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Case Report

Lupus profundus limited to a site of trauma: Case report and review of the literature☆

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ABSTRACT

Lupus erythematosus profundus (LEP) is a rare form of chronic cutaneous lupus erythematosus. We report on a case of a 56-year-old Caucasian woman who presented with a single, persistent, painful rash on the left hip and lateral aspect of the left upper thigh, which had been present for 2.5 years. The patient had a history of previous injury to this area before the rash started. Clinical findings showed an inflamed, hyperpigmented, and indurated plaque with a linear skin invagination and no associated systemic symptoms. A skin biopsy test result confirmed the diagnosis of LEP and the clinical and laboratory examinations ruled out systemic lupus erythematosus. After 2 months of treatment with methotrexate 20 mg weekly and 1 month of prednisolone 7.5 mg daily, the skin rash improved considerably. We also present a brief review of the epidemiology, etiology, clinical features, histopathology, laboratory findings, differential diagnosis, and treatment of LEP.

Case report

A 56-year-old Caucasian woman presented with a persistent painful rash on the left hip and lateral aspect of the left upper thigh, which had been present for 2.5 years. The patient had a fall with blunt contusion to the same area 2 months before the rash started, which caused persistent left-sided tenderness and hip pain. The patient underwent magnetic resonance imaging and the scan demonstrated an extensive subcutaneous contusion with fat necrosis in the left gluteal region with no muscle or tendon injury. Over the past years, the patient reported only persistent left hip, gluteal, and upper lateral left thigh tenderness that was associated with the development of a hyperpigmented and indurated plaque and intermittently became very inflamed but no other systemic symptoms. In the year immediately prior to presentation, linear skin invagination had developed and was enlarging gradually on the upper border with more induration, allodynia, and tenderness around this area. The patient was otherwise healthy with a history of osteoporosis and no current treatment and she had no personal and family history of autoimmune diseases.

During a physical examination, the patient was determined to have a large, indurated, tender, erythematous-to-violaceous, poorly demarcated plaque on the left hip and lateral aspect of the left upper thigh. Inside the plaque was a large linear skin depression (Fig 1A). She had no other skin lesions or symptoms, except for arthralgias on the hand joints.

Laboratory test results disclosed normal levels of blood cell counts, urinalysis, complements (C3, C4, CH50), and renal function. Some liver function tests results showed slightly elevated levels (gamma-glutamyl transferase 63 U/L [normal, 0-30 U/L], aspartate aminotransferase 52 U/L and alanine aminotransferase 55 U/L [normal, <45 U/L], and erythrocyte sedimentation rate 30 mm/hr [normal, 0-20 mm/hr]). Serological study results showed low grade antinuclear antibody results (antinuclear antibody, titer 1:320, homogenous pattern; titer 1:80, nucleolar; 1:80, cytoplasmic) and anti-ribonucleoprotein/Sm antibody and anti-nucleosomes antibody test results were positive. Anti-ds-DNA antibody, anti-Sm antibody, rheumatoid factor, and anti-cyclic citrullinated peptide antibody test results were negative.

An examination of deep skin biopsy tissue of the lesion revealed an epidermis of normal thickness. The underlying dermis showed perivascular and interstitial lymphocytes with dermal edema and

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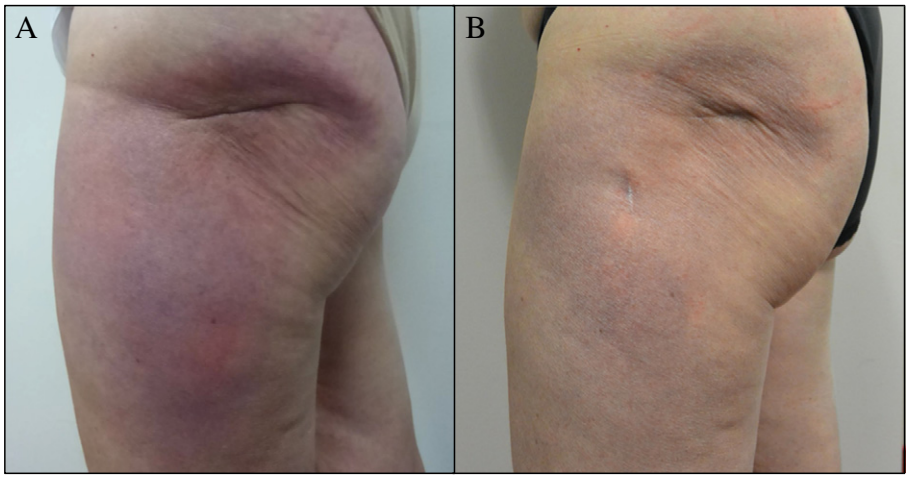

