Lupus Erythematosus Panniculitis: Clinical and Histopathological Diagnostic Challenge

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Abstract: Panniculitis is the inflammation of subcutaneous fat that sometimes associates with connective tissue diseases. One of the well-described forms of connective tissue panniculitis is lupus erythematosus panniculitis (LEP). We report a 35-year-old female patient with skin atrophic lesions on the lateral aspect of the upper arms and cheeks for at least 8-year duration. The atrophic lesions were followed by recurrent multiple small nodules on the right jaw and neck, on which excisional biopsy was performed. Histopathology examination revealed lobular panniculitis consistent with LEP. However, slight hyalinosis and thickened collagen bundles were also observed that deep morphea could not be ruled out. The patient was treated with hydroxychloroquine 200 mg/day and methotrexate 7.5 mg a week, showing improvement by decreased ANA titer. No new nodules and enlargement of atrophic areas were found after the one-month course of therapy.

1 INTRODUCTION

Inflammation of the subcutaneous fat known as panniculitis can be seen in many disorders, including connective tissue diseases. Panniculitis occurring in connective tissue diseases are lupus erythematosus panniculitis (LEP), panniculitis associated with dermatomyositis, morphea, and scleroderma, which were also known as connective tissue panniculitides and associated with autoimmune phenomena. (Gupta P et al., 2016; Braunstein I et al., 2012) LEP, or also known as Kaposi-Irgang disease, is a rare form of chronic cutaneous lupus erythematosus characterized by inflammatory lesions in the lower dermis and subcutaneous tissue. (Costner et al., 2012; Aronson IK et al. 2012). The most important differential diagnosis of LEP is deep morphea. Morphea or localized scleroderma is a chronic autoimmune disease characterized by sclerosis of the skin. (Costner et al., 2012; Saxton-Daniels et al., 2012). Diagnosing panniculitis is often difficult due to inadequate clinical details, overlapping clinical and histopathological features, inadequate biopsy specimens, and evolving morphology of different types of panniculitides at different stages. (Panniculitis associated with connective tissue diseases resolves with depressed atrophic scar leading to cosmetic disfigurement and decrease in quality of life. (Braunstein I et al., 2012; Hansen CB et al., 2010). report a case of connective tissue panniculitis featuring atrophic lesions on upper arms and cheeks for at least 8-year duration. Despite previous histopathology evaluation, it was not correctly diagnosed that definitive treatment had been delayed leading to permanent atrophy. This case report aimed to raise the awareness of the entity, the importance of skin biopsy for diagnosis, and prompt treatment to improve quality of life.

2 CASE

A 35-year-old female presented with skin atrophy on the lateral aspect of the upper arms for 12 years and cheeks for eight years. The lesions started as bluish-red bumps without pain or itch. Over six months, the lesions progressed to atrophic scar with healthy skin appearance. She also had suffered from a similar process on her cheeks for eight years, followed by...
multiple small nodules on the right jaw and neck. She underwent surgical excision and was diagnosed with tuberculosis lymphadenopathy by an internist. She was treated with a fixed-dose combination of antituberculosis drugs for six months, and the nodules were improved. Over the past ten months, multiple recurrent nodules had developed on the right neck. She underwent fine-needle aspiration biopsy, resulted as a benign submandibular lesion, and she was referred to oncology surgeon in our hospital. An excisional biopsy was performed, histopathology and immunohistochemistry examination confirmed a reactive polyclonal lymphoproliferative process (lymphocytes positive for CD30, CD20, CD138, CD4, CD8, and Ki67 ±20% of a nucleus). She was consulted to the hemato-oncology division and dermatology-immunology division. No history of skin trauma, fever, malaise, weight loss, stomatitis, joints, pain, or hair loss was found. There was no history of malignancy or similar symptoms in the family.

Physical examinations revealed multiple atrophic lesions on the cheeks and lateral aspect of the upper arms with the normal skin surface. There were two immobile and painless lymph node enlargement in the neck and submandibular region, 1x1x0.5 cm in size. Chest X-ray examination result was within normal limits. Ultrasonography of neck showed right mandible isoechogenic lesion and partially bilateral multiple conglomerated right intraparticle lymph nodes. Level II right neck lymphadenopathy was found in CT scan of the neck with contrast.

