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Teaching Point
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Falling through the cracks of vasculitis classification—a report of three patients

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Introduction

The systemic vasculitides are a group of multisystem diseases characterized by inflammation of blood vessels. Classification schema have been proposed by The American College of Rheumatology (ACR) [1] and by the Chapel Hill Consensus conference (CHCC) [2]. The current classification system for vasculitides is based on vessel size and clinicopathological features.

Precise recognition and accurate diagnostic categorization of the vasculitides is crucial for optimal management. Yet, some patients with vasculitis can have features consistent with more than one type of vasculitis syndrome during their disease course that is not captured by the current classification systems [3–7]. Another less recognized problem is that a patient may present with one form of vasculitis and develop years later another form. To our knowledge, only three patients who have transitioned from one form of vasculitis to another have been reported [8]. These three patients had Wegener's granulomatosis (WG) and developed IgA nephropathy while the WG was in remission. To bring attention to this important issue, we now report three patients who presented with a distinct type of vasculitis and subsequently developed a phenotype of a different type of vasculitis after a prolonged period of remission of their initial vasculitis presentation.

These cases raise important questions about the underlying mechanisms and the potential relationship between these distinct pathological entities. Additionally, treatment becomes challenging in these cases; after the second biopsy, should therapy take into consideration the results of the first biopsy?

Case 1

A 50-year-old white male presented at age 36 with fever, chills, malaise and hemoptysis. His laboratory tests were notable for a serum creatinine of 10.3 mg/dL, elevated erythrocyte sedimentation rate (ESR), anemia, microscopic hematuria and proteinuria. His serologies were negative for anti-neutrophil cytoplasmic antibody (ANCA), hepatitis B and C and his serum complements were normal. His chest imaging revealed a right lower lobe infiltrate. He was dialysis dependent on presentation. His renal biopsy revealed a necrotizing and crescentic pauci-immune glomerulonephritis (GN) (Figure 1). He was diagnosed with ANCA-negative microscopic polyangiitis (MPA) and treated with steroids and cyclophosphamide for 18 months. His renal function recovered and 2 months later his creatinine improved to 1.1 mg/dL. He was reevaluated 14 years later for hematuria and rise in serum creatinine to 1.7 mg/dL. His serologies were negative for ANCA, proteinase 3 antibody ELISA and myeloperoxidase antibody (MPO) ELISA. Renal biopsy revealed crescentic IgA nephropathy with mesangial IgA (3+) staining on immunofluorescence and mesangial-dense deposits on electron microscopy (Figures 2 and 3). He was treated with prednisone and rituximab with good response. This patient had the phenotype of MPA initially and subsequently developed IgA nephropathy.

Case 2

A 38-year-old white female was diagnosed with p-ANCA-positive and MPO ELISA-positive MPA at age 23 when she presented with fever, arthralgias, pulmonary-renal syndrome and had biopsy-proven pauci-immune GN. She was treated with steroids and cyclophosphamide for 6 months and went into remission. She was reevaluated 4 years later for rise in serum creatinine, hematuria and

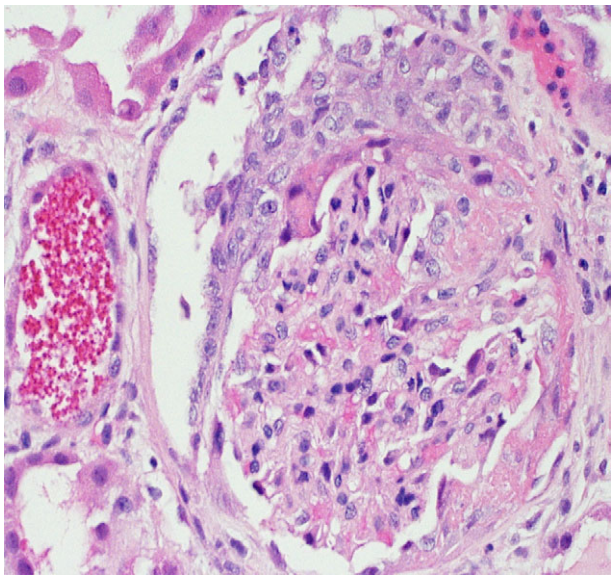

Fig. 1. Renal histology taken from Case 1, age 36 showing crescentic GN. Glomerulus compressed by a cellular crescent (hematoxylin and eosin, ×40).

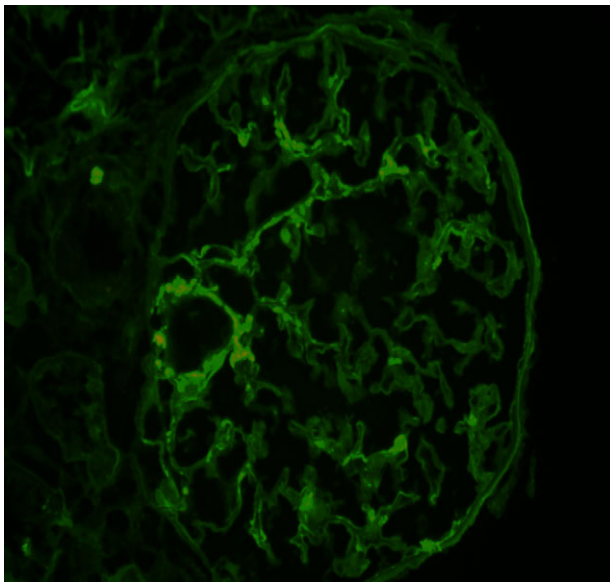

Fig. 3. Renal histology taken from Case 1, age 50, showing bright mesangial IgA staining (IgA, ×40).

