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Atypical presentation in a case of granulomatosis with polyangiitis

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is part of the anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis, mostly being ANCA-c (anti proteinase 3) positive. Primarily it involves the upper respiratory tract and kidneys having an increased mortality in the absence of early diagnosis and correct treatment. The most common renal involvement is pauci-immune crescentic glomerulonephritis. We present the case of a patient with GPA with a particular onset of interstitial nephritis, possible by vasa recta vasculitis, in the absence of glomerulonephritis.

Keywords: acute kidney injury, deep vein thrombophlebitis, granulomatosis with polyangiitis, vasa recta vasculitis

CASE PRESENTATION

A 71-year-old woman was admitted for oliguria and palpebral edema occurred in the last 36-48 hours. She had been in her usual health until 3 weeks before admission, when she gradually manifested non-productive cough, feeling of coldness, diaphoresis, and slight muscle aches, along with fatigue, loss of appetite and weight loss. Nine days before admission she started orally treatment with amoxicillin (2 g/day) and ibuprofen (1.2 g/day) for five days and because symptoms did not improve she switched to ciprofloxacin alone (1.5 g/day) for the next two days. During these she became oliguric and felt increasingly sick, so she stopped the antibiotic.

The patient had left breast cancer with total mastectomy followed by radio- and chemotherapy 38 years ago, complicated with left upper limb lymphedema and recurrent episodes of cellulitis, hysterectomy with bilateral anexectomy for intermittent metrorrhagia followed by successive endometrial biopsy showing focal atypia (in 2013). She also had arterial hypertension diagnosed in her fifties and her chronic medication during the last ten years was a angiotensin-receptor blocker (candesartan 8 mg/day).

Six months before, at a routine check-up, she had a normal kidney function (serum creatinine 1mg/dL). She had no history of food or drug allergies, did not drink alcohol, smoke or use illicit drugs. There is a family history of cancers and hypertension.

On admission, the patient appeared well and was in no acute distress. The physical examination was unremarkable except for a mild pallor, palpebral edema and oliguria (400 mL). No skin rash, no deformity or joints inflammatory signs, no lung rales or significant cough were found. The blood pressure was 140/80 mm Hg, the pulse 72 beats/minute, the temperature 36.4°C, the respiratory rate 15 breaths/minute and oxygen saturation 98% while the patient was breathing ambient air. Her serum creatinine was 3.74 mg/dL (327.9 μmol/L), serum urea 118 mg/dL, and urinalysis revealed clear, yellow urine, protein 1+, 250 white cells (with 1.4% eosinophils), 30 red isomorphic cells, and no hyaline cast per high-power field. Also, she had mild acidosis, mild thrombocytosis, leukocytosis and anemia (PLT 429000/μL, WBC 9800/μL with 3% eosinophils, Hb 10.7 g/dL), marked inflammatory syndrome (erythrocytes sedimentation rate 92 mm per hour, C-reactive protein

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147 mg/L), and elevated anti-neutrophil cytoplasmic antibodies anti-proteinase 3 (PR3-ANCA 288 UI/mL, i.e. 14-fold the upper limit of the reference range), with normal serum C3 and C4 complement fractions. Serum glucose, lipids and proteins, as well as the results of coagulation and liver-function tests were in normal range. A 24-hour urine collection revealed moderate proteinuria with an albumin/creatinine ratio of 132 mg/g and showed a fractional excretion of sodium (FENa) of 1.4%. Urinary beta-2 microglobulin was normal. The ECG and the chest radiograph described no abnormalities, while the abdominal ultrasound revealed both kidneys with normal size and parenchymal echogenicity, without urinary tract dilatation.

