

Case Report

Fulminant primary manifestations of Wegener's granulomatosis might not be pauci-immune

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Abstract

Wegener's granulomatosis is an ANCA-associated small vessel vasculitis. Because histologically immune complex deposits are frequently lacking, the term pauci-immune has been introduced for this subgroup. We report a patient with fulminant, severe PR3-ANCA-positive Wegener's granulomatosis and multi-organ involvement (upper respiratory tract, lung, kidneys, skin and general symptoms), who showed pronounced immunoglobulin and complement deposits within the skin biopsy. Our observation supports the hypothesis that immune complex deposits may be under-recognized in early lesions of ANCA-associated Wegener's granulomatosis.

Keywords: ANCA; pauci-immune; vasculitis; Wegener's granulomatosis

Introduction

Wegener's granulomatosis (WG) is a primary systemic vasculitis affecting small-sized blood vessels and capillaries. It is typically characterized by granulomatous inflammation of the upper and lower respiratory tract and necrotizing vasculitis in multiple organs, in particular the kidneys. The disease is highly associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA) directed against proteinase 3 (PR3) or myeloperoxidase (MPO) [1]. Cutaneous manifestations occur in up to 40–50% of WG patients. Skin findings include palpable and non-palpable purpura, papules, subcutaneous nodules, ulcers, digital necrosis, splinter haemorrhages, and vesiculobullous lesions [2,3].

WG is generally considered a pauci-immune systemic vasculitis indicating the low incidence of overt immunoglobulin and complement deposits demonstrated by direct immunofluorescence techniques [1,3,4], although low amounts of immunoglobulins or complement are often found in the affected tissues [1,5,6]. Here, we present a patient with fulminant, severe WG with high amounts of cutaneous immune deposits, supporting the hypothesis that im-

mune complex depositions are involved in the pathogenesis of WG.

Case report

A 39-year-old man was referred to the intensive care unit with acute respiratory distress syndrome and renal failure, requiring catecholamine therapy, extracorporeal membrane oxygenation, and continuous renal replacement therapy. His condition had developed after a vacation in Turkey and deteriorated quickly within 2 weeks. Pathological laboratory parameters on admission included serum creatinine (17.9 mg/dL), CRP (17.7 mg/dL) and haemoglobin (7.7 g/dL). The differential diagnosis at admission to our hospital included viral, bacterial and fungal infection, and the patient was initially treated with broad-spectrum antibiotics and antiviral therapy. However, despite an extensive search, no relevant infection could be detected at time of admission. A working hypothesis of fulminant WG was made on clinical grounds, which was rapidly confirmed by demonstration of elevated c-ANCA (titre 1:128) with specificity for PR3 (429 U/mL, normal value <15). Antinuclear antibodies, complement factor C3 and C4, and anti-GBM antibodies were within normal limits. The diagnosis of severe WG with involvement of the upper respiratory tract, lung, kidney and skin prompted the initiation of immunosuppressive therapy with methylprednisolone and low-dose daily cyclophosphamide. We refrained from taking a kidney or lung biopsy because of the patient's poor condition.

Skin findings at time of admission included a moderate manifestation of purpura (Figure 1A). Histological examination of a skin biopsy from the lower leg revealed an older stage of leucocytoclastic vasculitis of small vessel walls with fibrinoid necrosis, perivascular neutrophilic infiltration, and extravasation of red blood cells together with discrete leucocytoclasia. Direct immunofluorescence showed intense staining for IgM and C3, and lesser amounts of IgG and IgA lining both the small and large cutaneous vessels (Figure 1B).