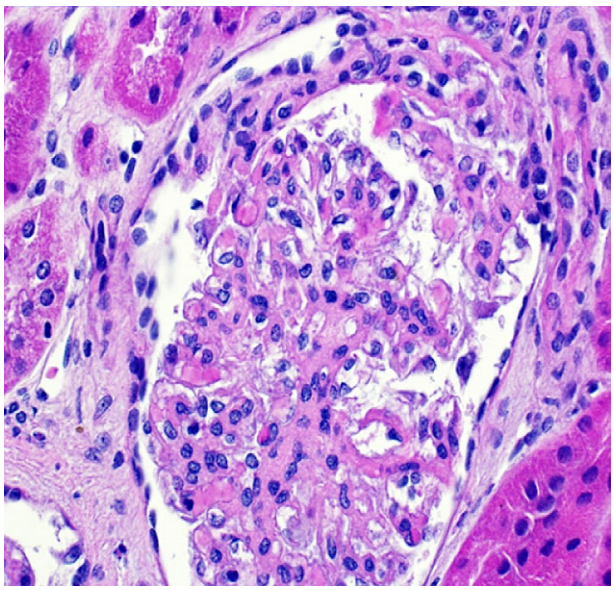

Fig. 2. Renal histology taken from Case 1, age 50, showing minimally proliferative IgA nephropathy. Glomerulus with a segmental cellular crescent (hematoxylin and eosin, ×40).

proteinuria. She was ANCA negative. Renal biopsy showed crescentic IgA nephropathy. She went into remission with a 6-month course of cyclophosphamide, steroids and azathioprine for 1 year. Over the ensuing 10 years, she developed a series of flares, predominantly with alveolar hemorrhage, palpable purpura and arthralgias that required cyclophosphamide, steroids and ultimately rituximab. Her creatinine is now stable at 1.1 mg/dL. This patient had initially presented with a phenotype of ANCA-positive MPA and subsequently developed Henoch–Schonlein purpura.

Case 3

A 24-year-old Hispanic female first presented at age 10 with recurrent upper respiratory infections, cough, cyanosis and systolic blood pressure of 160 mmHg and an ESR of 90 mm/h. The patient underwent magnetic resonance imaging, which showed severe stenosis of the mid-thoracic aorta, and impaired left ventricular function on echo and was diagnosed with Takayasu's arteritis (TA). She received corticosteroids, her ESR decreased from 90 to 15 mm/h, but she still had uncontrolled hypertension and persistent aortic abnormalities on imaging. She underwent aortic arch reconstruction with graft. She was treated with methotrexate and prednisone. Her prednisone was stopped after a year and her methotrexate was stopped after 4–5 years. At the age of 16, she had recurrence of hypertension and apparent renal involvement. Methotrexate was restarted. A short course of corticosteroids was also given. At age 22, she underwent an MRI/magnetic resonance angiogram that showed stable narrowing of the proximal descending aortic lumen with poststenotic dilatation, occlusion of the left subclavian artery and narrowing of the left main pulmonary artery (Figure 4). Due to the risk of teratogenicity, methotrexate was tapered and stopped. She developed recurrent sinusitis and nasal crusting, unresponsive to antibiotics and saline. Three months later, she presented with cough, dyspnea, bilateral infiltrates on chest X-ray and acute kidney injury with a serum creatinine of 5.3 mg/dL. Her serologies revealed a positive p-ANCA and MPO ELISA. Her renal biopsy revealed a necrotizing and crescentic pauci-immune GN. She became dialysis dependent. She was treated with corticosteroids and cyclophosphamide for 6 months and was switched to azathioprine. This patient had the phenotype of TA initially and subsequently developed features of WG.

In contrast to the first two cases of small vessel vasculitis developing another type of small vessel disease, our third

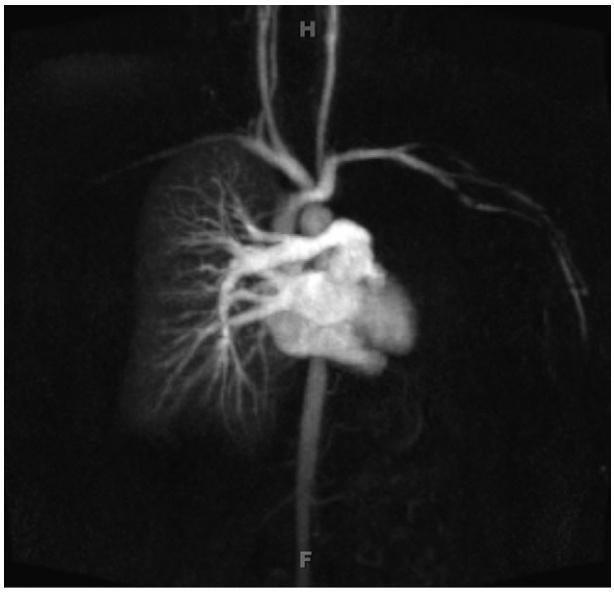

Fig. 4. Case 3, age 22. Coronal T1-weighted magnetic resonance angiogram with Gadolinium of the major vessels demonstrating nonenhancing proximal left subclavian which is reconstituted distally and a narrow or atretic left main pulmonary artery.

