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Case report

Eosinophilic fasciitis/generalized morphea overlap successfully treated with azathioprine

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Case report

A 66-year-old man had a right radical nephrectomy due to a renal cell carcinoma 10 years previously. He now presented with a 2-month history of erythematous, violaceous, indurated plaques on the upper limbs and chest, and violaceous patches on the thighs. The histopathologic findings from a 5-mm punch biopsy of the chest proposed differential diagnoses among interstitial mycosis fungoides, borreliosis, and the inflammatory stage of scleroderma. The molecular study revealed a rearrangement of the T-cell receptor gene.

Laboratory tests showed peripheral eosinophilia. Inflammatory markers, renal and liver function, peripheral blood immunophenotype, and serologic test for Lyme disease and HTLV-1 virus were normal or negative. A chest, abdominal, and pelvic computed tomography revealed no abnormalities. The patient began treatment with oral psoralen + ultraviolet A therapy with a suspected diagnosis of mycosis fungoides.

Two months later, the patient presented with asthenia, arthromyalgias, and progressive woody induration of the skin of the upper and lower limbs (Figure 1). The patient denied toxic, environmental, or drug exposures. Complete laboratory tests revealed persistent peripheral eosinophilia (3400/mm^3) and elevation of C-reactive protein (64.9 mg/l). Immunoglobulin levels, proteinogram, and muscle enzymes were within normal limits, and autoimmune testing, including antinuclear, anticentromere, and anti-Scl-70 antibodies, was negative. Lung high-resolution computed tomography, spirometry, scintigraphy of the esophagus, echocardiogram, and electromyogram showed no pathological findings.

A second incisional skin biopsy specimen from the right arm showed similar changes to the first biopsy (Figure 2). These changes were mainly an interstitial mixed infiltrate of lymphocytes, plasma cells, and eosinophils that involved the whole dermis to some extent and mild widening of septal subcutaneous fat. The collagen bundles of the deep reticular dermis were thickened and accompanied by some pseudorosette figures. No elastic fiber loss, epidermotropism, or mucin deposits were seen. A muscle biopsy of the tibialis anterior was performed (Figure 3). The muscle fascia presented a focal lymphohistiocytic inflammation with exceptional eosinophils without fibrosis.

A diagnosis of eosinophilic fasciitis (EF)/generalized morphea overlap was made based on the clinical, analytical, and histopathological findings. The patient began treatment with oral prednisone at 80 mg/day (1 mg/kg per day). After three weeks, he reported improvement in asthenia and arthromyalgias but complained of visual impairment. After ophthalmologic examination, he was

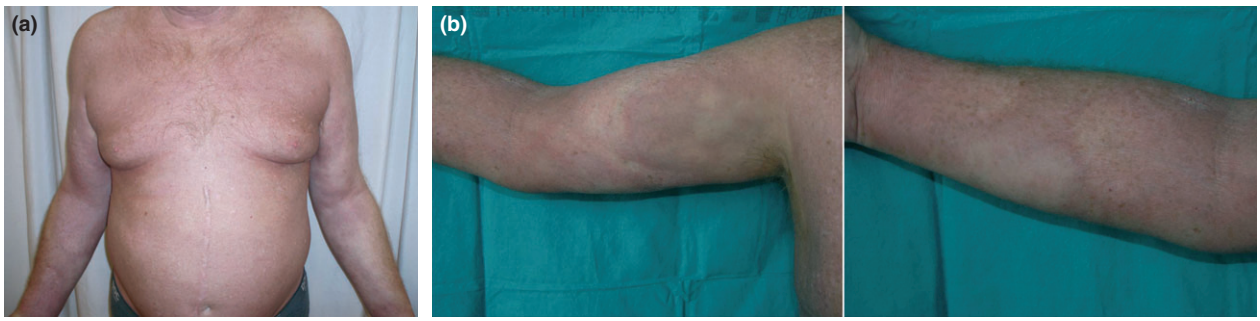

Figure 1 (a) Woody induration of the skin of the upper limbs and chest. (b) Erythematous violaceous and hypopigmented indurated plaques on the right arm

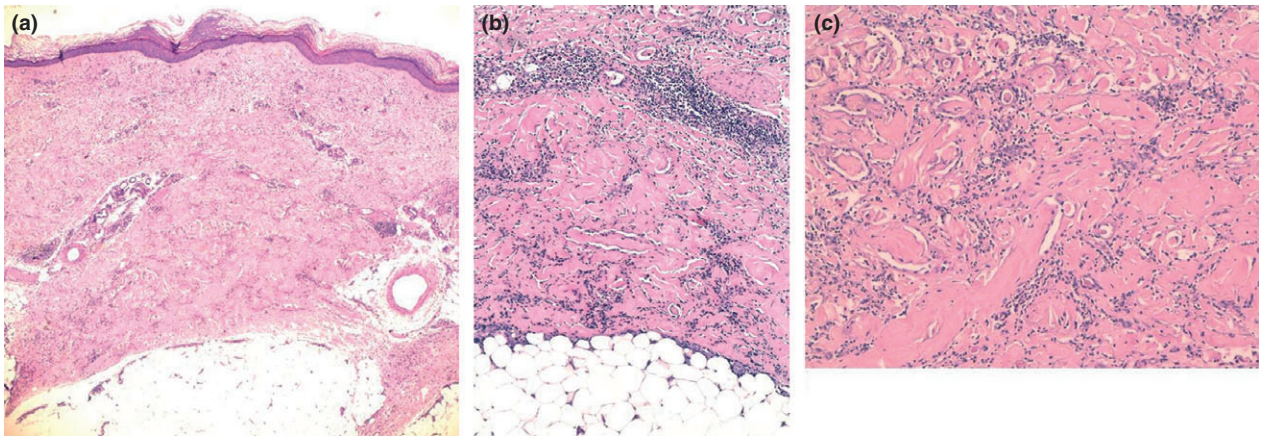

Figure 2 (a) Superficial and deep chronic interstitial dermatitis showing some extent and mild widening of septal subcutaneous fat (hematoxylin and eosin, ×4). (b) Higher power that highlights the inflammatory infiltrate composed mostly of lymphocytes with some plasma cells and eosinophils (hematoxylin and eosin, ×10). (c) Detail of the thickened collagen bundles of the deep reticular dermis with some pseudorosettes figures on the left top (hematoxylin and eosin, ×20)

