CASE REPORT

A tale of two vasculitides: biopsy-proven giant cell arteritis followed by the independent development of renal-limited microscopic polyangiitis

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ABSTRACT

We describe an 80-year-old woman who presented with headaches, bilateral jaw claudication and visual symptoms. She was diagnosed with giant cell arteritis, which was confirmed by temporal artery biopsy. She was treated with high-dose prednisone followed by a slow taper, with complete resolution of symptoms. Approximately 4 years later, she developed progressively worsening renal function associated with haematuria. Serological workup revealed a high-titre perinuclear antinuclear cytoplasmic antibody and antibodies to myeloperoxidase. Renal biopsy demonstrated a pauci-immune focal crescentic glomerulonephritis. Extensive review of systems, physical exam and diagnostic studies demonstrated no evidence of extra-renal disease, and she was diagnosed with renal-limited microscopic polyangiitis. High-dose prednisone was resumed, but she refused treatment with either cyclophosphamide or rituximab due to concern for toxicity. Her prednisone dose was tapered and renal function stabilised. Our case highlights the need to recognise the successive occurrence of two distinct vasculitides in a single patient and monitor accordingly.

BACKGROUND

Giant cell arteritis (GCA) is a common granulomatous vasculitis involving large-sized and medium-sized arteries, especially branches of the proximal aorta.[1] The most typical presenting symptoms of GCA in order of occurrence are headache, jaw claudication, fever and fatigue.[2] Inflammatory markers, such as erythrocyte sedimentation rate (ESR) and serum C reactive protein, are often elevated at the time of clinical presentation. The 1990 American College of Rheumatology criteria for the classification of GCA specify five criteria, of which at least three should be satisfied: age at disease onset >50 years, new headache, temporal artery tenderness to palpation or decreased pulsation, ESR >50 mm/hour and abnormal artery biopsy.[3] The most catastrophic consequence of GCA is vision loss, which is often permanent. Visual loss is caused by ischaemia of the optic nerve secondary to an inflammatory vasculitic process resulting in occlusion or narrowing of the posterior ciliary arteries.[4] Temporal artery biopsy remains the gold standard for diagnosis of GCA. Studies have shown that 40%–60% of patients with GCA have comorbid polymyalgia rheumatica, which is an inflammatory condition characterised by aching and morning stiffness in the shoulders, hip girdle and neck.[1]

Epidemiologically, the peak incidence of GCA is between the ages of 70–79 years, and there is a decreasing incidence with a north-to-south geographic gradient.[5] The highest incidence of GCA is observed in Scandinavian countries and in US communities with a Scandinavian ethnic background.[6] For years, glucocorticoids have been the mainstay of treatment for GCA, with initial doses of prednisone started at 40–60 mg/day, gradually tapered over 1–2 years.[1] Low-dose aspirin is added to reduce the risk of visual loss and ischaemic events.[7 8] There is also a role for disease modifying antirheumatic drugs (DMARDs) in the management of GCA that is refractory to steroid taper. Methotrexate (MTX) has shown moderate efficacy compared with placebo when used in combination with prednisone. The addition of MTX in patients who developed or are at high risk for adverse effects of prednisone is a common steroid-sparing strategy.[9] The evidence supporting the use of other DMARDs is limited and requires further investigation.[10]Several studies of various TNF-α inhibitors have proven disappointing for the management of GCA.[11–13] Interestingly, a recently completed Phase III trial demonstrated that the interleukin-6 receptor blocker tocilizumab was significantly more effective in achieving sustained remission in combination with a steroid taper compared with steroid therapy alone.[14]

Microscopic polyangiitis (MPA) is a small vessel necrotising vasculitis characterised by few or no immune deposits affecting vessel walls.[15] In contrast to other forms of small vessel vasculitis and in contrast to GCA, there is absence of granulomatous inflammation in MPA. Unlike GCA, MPA commonly involves the kidneys, which may be demonstrated on biopsy with a pauci-immune focal crescentic glomerulonephritis. Other organ involvement may include the lungs with alveolar haemorrhage and the peripheral nervous system with mononeuritis multiplex. Approximately 80%–90% of patients with MPA have a positive antinuclear cytoplasmic antibody (ANCA), most commonly with a perinuclear immunofluorescence pattern (p-ANCA).[16] The two most commonly occurring targets of ANCAs are myeloperoxidase (MPO) and proteinase-3 (PR3). Anti-MPO is most commonly associated with MPA, whereas anti-PR3

