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Complex Extra-intestinal Complications of Ulcerative Colitis in a Patient with α1-Antitrypsin Deficiency

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Abstract: Ulcerative colitis (UC) can manifest with a variety of extra-intestinal disorders frequently affecting the skin, joints, and liver. An aetiologic role of α_1-antitrypsin deficiency in chronic inflammatory bowel disease has recently been suggested. We report a patient with UC and α_1-antitrypsin deficiency who presented with disseminated cutaneous leucocytoclastic vasculitis clinically appearing with target-like purpuric patches and haemorrhagic oedemas. In addition, he displayed acute haemorrhage of the eyes and the respiratory tract consistent with a systemic vasculitic process. Moreover, he had autoimune haemolytic anaemia. Systemic vasculitides, such as Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis, could widely be excluded. Systemically administered glucocorticosteroids and azathioprine led to dramatic improvement of extra-intestinal symptoms. On the basis of α_1-antitrypsin deficiency and UC, the present patient likely develolped severe systemic vasculitis with multi-organ involvement. UC should at times be viewed within the context of a more generalized immune imbalance affecting multiple organs, and not as an isolated pathological entity. Testing for α_1-antitrypsin deficiency in UC patients may detect individuals at higher risk of severe extra-intestinal involvement.

Key words: Inflammatory bowel disease; alpha-1 antitrypsin; pulmonal vasculitis; haemorrhagic conjunctivitis; Seidlmayer syndrome.

Introduction

Ulcerative colitis (UC) is a common chronic inflammatory disease of the large intestine. The pathogenesis of UC is still unclear, but both autoimmune and immune-mediated phenomena are involved. Autoimmune phenomena may include the occurrence of serum and mucosal autoantibodies against intestinal epithelial cells and antineutrophil cytoplasmatic antibodies. Immune-mediated phenomena include a variety of disturbances of humoral and cell-mediated immunity, and a generalized increased reactivity against intestinal bacterial antigens. A variety of associations between UC and autommune or immune-mediated conditions have more or less frequently been observed including idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, autoimmune hepatitis, primary sclerosing cholangitis, systemic lupus erythematosus, linear IgA disease, non-infectious arthritis, and systemic vasculitides such as Wegener's granulomatosis, Takayasu's arteritis, and giant cell arteritis [1-4]. We report a patient with UC and α_1-antitrypsin deficiency who developed autoimmune haemolytic anaemia (AIHA) and severe systemic vasculitis mainly affecting the skin, eyes, and respiratory tract.

Case Report

A 51-year-old man with a 5-year history of biopsy proven ulcerative colitis (medication: mesalazine 1.5 g daily) presented to our dermatological department with transitory rashes of non-tender purpuric skin lesions which had firstly developed about three months ago. He suffered from constitutional upset comprising pyrexia, anorexia, abdominal pain, and flu-like symptoms. On examination, there were well-defined purpuric target-like lesions, partly with rosette-shaped borders on the upper and lower extremities and partly haemorrhagic oedema mainly affecting his genital region, hands and feet. A few days later he developed acute haemorrhage of the eyes and the respiratory tract including slight epistaxis and bloodstained sputum (Fig. 1). Otherwise his medical history was unremarkable (e.g., no asthma, no malignancies, no smoking).

Routine histology of two skin biopsies revealed small-vessel leucocytoclastic vasculitis with endothelial swelling, extravasation of erythrocytes, and fibrinoid degeneration of the vessel wall, affecting the entire dermis. The cell infiltrates mainly consisted of neutrophil granulocytes. Direct immunofluorescence showed strong fibrinogen deposits around the small vessels of the upper dermis. However no significant specific imunoglobulin deposits were detected. High resolution computed tomography of the lung displayed bidorsobasilar infiltrates. Bronchoscopy revealed a highly florid discontinuous, inflammation including fibrin deposits and ulcerations affecting the trachea and bronchial tree (Fig. 2). Histology of a biopsy taken from the bronchus intermedius displayed an acute non-granulomatous, mainly neutrophilic fibrinoid inflammation consistent with the clinical diagnosis of necrotizing vasculitis. Bronchoalveolar lavage cytology mainly showed neutrophilic granulocytes but was negative for eosinophils. Culture was negative for bacterial and fungal agents. A bone marrow biopsy ex-

