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CLINICAL VIGNETTE

ABATACEPT-induced Lupus Erythematosus Panniculitis in a Patient with Rheumatoid Arthritis

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Abstract

Lupus erythematosus panniculitis (LEP), also called lupus profundus, is a rare variant of cutaneous lupus erythematosus that may occur alone or in combination with systemic lupus erythematosus (SLE). Characterized by erythematous subcutaneous nodules and plaques of the face, proximal upper and lower extremities and trunk, LEP accounts for one to three percent of cases of cutaneous lupus erythematosus[1-3]. Histologically, LEP lesions are characterized by an inflammatory infiltrate, composed mainly of lymphocytes, in the adipose tissue and dermis[4]. While the etiology of LEP in not known, environmental, hormonal, and genetic factors have been proposed. The diagnosis of LEP is based on clinical assessment and pathologic diagnosis. In this report, we describe a patient with severe rheumatoid arthritis, who, while receiving treatment with Abatacept, developed subcutaneous nodules of the lower extremities that were histopathologically consistent with LEP without evidence of systemic involvement.

Case Report

A 60 year-old woman with rheumatoid arthritis presented with a two-month history of tender erythematous nodules along the flexor aspects of her bilateral lower extremities.

The patient's medical history dated back to 1992, when she developed polyarthralgias and tender lower extremity joints and was diagnosed with ankylosing spondylitis. During her initial work-up, her labs were notable for a positive HLA-B27, as well as a positive anti-nuclear antibody (ANA) with a titer of 1:80 with a homogeneous pattern. Over the next several years, she was treated with various systemic medications, including methotrexate, penicillamine, minocycline, cyclosporine and prednisone, without significant improvement in her symptoms.

She presented to the rheumatology clinic with recurrent swollen lower and upper extremity joints. At that time, her labs were notable for a positive rheumatoid factor of 525, a positive ANA of 1:80, and an elevated ESR at 45. Based on this presentation, the patient was diagnosed with rheumatoid arthritis, and treatment with systemic methotrexate was initiated. Infliximab was added because of refractory joint pain. The patient developed a productive cough, and computed tomography (CT) of the chest identified two ten-millimeter pulmonary nodules in her right upper lobe. Because of concern for pulmonary toxicity, methotrexate was discontinued. An additional work-up, including a lung biopsy, demonstrated no evidence of malignancy associated with the pulmonary nodules.

Following the lung biopsy, leflunomide and infliximab were initiated for management of the patient's rheumatoid arthritis. The patient however, continued to have persistent joint tenderness and in December 2007, therapy was initiated with rituximab. In December 2007, the patient underwent her first cycle of rituximab (one gram intravenously on days 0 and 14) in combination with leflunomide daily. The patient was also taking nonsteroidal anti-inflammatory agents for her pain. In June 2008, the patient developed fevers with diarrhea, and had developed gram negative bacteremia and colonic strictures. Due to concern for bacteremia, rituximab was halted temporarily for colon stricture resection. Following surgical resection in June 2008, two additional cycles of rituximab followed (in June and August 2008, respectively) with mild improvement in the patient's joint

tenderness. Despite rituximab therapy, the patient continued to experience joint pain. In March 2009, treatment with abatacept, a novel recombinant T- cell inhibitor, was initiated at a dose of 750 mg IV monthly. Over the next two months, the patient developed tender, firm, erythematous subcutaneous nodules, first along the extensor surfaces of her upper extremities, followed by the flexor and extensor surfaces of her bilateral lower extremities. Review of systems was negative for photosensitivity, malar rash, oral ulcerations, alopecia, or increased fatigue from baseline.

