CLINICAL OBSERVATIONS

Lupus panniculitis: diagnostic difficulties

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The paper describes a clinical case of a female patient with systemic lupus erythematosus. The features of this case are lobular panniculitis (Pn) concurrent with other typical clinical and laboratory signs of the underlying disease, as well as the absence of the effect of previous therapy. The main directions of the differential diagnosis of idiopathic lobular Pn and lupus Pn that required exclusion of other rheumatic diseases are highlighted.

Keywords: *idiopathic lobular panniculitis; lupus panniculitis; diagnosis.*
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Rheumatic diseases (Rd) associated with panniculitis (Pn), arouse increased interest in domestic and foreign rheumatologists. Currently, Pn is regarded as a set of heterogeneous inflammatory diseases characterized by damage to the subcutaneous fatty tissue (SFT) and often involving the musculoskeletal apparatus and internal organs [1–4].

is believed that a certain role in the development of Pn may be played by infections (viral, bacterial), injuries, hormonal and immune disorders, medical drugs, pancreatic diseases, malignant neoplasms, etc. [2–4, 5]. Nosological affiliation of types and variants of Pn in rheumatic diseases (Rd) is of special interest. The frequency of development of this pathology in Rd varies from 0.5% to 5% [1, 3, 5, 6], and the causes of its development are not fully clarified. In the available literature there are scarce data on the specific features of Pn during Rd [7–10], which may be the first manifestation of the disease.

One of the striking examples of Rd, in which skin and SFT lesions are of paramount diagnostic value, is systemic lupus erythematosus (SLE). There are lupus-specific and lupus-nonspecific changes in the skin and SFT, the latter occurring in SLE several times more often [11]. Lupus-specific manifestations include the so-called chronic lupus erythematosus (LE) (discoid rashes, verrucous lupus erythematosus, lupus Pn, tumor-like lupus erythematosus), subacute cutaneous LE (anular-polycyclic type, psoriasiform type, Rowell syndrome) and acute LE (the typical sign is «butterfly»). Non-specific skin manifestations include photosensitivity, leukocytoclastic and urticarial vasculitis, telangiectasias, livedo reticularis, malignant atrophic papulosis, Raynaud's syndrome. With such an abundance of «specific» signs, verification of the diagnosis, especially with atypical variants of the disease, is complicated. Morphological examination and the timing of the development of skin rashes are important for determining specificity. In this regard, the correct assessment of clinical and laboratory manifestations in such patients, search for diagnostic markers of a systemic disease are of great importance.

Hereafter we present our clinical observation.

Patient F.*, 33 years old, was hospitalized to V.A. Nasonova Research Institute of Rheumatology in April 2019 with complaints of widespread erythematous rashes on her face, chest, upper limbs and lumbar region; crimson painful dense area extending to the right lumbar and gluteal regions with an ulcerative defect producing transparent exudate; pain in the inguinal region, frequent headaches, dry mouth, sensation of «sand» in the eyes.*

From the history it is known that in 2006, the patient was stung by a wasp in the right lateral surface of the trunk, after which a red painless spot appeared. For 9 years, similar rashes occurred periodically in the lumbar region and on the right shoulder, but the patient did not seek medical aid. In November–December 2016, she first noted a painful lump in the lumbar region. In May 2017, during pregnancy, she felt increased pain and the lumbar compaction area began to spread. In November 2017, she had a healthy baby. In February 2018, the patient developed a high temperature, increased pain and increased compaction in the lumbar and gluteal regions: she also had increased hair loss. The patient was taken to a local hospital with a diagnosis of idiopathic lobular panniculitis (ILP), infiltrative type, infiltration of the gluteal region on the right. Treatment with antibacterial agents (intramuscular ceftriaxone 2 g/day for 7 days) had no effect. In March 2018, the infiltrate lancing was performed with a subsequent biopsy of the skin and SFT. Histological examination showed a fragment of granulation tissue with massive petrification. A month later, the dense area spread to the right lumbar region with a persistent non-healing wound after the biopsy.

In June 2018, the patient underwent hospital treatment with a diagnosis of systemic scleroderma, proximal scleroderma, Pn, cutaneous vasculitis, Sjogren's syndrome, infected non-healing wound on the right gluteal region. The wound was re-examined and drained. Repeated biopsy of the skin and SFT showed that the morphological picture corresponded to crystalline Pn, macrophage stage. Given the activity of the disease, prednisone 15 mg/day and plaquenil 200 mg/day were prescribed for the first time with a satisfactory effect.