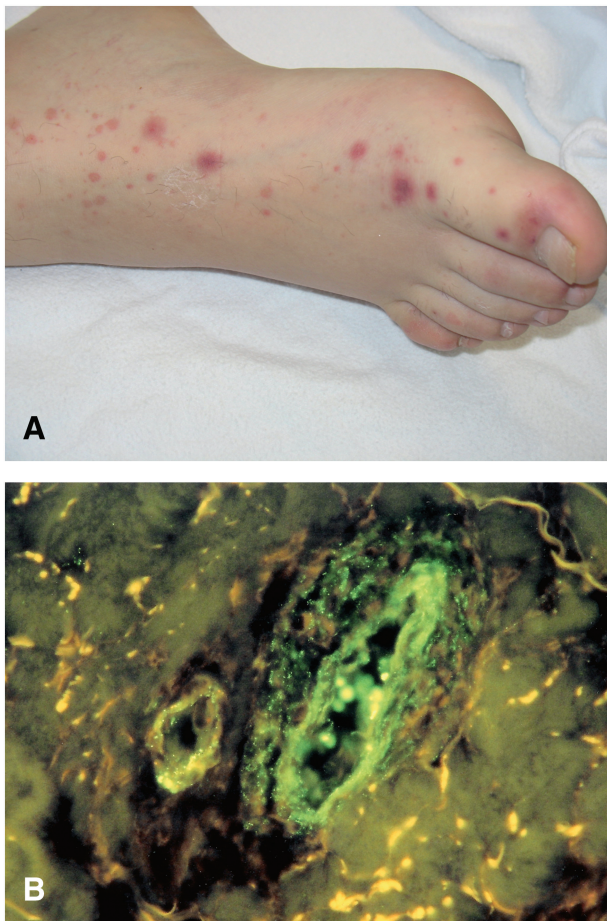


Fig. 1. (A) Clinical presentation of our patient's right foot with multiple skin lesions of WG, as present on admission to hospital. (B) Immunohistology of the skin biopsy from the lesions depicted in A: very intense IgM fluorescence (score 4, fluorescein isothiocyanate staining) in a dermal vessel wall and moderate granular perivascular deposits in the reticular dermis (original magnification $\times 400$). The intensity of the immunofluorescence staining was evaluated by a semi-quantitative scoring scale from 0 to 4 (0 = no staining; 1 = weak staining; 2 = moderate staining; 3 = intense staining; 4 = very intense staining). Vascular deposits were also scored for IgA (2), IgG (3), IgE (0), complement C3 (4), C4 (2) and fibrinogen (3).

Initially, the patient showed good response to the immunosuppressive treatment. PR3-ANCA titres decreased and were within normal limits after 7 weeks. However, the patient developed multiple complications including heparin-induced thrombocytopenia, bleeding, infections and hepatic failure. He died 4 months after initial presentation due not to active vasculitis, but to multi-organ failure.

Recently, we reported another case of PR3-ANCA-associated WG [7], sharing many similarities with the actual case. Both were young males with fulminant primary manifestation and multi-organ involvement. Kidney biopsy in the previously reported case revealed focal and segmental crescentic glomerulonephritis with scarce deposits of IgM but lacked deposition of IgG, IgA and C3. However, skin biopsies showed in both cases leucocytoclastic vasculitis of small- and medium-sized dermal vessels with fibrinoid vessel wall necrosis, extravasated red cells and a neutrophilic infiltrate with nuclear dust, as well as strong IgM and C3 deposits.

Discussion

WG is commonly described as pauci-immune vasculitis. Using direct immunofluorescence, significant amounts of immune deposits are usually absent, but small amounts of deposits, mostly IgM and complement, are often present in kidney biopsies [1,4–6]. Only a few small-sized studies have investigated the presence of immune deposits in skin biopsies, demonstrating that immune deposits may be present in fresh cutaneous while absent in renal lesions [8].

The pathogenesis of WG is multifactorial. Clinical and experimental data suggest a direct role for ANCA, although this is more evident for MPO-ANCA than for PR3-ANCA [1,4]. In an experimental animal model, a transient immune complex deposition could be detected at an early stage of ANCA-associated glomerulonephritis [9]. Recent studies also support the pathogenic role of complement activation [10]. Immune complex deposits could sustain and amplify neutrophil recruitment and activation, which in turn degrade immune complexes within a short time and result in the development of necrotizing vascular injury [4]. These experimental data suggest the involvement of immune complexes in the initial phase of the disease.

The presence and detection of immune complex deposits might be time-dependent. High amounts of immune complex deposits will be most likely present in newly developed skin lesions, which are usually taken for biopsy. Furthermore, cutaneous manifestation in WG occurs most likely in patients with multiple organ involvement, and the presence of leucocytoclastic vasculitis is often associated with a rapidly progressive course [2,3]. The discrepancy that immune deposits may be present in cutaneous but absent in renal lesions could be the result of differences either in the development of lesions over time or in the degradation of immune complexes within the cutaneous and renal microenvironment.

In conclusion, we present further clinical evidence supporting the hypothesis that immune depositions are involved in the pathogenesis of ANCA-associated WG. Biopsies taken from fulminant WG lesions, and in particular skin biopsies, may show pronounced immunoglobulin and complement deposition, despite the common classification of WG as pauci-immune vasculitis. This fact is clinically important, as misinterpretation of immune deposits may confuse or delay proper diagnosis of WG. Our findings emphasize the importance of time course considerations in interpretation and classification of ANCA-associated vasculitis.

Conflict of interest statement. None declared.

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