Case report

A case of arthritis and vasculitis associated with the refractory anemia with excess of blasts syndrome resistant to glucocorticoid treatment that responded favorably to TNF-alpha blockade

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematological disorders characterized by ineffective hematopoiesis resulting in peripheral blood cytopenia. Various rheumatic disorders, particularly arthritis and small-vessel vasculitis, have been described in association with the MDS (1-4). Glucocorticoids (GC) have been reported as being mostly effective in the treatment of both arthritis and small-vessel vasculitis secondary to MDS (1). We describe a patient with a MDS, the refractory anemia with excess of blasts (RAEB) syndrome, who developed arthritis and vasculitis resistant to GC but responsive to TNF-α blockade. To our knowledge, this is the first case in the literature of arthritis and vasculitis secondary to the RAEB syndrome successfully treated with TNF-α blockade.

Case report

M. L., a 65-year old man, was referred in June 2004 to our department for a 2-month history of bilateral shoulder and knee pain. The pain was typically inflammatory in nature, worse at night, and EMS (early morning stiffness) lasted several hours. Swelling had been noted in the knees. No recent constitutional symptoms were reported other than a modest (2 kg) weight loss. The patient denied cutaneous lesions including photosensitivity, Raynaud's phenomenon, oral ulcers, genito-urinary infection, and respiratory or abdominal complaints. Past medical history revealed mechanical neck and low back pain with X-ray changes consistent with osteoarthritis, allergic rhinitis, surgery for right inguinal hernia, and transurethral resection of prostate. RAEB syndrome had been diagnosed 13 years previously when the patient was referred to the Hematology Department because of leucopenia detected at a routine screening test. At that time, white cell count was 2,000/mm^3 with a differential of 46% neutrophils, 38% lymphocytes, 6% monocytes and 10% eosinophils; hemoglobin was 15 g/dl. A bone marrow aspirate disclosed 18% myeloid blasts. The caryotype was normal. Since the patient was asymptomatic, no treatment was instituted. In May 2002, after a number of episodes of recurrent hematuria, an isolated κ Bence-Jones proteinuria was found, but the bone marrow remained unchanged. Family history disclosed osteoarthritis and ischemic heart disease but no psoriasis or inflammatory bowel disease. The patient was a retired owner of a candy store. He did not drink and was on no medications; he had quit smoking 15 years previously. Recent laboratory investigations showed leucopenia (white cells 1020 mm^3) with 40% neutrophils, erythrocytes 4.0 million/mm^3, hemoglobin 10.7 g/dl, and normal platelet count. Uric acid levels, creatinine, anti-nuclear antibodies, RA test, and Rose-Waaler were normal or negative. Liver function tests were within limits except for a slightly raised (355 U/l) alkaline phosphatase (normal range 91-258). Erythrocyte sedimentation rate (ESR) was 84 mm/1st hour and C-reactive protein (CRP) was 18.40 mg/dl (normal values < 0.5 mg/ml).

Physical examination revealed tender shoulders with a limited range of movements. There were no lymphadenopathy, nodules, skin rash, abdomi-

nal masses, and heart and lung auscultation was within limits. At that time, it was felt that no conclusive diagnosis could be made, but polymyalgia rheumatica, seronegative rheumatoid arthritis, and spondyloarthropathy were considered. Empirical treatment with methylprednisolone 12 mg mane with a tapering scheme associated with etoricoxib 90 mg per day as required was prescribed.

The patient attended for review six weeks later. He reported no benefit from the treatment and complained of bilateral shoulder and left knee pain with prolonged EMS. Blood tests confirmed a raised ESR (68 mm/1st hour) and CRP (13.8 mg/dl). On examination, the shoulders were tender and the left knee was warm and swollen. Synovial fluid was aspirated from the affected knee and triamcinolone 40 mg was injected intra-articularly. Analysis of the synovial fluid showed no crystals, but the white cell count was elevated (++--).

The patient was admitted to our ward for further investigations two weeks later (August 2004). On admission, he reported severe pain in the shoulders, knees, and sterno-clavicular joints for which tramadol had been prescribed with only limited benefit. The left foot was also painful at the calcaneal insertion of the plantar fascia. Physical examination showed tender shoulders with markedly limited movements, swelling of the right sterno-clavicular joint and of the right knee, and left plantar fasciitis. Laboratory tests showed an abnormal complete blood count with 0.88 million/mm^3 white cells; neutrophils were 34% (0.3 x 1000/mm^3), lymphocytes 40% (0.35 x 1000/mm^3), and monocytes 23%. Erythrocytes were 4.28 million/mm^3 with a hemoglobin level of 11 g/dl. Routine investigations including electrolytes, liver and renal function tests, serum lipids and urinalysis were within limits; serum protein electrophoresis (SPEP) showed elevated α_2 (17.8%) consistent with active inflammation, while ESR was 60 mm/1st hour and CRP was 8.33 mg/dl. C3 and C4 levels were in the normal range, and tumor markers including prostate-specific antigen were also normal. A chest X-ray and abdominal ultrasound scan showed no significant abnormalities, whereas a CT scan of the sterno-clavicular joints revealed bilateral erosions at the clavicular margins. A diagnosis of undifferentiated seronegative spondyloarthropathy was made on the basis of the clinical, laboratory, and imaging findings. The patient was initially treated with three pulses of intravenous methylprednisolone (250 mg each) and subsequently discharged on ciclosporin 100 mg twice daily, methylprednisolone 8 mg mane post cibum, and tramadol pro re nata. His ESR normalized completely (1 mm/1st hour), but he continued to complain of bilateral knee pain intermittently associated with joint effusions. Three months after his discharge, he came to see us again because of a flare of the shoulder and knee pain; swelling was observed in the right knee. The patient was treated with three pulses of intravenous methylprednisolone 250 mg in addition to the usual regimen with limited benefit. In February 2005, however, he suffered a severe exacerbation of the arthritis; at the same time, he developed widespread papulo-pustular lesions over the trunk and limbs. He was admitted again to the ward for investigations.