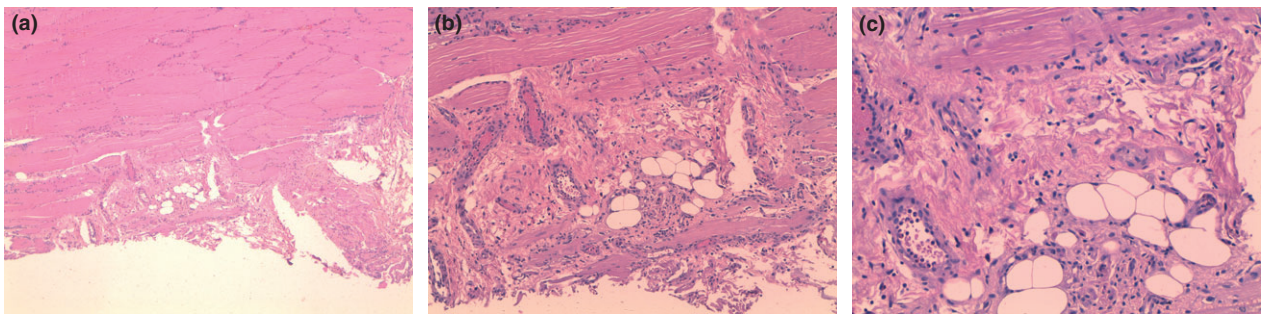

Figure 3 (a) Muscle biopsy of the tibialis anterior with inflammation of the muscle fascia (hematoxylin and eosin, ×4). (b) Higher power that highlights a focal lymphohistiocytic inflammation without fibrosis (hematoxylin and eosin ×10). (c) Exceptional eosinophils within the inflammatory infiltrate (hematoxylin and eosin, ×20)

diagnosed with central serous chorioretinopathy (CSCR) probably related to systemic glucocorticoids, and a progressive rapid tapering of prednisone was recommended. Treatment with azathioprine was started at 200 mg/day. After two months, the patient improved significantly, with marked reduction of induration and

increased skin flexibility. Six months after the introduction of azathioprine, he developed positive antinuclear antibodies (titer 1 : 1280), and serial antibody tests showed a maintained titer of 1 : 640 until December 2011 when it decreased to 1 : 160; eosinophilia reverted to normal with no other laboratory abnormalities. Because of the significant clinical improvement, the dosage of azathioprine was tapered to 150 mg/day after six months and 100 mg/day after 12 months of treatment. The patient had regular ophthalmologic checkups, and visual symptoms gradually improved. After 18 months of follow-up, the patient has continued in complete remission with only two circumscribed hypopigmented and atrophic lesions on the right arm.

Discussion

EF is an uncommon connective tissue disease/scleroderma-like disorder, first described in 1974 by Shulman. Controversy exists whether EF is a variant of morphea or a distinct entity. It is characterized by woody induration of the skin typically affecting the limbs, and most patients start with an edematous phase with pitting edema of the extremities.[1] Localized lesions of morphea may be seen in up to 30% of patients.[2] Laboratory tests may show hypergammaglobulinemia, peripheral eosinophilia, and an elevated erythrocyte sedimentation rate. Diagnosis is often delayed; the typical pathological findings include thickening and fibrosis of the fascia with a lymphohistiocytic inflammatory infiltrate with plasma cells and eosinophils, which are not mandatory for the diagnosis.[3] Both morphea and EF show homogenization of collagen bundles, which are differentiated by the depth of skin involvement. Morphea predominantly affects dermis and superficial panniculus, and EF is characterized by involvement of the deep subcutis and fascia,[4] but there is a great overlap between these entities, and they may represent a spectrum of scleroderma-like diseases.[1] Cases with morphea lesions presenting before the onset of EF have been reported[2] as well as patients with an eosinophilic fasciitis/generalized morphea overlap.[5]

Treatment of EF is often challenging. High-dose systemic corticosteroids remain the first-line therapy, although spontaneous remission is possible. Complete recovery may take up to 1–3 years.[6,7] In our case, we had to discontinue systemic corticosteroids because of ocular complications. Glucocorticoids were widely used as a treatment for CSCR; however, in the past 10 years it has been noted that CSCR is associated with exposure to increased levels of endogenous and exogenous glucocorticoids. Many cases have been described during treatment with corticosteroids, administered by any route.[8] Cyclosporine, azathioprine, methotrexate, cyclosphosphamide, photochemotherapy, hydroxychloroquine, cimetidine, extracorporeal photochemotherapy, or infliximab have been reported as adjuvant treatments for EF.[3] Because of the history of nephrectomy, we chose azathioprine, which is an immune-modulating drug widely used in medicine for immune-mediated diseases. In most European countries, the use of azathioprine in dermatology is licensed for pemphigus vulgaris and dermatomyositis, but it is frequently used off-label.[9] To our knowledge, few cases of recalcitrant EF treated with azathioprine have been reported without description of their clinical characteristics.[10] Our patient showed excellent clinical response with no side effects.

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