The first diagnostic hypothesis was acute kidney injury (AKI), most probably due to an intrinsic renal cause. Even no signs of dehydration were found, the patient added a nonsteroidal anti-inflammatory drug (NSAID) to her previous sartan medication for a few days. It is well known that angiotensin receptor blockers (ARBs) decrease intraglomerular pressure, and consequently the glomerular filtration rate, by selective inhibition of angiotensin II-mediated vasoconstriction at the efferent arteriole (1). On the other hand, ibuprofen, a NSAID, inhibits the prostaglandin-mediated dilation of the afferent renal arteriole, and the combination of renin-angiotensin system inhibitors with NSAID is recognized as potential nephrotoxic due to their additive unfavorable effects on glomerular hemodynamics, resulting in pre-renal AKI (2). However, the abnormal urinalysis and the FENa >1% suggested an intrinsic renal disease (3). Our patient recently used potential nephrotoxic medications, so a drug-induced tubulo-interstitial nephritis was the supposed cause of AKI. The predominance of leukocytes with eosinophiluria above 1%, the absence of casts and the low degrees of hematuria and proteinuria were considered arguments for an acute interstitial nephritis (AIN) most likely caused by amoxicillin (ciprofloxacin was introduced just for two days in medication). The onset of AIN typically occurs within 3 weeks of starting the offending drug in 80% of cases, with an average delay of ~10 days for antibiotics (4). NSAIDs-induced AIN occurs after months of exposure with a mean duration of six months and patients with NSAIDs-related nephropathy can develop even nephrotic syndrome (4). Since AIN should be considered in all patients with unexplained AKI and recent exposure to any of the potential causative agents, even in the absence of peripheral eosinophilia (5), corticosteroid therapy was started. The use of corticosteroids has been supported by many even not all retrospective studies (6,7), some reporting rapid return to baseline kidney function (after a mean of 9.3 days), but was not confirmed by prospective randomized controlled trials (5).

The only peculiar finding in our case was the presence of elevated PR3-ANCA. This raised the suspicion of systemic vasculitis with granulomatous interstitial nephritis, a condition reported in 5-16% of granulomatosis with polyangeitis patients (4). Nevertheless, commercially available PR3- and MPO-ANCA direct ELISA kits were found to have poor sensitivity (8), and false positive results for proteinase 3 ANCA in the absence of suggestive clinical symptoms were reported in 24% of a case series (9). Even the association of cephalosporin-induced AIN with positive ANCAp was described (10).

However, since a definitive diagnosis of AIN can be established only by histopathology and some features in the clinical presentation of our case (flu-like onset associated with AKI, marked inflammation and increased PR3-ANCA titre) could point to systemic vasculitis, a kidney biopsy was performed in the fourth day of corticosteroid treatment. Seven glomeruli were present in the bioptic fragment, six of which were normal (Figure 1) and one showed diffuse sclerosis. Focal interstitial inflammation in the recovery phase without granuloma and eosinophils was also seen in light microscopy, while the immunofluorescence and electron microscopy were unremarkable. Therefore, the biopsy had limited diagnostic utility, except for the fact that it ruled out a crescentic glomerulonephritis.

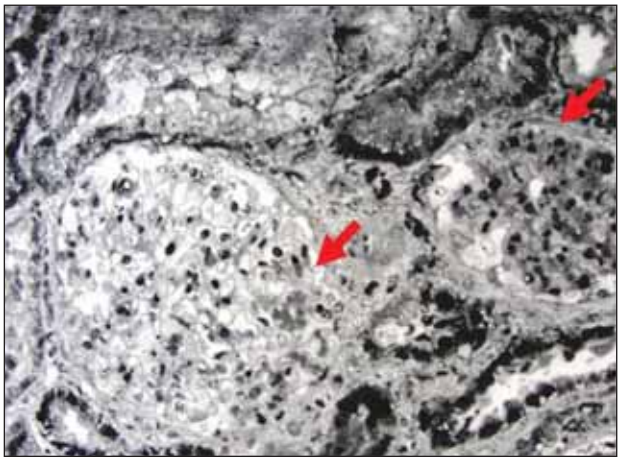

FIGURE 1. *Kidney biopsy (light microscopy) showing normal glomeruli (red arrows). Courtesy of Dr. Eugen Mandache*

CLINICAL COURSE

Methylprednisolone (1 g daily) was administered intravenously for 3 days beginning with the second day of hospitalisation, was continued with oral corticosteroids (prednisone) 0.5 mg/kcg/day in the next 4 days, and then was rapidly tapered over 1 month. The clinical course was favorable with fast increase in diuresis (4,000 mL in the fourth day) and regressive serum creatinine levels (Figure 2), so the patient was discharged after 14 days, when the diuresis was normal (2,000 mL) and she was free of symptoms.