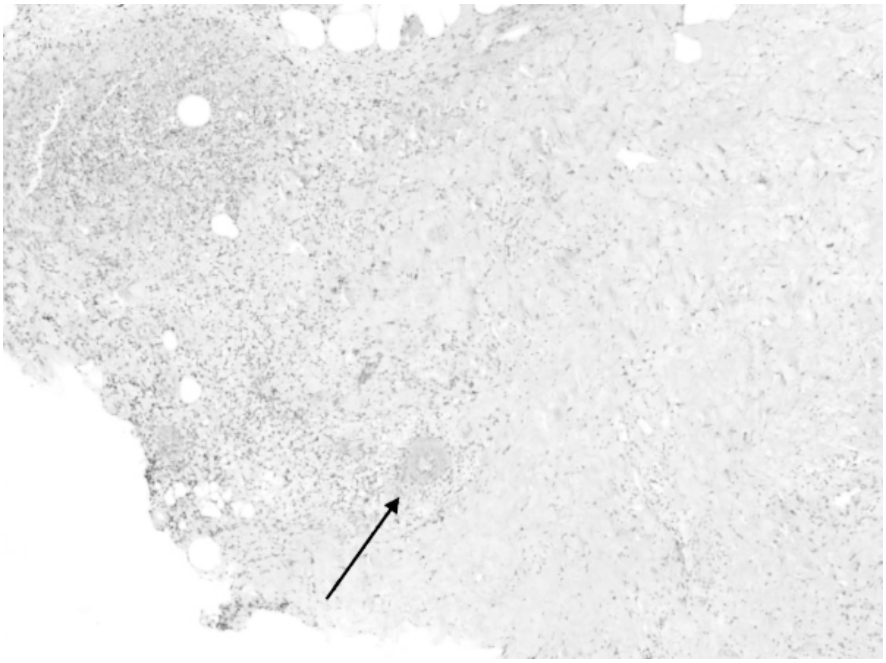

Fig. 1. Skin biopsy of an active lesion (H&E, 40x). Necrosis and abscesses of the deep derma associated with necrotizing vasculitis; (arrow) small vessel with thickened, hypereosinophilic wall, suggestive of fibrinoid necrosis.

On admission, the patient appeared in distress, with tender shoulders and knees; the right knee was warm and swollen. Examination of the skin revealed diffuse papulo-pustular lesions, some of which showed central necrosis. Heart and lung auscultation was within limits. Due to severe pain, ketoprofene 200 mg daily and fentanyl 25 μg/h every 72 hours were immediately prescribed. Blood tests demonstrated a white cell count of 1.15 million/mm^3, while the ESR was 73 mm/1st hour and CRP was 16.50 mg/dl. SPEP showed an increased α_2 fraction (18.9%) and reduced albumin (49.8%), both consistent with active inflammation. The remaining laboratory tests were non-contributory. Body temperature on ketoprofen was in the range of 36.5°C to 37.2°C. A staphylococcal skin infection was suspected and blind treatment with rifampicin 600 mg and moxifloxacin 400 mg daily was started; ciclosporin was withdrawn. However, a 9-day course of antibiotic treatment proved not effective, while echocardiography ruled out heart valve vegetations suggestive of endocarditis. A biopsy of three active papulo-pustular skin lesions was performed: histology