Her physical examination demonstrated mildly indurated, erythematous and tender nodules along her upper and lower extremities. Laboratory findings revealed a positive ANA (1:160) in a homogeneous pattern, as well as a positive anti-histone antibody. Complete blood count was notable for normocytic anemia, but complete metabolic panel, aldolase, anti-double stranded DNA antibody, Anti-RNP, C3 and C4 were within normal limits. ESR was mildly elevated at 45. A skin biopsy of a lesion from the right shin demonstrated a superficial and deep perivascular lymphocyte-predominant inflammatory infiltrate extending into the subcutis. The inflammation in the subcutis was predominantly in a lobular pattern (Figure 1). Overlying hyperkeratosis, as well as interstitial dermal and subcutaneous mucin were also noted (Figure 2). These biopsies were representative of lupus panniculitis.

Abatacept was discontinued shortly after the skin biopsy. Furthermore, the patient was treated with hydroxychloroquine 200 mg twice daily. Her LEP lesions resolved within 2 weeks after the discontinuation of abatacept and 1 week after initiation of hydroxychloroquine.

Discussion

First described by Kaposi in 1883, LEP is a rare chronic inflammatory condition of the adipose tissue and dermis characterized by tender, erythematous subcutaneous nodules and plaques over the buttocks, proximal lower extremities, and trunk[5]. More recently, the distribution of LEP has been described as including the head (predominantly on the face) and upper arms[6-9]. Its occurrence may serve as a marker of incipient lupus erythematosus, or of less severe disease when observed in patients with already diagnosed SLE[10,11,12]. Occurring in only two to three percent of systemic lupus patients, lupus panniculitis most often occurs in the absence of SLE[12]. Conversely, 10-15% of patients with LEP may develop SLE, and in a few cases, LEP has been identified as the presenting symptom of SLE[13,14]. The etiology of lupus panniculitis is unclear, but may involve genetic, environmental, or hormonal factors.

Some studies suggest that there is a genetic susceptibility to SLE via HLA DR2 and HLA DR3 gene loci, and interferon gamma expressing genes[15,16]. Other theories center upon the role of hormonal factors such as estradiol, dehydroepiandrosterone (DHEA), testosterone, and prolactin as risk factors for lupus erythematosus[17]. Finally, environmental factors, such as medications, ultraviolet light, viral infections and smoking, may also contribute to the pathogenesis of lupus panniculitis, but their roles are not yet known. Smoking may contribute to increased disease area and severity, and has been shown to be predominantly associated with cutaneous disease[18-20]. The clinical course for LEP is characterized by relapse and remission. The target lesions may resolve spontaneously or after therapy and cessation of offending agents, leaving in their place a deep depression and/or scar.

The diagnosis of LEP is based on pathologic examination, and clinical assessment. The differential diagnosis for panniculitides is broad. Histopathologically, panniculitides may be differentiated into septal versus lobular forms[21-22]. LEP is characterized by a marked lobular lymphocytic infiltrate in the adipose tissue and dermis, mucin accumulation, lymphoid follicles with germinal centers, hyaline fat necrosis (eosinophilic degeneration of fat lobules), and immunoglobulin and complement deposition in the vessels of the subcutis[23]. In addition, serologic markers such as anti-nuclear antibody (ANA) and clinical history may be used to support the pathologic diagnosis. Patients with LEP typically have positive ANA. In a recent study, 65% of patients with LEP had positive ANAs of low titer[12]. The combination of clinical history, pathology, and serology permit the diagnosis of lupus panniculitis.

This is the first case of drug-induced lupus panniculitis, which is a subset of drug-induced lupus erythematosus (DILE). DILE is a lupus-like syndrome associated with continuous

exposure to a medication that resolves after cessation of the offending agent. Accounting for approximately 10% of SLE cases, DILE is reported in association with a growing number of medications including hydralazine, minocycline, sulfadiazine, fluorouracil agents, and recently, tumor necrosis factor-alpha (TNF-α) inhibitors such as those used in rheumatoid arthritis[24]. The diagnosis of DILE is based on clinical history. Furthermore, DILE may be supported by positive anti-histone antibody serologies[25], which was also noted in our patient. In the literature, infliximab-induced SLE has been reported in multiple case reports[25-27], as has etanercept-induced lupus[28-30]. Abatacept was recently approved for the treatment of rheumatoid arthritis refractory to TNF-α inhibition[31]. A recent Cochrane review found that, although abatacept had a moderate level of efficacy and safety in reducing disease activity and improving function in the treatment of rheumatoid arthritis, long-term studies would be needed to assess the medication's overall side effect profile in terms of sustained harm and efficacy[32]. Indeed, although numerous cases of TNF-α-induced SLE have been reported, this is the first case of LEP induced by a biologic agent, and also the first case of cutaneous lupus associated with abatacept.