Three weeks after discharge, the patient returned in clinic for massive swelling, erythema and tenderness in the left lower limb. Doppler ultrasound exam revealed left iliofemoral-popliteal deep vein thrombosis (DVT). No obvious cause for DVT was detected. The chest radiograph, the abdominal ultrasound exam, the tumor markers (alpha fetoprotein, CA-125, carcinoembryonic antigen), the anti-dsDNA antibodies, anti-cardiolipin antibodies, the anti Ro/SSa and anti La/SSb antibodies were all negative. Serum creatinine and urinalysis was normal. The anticoagulant treatment was rapidly started (initially low-molecular-weight heparin followed by continuous oral anti-vitamin K) and slow remission of symptoms was obtained.

Shortly afterwards the patient manifested again dry cough, associated with dyspnea on exertion, arthralgias and weakness. The kidney function was stationary (normal serum creatinine; estimated glomerular filtration rate 50 mL/min by abbreviated MDRD equation) and urinalysis unchanged (there were no proteinuria, no dysmorphic hematuria). The inflammatory syndrome was present and the ANCA-PR3 was still elevated (203 UI/mL), while serology for hepatitis B and C viruses was negative. A native and contrast medium thoracic computed tomography scan showed no signs of pulmonary embolism but detected bilateral ground-glass, pleural based pulmonary nodules of 1.3-4.2/1-2 cm in diameter, with contrast uptake (Figure 3), without mediastinal lymph nodes. Pleural or lung biopsy was not performed because of the patient's refusal.

At that moment, the recent medical history of the patient was reviewed and the following association was retained: constitutional symptoms in the preceding two months + pulmonary nodules + idiopathic deep vein thrombosis + persistently increased serum PR3-ANCA. In this clinical setting a presumptive diagnosis of ANCA-associated vasculitis was made with a high probability.

Intravenous (IV) cyclophosphamide pulses was commenced as induction therapy monthly (a total of 5 doses), associated with the re-initiation of corticosteroids (IV methylprednisolone and then oral prednisone). During the therapy the kidney function remained stable, in normal range, while the inflammatory syndrome disappeared and the PR3-ANCA serum level normalized promptly. After the fifth month of complete remission the maintenance therapy with azathioprine 2 mg/Kgc/day was introduced in association with low-dose prednisone. At the end of follow-up (13 months) the patient has persistent remission of the disease and continues the maintenance immunosuppressive therapy.

DISCUSSIONS

The current report describes a case consistent with ANCA-associated vasculitis, most probably

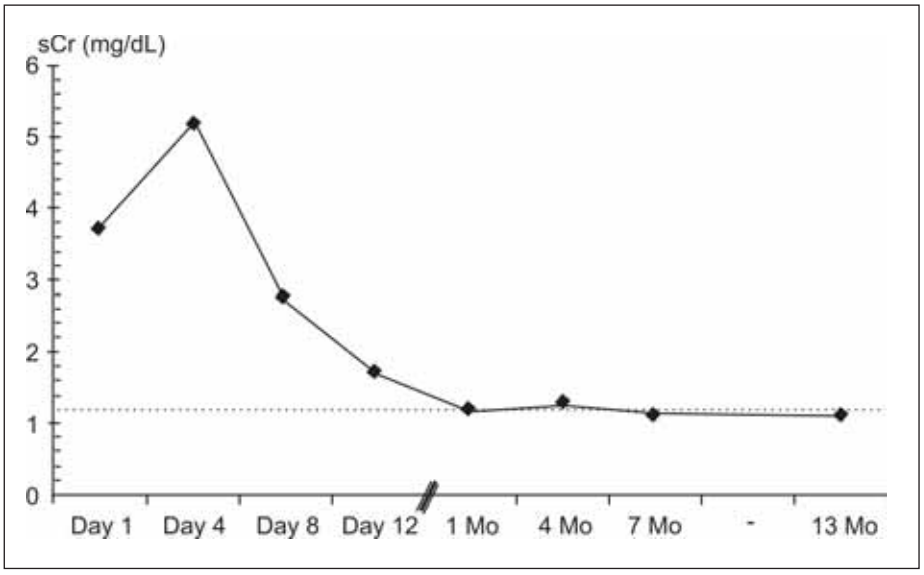

FIGURE 2. *Kidney function outcome (measured by serum creatinine) during the 13 months follow-up period*

