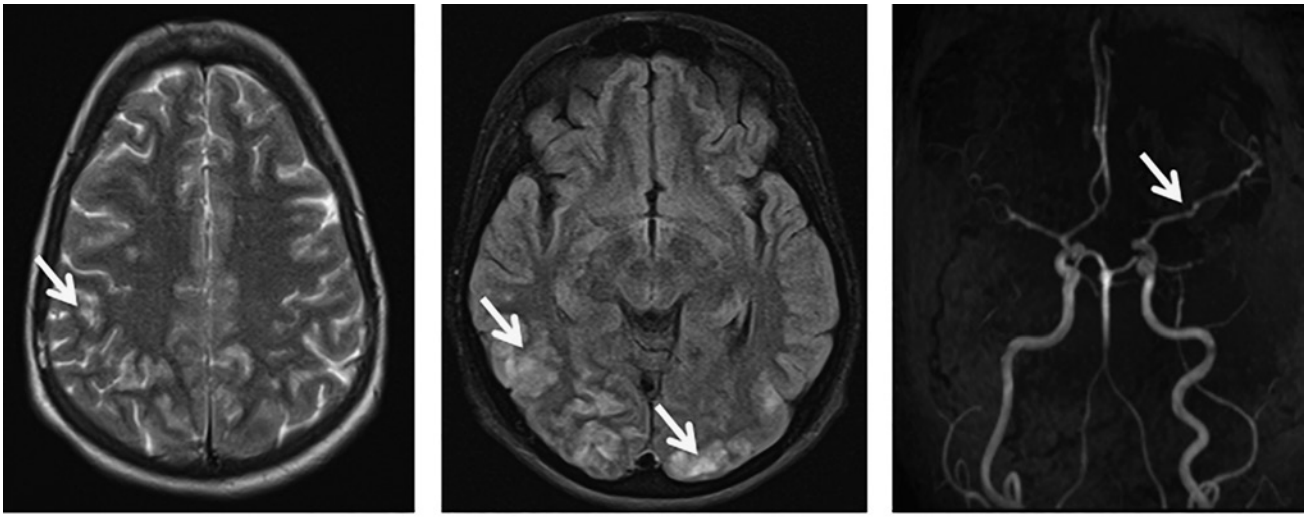
After 2 years of AAV diagnosis, while on maintenance treatment with azathioprine 100 mg/day, she was admitted to the emergency department with seizures. She had started oral ciprofloxacin 2 days before for acute gastroenteritis and had worsening hypertension for the previous 2 months. No illicit drugs were noticed. She presented in post ictal status and had two new ictal episodes during initial evaluation, described as focal motor evolving to bilateral tonic-clonic seizures. The remaining physical examination showed hypertension (160/105 mmHg), heart rate of 101 beats per minute, peripheral oxygen saturation of 96%, temperature 36.8° C, with no abnormalities on cardiac, pulmonary, abdominal or skin examination. After anticonvulsant administration and once the ictal phase was resolved, no asymmetries in strength or sensitivity were detected. Blood tests showed leucocytosis with neutrophilia and raised myoglobin but were otherwise unremarkable. No drug was detected in the urine test except for benzodiazepines (diazepam was used for seizure treatment on admission). Cerebral computed tomography was normal. Cerebrospinal fluid (CSF) analysis showed only erythrocytes, with probable traumatic origin, but was otherwise unremarkable. Magnetic resonance imaging (MRI) showed diffuse cortico-subcortical lesions with T2 and proton density hypersignal, suggesting recent cortical ischemia, as well as segmental irregularities of medium and anterior cerebral branches, consistent with small and medium size vessel vasculitis (Figure 1). Chest CT scan was repeated, and subtle ground-glass opacities were, again, observed, suggesting possible lung bleeding, favouring the vasculitis flare scenario, but could also be attributed to cigarette associated bronchiolitis. In addition, centrilobular emphysema was also reported. MPO-ANCA remained elevated (>200 RU/mL).

Given the suspicion of CNS vasculitis, intravenous methylprednisolone was started, 1g/day for 3 days, followed by oral prednisone, and oral cyclophosphamide 2mg/kg/day.

The patient completed 6 months of oral cyclophosphamide, followed by azathioprine. A favourable clinical course was observed, with no neurological sequelae, and with normalization of MPO-ANCA. No other vasculitis relapses occurred since then.

