

# Lupus erythematosus panniculitis in children and adolescents

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## ABSTRACT

**Introduction:** Lupus erythematosus panniculitis (LEP) or lupus erythematosus profundus is a rare form of chronic cutaneous manifestation affecting both adults and pediatric patients. The prevalence of this manifestation was seldom reported in juvenile systemic lupus erythematosus (JSLE).

**Case reports:** From January 1983 to December 2010, 5,506 patients were followed at the Pediatric Rheumatology Unit of our University Hospital and 278 (5%) of them met the American College of Rheumatology classification criteria for JSLE. Two (0.7%) of them had LEP at JSLE onset. These two cases had tender deep inflammatory subcutaneous nodules or plaques at the time of diagnosis, and the histopathologic pattern evidenced lobular or mixed panniculitis with lymphocytic inflammatory cells of the fat lobule. Treatments for LEP included mainly antimalarials, systemic corticosteroids and sunscreen protection. One male patient required thalidomide and immunosuppressive drugs, including mycophenolate mofetil, cyclosporin and intravenous cyclophosphamide. However, skin lesions improved only after rituximab treatment.

**Discussion:** LEP was rarely observed in our cohort of JSLE patients as the first lupus manifestation. Anti-CD20 monoclonal antibody therapy may be an option for refractory LEP treatment in children.

**Keywords:** Panniculitis; Autoimmune; Children; Juvenile Systemic Lupus Erythematosus; Rituximab.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder that may affect multiple organs and systems<sup>1</sup>, including cutaneous involvement<sup>2</sup>. Skin manifestations are frequent in adult and juvenile SLE (JSLE) patients, and are the first symptoms of the disease in 23% to 28% of patients<sup>2</sup>.

A variety of cutaneous features can be evidenced in lupus patients, including lupus erythematosus panniculitis (LEP) or lupus erythematosus profundus<sup>3,4</sup>. LEP is a rare form of chronic cutaneous lupus erythematosus (CCLE) and it is characterized by recurrent nodules or plaques in deep dermis and subcutaneous tissues, mainly affecting the proximal limbs, buttocks and face, leading to local swelling and skin atrophy. Of note, the prevalence of this manifestation in paediatric lupus population was not reported.

Therefore, we reviewed our data from January 1983 to December 2010 that included the 5,508 patients of Paediatric Rheumatology Unit of the Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo. We identified 278 (5%) cases that met the American College of Rheumatology (ACR)<sup>5</sup> classification criteria for JSLE. Two (0.7%) of them had JSLE and were described herein. This study was approved by the Local Ethics Committee of our University Hospital.

## CASE REPORTS

### CASE 1

An 8-year old boy was admitted in our University Hospital with one-year history of fever and recurrent tender erythematosus nodules, with skin hyperpigmentation and atrophy affecting the face, proximal upper limbs, back and trunk. At that time, laboratory exams revealed hemoglobin 14g/dL, hematocrit 38.6%, white blood cell count 9,700/mm<sup>3</sup> (60% neutrophils, 35%

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**Figure 1.** Skin vasculitis and diffuse tender erythematous nodules in right hand with loss of distal segment of the second finger in an 11-year old boy patient with lupus erythematosus panniculitis.

lymphocytes, 2% eosinophils and 3% monocytes), platelets  $216,000/\text{mm}^3$ , urinalysis (1,000 leukocytes and zero erythrocytes), C3 184 mg/dL (normal 90-180), C4 22 mg/dL (normal 10-44), IgG 2000 mg/dL (normal 570-1320), IgA 306 mg/dL (normal 65-240), IgM 149 mg/dL (normal 60-175), erythrocyte sedimentation rate (ESR) 45 mm 1<sup>st</sup> hour (normal < 20), C-reactive protein (CRP) 2.75 mg/L (normal < 5) and proteinuria 0.22 g/24h. Immunological tests were positive for antinuclear antibodies (ANA) 1:80 (fine speckled pattern) and negative for other serum antibodies: anti-double stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-Ro, anti-La, anti-Jo-1, anti-Scl-70, antineutrophil cytoplasmic antibody (ANCA), and IgG and IgM anticardiolipin. Skin biopsy from upper back region showed septal and lobular panniculitis, with inflammatory infiltrate predominantly composed of lymphocytes in fat lobules and paraseptal regions, hyaline fat necrosis, without vasculitis. Dermoepidermal changes evidenced loss of the normal organization and orientation of basal cells, basement membrane thickening, and superficial and deep perivascular dermal lymphocytic infiltrates. Direct immunofluorescence study of lesional skin was negative to IgG, IgM, IgA and C3. Diagnosis of LEP was established and the patient was treated with prednisone (2 mg/kg/day, progressively tapered to 20 mg/day), chloroquine diphosphate (5 mg/kg/day), cyclosporine (3 mg/kg/day) and sunscreen protection, with improvement of all clinical manifestations. At 9 years of age, he presented headache and seizures. Brain magnetic resonance imaging