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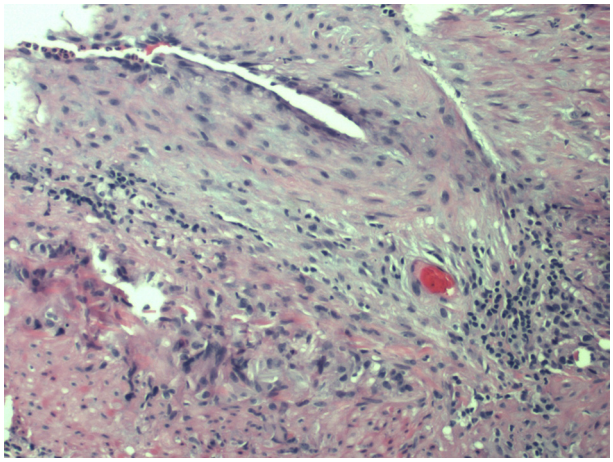

Figure 1 Temporal artery biopsy. Moderately intense chronic inflammation within the arterial wall along with a few multinucleated giant cells and destruction of the internal elastic membrane.

is largely associated with granulomatosis with polyangiitis. There are other autoantigens recognised by ANCAs that are seen with inflammatory bowel disease, drug-induced ANCA-associated disease and IgA vasculitis.[17]

Herein we describe a patient who developed biopsy-proven GCA and was treated successfully with tapering prednisone, who presented 4 years later with biopsy-proven renal-limited MPA. To our knowledge, the successive occurrence of these two different types of vasculitides has not previously been reported in the literature. Our case highlights the need for clinicians to consider this possibility and monitor patients accordingly, especially in the ageing population.

Case presentation

An 80-year-old Caucasian woman with a history of osteoporosis, atrial fibrillation and osteoarthritis presented with bilateral jaw claudication, with pain radiating to her neck and shoulders. The patient also reported new-onset headaches and intermittent bilateral scotomas and was originally diagnosed with ocular migraines by an ophthalmologist. She denied any proximal muscle weakness or pain, fatigue, joint pain, fever, chills or weight loss. On physical exam, the patient exhibited tenderness of her temporomandibular joints bilaterally, but there was no scalp tenderness. Temporal artery pulses were +1 bilaterally. She had no visual deficits, proximal muscle tenderness, weakness or synovitis. ESR was 54 mm/hour and serum creatinine was 0.85 mg/dL. Urinalysis and ANCA were not obtained at the time. She was immediately started on prednisone 60 mg daily and subsequent bilateral temporal artery biopsies confirmed the diagnosis of GCA (figure 1). The patient was followed over the course of 4 years and her prednisone dose was gradually tapered down to 1 mg daily over this period, with complete resolution of symptoms. She was additionally treated with zoledronic acid for steroid-induced osteoporosis.

During the following year, the patient exhibited a gradual worsening of her renal function over the course of 4–5 months. Her baseline serum creatinine was 1.1 mg/dL, and this had progressively risen to 1.64 mg/dL. Urinalysis was significant for large haematuria and a urine protein-to-creatinine ratio of 1.63 mg/g creatinine. She was initially diagnosed with a urinary tract infection by her primary care physician. Ultimately, serologies were notable for the presence of p-ANCA at a titre of 1:320 and IgG antibodies to MPO by ELISA at a level of 328 AU/mL. Antinuclear antibodies (ANA), antibodies against glomerular basement membrane and hepatitis serologies were all negative. C3 and C4 complement levels were within normal limits. Shortly thereafter, the patient sustained a right intertrochanteric hip fracture following a fall and was found to have acute kidney injury (serum creatinine=3.47 mg/dL). Renal biopsy at that time demonstrated a pauci-immune focal crescentic glomerulonephritis (figure 2A & B). Extensive review of systems, physical exam and diagnostic studies revealed no evidence of extra-renal disease at the time, and the patient was diagnosed with renal-limited MPA.

