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CASE REPORT

An Unusual Presentation of Classic Idiopathic Polyarteritis Nodosa as Acute Interstitial Nephritis

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Abstract: In the medical literature, there have been few reported cases of classic Polyarteritis Nodosa (cPAN) presenting with acute renal failure (ARF) and, unlike microscopic polyangiitis (MPA), no documentation to our knowledge of cPAN with clinical presentation similar to acute interstitial nephritis. We describe a case of ARF and a clinical picture suggestive of acute interstitial nephritis (AIN). However, renal biopsy of this patient showed acute necrotizing intrarenal vasculitis, suggestive of cPAN. Although no guidelines exist for the most appropriate therapy for patients presenting in this fashion, combination therapy with cyclophosphamide and steroids, in our patient, resulted in clinical improvement and resolution of dialysis-dependent renal failure. These findings suggest the potential for good prognosis in patients with cPAN who present with a presumed diagnosis of AIN and dialysis-dependent ARF.

Keywords: classic polyarteritis nodosa, acute interstitial nephritis, microscopic polyangiitis, renal biopsy, eosinophiluria, MPO-ANCA

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Introduction

Classic polyarteritis nodosa (cPAN) is a multisystem disease characterized by necrotizing nongranulomatous vasculitis of medium-sized or small muscular arteries without glomerulonephritis[1] and was first described by Kussmaul and Maier in 1866.[2] The clinical features vary widely depending on the size and extent of involvement of the vessel.[3,4] The organs commonly affected are soft tissue, muscles, the gastrointestinal system, and the nervous system, but, unlike microscopic polyangiitis (MPA), it spares the lungs.[5]

Involvement of visceral and renal arteries is characteristic, but although polyarteritis nodosa is known to involve the kidneys,[6] it is uncommon for it to present as acute renal failure (ARF), and, to our knowledge, cPAN presenting as acute interstitial nephritis is virtually unknown. Acute interstitial nephritis, as described by Councilman in 1897, is an acute inflammation of kidney characterized by cellular and fluid exudation in interstitial tissue, accompanied by degeneration of epithelium.

Additionally, although corticosteroids and immunosuppressants improve prognosis of patients with cPAN, there is no consensus on the most appropriate therapy for cPAN with ARF, and prognosis of the disease remains uncertain. Here we present a patient with ARF due to polyarteritis nodosa manifesting clinically as acute interstitial nephritis who responded to immunosuppressants.

Case report

A 69-year-old woman presented to our hospital with a 2-week history of nausea, abdominal pain, extreme generalized weakness and fatigue, and a 1-week history of poor oral intake. Additionally, she had noticed a new onset of pruritic rash over the abdomen, spreading over the trunk. Two weeks prior to the onset of her symptoms, she had presented with dysuria to her primary care physician and was treated with a week's course of ciprofloxacin for presumed urinary tract infection, but, despite this, her symptoms persisted.

Her past medical history was significant for atrial fibrillation, lumpectomy for breast cancer, done six years previously, and diverticulosis.

On examination at our institution, her temperature was 37.2 °C, her blood pressure was 110/70 mmHg, and her pulse rate was 156 beats per minute. Positive physical examination findings were a diffuse, predominantly truncal, maculopapular, erythematous rash. This was nonpalpable and nonblanching. Cardiovascular exam was positive for rapid atrial fibrillation. Examination of her lower extremities revealed severe tenderness over both calf areas but no pedal edema. A separate petechial rash was noted over the shins. Abdominal examination revealed no masses, but she demonstrated generalized tenderness on palpation.

Laboratory data revealed hemoglobin (Hb) 9.7 g/dL, hematocrit 32.2%, leukocyte count of 9300 cells/UL (differential: granulocytes 91%, lymphocytes 2%, monocytes 6%, and eosinophils 1%), platelets of 276,000/mm3, blood urea nitrogen (BUN) of 134 mg/dL (normal, 10–20 mg/dL), creatinine, 11.6 mg/dL (her baseline creatinine a month prior to her presentation was 1.1 mg/dL). In addition, her sodium was 125 mmol/L (normal, 135–146 mmol/L); chloride, 88 mmol/L (normal, 96–106 mmol/L); potassium, 4.2 mmol/L (normal, 3.5–5.1 mmol/L); phosphorus, 7.5 mg/dL (normal, 2.7–4.5 mg/dL); and bicarbonate, 18 mmol/L (normal, 24–32 mmol/L). Urine analysis showed specific gravity of 1.010; trace proteins, 3 to 5 dysmorphic red blood cells; no casts and no leucocytes; and glucose, 50 mg/dL. The 24-hour urine microalbumin/creatinine ratio was 797 mcg/mg with a urine creatinine of 30.6 mg/dL. Although there was no peripheral eosinophillia, her urine was positive for eosinophils by Wright's stain. Liver function tests were normal.

Serum protein electrophoresis was normal, while her antinuclear antibody and serologies for hepatitis B and C were all negative. Her Complement component 3 (C3) was normal at 112 and Complement component 4 (C4) was mildly depressed at 15.1.

