CLINICAL VIGNETTE

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

Cindy Mong, MD[1]; Monica Tsai[2] BA; Nima M Gharavi, MD, PhD[3]; Chandra Smart, MD4, Delphine J. Lee, MD, PhD[5]; Lorraine Young, MD[3]; [1]Department of Internal Medicine, Olive View UCLA Medical Center, Sylmar, CA. [2]Department of Medicine, [3]Division of Dermatology, and [4]Department of Pathology and Laboratory Medicine, UCLA David Geffen School of Medicine; Los Angeles, CA. [5]Dirks/Dougherty Laboratory for Cancer Research, Department of Translational Immunology, John Wayne Cancer Institute, Santa Monica, CA.

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

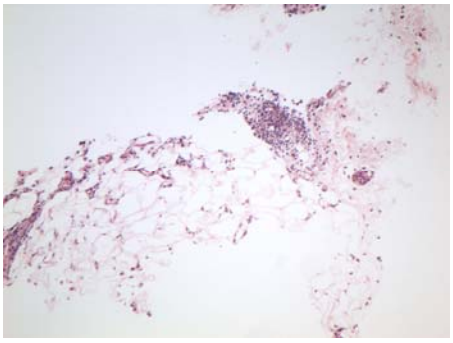

Figure 1-Para-septal lymphoid aggregate with extension into the lobule (100x magnification)

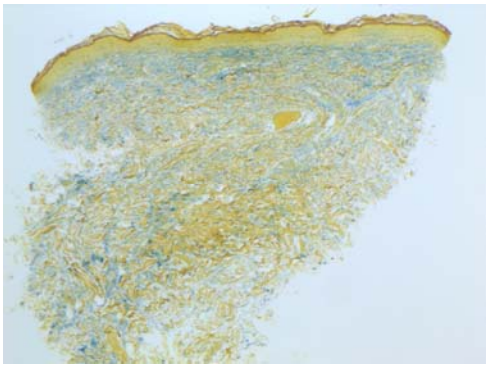

Figure 2--Colloidal iron stain highlighting a diffuse increase in interstitial dermal mucin (40x magnificiation)

Financial Disclosures/Sponsors – Dr. Lee is supported by NIAMS and the Joseph B. Gould Foundation.