Laboratory test results showed normal levels of complete blood count, renal and liver function tests, but a decrease in vitamin D 25-OH level (21ng/dl). HIV screening assays, HBsAg, anti-HCV, C3, C4 levels, and anti-dsDNA test were negative. ANA 1/1000, coarse speckled pattern, possible antibodies on hnRNP, U1RNP, Sm, RNA Polymerase III. Ro-52 recombinant borderline and SS-B positive in ANA profile.

In the dermatology-immunology clinic, patients were suspected of LEP, different from the earlier histopathologic result. So, we asked for a reevaluation of the biopsy specimens to dermatopathology division. Histopathology reading revealed epidermal atrophy, vacuolar alteration, and flattening of rete ridges; perivascular and periadnexal lymphohistiocytic infiltrates forming lymphoid follicles; and lymphohistiocytic infiltrates among fat lobules which showed partial necrosis with corresponding Touton giant cells, and lipophagia, supporting a diagnosis of LEP. Ziehl-Neelsen, Periodic Acid-Schiff (PAS), and Gram staining did not demonstrate acid-fast bacilli, thickened basement membrane, and bacteria respectively. However, as there was suspicion for morphea, another reading was done that found what was considered as hyalinized and thickened collagen bundles. The diagnosis of LEP with deep morphea as a differential diagnosis was made.

After confirming a normal glucose-6-phosphate dehydrogenase (G6PD) level and no ophthalmic contraindication to an antimalarial drug, the patient began treatment with hydroxychloroquine 200 mg a day and topical sunscreens. Later at one month follow upslesions were stable without new nodules, and ANA titer decreased to 1/320. Methotrexate was given in initial dose 5 mg a week, escalated to 7.5 mg a week accompanied with folic acid 5 mg a week orally in addition to hydroxychloroquine. During the last three months, the atrophic lesions were stable, no new nodules were found, and multiple nodules on the right neck decreased in size.

Figure 1. A–E. Multiple atrophic lesions with normal skin surface (arrow).
3 DISCUSSION

Panniculitis associated with connective tissue disease begins with active inflammation and develops into atrophy, scar, and calcification. (Gupta P et al., 2016; Braunstein I et al., 2012; Hansen CB et al., 2010) Diagnosis of LEP and deep morphea as a differential diagnosis were established based on clinical, laboratory, and histological findings. LEP is characterized by inflammatory of the lower dermis and subcutaneous tissue, estimated to comprise 1–3% of cutaneous LE cases. (Costner et al., 2012; Aronson IK et al., 2012) LEP lesions begin with subcutaneous nodules without or with any surface changes including erythema and discoid lupus erythematosus (DLE) features. The most common sites are on the lateral aspect of upper arms, shoulders, face, scalp, hips, breasts, and buttocks. The mean duration of the disease is six years and resolves with depressed lipoatrophic areas. (Aronson IK et al., 2012). Clinically, the disease’s course and location in our patient matched with those of LEP. Fifty percent of LEP patients could develop systemic lupus erythematosus (SLE) with mild manifestations. (Fett N et al., 2011; Castrillon MA et al., 2017). On the other hand, Deep morphea is a chronic autoimmune disease characterized by skin sclerosis that involves the deep dermis, subcutaneous tissue, fascia, and muscle. Both diseases are more common in females aged 30–60 years old and resolve with depressed atrophic scar. (Costner et al., 2012; Saxton-Daniels et al., 2012; Fett N et al., 2011)

Serologic analysis for LEP are often normal, and sometimes variable positive ANA titer demonstrated ranging from 27–95.4% of cases. Less frequently, anti-ds-DNA antibodies are present. (Aronson IK et al., 2012; Castrillon MA et al., 2017; Zhao YK et al., 2016) In our patient, the laboratory showed ANA titer 1/1000. However, anti-dsDNA is not present. Positive ANA could also be found in 39–80% morphea with speckled pattern (81%) and titer >1/1280. (Saxton-Daniels et al., 2012; Teke MN et al., 2017)