showed high signal intensity on T2-weighted images predominantly in the posterior regions compatible with reversible posterior leukoencephalopathy, and cyclosporine was replaced by azathioprine (100 mg/day). One year later, he developed recurrent erythematous nodules with hyperpigmentation on the face, neck, arms, back, trunk and inferior limbs. Mycophenolate mofetil (30 mg/kg/day) and thalidomide (2 mg/kg/day) were started. At 11 years, he presented severe ischemia and loss of distal segment of the second finger of right hand and generalized skin vasculitis, diffuse tender erythematous nodules (Figure 1), affecting face, arms, shoulders, trunk, hands, legs and feet and pericarditis. At that moment, his exams showed: white blood cell count  $1,900/\text{mm}^3$  (54% neutrophils, 39% lymphocytes, 6% monocytes and 1% eosinophils), platelets  $108,000/\text{mm}^3$ , proteinuria 0.7 g/24h, ANA 1:160 (fine speckled pattern), anti-Ro 1:40 UI/mL and the diagnosis of JSLE was confirmed according to the ACR criteria<sup>5</sup>. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score was 13<sup>6</sup>. He was treated with monthly intravenous cyclophosphamide (750 mg/m<sup>2</sup>/dose) and three pulses of intravenous methylprednisolone on a monthly basis for four consecutive months. However, after four months, he developed diffuse tender erythematous nodules, palpable purpura, skin ulcers, and ischemia of distal segment of the third finger of left hand. A treatment with four weekly doses of rituximab (375 mg/m<sup>2</sup> per dose) showed a remarkable improvement of the skin vasculitis, despite the persistence of both diffuse skin hyperpigmentation and atrophy. No adverse events were observed after anti-CD20 monoclonal antibody therapy. The patient has remained symptom free for over 12 months.

## CASE 2

A 13-year old girl presented with a history of fever, polyarthritis in shoulders, left elbow, knees and ankles, and cervical lymphadenopathy for the last 20 days. Two subcutaneous, erythematous and tender nodules were evidenced on the left leg. The patient was hospitalized in our University Hospital and laboratory exams revealed hemoglobin 10.5g/dL, hematocrit 31.2%, white blood cell count  $1,500/\text{mm}^3$  (40% neutrophils, 43% lymphocytes, 7% eosinophils and 10% monocytes), platelets  $202,000/\text{mm}^3$ , C3 0.88 g/L (normal 0.5-1.8), C4 0.08 g/L (normal 0.1-0.4), urinalysis (2,000 leukocytes, zero erythrocyte), proteinuria 0.7 g/day, ESR 57 mm 1<sup>st</sup> hour and CRP 162

mg/L. Immunologic tests revealed ANA titers of 1:160 (homogeneous pattern), positive anti-dsDNA, anti-thyroid peroxidase, anti-thyroglobulin, anticardiolipin IgG (67.3 GPL) and IgM anticardiolipin (15.4 MPL) antibodies. Serologic tests for hepatitis virus A, B and C, Epstein-Barr virus, parvovirus B19, cytomegalovirus, toxoplasmosis and human immunodeficiency virus (HIV) infections were negative. Bone marrow aspirate was normal. After five days of hospitalization, the other serum autoantibodies were negative: anti-Sm, anti-RNP, anti-Ro and anti-La. The skin biopsy from left leg showed lobular panniculitis with inflammatory infiltrate composed of lymphocytes and lymphocytic vasculitis in the small-sized vessels. No deposits of IgG, IgM and C3 were observed in direct immunofluorescence of lesional skin. Therefore, the diagnosis of JSLE<sup>5</sup> and LEP were established. At that moment, the SLEDAI-2K score was 20<sup>6</sup>. At the same day of lupus diagnosis, she had sepsis despite previous ceftriaxone use, and died after 12 days of hospitalization. The autopsy showed acute tubular necrosis, diffuse alveolar damage compatible with acute respiratory distress syndrome, and diffuse cerebral edema, cerebellar infarcts and brain herniation with multiple hemorrhages compatible with sepsis.