Fig. 1. Clinical manifestation of lupus erythematosus profundus. A) Before treatment. A large, indurated, erythematous-to-violaceous, poorly demarcated plaque on the left hip and lateral aspect of the left upper thigh within a large linear skin invagination of lipoatrophy. B) Plaque with less edema, inflammation, and induration, after 2 months of therapy, showing signs of postinflammatory hyperpigmentation.

mucin. The inflammation was more marked in the deeper dermis and subcutis where there were lymphoid aggregates with focal germinal center formation. Fat lobules were reduced in size and associated with hyaline fat necrosis. The inflammation and lobular panniculitis extended the full depth of the biopsy tissue. Lymphocytes surrounded the vessels and permeated the walls but vascular destruction was not evident (Fig 2A and B). The test results of a direct immunofluorescence examination (DIF), and fungal and bacterial cultures of skin specimens were negative.

A diagnosis of lupus erythematosus profundus (LEP) was made on the basis of a combination of clinical (indurated erythematous-violaceous patch with hypodermis atrophy) and histological findings of lymphocytic cells infiltration over the dermis (more marked within the deeper dermis) and subcutaneous tissues, and hyaline fat necrosis in the context of antinuclear antibody positive test results. Treatment with hydroxychloroquine 200 mg twice daily was initiated but the patient developed a drug eruption within 2 weeks, which was confirmed by an examination of skin biopsy tissue. Treatment with hydroxychloroquine was stopped and methotrexate 5 mg/week was initiated with gradual increases up to 20 mg/week, along with prednisolone 7.5 mg daily for 1 month. After 2 months of methotrexate 20 mg weekly, the skin rash improved considerably, showing less induration, edema, and erythema (Fig 2B). The patient continued treatment with methotrexate 20 mg/week for 6 months without complications or flare-ups.

Discussion

LEP is an infrequent form of chronic cutaneous lupus erythematosus (Massone et al., 2005; Tuffanelli, 1971). The term *lupus profundus* is used with dermal and subcutaneous involvement. When there is solely subcutaneous involvement, it is called lupus panniculitis (Walling and Sontheimer, 2009). Studies have described the frequency of LEP at 1% to 3% of patients with cutaneous lupus erythematosus (Requena and Sánchez Yus, 2001; Walling and Sontheimer, 2009). LEP may manifest as a unique entity or can be associated with discoid lupus erythematosus (DLE) or systemic lupus erythematosus (SLE). A patient with LEP has approximately 50% of probability to develop SLE (Kundig et al., 1997). When LEP is present in combination with SLE, the prognosis of the systemic disease is often better because the patient usually develops a mild form of SLE with infrequent neurological and renal manifestations (Fraga and García-Díez, 2008; Kundig et al., 1997). Our patient did not fulfill the American College of Radiology criteria for SLE.

Epidemiology

LEP frequently occurs as a separate disease. However, 2% to 5% of patients with SLE and approximately 10% of those with DLE develop lupus panniculitis. LEP presents more frequently in women. The percentages of frequency are variable with a female/male ratio between

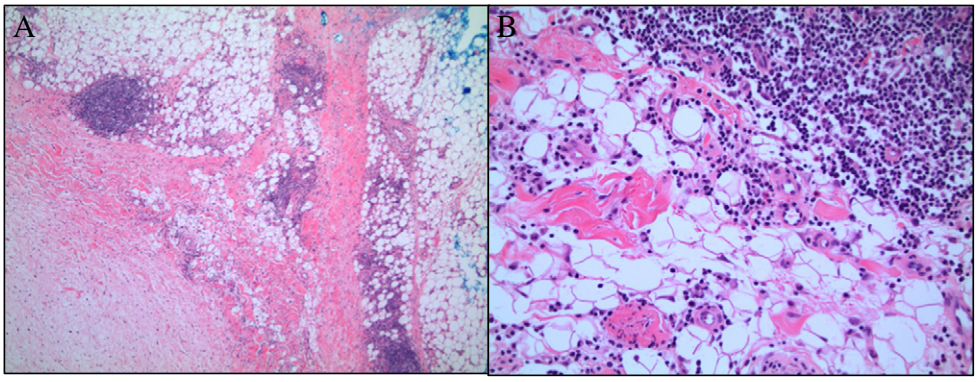

Fig. 2. Histopathology. A) Dermis with perivascular and interstitial lymphocytes, edema and mucin. The inflammation is more marked within the deeper dermis and subcutis where there are aggregates with focal germinal center formations. B) Subcutis with interstitial lymphocytes and plasma cells. Fat lobules are reduced in size and associated with hyaline fat necrosis.