Figure 1

Magnétic ressonance imaging (T2, proton density and angiopathy)



T2 (left) and proton density (middle) show diffuse hypersignal cortico-subcortical lesions located on the right posterior temporal lobe and on the frontal, parietal and occipital lobes, suggesting recent cortical ischaemia. Angiography (right) shows decreased diameter of medium and anterior cerebral arteries and vertebral artery, with segmental irregularities of M1 and M2 segments of medium cerebral arteries, consistent with small and medium size vessel vasculitis.

DISCUSSION

We describe here a case of MPO-ANCA vasculitis that presented with end stage renal disease and pulmonary involvement, but no CNS symptoms, and recurred 2 years after diagnosis with primarily neurologic disease. CNS vasculitis is not very common and when it happens, it has been mostly described as part of a multisystemic phenotype[2,3,9-11]. In addition, CNS AAV recurrences, in general, have been reported after a first presentation with cerebral involvement as well[8,11], although we found one case, described by Seror et al, of AAV associated pachymeningitis presenting with headache 6 years after the diagnosis of AAV that presented without SNC symptoms[10]. It is important to recognise that CNS manifestations in ANCA vasculitis may be due to vasculitis affecting the brain, but also to granulomata, hypertension, sepsis or coagulation disorders[7-9]. Distinguishing CNS vasculitis from other causes of cerebral lesions is challenging due to the scarcity of published data and difficulty in confirming this entity.

Here, the diagnosis of cerebral vasculitis was made on the basis of the clinical manifestations, characterised by seizures, by the abnormal brain MRI findings consistent with vasculitis[8,12], and by the absence of other obvious causes of cerebral lesions. Infectious cause was ruled out on the basis of absence of fever or relevant increase inflammatory markers, as well as innocent CSF analysis. CSF may actually show pleocytosis, increased protein content, or both, in infections and in active CNS disease related to AVV[10,13]. However, CSF may also be entirely unremarkable[14], as in our case.

Uncontrolled hypertension was present and, together with RMI findings, made us consider reversible posterior leukoencephalopathy syndrome (PRES) in our differential diagnosis. Cases of AAV associated PRES have been reported[15-18]. However, the asymmetrical nature of the lesions and the segmental irregularities of cerebral arteries branches with multiple stenosis was strongly evocative of vasculitis in our patient. This together with the clear response to the standard AAV immunosuppressant treatment reinforced our hypothesis of SNC relapse of AAV. CNS biopsy is considered the gold standard to diagnose intracranial vasculitis, but it is rarely performed because of its invasive nature and potential risks[19,20].

Possible risk factors for recurrence in this patient could have included involvement of the lung at presentation and constantly positive ANCA titers, although there is still some controversy on the last issue[21-23]. Some authors believe that there is significant interindividual variability in the correlation between ANCA titer and activity of the disease[21]; others have found that ANCA is nearly always present in patients with renal involvement and correlates with activity, but is mainly negative in patients with nonrenal disease[5]. It has then been suggested that longitudinal ANCA measurements may be useful in patients with renal involvement but is less valuable in patients with nonrenal disease[2]. However, there is no established indication to guide treatment decisions only upon serial ANCA measurements during disease remission. Another precipitant for relapse could have been recent infection, possibly because acute-phase or cellular response to infection may enhance quiescent disease[24,25]. Our patient had been diagnosed with acute gastroenteritis two days prior to admission. She was treated with ciprofloxacin and we believe that the fluoroquinolone might have additionally contributed to the convulsive episodes, by lowering the convulsive threshold.

Finally, pulmonary changes observed at the last chest CT might suggest that some degree of pulmonary involvement could be present as well. The ground-glass opacities seen could represent lung bleeding. However, they could also represent bronchiolitis associated with cigarette smoking, as our patient remained an active smoker. Centrilobular emphysema, which we know is frequently associated with cigarette smoking, was also reported in this last CT. We cannot also affirm if the opacities seen were new/active or persistent/chronic, given the fact that they overlapped with those described in the previous CT scan. Regardless, we think that the involvement of the CNS was more exuberant than any other involvement, making it a challenge for us.

In conclusion, diagnosis of ANCA associated CNS vasculitis is challenging and should be suspected in patients with AAV if there is clinical evidence of cerebral involvement and if MRI shows multiple ischemic lesions and vascular branches irregularities. Awareness of this rare but severe complication is critical for timely recognition and prompt treatment.

Disclosure of potential conflicts of interest: none declared.

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