CASE REPORT

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A rare cause of crescentic glomerulonephritis

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ABSTRACT

Crescentic necrotising glomerulonephritis is a morphologic manifestation of severe glomerular injury, usually associated with poor outcome. It can be caused by different aetiologies, and rare causes should always be considered as part of the differential diagnosis. We present a case report of a 57-year-old woman with constitutional symptoms, auricular perichondritis, anaemia and rapidly progressive renal dysfunction. Kidney biopsy revealed a pauci-immune crescentic necrotising glomerulonephritis with undetectable ANCA in the serum. Treatment with corticosteroids and intravenous cyclophosphamide for one year led to resolution of the cartilaginous involvement and improvement and stabilisation of the renal function. She spent ten years symptom-free and with normal progression of chronic kidney disease before suddenly developing fever, malaise, worsening renal function and shortness of breath with stridor. Laryngotracheobronchial inflammation was detected, and she was treated with intravenous high dose corticosteroids with resolution of respiratory complaints. Her renal function, however, did not improve and progressed to end-stage kidney disease in a few months.

This is a case of relapsing polychondritis with systemic vasculitis and renal involvement. This is a rare inflammatory multisystemic condition with chronic relapsing features mainly affecting cartilaginous structures. A brief revision of the disease is provided by the authors.

Key Words:
Crescentic pauci-immune glomerulonephritis; relapsing polychondritis; systemic vasculitis.

INTRODUCTION

Crescentic necrotising glomerulonephritis is a morphologic manifestation of severe glomerular injury that can be caused by different aetiologies and pathogenic mechanisms. It is usually associated with poor outcome. It is most commonly caused by small vessel vasculitis, characterised by an absence or paucity of staining for immunoglobulin (*i.e.* pauci-immune). It can occur as a renal limited process or as a component of systemic small vessel vasculitis, classically Wegener granulomatosis, microscopic polyangiitis or Churg-Strauss syndrome. However, one has to bear in mind that some patients have this type of kidney damage in association with less common diseases, such as the case presented below.

CASE REPORT

We present a case of a 57-year-old Caucasian woman who presented at the emergency room (ER) with pain, swelling and erythema in her left auricle. She had noticed these changes the previous week, but also complained of occasional low-grade fever, malaise and weight loss in the three months preceding. Her past medical history was unremarkable except for episodic arthralgias without joint swelling, which resolved spontaneously. At the ER, she had a normal physical examination, except for pale skin and the presence of inflammatory signs on the left auricle with cartilaginous deformation, interpreted as auricular perichondritis.

Her initial work-up revealed a normochromic, normocytic anaemia (haemoglobin 9.2g/dL), impaired renal

function (serum creatinine 2.2mg/dL, with previously normal values, 3 months earlier) with microscopic haematuria and elevated C-reactive protein (CRP 5.7mg/dL) and erythrocyte sedimentation rate (ESR 113mm/h). Her chest X-ray and renal ultrasound showed no abnormalities. She was then admitted to the nephrology ward for further investigation. Levels of complement components (C3, C4), and immunoglobulins (IgA, IgG, IgM) were normal, and no monoclonal component was found in the serum protein electrophoresis. Antinuclear antibodies (ANA) titer was 1/80. Autoantibodies studied (anti-dsDNA, anti-Sm, anti-nRNP, anti-SSA, anti-SSB, ANCA, anti-glomerular basement membrane) and rheumatoid factor were negative. The viral serology (HBV, HCV, HIV) was negative. Serum creatinine kept rising, reaching a maximum of 2.9mg/dL. She underwent a renal biopsy, which showed 7 out of 11 glomeruli with fibrinoid necrosis and fibrocellular crescents, 2 globally sclerosed and 2 with no lesions on light microscopy (Fig. 1). A chronic interstitial inflammatory infiltrate without granulomas and significant interstitial fibrosis was also present (Fig. 2). No immune deposits were identified in the immunofluorescence. She began treatment with cyclophosphamide intravenous (I.V.) pulses (500mg/month) and methylprednisolone I.V. pulses (1000mg/day for three days), followed by oral prednisolone (60mg/day).

Meanwhile, full bone X-ray survey showed no bone lesions, but a moderate uptake of Technetium-99m methylene diphosphonate was seen in the left auricle, nose, left knee and left ankle joints when a bone scintigraphy was performed. These changes were suggestive of an inflammatory osteoarticular process, which, along with the perichondritis in the left auricle and the pauci-immune crescentic necrotising glomerulonephritis prompted a clinical diagnosis of polychondritis featuring systemic vasculitis.