Abatacept, etanercept, and infliximab are biologic agents used to treat rheumatoid arthritis. Etanercept is a soluble TNF-α receptor antagonist that competitively binds TNF-α. Infliximab is a chimeric monoclonal antibody directed against TNF-α. Both of these agents inhibit the action of TNF-α, thereby inhibiting T-cell activation. There are two hypotheses that may explain TNF- α -induced SLE. First, anti-TNF-α agents are postulated to suppress Th-1-mediated immune responses and promote a shift toward predominantly Th-2 responses, which may promote the development of lupus[33]. In addition, it is postulated that TNF-α inhibitors induce cell apoptosis, which may lead to the release of nucleosomal antigens and the subsequent production of auto-antibodies[34]. In contrast, abatacept has a different mechanism of action. Abatacept is a fusion protein of cytotoxic T-lymphocyte associated antigen-1 (CTLA-1) and immunoglobulin G-1 (IgG-1) that inhibits T-cell activation by blocking the binding of co-stimulatory CTLA-1 with its target cell receptor B7, a necessary step in T-cell activation[35]. The mechanism by which abatacept may be involved in pathogenesis of LEP, however, remains unclear.

The treatment of LEP is based on clinical experience rather than randomized clinical trials. Most cases of chronic cutaneous lupus respond to oral anti-malarial agents. Hydroxychloroquine at doses of 250 mg-500 mg daily is considered the first line treatment for LEP[36-37]. Hydroxychloroquine may be combined with quinacrine for refractory LEP. For treatment failure with anti-malarial agents, thalidomide at doses of 50-150 mg daily has been used[37-40]. Furthermore, case reports have also supported the use of mycophenolate mofetil for LEP, demonstrating complete remission[41]. In drug-induced lupus erythematosus, withdrawal of the offending agent results in remission of the cutaneous manifestations. In this case of abatacept-induced LEP, withdrawal of abatacept and initiation of hydroxychloroquine resulted in complete remission of the patient's lesions.

FIGURES

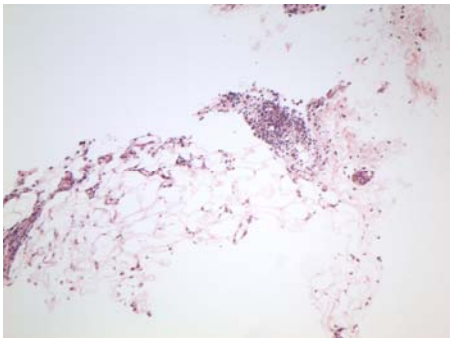

Figure 1-Para-septal lymphoid aggregate with extension into the lobule (100x magnification)

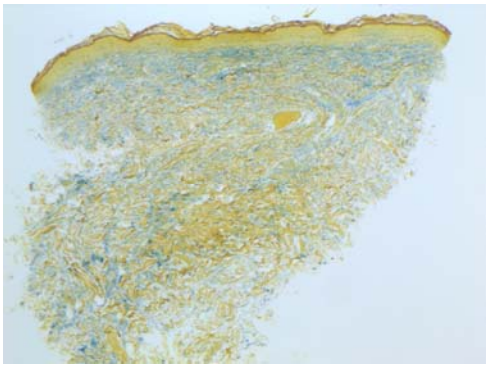

Figure 2--Colloidal iron stain highlighting a diffuse increase in interstitial dermal mucin (40x magnificiation)

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