2:1 and 9:1 among different series. The age of onset varies as well but the majority of patients fluctuate between 30 years to 60 years of age (Bednarek et al., 2015; Fraga and García-Díez, 2008). In the Asian population, LEP seems to occur at an earlier age (Ng et al., 2002). LEP in children is less frequent (Wimmershoff et al., 2003). Exceptionally, LEP can be a manifestation of neonatal lupus (Nitta, 1997).

Etiology

The etiology of LEP is not completely understood. Sometimes, there is a history of prior trauma on the sites of cutaneous lesions (Lee et al., 2011; Tuffanelli, 1971). Clinical cases have been described in which the cutaneous manifestations worsened on the sites where biopsies or injections were performed (Fraga and García-Díez, 2008). Our case is of interest because the LEP appeared solely in an area of previous injury and the clinical manifestations of LEP started 2 months after the trauma occurred. We believe that the trauma contributed significantly to the development of LEP in this case. Tuffanelli (1971) reported on six cases of LEP of which four had a probable relationship to trauma with affected skin sites on the face, upper arms, chest, abdomen, and buttocks. Lee et al. (2011) reported on a case of LEP that initially started on the patient's right upper thigh after trauma. Unfortunately, the amount of time between injury and development of LEP in all these cases was not included.

Also, some cases of DLE that are described in the literature developed after trauma (Eskreis et al., 1988; Kern and Schiff, 1957; Ruocco et al., 2013; Schiff and Kern, 1954). The mechanism behind the trauma that induces cutaneous lupus is unknown. Ruocco et al. (2009, 2014) introduced the concept of *immunocompromised district* to explain how different skin injuries may generate some skin diseases. The researchers proposed that after certain clinical events on the skin such as persistent lymph stasis, herpetic infections, ionizing radiation, or thermal or mechanical injuries, the affected sites are damaged and immunologically compromised. Consequently, these areas are more susceptible to develop skin disorders such as opportunistic infections, tumors, and allergic or hyperimmune reactions. The researchers explained that the neuro-immuno-cutaneous system that is essential for a normal and well-balanced immune response is damaged, which results in a dysregulated local immune response that may remain destabilized forever. In addition, a study of Murphy Roths Large/++ lupus-prone mice suggested that severe tissue trauma (i.e., a large, full-thickness, cutaneous burn injury) triggers and exacerbates inflammatory skin disease and severe multi-organ pathogenesis in lupus-prone mice (Anam et al., 2009).

Chronic minor trauma also plays a part in other autoimmune skin diseases such as the Köebner phenomenon that is observed in psoriasis and lichen planus as well as diseases that mainly occur in trauma-prone sites including epidermolysis bullosa acquisita.

Cutaneous lupus erythematosus in general is an interplay between ultraviolet irradiation, autoantibody generation, and dysregulation of T cells, dendritic cells, and other immune cells (Yu et al., 2013).

Clinical features of lupus erythematosus profundus

LEP is characterized by tender, deep, subcutaneous nodules or plaques, which are usually localized on the scalp, face, proximal extremities, and especially the lateral aspects of the arms and shoulders, breast, trunk, and buttocks. Cutaneous lesions can be single or involve multiple areas of the body; however, the latter form of presentation is infrequent. The face is often affected in children with LEP. The disease has a chronic course that is characterized by remission and flare-ups. Erythema is a common clinical feature in the overlying skin although classic DLE can present also on the skin surface with characteristic features such as scaling, depigmentation, follicular plugging, atrophy, telangiectasias, or ulceration.

In addition to the classical form of LEP (i.e., deep dermal or subcutaneous nodules or plaques), other clinical presentations such as linear (Lee et al., 2011; Marzano et al., 2005; Mitxelena et al., 2013), morphea-like lesions (Stork and Vosmík, 1994), sclerodermoid linear lesions (Marzano et al., 2005), and annular configurations (Bacanli et al., 2005; Mitxelena et al., 2013) have been described in the literature. Other unusual manifestations include the involvement of salivary glands (White et al., 1993) and periorbital edema as the presenting skin symptom of lupus erythematosus panniculitis of the peribulbar fat pads (Franke et al., 1999). When the lesions have resolved, skin characteristically develops areas of lipoatrophy that present as depressions or skin retraction. This may produce great morbidity that causes destructive cosmetic results and disability that is related to painful lesions. For example, one case has been reported of LEP of the scalp that was associated with Parry Romberg syndrome, which caused significant disfiguration to the patient (Grossberg et al., 2001).