showed evidence of leukocytoclastic vasculitis with fibrinoid necrosis (Fig. 1). Search for acid-fast bacilli (AFB) and fungi was negative. In view of the poor clinical response to ciclosporin and low-dose steroids, etanercept 25 mg subcutaneously twice weekly was commenced; as a matter of precaution, we also initiated therapy with recombinant human granulocyte-colony stimulating factor (Lenograstim 33.6 MIU) subcutaneously every other day, which was gradually tapered to a weekly schedule after a few weeks. The patient was discharged after one month. He described a substantial improvement in joint pain, and the skin lesions cleared within a couple of weeks. However, two months later he presented to the Emergency Room because of acute intestinal and urinary retention. On examination, there was no sensory, reflex, or motor level, joint swelling, or evidence of skin lesions. Blood tests showed a white cell count of 0.72 million/$mm^{3,}$ an ESR of 99 mm/1^{st} hour and a CRP elevated at 11.50 mg/dl. Electrolytes were basically normal except for a moderately decreased serum potassium at 3 mmol/l (normal range 3.5-5). Magnetic resonance imaging (MRI) of the spine showed a few disk bulges, none impinging on the spinal cord, but no cord abnormality suggestive of acute transverse myelitis. Despite the negative MRI, we felt that the neurologic manifestations might be possibly related to vasculitis (5) triggered by etanercept (6, 7). Etanercept was withdrawn and the patient was treated with enemas and bladder catheterization. He resumed normal sphincter function in a few days. The patient was discharged with intravenous infliximab 3 mg/kg every eight weeks, while treatment with Lenograstim 33.6 MIU subcutaneously was resumed, initially every other day tapering to every second week. After the onset of therapy with infliximab, there was a prompt, marked improvement in the articular manifestations and no re-appearance of the cutaneous lesions. So far the patient is doing reasonably well on this regimen, requiring only occasionally the use of NSAIDs or analgesics; knee swelling occurred only on two occasions. Synovial fluid analysis revealed modest hypercellularity (+---) and absence of crystals on polarized light microscopy, while tests for Mycoplasma and AFB were repeatedly negative.

Discussion

The MDS are a heterogeneous group of hematological disorders affecting mainly the elderly characterized by peripheral blood cytopenia despite hypercellularity of the bone marrow. Different classifications have been proposed to stratify MDS patients. The French-American-British (FAB) classification, published in 1982, has served as the standard for assessment of MDS patients for nearly two decades and is still the most widely used system (8). According to the FAB system, MDS patients are classified depending on the proportion of blasts in the bone marrow as having refractory anemia or refractory anemia with ringed sideroblasts (< 5% of blasts), RAEB (5-20%), and RAEB in transformation (21-30%) or chronic myelomonocytic leukemia. A subsequent classification by the working group of the World Health Organization proposed in 1999 split RAEB into RAEB-1 (blasts < 10%) and RAEB-2 (blasts >10%) (9).

The pathogenesis of the MDS is still incompletely elucidated, but they are thought to result from a clonal abnormality in the bone marrow stem cell, with an increased (30%) risk of transformation to acute myeloid leukemia (10). The expansion of the abnormal clone is characterized by morphologic dysplasia, impaired differentiation, defective cell function, and genetic instability (10). In turn, ineffective hematopoiesis results in peripheral cytopenia that may involve all blood cell lineages (erythroid, granulocytic, and megakaryocytic) (10).

With specific regard to TNF-α, a dual pathogenic role has been suggested, in that TNF-α may both induce apoptosis in maturing cells causing peripheral cytopenia and stimulate proliferation of primitive progenitor cells resulting in a hypercellular bone marrow (11). Trials with the TNF-α inhibitors infliximab (12) and etanercept (13) have shown some degree of hematological improvement, although the degree of the benefit conferred appeared to be of limited magnitude and confined to some patients, suggesting that TNF-α is but one component in a complex interplay of different pathogenic factors.

Various rheumatic diseases, including arthritis and cutaneous vasculitis, have been reported in associations with MDS, in particular with the RAEB syndrome (1-4). A retrospective review of 162 patients with various MDS found that 16 patients (10%) had evidence of rheumatic diseases, including 7 cases of cutaneous vasculitis, 3 cases of lupus-like manifestations, and 1 case of mixed connective tissue disease, Sjögren's syndrome, and rheumatoid arthritis, respectively; 9 patients had evidence of undifferentiated arthritis, which was usually rheumatoid factor- and ANA-negative (1). In most cases, the rheumatic manifestations appeared shortly before, or concurrent with the diagnosis of MDS; the majority of patients with rheumatic complaints had a diagnosis of RAEB syndrome (1). Other rheumatic diseases reported more anecdotally in association with the MDS include large-vessel vasculitis (14), Sweet's syndrome (15, 16), and Adamantiades-Behçet's disease (17). GC therapy is perceived as being usually effective in the treatment of both arthritis and of vasculitis (1, 18).

Our case is unusual because the rheumatic complaints occurred long after the diagnosis of the MDS RAEB was made, and because of the lack of response to GC therapy. By contrast, the patient responded well to TNF-α blockade. Therefore, although the link between MDS and rheumatic complaints and, more specifically, the role of TNF-α in these disorders remains to be established, our case suggests that TNF-α may be involved in the pathogenesis of arthritis and vasculitis associated with MDS.

To our knowledge, this is the first reported case (Medline search until October 2005) of successful treatment of MDS-associated arthritis and vasculitis with TNF-α blockade. Since TNF-α inhibitors may also induce hematological improvement (12, 13),

they may be potentially be able to "hit two birds with one stone". At the same time, preliminary data on the use of etanercept in MDS have fueled concerns that this treatment may precipitate progression from a pre-malignant to a malignant state (19). Proper clinical trials are thus needed to define not only the efficacy, but also the safety profile of TNF-α inhibitors in the treatment of the MDS and of their rheumatic complications.

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