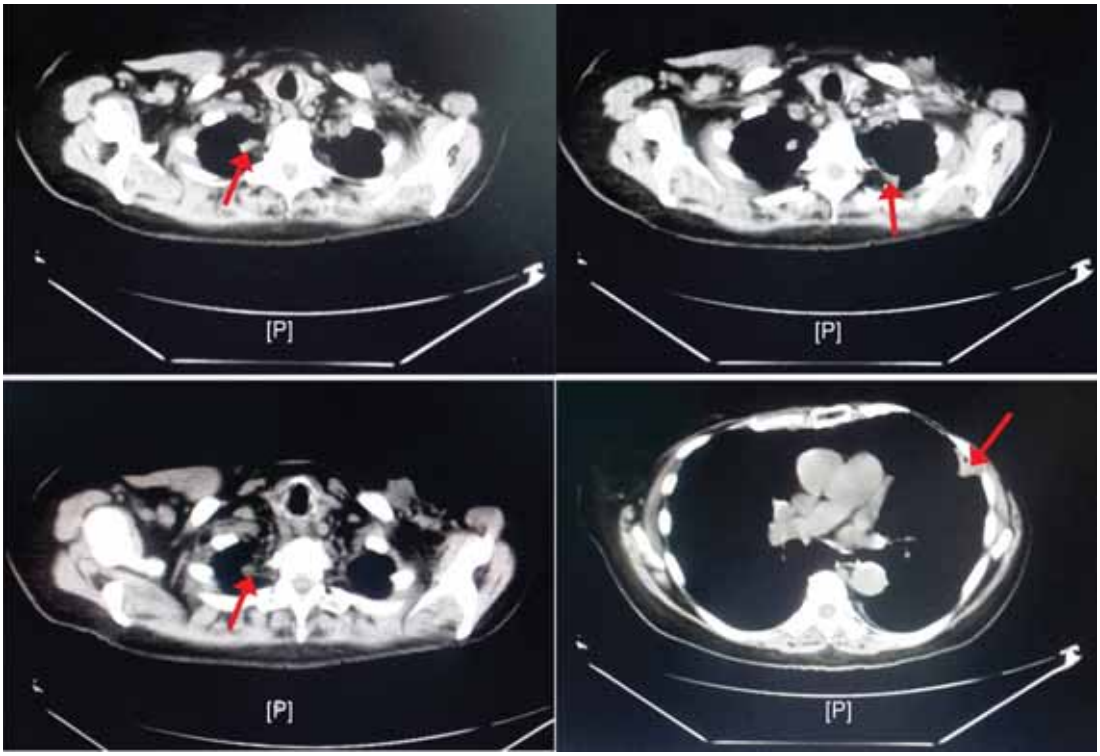

FIGURE 3. *Thoracic computed tomography showing bilateral pleural-based nodules (arrows)*

granulomatosis with polyangiitis, who had an unusual onset as reversible acute kidney injury due to interstitial nephritis without glomerular involvement.

Antineutrophil cytoplasmic antibody-associated vasculitides (AAV) are a group of pauciimmune small vessel vasculitides that often affect the kidneys and commonly have increased levels of serum ANCA (11). According to the latest classification (International Chapel Hill Consensus Conference criteria, revised in 2012) four distinct entities are included in AAV: granulomatosis with polyangiitis (formerly Wegener), microscopic polyangiitis (MPA), renal-limited vasculitis (RLV), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) (11,12).

GPA is a rare disease with an incidence described between 0.5 to 8.5 pmp, that has probably risen in the last decades due to the increase awareness (13,14). A north-to-south decreasing frequency was described in Europe, the incidence of GPA being more frequent in the Nordic countries. There is no gender difference and there are rare cases in black subjects or in children (15). GPA is a systemic necrotizing vasculitis affecting small- and medium-sized blood vessels, associated with PR3-ANCA in 80-90% of cases (12,15), which most often presents with respiratory and kidney involvement. The primary kidney involvement is a focal and segmental pauci-immune necrotizing glomerulonephritis with extra-capillary proliferation (crescent formation). It usually leads to dysmorphic hematuria and subnephrotic proteinuria, a real nephritic syndrome with rapidly progressive loss of glomerular filtration rate (16). Even at presentation only one in five patients had signs of glomerulonephritis, it subsequently developed in the first two years of the disease onset in more than 80% of cases (12).