The signs of auricular perichondritis rapidly improved after the corticosteroids I.V. pulses. Renal function stabilised but did not fully recover (serum creatinine 1.6mg/dL), which was consistent with the chronic changes seen in the renal biopsy. She maintained treatment with oral prednisolone (60mg/day during the first month, tapered down to 20mg/day by the end of the third month, and slower taper afterwards) and cyclophosphamide I.V. pulses (500mg/month for six months, and then additional pulses each three months until completing one year of therapy). By that time, she was only on low-dose prednisolone (5mg/day). During this first year of therapy, she attained complete remission of the cartilaginous involvement and showed no progression of kidney disease. At this time, she had an estimated glomerular filtration rate (eGFR – MDRD formula) of 36ml/min/1.73m^2, and no active urinary sediment. She had, however, some complications related to the immunosuppression, namely some mild

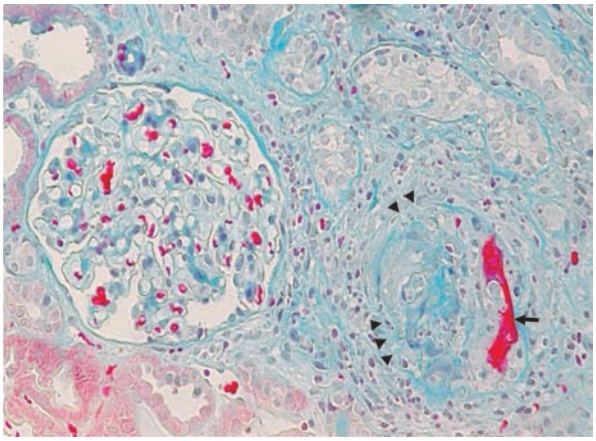


Figure 1

Renal biopsy showing two glomeruli. The one on the left has no apparent lesions on light microscopy. The other, on the right, shows a large fibrous-cellular crescent, with an irregular focus of fibrinoid necrosis (arrow) and Bowman's capsule disruption (arrowheads). Chromotrope Aniline Blue Trichrome ×400.

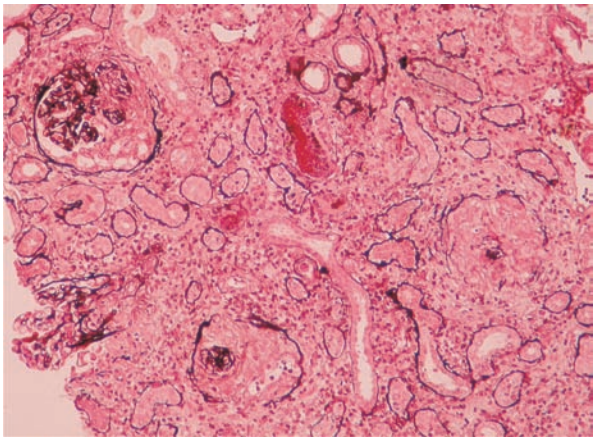


Figure 2

Renal biopsy showing three glomeruli with fibrous-cellular crescents, with almost complete destruction of the glomerular tuft in two of them and disruption of Bowman's capsule. Note the significant interstitial enlargement, with inflammatory infiltrate and fibro-oedema. (Silver ×200)

to moderate urinary and respiratory tract infections. She complained of the cosmetic changes induced by the corticosteroid therapy and moderate to severe osteopaenia was diagnosed. For these reasons, prednisolone was tapered-off, successfully.

She remained symptom-free for ten years after stopping the medications. Her renal function slowly declined, to an eGFR of 20ml/min/1.73m^2. Suddenly, the patient developed fatigue, anorexia and asthenia, followed by cough, shortness of breath and bloody sputum. Her physical examination was remarkable for skin pallor and mild to moderate respiratory distress, with inspiratory stridor and bilateral expiratory wheezing. Blood analysis confirmed normochromic, normocytic anaemia (haemoglobin 8.0g/dL), worsening renal function (serum creatinine 5.6mg/dL), haematuria and elevated CRP and ESR (2.0mg/dL and 120mm/h). Chest X-ray showed bilateral prominent pulmonary vascularisation. Upper airway evaluation disclosed inflammation with mild narrowing of the lumen, consistent with a polychondritis relapse with laryngotracheobronchial involvement.

She was treated with methylprednisolone I.V. pulses (1000mg/day for three days) followed by oral prednisolone (60mg/day) with improvement of the respiratory symptoms. Her renal function, however, did not recover. About 1 month postdischarge from the hospital she had an eGFR of 9ml/min/1.73m^2. She had a radio-cephalic arteriovenous fistula done in her left forearm, and three months later, she started haemodialysis for uraemic symptoms. The corticosteroid dose was tapered down to 5 mg/day, which she maintains. The dialysis treatments are event-free and she is asymptomatic in terms of extra-renal manifestations. Her haemoglobin levels are within the 10-12g/dL interval, with an erythropoiesis stimulating agent and CRP and ESR are normal.

DISCUSSION

Relapsing polychondritis is a severe, episodic and progressive inflammatory condition involving cartilaginous structures, predominantly those of the ears, nose and laryngotracheobronchial tree, described many years ago[1].