## DISCUSSION

To our knowledge, this is the first study that evaluated the prevalence of LEP in a large population of Paediatric Rheumatology University Hospital, showing a rare frequency of this type of skin involvement as the first disease manifestation.

Of note, LEP is a rare chronic lupus cutaneous involvement, and was reported in adult SLE and discoid lupus, as a single skin abnormality (with and without systemic manifestations)<sup>7,11</sup>, and was rarely described in JSLE population<sup>11</sup>. Indeed, the prevalence of LEP associated with SLE ranged from 2% to 5%, and this alteration may occur before or after the disease onset<sup>7</sup>. Contrary to other subtypes of cutaneous lupus, these lesions occur frequently in female gender<sup>8,10,11</sup>.

Usually, LEP manifests as tender deep subcutaneous nodules or plaques that involve shoulders, upper arms, trunk, buttocks, and legs<sup>7,11</sup>, as observed herein. Interestingly, a predilection for facial involvement was evidenced in pediatric cases<sup>7</sup>, regardless of the absence of clinical and histopathologic signs of discoid lupus on the overlying skin, as shown in our two JSLE cases.

In our series, other initial clinical manifestations in LEP patients included fever and pericarditis<sup>8,11</sup>.

Although there are no specific serologic findings in LEP, some studies suggest a high probability of systemic involvement in patients with LEP and ANA<sup>12</sup>.

Of note, one of our cases had reversible posterior leukoencephalopathy possibly associated with cyclosporine treatment. This is a neurologic abnormality characterized by headache and seizure. The imaging study confirms the diagnosis, showing posterior leukoencephalopathy, which was rarely reported in JSLE patients<sup>13</sup>.

Histopathologic pattern in LEP patients is characterized by lobular or mixed panniculitis with lymphocytic inflammatory cells of the fat lobule<sup>9,10,14</sup>. Other characteristics include dermoepidermal changes and lymphocytic vasculitis in the small vessels of the fat lobule, as described in our cases. Importantly, differential diagnosis encompass subcutaneous panniculitis-like T-cell lymphoma, deep morphea, erythema nodosum, erythema induratum of Bazin, post-steroid panniculitis<sup>7-8</sup>, Weber-Christian disease and sarcoidosis.

Treatments of LEP include mainly antimalarials, which is the first therapy option<sup>10,11</sup>, mainly in non-smokers patients<sup>7</sup>. Corticosteroids are the second line of therapy, although severe adverse events may be observed<sup>7,11</sup>. Topical corticosteroids are generally ineffective, and the intralesional administration can lead to local atrophy and ulcerations<sup>10</sup>. The depth and extension of the lesion suggest that the ultraviolet light may participate in the disease's pathogenesis. Therefore the use of sunscreen protection is indicated, as it was in our patients<sup>10</sup>.

Other treatment modalities for refractory cases have included thalidomide<sup>7,10</sup>, and immunosuppressive drugs, such as methotrexate<sup>14</sup>, mycophenolate mofetil<sup>10</sup> cyclosporin and intravenous cyclophosphamide<sup>7</sup>, as used in our first case. Rituximab was the only therapy to induce skin improvement in one of our patients, as previously described in one adult with lupus panniculitis<sup>15</sup>. To our knowledge, this was the first case reported with LEP and JSLE that was treated with anti-CD20 monoclonal antibody therapy. In addition, one of our patients, who had acute and severe lupus, had severe sepsis, even before receiving lupus treatment.

In conclusion, LEP proved to be rare in our pediatric population with lupus and it may be the first lupus manifestation. Anti-CD20 monoclonal antibody therapy may be an option for refractory LEP treatment in children.

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