REFERENCES

1. **Lipsker D**. Classification of specific cutaneous manifestations in patients with lupus erythematosus: a time for change? The concept of dermal lupus erythematosus. *Dermatology*. 2006;212(4):324-6. PubMed PMID: 16707881.
2. **Crowson AN, Magro C**. The cutaneous pathology of lupus erythematosus: a review. *J Cutan Pathol*. 2001 Jan;28(1):1-23. Review. PubMed PMID: 11168747.
3. **Requena L, Sánchez Yus E**. Panniculitis. Part II. Mostly lobular panniculitis. *J Am Acad Dermatol*. 2001 Sep;45(3):325-61; quiz 362-4. Review. PubMed PMID: 11511831.
4. **Sánchez NP, Peters MS, Winkelmann RK**. The histopathology of lupus erythematosus panniculitis. *J Am Acad Dermatol*. 1981 Dec;5(6):673-80. PubMed PMID: 7033308.
5. **Kaposi M**. Pathologie und Therapie der Hautkrankheiten [Pathology and therapy of skin diseases]. 2nd ed. Vienna: Urban & Schwarzenberg, 1883:624.
6. **Bacanli A, Uzun S, Ciftcioglu MA, Alpsoy E**. A case of lupus erythematosus profundus with unusual manifestations. *Lupus*. 2005;14(5):403-5. PubMed PMID: 15934442.
7. Jacyk WK, Bhana KN. Lupus erythematosus profundus in black South Africans. Int J Dermatol. 2006 Jun;45(6):717-21. PubMed PMID: 16796635.
8. **Pérez-Pastor G, Valcuende F, Tomás G, Moreno M**. [Lupus erythematosus panniculitis presenting as palpebral edema and parotiditis]. Actas Dermosifiliogr. 2007 Oct;98(8):549-52. *Spanish*. PubMed PMID: 17919430.
9. **Tsuzaka S, Ishiguro N, Akashi R, Kawashima M**. A case of lupus erythematosus profundus with multiple arc-shaped erythematous plaques on the scalp and a review of the literature. *Lupus*. 2012 May;21(6):662-5. Epub 2012 Jan 13. Review. PubMed PMID: 22247340.
10. **Weingartner JS, Zedek DC, Burkhart CN, Morrell DS**. Lupus erythematosus panniculitis in children: report of three cases and review of previously reported cases. *Pediatr Dermatol*. 2012 Mar-Apr;29(2):169-76. doi: 10.1111/j.1525-1470.2011.01544.x. Epub 2011 Nov 8. Review. PubMed PMID: 22066977.
11. **Yell JA, Mbuagbaw J, Burge SM**. Cutaneous manifestations of systemic lupus erythematosus. *Br J Dermatol*. 1996 Sep;135(3):355-62. PubMed PMID: 8949425.
12. **Martens PB, Moder KG, Ahmed I**. Lupus panniculitis: clinical perspectives from a case series. *J Rheumatol*. 1999 Jan;26(1):68-72. PubMed PMID: 9918242.
13. **Tuffanelli DL**. Lupus erythematosus panniculitis (profundus). *Arch Dermatol*. 1971 Mar;103(3):231-42. PubMed PMID: 4100949.
14. **Díaz-Jouanen E, DeHoratius RJ, Alarcón-Segovia D, Messner RP**. Systemic lupus erythematosus presenting as panniculitis (lupus profundus). *Ann Intern Med*. 1975 Mar;82(3):376-9. PubMed PMID: 1115472.
15. **Barcellos LF, May SL, Ramsay PP, Quach HL, Lane JA, Nititham J, Noble JA, Taylor KE, Quach DL, Chung SA, Kelly JA, Moser KL, Behrens TW, Seldin MF, Thomson G, Harley JB, Gaffney PM, Criswell LA**. High-density SNP screening of the major histocompatibility complex in systemic lupus erythematosus demonstrates strong evidence for independent susceptibility regions. *PLoS Genet*. 2009 Oct;5(10):e1000696. Epub 2009 Oct 23. PubMed PMID: 19851445; PubMed Central PMCID: PMC2758598.
16. **Kariuki SN, Kirou KA, MacDermott EJ, Barillas-Arias L, Crow MK, Niewold TB**. Cutting edge: autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. *J Immunol*. 2009 Jan 1;182(1):34-8. PubMed PMID: 19109131; PubMed Central PMCID: PMC2716754.
17. **Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW**. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum*. 2007 Apr;56(4):1251-62. PubMed PMID: 17393454.
18. **Dutz J, Werth VP**. Cigarette smoking and response to antimalarials in cutaneous lupus erythematosus patients: evolution of a dogma. *J Invest Dermatol*. 2011 Oct;131(10):1968-70. doi: 10.1038/jid.2011.237. PubMed PMID: 21918570; PubMed Central PMCID: PMC3263354.
19. **Piette EW, Foering KP, Chang AY, Okawa J, Ten Have TR, Feng R, Werth VP**. Impact of smoking in cutaneous lupus erythematosus. *Arch Dermatol*. 2012 Mar;148(3):317-22. Epub 2011 Nov 21. PubMed PMID: 22105815; PubMed Central PMCID: PMC3309110.
20. **Zandman-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y**. Environment and lupus-related diseases. *Lupus*. 2012 Mar;21(3):241-50. Epub 2011 Nov 7. Review. PubMed PMID: 22065092.
21. **Requena L**. Normal subcutaneous fat, necrosis of adipocytes and classification of the panniculitides. *Semin Cutan Med Surg*. 2007 Jun;26(2):66-70. Review. PubMed PMID: 17544956.
22. **Rose C, Leverkus M, Fleischer M, Shimanovich I**. Histopathology of panniculitis--aspects of biopsy techniques and difficulties in diagnosis. *J Dtsch Dermatol Ges*. 2012 Jun;10(6):421-5. doi: 10.1111/j.1610-0387.2011.07831.x. Epub 2011 Nov 16. PubMed PMID: 22084866.
23. **Park HS, Choi JW, Kim BK, Cho KH**. Lupus erythematosus panniculitis: clinicopathological, immunophenotypic, and molecular studies. *Am J Dermatopathol*. 2010 Feb;32(1):24-30. PubMed PMID: 20098081.
24. **Hess E**. Drug-related lupus. *N Engl J Med*. 1988 Jun 2;318(22):1460-2. PubMed PMID: 3259288.
25. **Schneider SW, Staender S, Schlüter B, Luger TA, Bonsmann G**. Infliximab-induced lupus erythematosus tumidus in a patient with rheumatoid arthritis. *Arch Dermatol*. 2006 Jan;142(1):115-6. PubMed PMID: 16415403.
26. **Favalli EG, Sinigaglia L, Varenna M, Arnoldi C**. Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. *Lupus*. 2002;11(11):753-5. PubMed PMID: 12475006.
27. **Shakoor N, Michalska M, Harris CA, Block JA**. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet*. 2002 Feb 16;359(9306):579-80. PubMed PMID: 11867114.