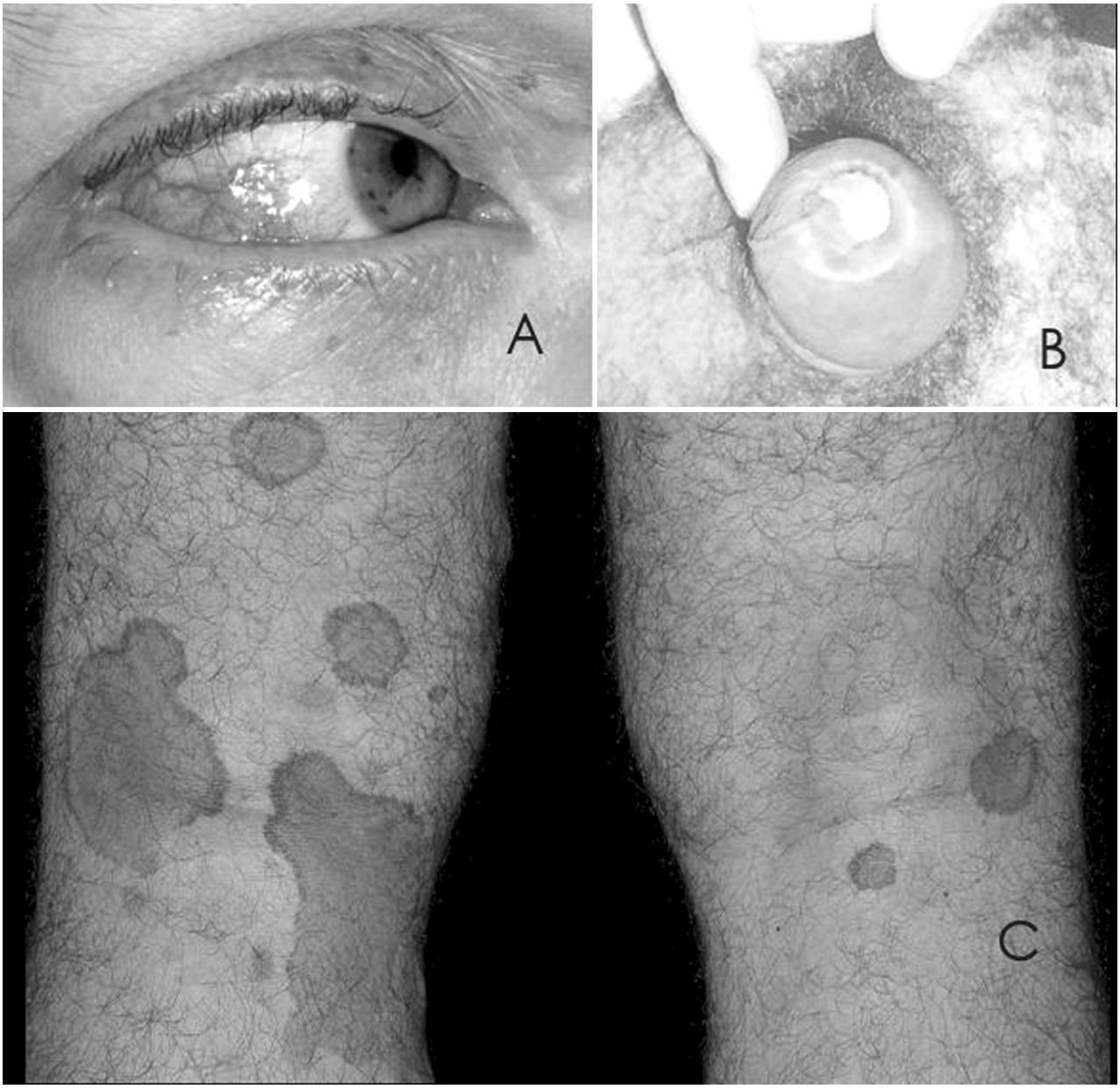

Fig. 1. Haemorrhagic conjunctivitis of the right eye (A), erythematous oedema of the penis (B), and target-like purpuic patches on the posterior aspect of the legs (C).

cluded any lymphoproliferative malignancy. However, an enhanced erythropoesis with abundance of CD61+ megacaryocytes was remarkable. Besides, there was a reactive plasmocytosis. Chest x-ray and sonographic lymph node staging did not reveal significant pathological findings. Abdominal ultrasound demonstrated splenomegaly (85 cm^2). Renal duplex-ultrasound was unremarkable. Colonoscopy and biopsy established the diagnosis of ulcerative colitis (proctocolitis totalis). Ophthalmologic investigation confirmed discrete scleral icterus and haemorrhagic conjunctivitis with bilateral hyposphagma.

