

Chronic Unilateral Facial Ulcer Revealing Wegener's Granulomatosis in a Patient with Rheumatoid Arthritis

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Wegener's granulomatosis (WG) is an autoimmune multisystem small-vessel vasculitis (1). The incidence of cutaneous manifestations of WG (nodules, ulcers, purpura, petechiae, haemorrhagic pustules, erythematous papules and plaques) was reported to range from 28 to 64% (2, 3). We report here the case of a 66-year-old man who presented with chronic unilateral facial ulcer and was proven to have biopsy-confirmed WG. It is noteworthy that the patient had pre-existing rheumatoid arthritis (RA), cutaneous candidiasis and onychomycosis.

CASE REPORT

A 66-year-old Chinese man presented with an 8-month history of non-painful ulcer on the left face. He had a 10-year history of arthritis of the extremities, resulting in symmetrical deformities of multiple small joints of the hands and feet. He was diagnosed with RA by typical clinical manifestations, elevated serum rheumatoid factor (RF) and typical X-ray findings in the department of rheumatology 6 years ago. He had intermittently administered low-dose prednisone since then. A productive cough with bloody sputa developed 2 years before presentation. He had a 30-year history of cigarette smoking. He had no history of tuberculosis or tuberculosis exposure. A purified protein-derivative skin test was negative.

Physical examination revealed a 7 × 9 × 11.5 cm deltoid-shaped sharply margined ulcer on his left face, with erythematous elevated borders, puruloid exudates, bloody crusts and irregular shaped hypertrophic scars in the centre (Fig. 1A). White patches were observed involving the proximal regions of 4 toenails (Fig. S1H; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1405>). Bilateral hallux valgus and stacking of the second and third toes on top of the great toe were also seen (Fig. S1H).

Laboratory tests showed a total white blood cell (WBC) count of $20.45 \times 10^9/l$ (3.97–9.15), leukocytosis (88.1%), elevated platelet $579 \times 10^9/l$ (85–303), and reduced haemoglobin 89 g/l (131–172). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF and anti-streptolysin O (ASO) were 84 mm/h, 140 mg/dl (0–8), 2470 IU/ml (0–30) and 649 IU/ml (0–116), respectively. Serum γ globulin was 31.4% (11.6–24.4). Serological tests for cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) and perinuclear ANCA were negative. Serum antibodies against HIV and syphilis were negative. Serum 1,3- β -D-glucan was negative.

Direct smears of thrush, sputum and pus in the ulcer showed spores and pseudohyphae, and cultures revealed *Candida albicans*. Deep scrapings of the white patches of the toenails and potassium hydroxide preparation of the materials showed numerous hyphae. Cultures on Sabouraud glucose agar revealed colonies of *Trichophyton rubrum*. Gram stains, bacterial cultures, acid-fast bacilli smears and mycobacterial cultures of pus and sputum were negative.

The biopsy specimen of the border of the ulcer showed necrosis with a dense infiltrate of mixed inflammatory cells composed

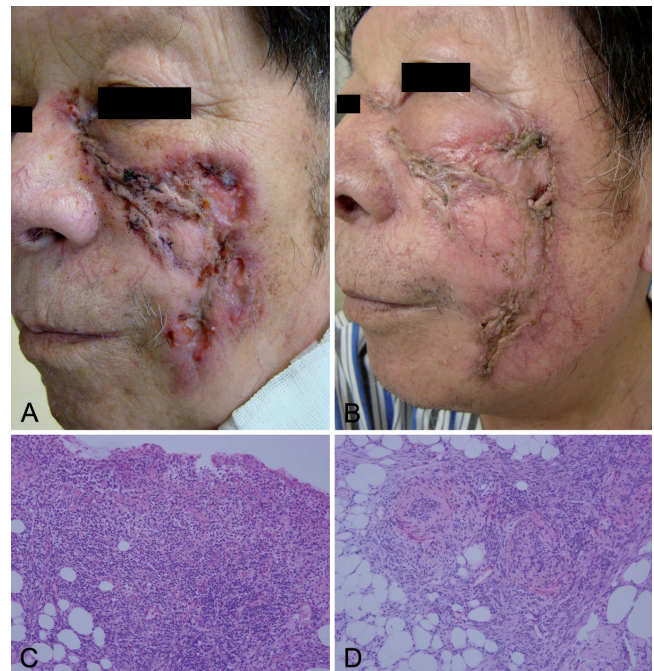


Fig. 1. (A) A sharply margined ulcer on the left side of the face, with erythematous elevated borders, puruloid exudates, bloody crusts and hypertrophic scars in the centre. (B) The ulcer healed after 3 months' treatment. (C, D) Histopathology revealed necrosis, granulomatous inflammation and vasculitis of small and medium-sized vessels in subcutaneous tissue (haematoxylin and eosin staining, original magnification $\times 200$).

mainly of neutrophils, as well as lymphocytes, plasma cells, histiocytes and multinucleated giant cells in dermis and subcutaneous tissue, revealing granulomatous inflammation and vasculitis of small and medium-sized vessels in subcutaneous tissue (Fig. 1C, D). Periodic acid-Schiff (PAS) stain was negative. Bone marrow smear and biopsy showed WBC left shift and thrombocytosis.