A positive ANCA test strongly suggests the diagnosis of vasculitis, but both false-positive and false-negative results were reported, so the histologic examination of bioptic tissue obtained from an affected organ remains the confirmatory method for diagnosis. Of note, significant clinical overlap exists, so diagnostic algorithms have insufficient sensibility and specificity to reliable distinguish between GPA and MPA, the presence of granulomatous changes on biopsy being the defining differentiation clue (12). In our patient the histologic proof of vasculitic process is lacking. In such cases, which are the common real life scenario in daily practice, presumptions based on clinical and laboratory features could be made and should support the early start of immunosuppressive therapy. Two out of the four surrogate markers suggested by the European Medicines Agency algorithm for the diagnosis of GPA in ab-

sence of histologic proof (fixed pulmonary nodules and positive ANCA serology) (12) were found in our case and substantiated the diagnosis.

In addition, the occurrence of deep vein thrombosis at the proximal level of lower left limb without a known favoring factor (no history of peripheral varices or venous insufficiency, no history of recent fractures or immobilization etc.) point also to ANCA-associated vasculitis as many studies suggested a hypercoagulable state and high incidence of venous thromboembolic events in vasculitis (six times more than in general population of the same age), especially when the disease is active (17). A causative factor could be changes in endothelial function, like the loss of anti-thrombogenic activity resulting from endothelium damage and activation during inflammation, since it is known that pro-inflammatory cytokines and ischemia can cause endothelial damage (17,18). Furthermore, high levels of D-dimers, thrombin-antithrombin III complexes and factor VIII were detected in patients with AAV. Increased platelet aggregation and decreased fibrinolytic capacity during active disease was described as well (17). Recently, a new contributing mechanism was proposed based on the fact that C5a-primed neutrophils stimulated with ANCA produce tissue factor-expressing microparticles and neutrophil extracellular traps which could promote hypercoagulability and activate the coagulation system by thrombin generation. Thus, the pro-inflammatory factor C5a, neutrophil-derived tissue factor an extracellular traps could play a role in the pathogenesis of hypercoagulability in vasculitis (18).

The most important particularity of the presented case is the atypical kidney involvement which prompted the patient to hospital in the first place. As previously mentioned, most AAV patients have pauci-immune focal segmental crescentic and/or necrotizing glomerulonephritis, but a few cases of isolate tubulointerstitial nephritis (TIN) were described too (19). In microscopic poliangiitis the prevalence of this unusual kidney lesion varies from 1 to 4.5% of cases (19). Other rare kidney lesions reported in vasculitis were obstructive uropathy due to ureteral granulomatous vasculitis and ruptured arterial aneurysm of the kidney caused by the involvement of larger vessels (20). Some cases of TIN are due to vasculitis of vasa recta (medullary angiitis) (12). In PGA, vasculitis of the renal vessels (usually the interlobular arteries, the medullary vasa recta, or branches of the spiral arteries) were found in ~8% of patients (14). Renal medullary angiitis involves the vasa recta of the medulla and the characteristic lesions (i.e. interstitial hemorrhage associated with polymorphonuclear leukocyte infiltrate and karyorrhectic debris surrounding peritubular capillaries) are not seen in the cortex (21). It was suggested that tubulointerstitial ischemia due to both peritubular capillary injury (capillaritis) and fibrinoid vasculitis of the interlobular arteries and arterioles at least partially account for the TIN in ANCA-associated vasculitis and is the major cause of renal dysfunction (19). The histologic diagnosis of these conditions is jeopardized because of the focal involvement which could explain the underestimation of the real extent of interstitial damage (19). Such patients who initially present only TIN may subsequently develop the classic pauci-immune necrotizing glomerulonephritis (12).

Even the hypothesis of a coincidental drug-induced AIN at the onset of the active vasculitis disease in our patient cannot be firmly rejected, the previous similar case reports and the general "rule" that simultaneous occurrence of different pathological processes in the same individual is a rarity, sustain the interpretation as an unusual presentation of the ANCA-associated vasculitis with acute, reversible, tubulo-interstitial kidney involvement.

CONCLUSION

GPA is a serious disease with a variety of clinical presentation forms, some of them misleading. Since the patient's prognosis depends on the early diagnosis and appropriate treatment, we should stay alert and closely monitor each case that seems to show at least one sign of ANCA-associated vasculitis. In particular, in all cases of acute kidney injury without a very clear etiopathogenic factor, or associated with extra-renal symptoms, marked inflammation or active urinary sediment, ANCA serology and kidney biopsy should be performed.

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