Significant clinical biochemistry results were: white cell count 29.580/µl (4.600-9.500), neutrophils 26.500/µl (1.800-7.200), eosinophils 20/µl (40-360), red cell count 3.5 x 10^6/ µl (4.6-6.2), haemoglobin 7.4 g/dl (14-18), reticulocytes 35.8%% (5-15), serum iron 14 µl/dl (70-180) lactate dehydrogenase 539 U/l (0-247), total bilirubin 1.6 mg/dl (0-1) immunoglobulin G 2160 mg/dl (700-1600), and C-reactive protein 273 mg/l (0-5). Indirect immunofluorescence as well as enzyme-linked immunosorbent assays (ELISA) for antineutrophil cytoplasmic antibodies (ANCA) were negative. Serological tests for hepatitis B and C virus were negative. Serum complement, circulating immune complexes, warm and cold agglutinins, and autoantibodies including antinuclear antibodies, double-strain DNA and thyroid antibodies, and HLA-B27 were negative or within the normal range. Blood and urine cultures were negative for viral and bacterial organisms. Serum creatinine and glomerular filtration rate were within the normal range. Blood test (full blood count, liver

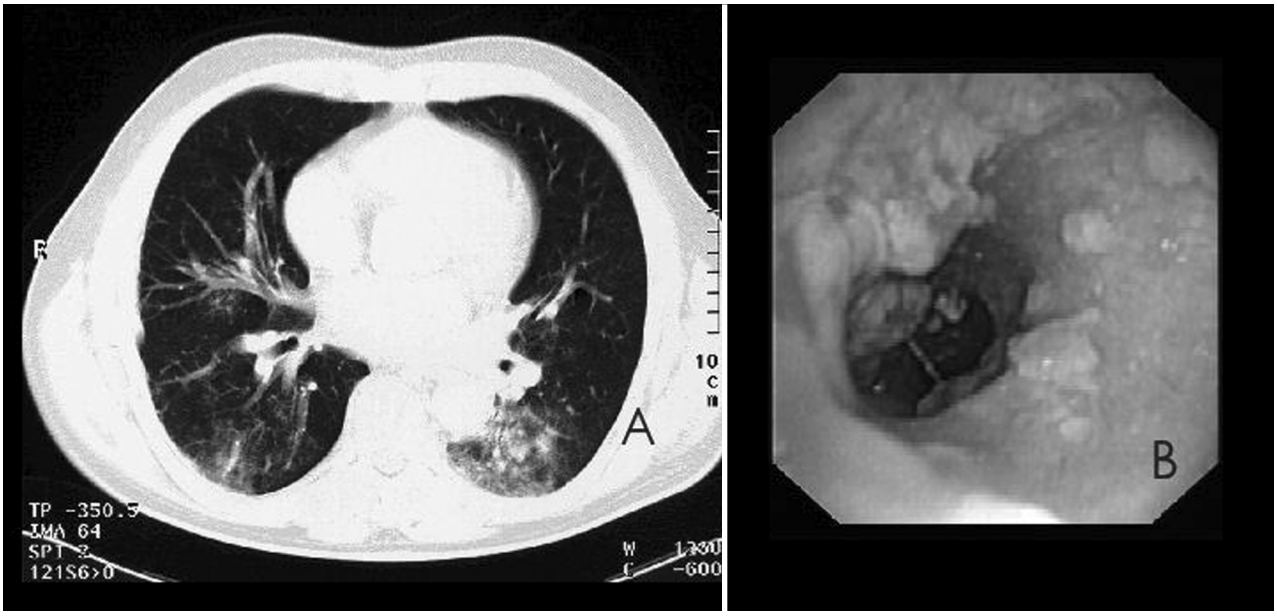

Fig. 2. High-resolution computed tomography of the lower lung segments showing dorsobasilar nodular infiltrates and increased density suggesting a vascular inflammatory process (A). Bronchoscopy demonstrating florid inflammation including fibrin deposits and haemorrhagic erosions within the bronchus intermedius (B).

and renal parameters, acute phase proteins etc.) done four months later revealed no pathologies, except for decreased α_1-antitrypsin 133 mg/dl (169-312).

Initially, the patient was treated with prednisolone 500 mg daily in tapered dosage regimen. A dramatic improvement was observed during the first days of treatment. A daily dosage of azathioprine 100 mg was later added to prednisolone 10 to 20 mg maintenance therapy. Apart from a significant clinical improvement, normalization of haematological and acute phase parameters was observed. On follow-up six months later, under prednisolone 5 mg and azathioprine 100 mg daily, the patient experienced transitory relapses of purpuric patches affecting the lower legs. Therefore, a daily dose of azathioprine 150 mg was prescribed. Otherwise his condition including UC was under good control with the aforementioned medication.