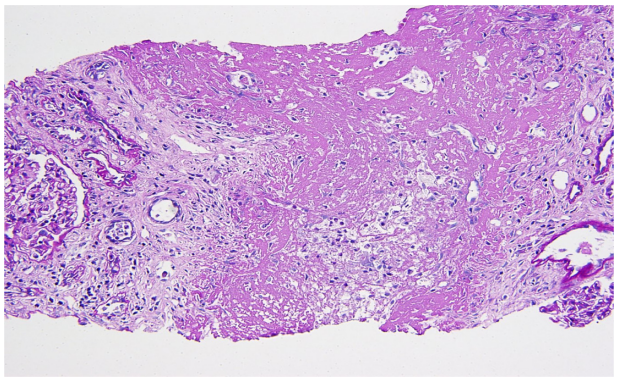

Figure 1. High magnification of the necrotic medium-sized artery showing extensive fibrinoid change with early central organization of the fibrinoid material, with adjacent infiltration of inflammatory cells, granulocytes and lymphocytes.

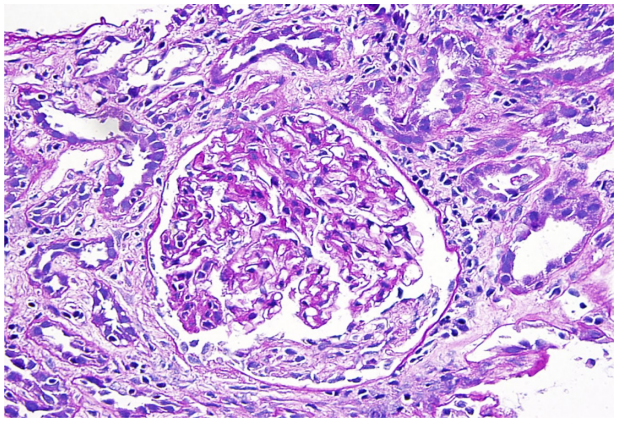

Figure 2. High magnification of a glomerulus surrounded by mild inflammatory infiltrate, showing a small cellular crescents in the Bowman space.

Enzyme-linked immunosorbent assay (ELISA) was used to test for presence of serum myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA); this was found elevated to 54 EU, (normal value is <20 EU). Her P-Anti-neutrophil cytoplasmic antibody titer was 1:40.

Human immunodeficiency virus was negative, so was the Antinuclear antibody (ANA). C-Reactive Protein (CRP) was 22.9 mg/dL and Erythrocyte sedimentation rate (ESR) was >140 mm/hr, the results of tests that were done after the biopsy diagnosis was made.

A renal biopsy was performed after admission, and it showed acute necrotizing intrarenal vasculitis with diffuse acute ischemic tubular injury. Low magnification showed an interlobular or arcuate artery showing full-thickness fibrinoid necrosis with luminal occlusion. One glomerulus out of 25 in the specimen showed a fibrocellular crescent and global glomerulosclerosis. The other glomeruli were unaffected. Additionally, there was no evidence of acute interstitial nephritis on the biopsy specimen.

An magnetic resonance image of the brain at that time revealed nonspecific white matter signal changes, likely representing small vessel ischemic disease but vasculitis could not be definitively ruled out. Renal arteriogram was negative for micro aneurysms.

Given her severe uremia, she was placed on intermittent hemodialysis via a split-tip tunneled hemodialysis catheter. In addition, she was started on a daily oral cyclophosphamide at a dose of 1 mg/kg/day and daily oral prednisone at a dose of 1 mg/kg/day initially. Six weeks into her treatment, her creatinine fell to 1.9 mg/dL and intermittent hemodialysis was discontinued (Table 1).

Table 1. Subjective and objective improvement pre- and post- treatment.

Clinical and laboratory findings	Before treatment	After treatment
Weakness	++++	+
Myalgia	+++	+
Fever (C)	38.2	36.5
Hb (g/dL)	10.7	11.6
Urinalysis	6–8 RBC and trace protein	1–2 RBC
Creatinine (mg/dL)	11.6	1.9

Discussion

Vasculitis is a rare entity, which comprises distinct groups often based on the size and site of the part of the vascular tree involved. Renal involvement is likely due to ischemic injury as a result of luminal vascular occlusion by the inflammatory process and manifests as varying degrees of renal insufficiency, hypertension, and hematuria. Polyarteritis nodosa is a systemic vasculitis that involves medium and small muscular arteries and presents with constitutional symptoms of fever, malaise, extremity and calf pains, purpura, and skin rash. Drug-induced acute interstitial nephritis, on the other hand, often manifests with rash, fever, eosinophilia, eosinophiluria, and acute renal failure, usually after ingestion of an offending drug.

Added to the usual protean symptoms of malaise, myalgia, and fatigue for months, our patient had presented with a new-onset diffuse rash and rapidly progressive acute renal failure. With a history of having been exposed to a quinolone antibiotic, the presence of a new-onset truncal rash, acute renal failure on laboratory data, and eosinophils in the urine, we made a presumptive clinical diagnosis of drug-induced acute interstitial nephritis.

