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Erythema elevatum et diutinum, Multiple Sclerosis and Interferon Beta

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Key Words

Erythema elevatum et diutinum · Multiple sclerosis · Interferon β

A 42-year-old woman was diagnosed as having multiple sclerosis based on a complex status epilepticus, a pathologic MRI with multiple lesions in the white matter, oligoclonal immunoglobulin in the cerebrospinal fluid and pathologic visual-evoked cerebral potentials. She was treated with carbamazepine and Rebif[®] (interferon β 1a, Serono, Geneva, Switzerland). One year later, she developed arthralgia of the hands, knees and ankles as well as a painful heel. Despite discontinuing interferon, the arthralgias persisted and skin lesions appeared.

At presentation, she had swollen proximal interphalangeal joints of the left second and third fingers and a swollen insertion of the Achilles tendon. She had 3 erythematous nodules at the medial aspect of the left index finger that exhibited a dermal infiltrate upon diascopy. A skin biopsy showed a dermal perivascular and interstitial mixed neutrophilic and mononuclear cell infiltrate. Many leukocytes exhibited signs of apoptosis. Extravascular erythrocytes were identified. The microvascular endothelium was turgescent, but no fibrinoid necrosis of the vessel walls was detected. The superficial dermis exhibited moderate fibrosis. A diagnosis of erythema elevatum et diutinum (EED) was made. ESR was 28 mm in the first hour (normal <10), CRP was 6.5 mg/l (normal <4) and the ANA titer was 1:320 (normal <1:80). Tests for blood chemistry including glucose-6-phosphate dehydrogenase, urinalysis, angiotensin-converting enzyme, an-

tistreptolysin titer, rheumatoid factor, antibodies to citrullinated peptide, anti-nDNA, anti-ENA, antinucleosome antibodies, CH50, C3, C4, immunoelectrophoresis and immune fixation, Bence-Jones proteinuria, immunoglobulin isotype levels, cryoglobulins and serology for *Borrelia* were normal or negative. X-ray of the left hand did not show erosion.

Dapsone was started at 50 mg/day and increased to 200 mg/day with a good clinical response on joint and skin manifestations. Despite normal glucose-6-phosphate dehydrogenase levels, anemia (94 g/l) without signs of hemolysis developed. Dapsone was discontinued, and the skin nodules and the arthralgias recurred. Dapsone was reintroduced at 100 mg/day and well tolerated. The joint pain and the skin nodules disappeared again. Six months later, Dapsone was stopped without cutaneous or articular relapse. An alternative treatment for multiple sclerosis was initiated.

EED is a form of neutrophil-rich vasculitis [1] often lumped together with Sweet syndrome, pyoderma gangrenosum, rheumatoid neutrophilic dermatosis, neutrophilic eccrine hidradenitis and Sneddon-Wilkinson subcorneal pustular dermatosis under the term of neutrophilic dermatoses. Behçet's disease is also associated with neutrophil-rich infiltrates of the skin. Aside from IgA paraproteinemia with or without myeloma, myelodysplastic and myeloproliferative diseases, lymphoma and POEMS syndrome, EED is associated with arthralgia and a number of autoimmune and inflammatory disorders such as rheumatoid arthritis [1], ulcerative colitis [2], Crohn's disease [3], relapsing polychondritis [4], type 1 diabetes [5], Wegener's granulomatosis [6], celiac disease [7], myasthenia gravis [8], hyper-IgD syndrome [9] and HIV infection [10]. We found no association of multiple sclerosis with EED. Pyoderma gangrenosum in a patient with ulcerative colitis and multiple sclerosis [11] and a patient with subcorneal pustular dermatosis and multiple sclerosis [12] have been reported. CNS involvement of Behçet's disease can mimic multiple sclerosis [13]. Interferon β could have precipitated EED, but we found no cases of histologically documented vasculitis or neutrophilic dermatosis associated with interferon β therapy. Skin ulcerations or vasculitis-like lesions observed after interferon β injection appear to be due to vascular thrombosis [14]. Webster et al. [15] reported 1 patient with multiple sclerosis undergoing treatment with interferon β and developing a pustular flare of her usually mild psoriasis. Treatment with interferon α which shares the receptor with interferon β has been associated with vasculitis including histologically documented leukocytoclastic vasculitis although leukocytoclastic vasculitis may rather be due to the underlying chronic hepatitis C in that case [16]. Other neutrophilic dermatoses such as pyoderma gangrenosum [17], 'granulomatous and suppurative dermatitis' [18] but not EED have been diagnosed during interferon α treatment. The relation between interferon α and neutrophilic dermatoses, however, is not clear because cases of Sweet's syndrome [19, 20] and pyoderma gangrenosum [21, 22] have regressed under treatment with this cytokine. Similarly, the relation between arthritis and interferon β treatment is not clear. While it appeared beneficial for rheumatoid arthritis [23, 24], appearance of arthritis during treatment with interferon β in a patient with multiple sclerosis has been reported [25].

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