Histopathology

The golden standard of an LEP diagnosis is the histopathology examination result of a deep skin biopsy of the lesional area. Histopathology of LEP shows a predominantly lymphocytic lobular or mixed panniculitis with frequent plasma cells and sometimes eosinophils. In 45% to 78% of cases, lymphoid follicles are present, sometimes with germinal centers (20% of the cases), with a perilobular distribution (Fraga and García-Díez, 2008).

Another characteristic feature is hyaline fat necrosis. Additional histopathology findings include pathological changes of DLE in the overlying skin, dermo-epidermal changes such as the thickening of the basement membrane, mucin deposition, calcification, and vascular changes such as lymphocytic vasculitis, fibrin thrombosis, and perivascular fibrosis. Vascular changes seem to be the cause of ulceration in some patients. The two most important histopathologic criteria for a diagnosis of LEP are the presence of lymphocytic infiltrates that involve fat lobules and the hyaline necrosis of the fat lobule. Direct immunofluorescence varies among the different series from 36% (Ng et al., 2002) to 90.5% (Arai and Katsuoka, 2009).

Laboratory findings

Serologic analysis results are often normal. Sometimes positive antinuclear antibody titer can be demonstrated and is variable among the published series, ranging from 27% to 95.4% (Arai and Katsuoka, 2009; Massone et al., 2005; Ng et al., 2002). As in all form of lupus, the antinuclear antibody titer alone cannot serve as a basis for diagnosing LEP but has to be considered as an auxiliary test to diagnose LEP. Less frequently, anti-double-stranded DNA antibodies are present. Syphilis serology test results may be falsely positive (Kundig et al., 1997). Other possible laboratory abnormalities may include lymphopenia, anemia, decreased C4 levels, and positive rheumatoid factor.

Diagnosis and differential diagnosis

The diagnosis of LEP may be extremely difficult, especially in patients who lack other skin or systemic manifestations of lupus erythematosus. The diagnosis of LEP is based on characteristic clinical features and confirmed by histopathology. The differential diagnosis includes the inflammatory diseases of subcutaneous fat such as erythema nodosum, erythema induratum of Bazin, subcutaneous panniculitis-like T-cell lymphoma (SPTCL), and traumatic fat necrosis. The distinction is based on routine histology, immunofluorescence, and serology. The particularly troublesome differential diagnosis is SPTCL (Arps and Patel, 2013).

Treatment

There are no randomized controlled trials of treatments for LEP. Topical therapy consists of glucocorticosteroid (Yell and Burge, 1993) and lubricant ointments. Injections of glucocorticosteroid medications into lesional areas are generally ineffective and can exacerbate the atrophy (Fraga and García-Díez, 2008). Systemic, first-line therapy for LEP as well as other forms of CLE traditionally has been antimalarial medications such as hydroxychloroquine (dose 200-400 mg daily) or chloroquine (250-500 mg daily) (Bednarek et al., 2015; Espírito Santo et al., 2010; Housman et al., 2003). Systemic corticosteroid medications are often useful for severe cases that are accompanied by SLE (Bednarek et al., 2015; Espírito Santo et al., 2010).

Other reported systemic therapies include thalidomide (Housman et al., 2003; Espírito Santo et al., 2010), dapsone (Espírito Santo et al., 2010; Ujiie et al., 2006), methotrexate (Espírito Santo et al., 2010; Grossberg et al., 2001), cyclosporine (Espírito Santo et al., 2010; Saeki et al., 2000; Wozniacka et al., 2007), cyclophosphamide (Espírito Santo et al., 2010; Grossberg et al., 2001), intravenous immunoglobulins (Espírito Santo et al., 2010), and rituximab (McArdle and Baker, 2009; Moreno-Suárez and Pulpillo-Ruiz, 2013).

Given the association between LEP and SLE (Martens et al., 1999; Patel and Marfatia, 2010; Zhao et al., 2016), patients with LEP should be regularly monitored for development of symptoms and signs that are related to SLE. Regular blood and immunologic tests have to be performed on these patients to make an early diagnosis and provide proper treatment. The biopsy with immunohistochemistry and T-cell receptor gene rearrangement studies should be repeated on those patients who are resistant to appropriate treatment to rule out SPTCL.

Conclusion

LEP is a relatively rare presentation of lupus that occasionally may occur in association with SLE. This patient presentation was unusual because it was localized only at a site of trauma.

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