case presented with a large vessel vasculitis and subsequently re-presented with small vessel disease.

Discussion

We report the presentation of systemic vasculitis in three patients in whom the initial presentation had the phenotype of one type of vasculitis and subsequently developed the phenotype of a different type of vasculitis after years of remission of the initial vasculitis presentation. The relationship between these apparently distinct entities has three possibilities; firstly, that these conditions are truly coincidental. Secondly, that these relapsing and remitting diseases have different phases of the same process and may represent diseases that cannot be classified by either the CHCC or ACR systems. Thirdly, and most interestingly, patients with one autoimmune disease are more likely to have another autoimmune disease and a shared immunogenetic predisposition may underlie these observations, and these distinct syndromes could be related at a molecular and genetic level.

The first two patients presented as MPA involving the kidneys and lungs initially and subsequently developed crescentic IgA nephropathy. The second patient had involvement of skin and lungs in addition to the kidney. Andrassy *et al.* [8] report de novo IgA nephropathy in three ANCA-positive patients with WG in remission. All three patients had no systemic symptoms and had a history of nonspecific recurrent respiratory infections preceding the diagnosis of IgA. In contrast, one of our patients had ANCA-positive MPA and had systemic signs during development of IgA nephropathy and the other patient had ANCA-negative MPA and did not have any systemic symptoms. However, the coexistence of ANCA positivity and crescentic IgA has been reported in several case reports and case series. In the two large series reported involving 14 patients, the systemic vasculitis symptoms, circulating ANCA and crescentic IgA nephropathy were demonstrated simultaneously during the initial presentation and the authors postulate that the patients may have had preexisting IgA nephropathy that was superimposed by ANCA vasculitis [3, 4]. The authors of these series concluded that the coexistence of IgA nephropathy and ANCA represented an overlap syndrome of IgA nephropathy and ANCA vasculitis presenting with rapidly progressive renal failure and responded well to immunosuppressive therapy. In contrast, our cases were negative for IgA staining on the initial biopsy and had strong staining for IgA with mesangial deposits on the subsequent biopsy that was performed after the initial vasculitis was in remission for years. This suggests de novo development of IgA nephropathy. Both ANCA vasculitis and IgA nephropathy can be triggered by infection but our patients did not have any preceding infections. A possible immunogenetic mechanism was suggested by the observation of HLA-DR-2 positivity in all three patients by Andrassy *et al.* The pathogenesis of IgA nephropathy involves aberrant glycosylation of IgA1 and glycosylation is determined by the B cells [9]. Both of our patients were treated with rituximab in view of their prior exposure to cyclophosphamide and possible role of B cells in both ANCA vasculitis and IgA nephropathy. They both responded well. However, because of limited experience with using rituximab for de novo IgA nephropathy, we cannot definitively recommend this as a standard treatment for these vasculitis overlap syndromes. It is known that the therapies for MPA have profound effects on B lymphocytes but it is not clear whether these therapies may set the stage for appearance of abnormally glycosylated IgA1 and development of IgA nephropathy.

Our third patient was diagnosed with classical TA and then developed the phenotype of WG after years of remission of her TA. Large vessel involvement has been reported in WG presenting as transmural aortitis, aortic dissection and rupture [10] in contrast to the predominantly stenotic complications of TA that our patient had. Renal manifestations of TA are confined to complications from ischemia. Although rare, glomerular involvement has been described with the majority showing a mesangial-proliferative or membrano-proliferative GN [11]. There have been cases of crescentic pauci-immune GN described concurrently with TA [5–7] and in patients with temporal arteritis [12]. Our patient reported here is the first case where features of WG appeared after her TA was in remission for years.

Together, the three cases illustrate the limitations of the current classification schema for vasculitis and demonstrate the possibility that vasculitis can transform from one type to another. We hope this report may be useful to experts involved in the proposed update of vasculitis classification systems by ACR and the European League Against Rheumatism. This observation of change in type of GN calls for repeat renal biopsies if clinical context suggests this possibility and is important to guide therapy.

Teaching points

(1) The current vasculitis classification schema does not account for cases of vasculitis that transform from one type to the other.

(2) The cases presented raise important questions about the underlying relationship between conditions, how to optimally classify and manage them and their ultimate clinical course.

(3) These cases emphasize the importance of repeating the renal biopsy when the clinical context raises suspicion for a second condition.

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