The aetiology of the disease is unknown, but it is recognised that autoimmune processes are implicated in the pathogenesis. This is supported by the evidence of both antibody and cell-mediated autoimmune mechanisms directed to extracellular matrix components of cartilage[2], and a high prevalence (up to 35%) of other autoimmune disorders found in patients with relapsing polychondritis, namely systemic vasculitis[3].

The reported incidence of the disease is 3.5 cases per million population, affecting mostly Caucasians and females. It usually becomes clinically apparent during the fifth decade of life[3,4].

The hallmark of relapsing polychondritis is the episodic inflammation and destruction of cartilaginous structures. However, some patients do not show the characteristic paroxystic course, instead having an indolent, relatively benign disease or, on the other hand, a fulminant downhill course resulting in death. The most common presentation (50% of the patients) is external ear inflammation. Other characteristic cartilaginous sites involved are the nose, large airways (including life-threatening laryngotracheobronchial disease), parasternal and peripheral joints. The disease can also affect other tissues and organs, namely the inner ear, the eye, heart valves and vessels, central nervous system, skin and the kidneys. This variability in presenting symptoms and course of the disease can significantly delay the diagnosis[4,5].

There is no specific test for relapsing polychondritis. The diagnosis is established with the combination of clinical findings, supportive laboratory data, imaging procedures, and eventually a biopsy of an affected cartilaginous site. Laboratory studies will often reveal an elevation of acute phase reactants, anaemia and measurable titres of some autoantibodies (ANCA may be present, especially in those with vasculitis). Biopsy of a typical lesion shows a mixed inflammatory infiltrate in the perichondrium and eventually fibrosis replacing the degenerated cartilage[6].

Renal involvement in relapsing polychondritis is best documented in reference 7. Chang-Miller *et al.*[7] summarised a variety of case reports showing renal involvement, typically in the form of a segmental necrotising glomerulonephritis, with a rapidly progressive course and crescent formation in some. They estimated an incidence of renal involvement of 22%.

Pathological biopsy findings included mild mesangial matrix expansion and cell proliferation, segmental necrotising glomerulonephritis with or without crescents, interstitial lymphocytic infiltrates, interstitial fibrosis, active tubulitis, and glomerulosclerosis. Renal disease was more common in older patients and in patients with arthritis or evidence of systemic vasculitis. The response to treatment varied from stabilisation of renal function to renal failure[7].

Treatment is based in case series and case reports experience. The goal of therapy is to control clinical apparent activity. Mild disease can be controlled with nonsteroidal anti-inflammatory drugs, dapsone or oral corticosteroids. Whenever there is evidence (even at subclinical level) of visceral involvement, a more potent immunosupression regimen is advocated. Given the data available, the choice of the second-line agent is largely empiric. The most used drugs are cyclophosphamide (oral dose of 1-2mg/kg/day or monthly I.V. pulses), azathioprine (2mg/kg/day), ciclosporin (5mg/kg/day), I.V. pulse methylprednisolone (1g/day for three consecutive days) or methotrexate (5-25mg per week). Other treatments have been used, with efficacy reported only in individual case reports. There are no guidelines indicating how long therapy should be maintained. An acceptable approach should be to maintain treatment at least for three months after clinical control of the disease[3,8].

A recent series reported a 94% survival rate at 8 years. The major causes of death related to the disease include infection (secondary to immunosuppression), respiratory failure following airway disease and vasculitis. Valvular heart disease with heart failure, renal disease and anaemia were identified as adverse prognostic features[3,4].

The case presented represents a typical case of relapsing polychondritis with renal involvement. In the differential diagnosis of the necrotising glomerulonephritis, the presence of glomerular lesions with various ages, together with the absence of immune deposits ruled out immune-complex-associated diseases or anti-glomerular membrane antibodies disease. The absence of ANCA in this patient helped in the differential diagnosis with ANCA-positive small vessels vasculitis, namely Wegener's granulomatosis, given the number of clinical features that both diseases can share and the lack of specificity of ANCA. In this case the evolution of the renal disease towards renal failure was consistent with the presence of poor prognostic features at baseline (particularly low GFR at the time of diagnosis and significant interstitial fibrosis).

The case illustrates the evolution of the disease associated with poor prognostic features (renal and respiratory disease and immunosuppression-related complications), as well as the relapsing feature of this condition, with a long period of time with symptoms. This characteristic poses a difficulty in the management of the disease, regarding the need for maintenance therapy. There is no data supporting long-term immunosuppression, but as in this case, the preemptive treatment strategy may lead to significant organ damage before treatment is initiated.

Relapsing polychondritis is an uncommon disease, occasionally associated with systemic vasculitis features that can affect the kidneys. The knowledge of its key manifestations and clinical course is critical for establishing a timely diagnosis and address end-organ complications properly and without delay.

Conflict of interest statement. None declared.

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