Differential diagnosis

The differential diagnosis of progressively worsening renal function in an elderly patient is broad. Our patient presented with worsening renal function associated with haematuria and proteinuria, suggesting some form of glomerulonephritis. Serological testing is useful in establishing the aetiology of glomerulonephritis. Systemic lupus erythematosus (SLE) would be suspicious in the setting of a positive ANA, as well as a positive antibody to double-stranded (ds) DNA and low C3 and C4 complement levels. ANA and anti-dsDNA antibodies were negative in our patient, and complement levels were normal. Hepatitis B and C can induce membranous and

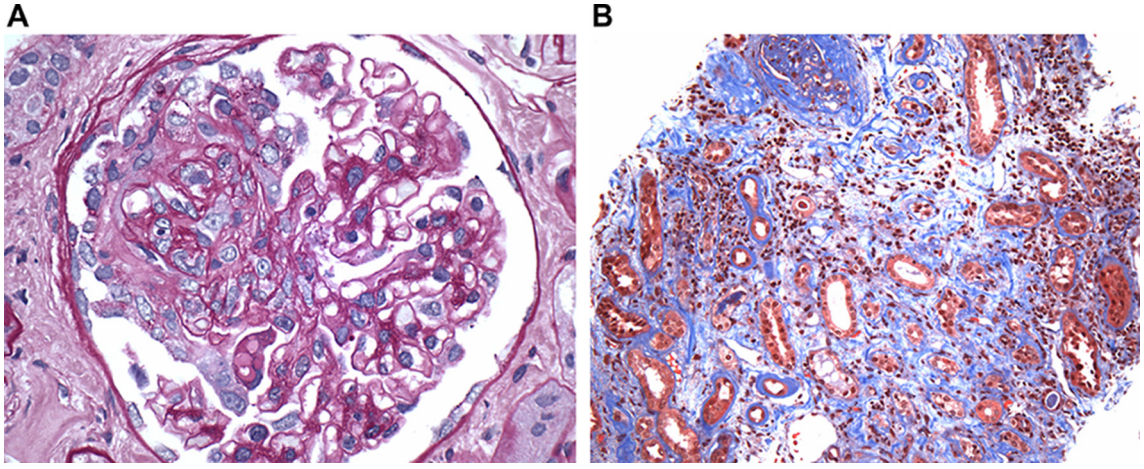

Figure 2 Renal biopsy. (A) Glomerulus with fibrocellular crescent, with macrophages and other inflammatory cells embedded in fibrin. (B) Moderate-to-severe interstitial fibrosis and tubular atrophy.

membranoproliferative glomerulonephritis; both viral hepatitis serologies were negative. Poststreptococcal glomerulonephritis (PSGN) and IgA nephropathy usually present following recent upper respiratory infection, with elevated antistreptococcal antibody titres found in PSGN. In our patient, the history was negative for any signs of antecedent infection. Goodpasture's syndrome may be diagnosed in the setting of positive antiglomerular basement membrane antibody, which was negative in our case. Our patient had a positive p-ANCA and antibodies to MPO, suggesting ANCA-associated glomerulonephritis. Nevertheless, renal histopathology provides essential information for establishing a diagnosis and assessing the activity and chronicity of disease.[18] Our patient had a pauci-immune focal crescentic glomerulonephritis on renal biopsy, which is consistent with ANCA-associated glomerulonephritis. There was no evidence of immune complex deposition that would be seen with SLE or IgA nephropathy or linear autoantibody deposition as seen with Goodpasture's syndrome. Granulomatosis with polyangiitis is also a consideration in the differential diagnosis, although the absence of upper or lower respiratory tract symptoms and the positive p-ANCA and MPO antibodies with an isolated pauci-immune glomerulonephritis make MPA a more probable diagnosis.

Treatment

The patient underwent intramedullary nail fixation for her hip fracture and was treated with pulse methylprednisolone 1000 mg daily for 3 days, followed by prednisone 60 mg daily. Despite extensive counselling, she refused definitive treatment for MPA with either cyclophosphamide or rituximab, due to concern for toxicity. Her prednisone dose was tapered down to 10 mg daily over the course of several months.

Outcome and follow-up

Her renal function stabilised (serum creatinine=1.82 mg/dL), however, moderate haematuria persisted. The patient remained on prednisone 10 mg daily and persistently refused any further pharmacological treatment.