Spirometry showed a forced vital capacity (FVC) of 3.14 l (84% predicted), and forced expiratory volume (FEV)₁ of 2.02 l (69% predicted), and an FEV₁/FVC of 0.64. Computed tomography (CT) scan showed chronic rhinosinusitis of the left side (Fig. S1G; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1405>), multiple bilateral nodules in both lung fields (Fig. S1E; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1405>).

The patient refused transthoracic fine-needle aspiration biopsy. WG, mucocutaneous *C. albicans* infection and proximal white subungual onychomycosis were diagnosed. Intravenous fluconazole 200 mg daily was given for 3 weeks. Thrush cleared within 3 days. Direct smears and fungal cultures of pus and sputum were negative. CRP decreased to 65.4 mg/dl. ESR, RF, ASO, pulmonary function tests and CT scan showed no improvement. Intravenous immunoglobulin 400 mg/kg was administered for 5 days. Oral cyclophosphamide 2 mg/kg daily and oral methylprednisolone 48 mg daily were administered.

Three months later, the ulcer healed with hypertrophic scars (Fig. 1B). WBC, haemoglobin, platelet, ESR, CRP, RF and ASO were all normal. Four months later, CT scan showed significant improvement (Fig. S1F; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1405>). Now he had been in remission for 1 year under regular follow-up and at a maintenance dose of prednisone 5 mg daily and cyclophosphamide 2 mg/kg daily.

DISCUSSION

To our knowledge, this is the first description of WG with facial ulcer as the presenting sign in a RA patient. Ulcerative lesions of WG are rare on the face and most commonly involve the ear, nose and throat (4). The present case is a limited form of WG without kidney involvement and pulmonary WG was suspected only after the diagnosis of cutaneous WG was made. Skin lesions may lead to an initial diagnosis of WG in 8.6–13% of patients (5). They typically include necrosis, granulomatous changes, and vasculitis. However, head and neck biopsies most often reveal findings compatible with, but rarely characteristic of, WG. A complete diagnostic triad is seen in only 3–16% of biopsy specimens (6). Positive ANCA is of diagnostic value, but in limited WG, 30% or more lack ANCA.

RA has been rarely reported to be associated with WG (7–9). In the present case, the long-standing disease duration and the characteristic symmetrical deformities of multiple small joints of the extremities confirmed the coexistence of RA and excluded the possibility of prodromal symptoms for WG from long-lasting polyarthralgia and elevated RF.

Rheumatoid vasculitis (RV) is a major differential diagnosis. RV usually occurs in seropositive RA patients with long-standing disease (10). Factors associated with the development of RV include male gender, high titers of RF, joint erosions, rheumatoid nodules, the number of disease-modifying drugs used (especially D-penicillamine or azathioprine), and current treatment with glucocorticoids. Cutaneous manifestations, seen in 75–89% of RV patients, include leg ulcers, purpura, digital infarcts, and gangrene, as well as non-specific maculopapular or nodular erythema, haemorrhagic blisters, livedo reticularis, erythema elevatum diutinum, and atrophie blanche. WG lesions show necrotizing granulomatous vasculitis of small-vessels, while the RV lesions mostly shows leukocytoclastic vasculitis (LCV). Systemic LCV or necrotizing vasculitis is fairly uncommon and is seen in <1% of patients with RV (10). Granulomatous changes are even more rare in RV. Moreover, nasal manifestations are rarely seen in RA. The pulmonary manifestations in RA may appear as single nodule or nodules in clusters that coalesce when significant peripheral arthritis and rheumatoid nodules are present (6). Rheumatoid nodules generally develop

as a later symptom of active RA and may often signal more severe systemic extra-articular manifestations and the development of vasculitis (10). In lesions of giant cell arteritis, characteristic necrosis of all layers of the arterial wall is seen. Moreover, fragmentation and disintegration of elastic fibres are closely associated with an accumulation of giant cells.

Other differential diagnoses include pyoderma gangrenosum, lymphoma, tuberculosis, sarcoidosis, and deep fungal infection. Typically, these conditions can be excluded through symptoms, signs, laboratory examinations, histopathology, appropriate stains and cultures for corresponding organisms. Mucocutaneous candidiasis might contribute partially to the elevated CRP, but not the elevated ESR, ASO or RF because systemic antifungal therapy decreased the serum CRP level to approximately half of the baseline CRP level.

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