The renal biopsy as previously mentioned, however, showed acute necrotizing and intrarenal vasculitis, diffuse acute ischemic tubular injury, fibrinoid necrosis, and a fibrocellular crescent.

One clinical dilemma is often to differentiate cPAN from MPA. ANCAs are seen in about 50% to 80% of patients with MPA and are positive in 10% of patients with polyarteritis nodosa.[9] In one series, 2 of

the 5 reported cPAN cases with RPRF were positive for MPO-ANCA.[7]

The Chapel Hill Consensus Conference, in 1994, suggested the term microscopic polyangiitis to describe the phenomenon of pauci-immune vasculitis affecting primarily small vessels and the presence of pulmonary capillaritis and glomerulonephritis.[1] The terminology sought to differentiate this syndrome from classic polyarteritis nodosa, which the conference felt needed to be restricted to arteritis involving medium-sized and small arteries without involvement of smaller vessels. Therefore, patients with vasculitis affecting arterioles, venules, or capillaries, including glomerular capillaries, were excluded from this class.

This reclassification has led to many more diagnoses of MPA and the concomitant decrease in the prevalence of polyarteritis nodosa.[10] However, despite this proposed distinction, separating these two phenomena clinically is not always straightforward, and our patient with the albeit rare crescent, positive myeloperoxiase-antineutrophil cytoplasmic antibodies, absence of hepatitis B, and negative arteriogram was initially classified in the MPA category. However, the absence of small vessel involvement, the absence of significant proteinuria, the dominant involvement of medium arteries on biopsy, and the paucity of glomerulonephritis pointed to cPAN. Also, she met 3 of the 10 criteria, that is, myalgias and calf tenderness, elevated BUN and creatinine not related to obstruction or dehydration, and a tissue biopsy with appropriate histological changes set forth by the 1990 American[11] College of Rheumatology criteria for classification of polyarteritis nodosa. Hence, she was reclassified as idiopathic polyarteritis nodosa.

Despite multiple attempts, there still remains a dilemma with classification of vasculitis.[13] There has been a revision of the International Chapel Hill Consensus (CHC) Conference nomenclature in 2012, which has differentiated cPAN from ANCA associated vasculitis (AAV) by the presence of ANCA.[13] Intriguingly, our case, based on the current nomenclature classification, could be classified under MPO-ANCA. However, it remains that there is predominant glomerulonephritis, mostly associated with small vessel disease. The majority of the MPO-ANCA vasculitis variants are associated with pulmonary capillaritis, with no clinical evidence in our case. It is also true that PAN and ANCA-associated vasculitis can exhibit clinically and pathologically indistinguishable necrotizing arteritis of medium and small arteries.[14] Thus, despite the new nomenclature for epidemiological differentiation, we believe this is idiopathic polyarteritis nodosa with a rare ANCA positivity.

This is an unusual clinical manifestation of cPAN. In one review of 10 cases of interstitial nephritis by Dixon et al,[12] one case was proven at necropsy to have polyarteritis nodosa. Therefore, on the one hand, this demands that clinicians bear this in mind when faced with a seemingly obvious case of drug-induced AIN and, on the other hand, demonstrates the potential for good response of this unique cPAN syndrome to chemotherapy even in the face of clinically severe renal failure requiring dialysis.

We believe the patient's overall prognoses improved due to earlier diagnosis, rapid initiation of treatment, and careful treatment monitoring. Early and accurate diagnosis is very important as delay in management worsens morbidity and mortality risks and also diminishes the odds for renal recovery.

Despite being dialysis-dependent on admission, a dramatic clinical response was observed in the subsequent weeks, with nearly complete resolution of the kidney injury with immunosuppressive combination therapy using cyclophosphamide and prednisone. Although this combination is frequently used for treatment of systemic vasculitis to induce remission, their use is often complicated by drug toxicity and deleterious side effects. However, inadequate dosing and treatment leads to relapses and thus organ damage from vasculitis.[8]

We therefore considered histological examination, in our case the kidney biopsy, as essential for correct diagnosis and appropriate treatment. As previously noted, she was successfully treated with immunosuppressive therapy using prednisone and cyclophosphamide.

In conclusion, we encountered a patient with biopsy-proven cPAN with a rare MPO-ANCA positivity who developed ARF but nevertheless showed good outcome with immunosuppressive treatment.

To our knowledge, there is a paucity of literature of cases of classic polyarteritis nodosa manifesting with ARF and clinical presentation of acute interstitial nephritis. Timely recognition of this clinical entity and obtaining histological confirmation are crucial

key steps in its management, while early initiation of immunosuppressive treatment potentially bodes well for the afflicted patient even in the face of dialysis-dependent renal injury.

Author Contributions

Conceived and designed the experiments: RS, NCO, PT. Wrote the first draft of the manuscript: RS, NCO, PT. Contributed to the writing of the manuscript: MT, VB. Agree with manuscript results and conclusions: RS, VB, MT, PT, NCO Jointly developed the structure and arguments for the paper: RS, VB, NCO. Made critical revisions and approved final version: RS, VB, NCO. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

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Disclosures and Ethics

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