28. **Cairns AP, Duncan MK, Hinder AE, Taggart AJ**. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. *Ann Rheum Dis*. 2002 Nov;61(11):1031-2. PubMed PMID: 12379532; PubMed Central PMCID:PMC1753946.
29. **Mohan AK, Edwards ET, Coté TR, Siegel JN, Braun MM**. Drug-induced systemic lupus erythematosus and TNF-alpha blockers. *Lancet*. 2002 Aug 24;360(9333):646. PubMed PMID: 12241965.
30. **Wetter DA, Davis MD**. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2009 Nov;84(11):979-84. PubMed PMID: 19880688; PubMed Central PMCID: PMC2770909.
31. **Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT, Dougados M**. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23. Erratum in: *N Engl J Med*. 2005 Nov 24;353(21):2311. PubMed PMID: 16162882.
32. **Maxwell L, Singh JA**. Abatacept for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009 Oct 7;(4):CD007277. Review. PubMed PMID: 19821401.
33. **Yung R, Powers D, Johnson K, Amento E, Carr D, Laing T, Yang J, Chang S, Hemati N, Richardson B**. Mechanisms of drug-induced lupus. II. T cells overexpressing lymphocyte function-associated antigen 1 become autoreactive and cause a lupuslike disease in syngeneic mice. *J Clin Invest*. 1996 Jun 15;97(12):2866-71. PubMed PMID: 8675699; PubMed Central PMCID: PMC507381.
34. **Marzano AV, Vezzoli P, Crosti C**. Drug-induced lupus: an update on its dermatologic aspects. *Lupus*. 2009 Oct;18(11):935-40. Review. PubMed PMID: 19762393.
35. **Moreland L, Bate G, Kirkpatrick P**. Abatacept. *Nat Rev Drug Discov*. 2006 Mar;5(3):185-6. Review. PubMed PMID: 16557658.
36. **Kündig TM, Trüeb RM, Krasovec M**. Lupus profundus/panniculitis. *Dermatology*. 1997;195(1):99-101. PubMed PMID: 9267758.
37. **Fox JN, Klapman MH, Rowe L**. Lupus profundus in children: treatment with hydroxychloroquine. *J Am Acad Dermatol*. 1987 Apr;16(4):839-44. PubMed PMID: 3571546.
38. **Winkelmann RK**. Panniculitis and systemic lupus erythematosus. *JAMA*. 1970 Jan 19;211(3):472-5. PubMed PMID: 5466921.
39. **Burrows NP, Walport MJ, Hammond AH, Davey N, Jones RR**. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol*. 1991 Jul;125(1):62-7. PubMed PMID: 1873207.
40. **Cuadrado MJ, Karim Y, Sanna G, Smith E, Khamashta MA, Hughes GR**. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med*. 2005 Mar;118(3):246-50. PubMed PMID: 15745722.
41. **Hanjani NM, Nousari CH**. Mycophenolate mofetil for the treatment of cutaneous lupus erythematosus with smoldering systemic involvement. *Arch Dermatol*. 2002 Dec;138(12):1616-8. PubMed PMID: 12472362.

Submitted on August 13, 2012