Discussion

The patient reported in this paper presented a complex combination of immune-related extra-intestinal manifestations of UC which may include a variety of potential differential diagnoses, particularly systemic vasculitides such as Wegener's granulomatosis, Churg-Strauss syndrome, or microscopic polyangiitis. Nevertheless, the absence of ANCAs (immunofluorescence and ELISA), granulomatous inflammation, eosinophilia, asthma, and renal impairment however widely excluded the aforementioned diagnoses [5, 6].

Extra-intestinal manifestations of UC are relatively common, and include skin conditions (e.g., erythema nodosum, pyoderma gangrenosum), biliary tract complications (sclerosing cholangitis), arthritis, and ocular inflammation (anterior uveitis, conjunctivitis) [8]. Previously, three patterns of conjunctival change have been reported to be associated with chronic inflammatory bowel disease: granulomatous; papillary hypertrophy with fibrovascular membrane formation; pyoblepharo-conjunctivitis with eosinophilic microabscesses [9]. Haemorrhagic conjunctivitis as observed in the present patient is an uncommon of UC-related manifestation of the eyes and may be considered a part-symptom of a systemic vasculitic process. Cutaneous leucocytoclastic vasculitis has rarely been reported in patients with UC. The skin lesions of our patient, who presented target-like purpura and haemorrhagic oedemas, predominantly resemble Henoch-Schönlein purpura and related disorders such as acute infantile haemorrhagic oedema (Seidlmayer syndrome). Nevertheless, direct immunofluorescence was negative for IgA deposits which are frequently observed in classic cutaneous small-vessel vasculitis. The latter is believed to be an immune complex disease triggered by drugs, infections, or autoimmune diseases. Leucocytoclastic vasculitis usually affects only the skin, but sometimes systemic manifestations, such as fever, arthritis and nephritis, may occur [10-13].

Involvement of the respiratory tract is rarely observed in UC. Pulmonary manifestations may include pulmonary vasculitis, fibrosing alveolitis, asthma, and chronic bronchial suppuration. Our patient had acutely developed haemorrhagic pneumonitis that histopathologically showed non-granulomatous fibrinoid necrotizing inflammation of the bronchial mucosa. Infectious aetiology of the condition could widely be excluded. In the presented case, the histopathology, high resolution computed tomography, and the dramatic response to medium-dosed glucocorticosteroids favour the diagnosis of pulmonal vasculitis. Therapy with 5-aminosalicylic acid (mesalazine) must also be considered a possible cause of the lung complications in UC. However, mesalazine-induced lung disease usually manifests with chronic interstitial pneu-

monia and poorly formed non-necrotizing granulomas [14-19].

We can however not fully exclude mesalazine as a cause of AIHA. This adverse effect of mesalazine has anecdotally been reported in the literature [20]. Anaemia is a common problem in patients with UC, and its aetiology is usually multifactorial (e.g., chronic blood loss, nutritional deficiencies) However, AIHA is a rare complication of UC that can be found in about 0.5% of patients, and although approximately 2% of patients with ulcerative colitis have a positive direct Coombs test without evidence of haemolysis. Presumably, the colon displays a role in the production of anti-erythrocyte antibodies [21].

Interestingly, the present patient had α_1-antitrypsin deficiency without evidence of the common organ manifestations such as emphysema and liver disease. A significant proportion of patients with α_1-antitrypsin deficiency are asymptomatic, however. A link between α_1-antitrypsin deficiency and UC has recently been suggested. Moreover a higher incidence of α_1-antitrypsin deficient phenotypes has also been seen in groups of patients with systemic vasculitis, in particular ANCA-positive conditions [22, 23]. It is well known that α_1-antitrypsin is an important regulatory protein in the suppression of immune and inflammatory responses. Hence decreased levels of this enzyme may have contributed to the pathogenesis of the disseminated vasculitic process observed in our patient. One may speculate that UC patients with α_1-antitrypsin deficiency are prone to develop severe extra-intestinal manifestations of their bowel disease. On the basis of α_1-antitrypsin deficiency and UC, the present patient likely developed severe systemic vasculitis with multiorgan involvement. UC should at times be viewed within the context of a more generalized immune imbalance affecting multiple organs, and not as an isolated pathological entity. Testing for α_1-antitrypsin deficiency in UC patients may detect individuals at higher risk of severe extra-intestinal involvement [22].

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