The gold standard of LEP diagnosis is the histopathology examination result from a deep skin biopsy of the lesional area. (Castrillon MA et al., 2017; Bednarek A et al., 2015). The histopathological finding of LEP shows mostly lobular or mixed panniculitis with a variable lymphocytic infiltrate. Meanwhile, panniculitis on deep morphea is predominantly septal. (Gupta P et al., 2016; Bednarek A et al., 2015) In our patient, the important findings included lymphoid follicles (that lead to the previous diagnosis of lymphoproliferative disorder), necrosis of fat lobules, and what was thought later to be hyalinized and thickened collagen bundles. With these overlapping clinical and histopathological features, diagnosis in our case was made with a degree of uncertainty. Lipoatrophic
panniculitis is a diagnosis of exclusion that requires evaluating for other causes of panniculitis. (Aronson IK et al., 2012; Hansen CB et al., 2010). In our patient, laboratory findings within normal limits and staining for Ziehl-Neelsen, Periodic Acid-Schiff (PAS), and Gram examination were used to eliminate infection, all returned negative. The differences between LEP and deep morphea are depicted in Table 1.

As immunohistochemistry examination confirmed a reactive polyclonal lymphoproliferative disease, another important differential diagnosis is subcutaneous panniculitis-like T-cell lymphoma (SPTCL), a lymphoma whose origin is from mature cytotoxic T cells.(Sugeeth et al., 2017;Lerma IL., 2018;Arps DP et al., 2013). As lymphocytes were positive for CD3, CD4, CD8, and CD20 (B cells marker) in our patient, SPTCL were excluded.

Antimalarial drugs such as hydroxychloroquine or chloroquine are usually the first-line treatment for LEP. Antimalarials interfere with inflammatory cytokines as well as TLRs, requiring at least three months to show effectiveness. (Costner et al., 2012;Aronson IK et al., 2012). The patient has treated with hydroxychloroquine 200 mg a day with good response, shown by decreased ANA titer from 1/1000 to 1/320, no new nodules or enlargement of atrophic lesion found after a month. Since methotrexate was recommended as a first-line treatment for morphea with dermal and subcutaneous involvement, five we also added methotrexate to previous hydroxychloroquine treatment.

Table 1. Summary of clinical features, laboratory findings, and histopathology in LEP and deep morphea. Bold words are found in our patient

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<th>Characteristics</th>
<th>LEP</th>
<th>Deep morphea</th>
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| **Clinical features** | - Subcutaneous nodules without or with any surface changes.  
- Location: lateral aspect of upper arms, shoulders, face, scalp, hips, breasts, and buttocks.  
- Resolve with atrophic scarring. | - Sclerotic plaque with hyperpigmented, ill-defined, or mildly inflamed.  
- The skin feels bound down to the underlying fascia and muscle.  
- Resolve with atrophy, hyperpigmentation, or discoloration. |
| **Laboratory findings** | - The serologic analysis is often normal.  
- Positive ANA titers ranging from 27–95.4%.  
- Anti-ds-DNA antibodies are less frequently present. | - Serologic analysis: peripheral eosinophilia, hypergammaglobulinemia, and raised ESR.  
- Positive ANA can be found.  
- Other autoantibodies: Anti ds-DNA, anti-histone, anti-Scl-70, and rheumatoid factor. |
| **Histopathology** | - Predominantly lobular panniculitis or mixed panniculitis.  
- Variable lymphocytic infiltrate, lymphoid follicles, and hyaline fat necrosis.  
- Other characteristics: DLE-like changes in epidermis, dermo-epidermal changes, mucin deposition, granuloma formation, plasmacytic infiltration, and calcifications. | - Predominantly septal panniculitis.  
- Lymphocyte and plasma cell infiltration and collagen tissue thickening and hyalinization in the subcutis.  
- Occasionally, lymphoid follicles devoid of germinal centers.  
- Lipophagic granuloma also may be present in the fat lobules. |

**4 CONCLUSION**

Diagnostic of panniculitis poses a challenge due to various factors. Many conditions that could cause panniculitis to need to be excluded. Histopathology examination from a deep skin biopsy is still remained to be the gold standard. Clinical and serologic characteristics should always be weighed in for a final diagnosis. Particularly in LEP, early diagnosis and appropriate therapy should be considered to prevent disfigurement and progression to systemic involvement.

**REFERENCES**


