Pyoderma gangrenosum associated with Wegener’s granulomatosis: partial response to mycophenolate mofetil

Sir, We report the history of a 41-yr-old Caucasian male with systemic Wegener’s granulomatosis (WG) associated with pyoderma gangrenosum (PG). Despite attenuation of clinical manifestations of WG, PG did not respond to several immunosuppressants and immunomodulating agents but regressed rapidly, albeit incompletely, under treatment with corticosteroids (CS) and mycophenolate mofetil (MMF).

Since December 1991, this man had suffered from histologically proven WG initially characterized by sinusitis and pulmonary nodules. Antineutrophil cytoplasm antibodies with a cytoplasmic labelling pattern (c-ANCA) were found and enzyme-linked immunosorbent assay (ELISA) detected anti-proteinase 3 (PR3) antibodies. Combining CS with 18 pulses of cyclophosphamide (CYC; cumulative dose 27 g) led to remission. The c-ANCA disappeared. In October 1995, he suffered a relapse characterized by pleuropericarditis, pulmonary nodules, slow atrial flutter, first-degree atrioventricular block, sinusitis and sciatalgia; he was weakly positive for c-ANCA. Combined CS and CYC therapy was reinitiated. CYC (cumulative dose, 18 g) again led to remission but was stopped because of haemorrhagic cystitis. CS were stopped during the summer of 1997. ANCA were undetectable and anti-PR3 were positive by ELISA [60 arbitrary units (AU), threshold for positivity >20 AU]. In September 1997, the patient presented headaches, crusted rhinitis, atrial flutter with complete heart block, interatrial septum nodules and pulmonary hypertension due to compression of pulmonary arteries. He again became weakly positive for c-ANCA and the anti-PR3 level rose (to 73 AU). A dramatic response was obtained under CS (three pulses of 15 mg/kg/day and then 1 mg/kg/day orally) in combination with intravenous immunoglobulins (IV Ig; 2 g/kg every 3 weeks for 8 months). In November 1997, a computed tomography (CT) scan of the chest showed regression of pulmonary and mediastinal abnormalities, and echocardiography showed regression of interatrial septum nodules; tapering of the CS dose was begun. One month later, numerous acneiform papular and pustular lesions of the trunk appeared (CS 0.95 mg/kg/day). They spread and evolved into PG—ulcers with clear-cut margins, deep, irregular, violaceous borders and a necrotic centre and showing chronic discharge. These multiple, painful, deep necrotic ulcers (1–3 cm in diameter) covered the trunk and neck (Fig. 1). Microbiological tests performed on histological sections showed no microorganisms, a finding confirmed by negative cultures. A skin biopsy showed an inflammatory suppurative dermal infiltrate harbouring neutrophils, lymphocytes and histiocytes. IV Ig were continued and CS tapered to 0.4 mg/kg/day. In February 1998, the skin area affected by PG decreased under treatment with IV Ig and CS (0.25 mg/kg/day). CS were further tapered (0.2 mg/kg/day). ANCA and anti-PR3 were no longer detectable. Sinusitis with periorbital oedema recurred in March 1998. A skin biopsy from the border of an ulcer showed intense inflammation of the superficial dermis with multinucleated macrophage-like cells. IV Ig was replaced with azathioprine (2 mg/kg/day) in May 1998. Five months later, skin lesions had regressed partially. Azathioprine was increased to 2.5 mg/kg/day but to no avail. Pulmonary nodules,
crusted rhinitis and right-sided deafness occurred in April 1999. c-ANCA were detected by immuno-fluorescence and anti-PR3 by ELISA (66 AU). Azathioprine was stopped, MMF (2 g/day orally) was started and the CS dose was increased to 1 mg/kg/day. For the first time, the PG regressed dramatically; complete healing was obtained within 3 weeks but proved transitory. CS were rapidly tapered (0.5 mg/kg/day at the end of April). No new lesions appeared over the next 2 months but, when CS reached 0.1 mg/kg/day at the end of June, small zones of PG reappeared on the left shoulder. This relapse was controlled by increasing prednisone to 0.15 mg/kg/day and MMF to 3 g/day. No side-effects of MMF were noted. WG was then in remission, with only minor zones of PG on the left shoulder; c-ANCA and anti-PR3 levels were also stable.

Although skin involvement has been observed in 14–47% of patients with WG [1–4], pyoderma-like ulcers or necrotizing ulcerations resembling PG are rare manifestations [5–8]. Cutaneous involvement may occur during the course of the disease or be present at onset [5–7] and may develop on unusual sites, e.g. the trunk [8], neck [5] and face [6], and may indicate an exacerbation of existing WG. Our case is unusual because cutaneous lesions became the predominant symptom, surpassing sinusitis and pulmonary signs at the time of the second relapse, and because of their persistence and spread despite appropriate treatment, including CS, IV Ig and azathioprine. Nowack et al. [9] were the first to report the successful use of MMF, as maintenance therapy after standard induction therapy, in 10 systemic WG patients, of whom four showed skin involvement. They also successfully prescribed MMF as induction treatment to replace CYC in a WG patient [9]. We used MMF because of its strong immunosuppressive effect and lymphocyte-selective mode of action and because it has few side-effects. As illustrated here, alternative treatments to high-dose CS combined with CYC, azathioprine or high-dose IV Ig and/or new drugs should be attempted in the therapeutic strategy of refractory ANCA-related vasculitides.

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