DISCUSSION

Herein we describe a case of biopsy-proven GCA, subsequently followed by the independent development of renal-limited MPA. Although GCA predominantly affects the cranial arteries, other organs including the lung, abdominal viscera and skin may occasionally be involved, with findings in the kidneys being extremely rare.[19] For our patient, the critical question is whether there is a link between these two seemingly independent vasculitic processes that developed consecutively. There are several studies that describe ANCA positivity in patients with GCA, with certain reports postulating that it could be a marker of earlier relapse.[20] Several case reports describe the concomitant development of GCA and MPA, with MPA hypothesised to be the likely primary pathogenesis in most reports.[21–23] One case report showed concurrent development of biopsy-proven GCA and MPA induced following an influenza vaccination.[24] The possibility of a systemic necrotising vasculitis (SNV) localised to the temporal arteries at the time of GCA diagnosis also needs to be carefully considered. Biopsy specimens of patients diagnosed with SNV show fibrinoid necrosis and polymorphonuclear leucocyte infiltrates. The absence of these histological findings in our patient makes the diagnosis of SNV less likely, but it cannot entirely be excluded since patients with SNV may also present with findings consistent with GCA on temporal artery biopsy.[25] Inflammation of the vasa vasorum of the temporal arteries as well as small arteries surrounding a normal temporal artery has been linked to several conditions.[26] It is plausible that the rapid initiation of glucocorticoid therapy may have masked the development of a systemic vasculitic process at the time of the initial diagnosis. Various authors have shown that the correct diagnosis at the onset of symptoms is critical to therapy selection and eventual outcomes.[27 28] However, our patient had no other obvious signs or symptoms to suggest a small vessel SNV at the time of her diagnosis of GCA.

Approximately 4 years elapsed between the development of GCA and renal-limited MPA in our patient, which is more likely indicative of two independent pathophysiological processes. In GCA, dendritic cells (DCs) located in the arterial adventitia of affected vessels are initially activated by an unknown antigen. Activated DCs are responsible for initiation of inflammatory cascade, which involves recruitment of CD4 T cells and macrophages. The inflammatory cells produce an array of cytokines subdivided into two well-recognised groups, IL-6/IL-17 and IL-12/IFN-γ.[29] It is hypothesised that in MPA an exposure to exogenous antigens is the initial stimulating factor responsible for development of pathogenic ANCAs.[17] Healthy individuals have circulating 'natural' antibodies against MPO and PR3.[30] ANCA-activated neutrophils release factors that activate the alternative complement pathway. Subsequently, an inflammatory amplification loop is created, which further causes attraction and priming of neutrophils. The neutrophils then continue to stimulate complement activation.[17]

Given that the pathogenic mechanisms for these two vasculitides are notably different, we postulate that one underlying process is unlikely to be responsible for both. Especially as the population ages, the general practitioner and specialist need to be aware of the possibility of two consecutive vasculitides occurring in the same patient. New clinical manifestations in patients with vasculitis or other autoimmune disease should prompt a careful review to identify other pathologies, and not simply be attributed to the underlying primary condition. This case reiterates the importance of close long-term monitoring of vasculitis patients for recurrence of disease, side effects of immunosuppressive therapy and for the occurrence of independent vasculitic or other autoimmune disease processes. To our knowledge, we report the first case describing the consecutive, independent development of MPA following successful treatment for GCA in an individual patient.

Due to the patient's significant concern for drug toxicity, she adamantly refused treatment with cyclophosphamide or rituximab, which are current standard-of-care medications for moderate-to-severe MPA. She therefore only received prednisone with a fairly rapid taper. Fortunately, the patient's renal function stabilised, but dysmorphic haematuria persisted. Studies comparing steroids used alone versus steroids with cyclophosphamide have shown that steroids alone are clearly inferior for inducing remission and preventing relapse.[31]

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Contributors RZ conceptualized and drafted the manuscript and assisted with the management of the patient. MP conceptualized and edited the manuscript and provided important inputs on the patient's renal disease. He also managed the patient. DRA conceptualized and assisted with drafting and editing the manuscript and also managed the patient.

Competing interests None declared.

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Learning points

- Giant cell arteritis and microscopic polyangiitis are distinct types of vasculitis with different pathogenic mechanisms, but may occur simultaneously or consecutively in a single patient.
- In an ageing population, it is important for the clinician to be aware that a patient may develop two independent types of vasculitis during his or her lifetime.
- New clinical manifestations in patients with vasculitis or other autoimmune disease should prompt a careful review to identify other pathologies and not simply be attributed to the underlying primary condition.
- Close long-term clinical follow-up of vasculitis patients is warranted for recurrence of disease, side effects of immunosuppressive therapy, and for the possible occurrence of independent vasculitic or other autoimmune disease processes.

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