In January 2019, the patient was hospitalized to the rheumatology department at the place of residence with complaints of diffuse painful compaction in the right lumbar and gluteal regions, ulcerative necrotic defect of the right gluteal region, red spots on the back and upper limbs, choking when eating, dry mouth and eyes, myalgia, arthralgia, periodic increase in body temperature.

The examination data: the upper limbs – single hemorrhagic punctuate eruptions, as well as crimson spots painless on palpation, 5 cm in size. In the region of the lumbar spine – a dark crimson dense area spreading to the right gluteal region. In the right gluteal region – massive infiltrate with marginal hyperemia, fistulous defect

without exudate, wound depth – about 3 cm. Visible mucous membranes – clean, pink; body temperature – 36.6 ℃; the pharynx – without changes; peripheral lymph nodes – not enlarged. Review of the systems was normal.

Laboratory findings: Hb – 101 g/L, tr. – 233 × 10⁹/L, l – 5.4 × 10⁹/L, p. – 5%; ESR – 25 mm/h; total protein – 72.9 g/L, alanine aminotransferase (ALT) – 92.2 mmol/L , aspartate aminotransferase (AST) – 48.2 mmol / L, creatinine – 63 μmol / L, urea – 5.21 μmol/L, creatinine phospholipase – 18 units/L, antibodies to double-stranded DNA (anti-DNA) – 200 IU/ml, antinuclear factor (ANF) – 1:320; antibodies to U1-, U2-, U4-ribonucleoproteins (anti-Sm), antibodies to histidine-tRNA synthetase (anti-Jo-1), antibodies to protein, associated with RNA Y1-Y5 / protein associated with RNA polymerase-3 (anti-SS-Ro/La), anti-scleroderma antibodies (anti-Scl-70), antibodies to protein components of a small nuclear nucleotide – U-1-RNA (anti-RNP) and rheumatoid factor (RF) were not detected; CRP – 0 mg/L. Analysis of urine – proteinuria 0.72 g/L and red blood cells up to 5 in the field of view.

Ultrasound of the abdominal organs revealed diffuse changes in the renal parenchyma, hepatomegaly, diffuse pancreatic changes and splenomegaly. The culture from the ulcerative necrotic focus in the right gluteal region did not reveal any growth of microorganisms. The patient was diagnosed with ILP, infiltrative-nodal form, with damage to the liver, spleen, joints, Sjogren's syndrome. Cyclosporin A (150 mg/day) was added to the therapy with prednisone in a daily dose of 15 mg and hydroxychloroquine 200 mg/day, but no effect was observed. The patient was referred to V.A. Nasonova Research Institute of Rheumatology for therapy correction. On admission, the patient's condition was of moderate severity, with clear consciousness and active position. Height – 168 cm, body weight – 100 kg, body mass index – 35.43 kg/m². Alopecia areata (Fig. 1), «chopped off» hair syndrome. Enanthema of the hard palate, cheilitis (Fig. 2), little free saliva. Common maculopapular rash on the cheeks, erythema on the upper limbs, in the decollete zone, suprascapular and scapular areas (Fig. 3, a). In the right lumbar region – diffuse crimson painful (80 mm on visual analogue scale, VAS) compaction spreading to the gluteal region, 30×20 cm in size (Fig. 3, b). In the region of the right buttock there was an ulcerative defect of 10 × 6 cm in size with transparent odorless exudate (Fig. 3, b). In the dense area the skin and SFT did not fold, the «saucer-like» symptom was positive. Peripheral lymph nodes were not enlarged. Joint movements were fully retained, the muscular system without pathology. Vesicular breathing, no wheezing. Heart sounds sonorous, rhythmic. Blood pressure – 140/90 mm Hg. The abdomen was soft, painless; the liver – at the edge of the costal arch; the spleen not enlarged. Pasternatsky's symptom was negative. Laboratory findings: Hb – 99 g/l, tr. – 228 × 10⁹/ L, l – 4.9 × 10⁹/L, p. – 2%; ESR – 23 mm/h; total protein –71.6 g/L, γ-globulin – 16.26%, ALT – 98.6 mmol /L; AST – 67.9 mmol/L; alkaline phosphatase – 100 U/L, γ-glutamyltransferase – 110.0 U/L, creatine kinase – 23 U/L, creatinine – 80 mg/L, CRP – 12.8 mg/L, anti-DNA >200 IU/ml, ANF –1/1280h, C3 – 0.668 g/L and C4 – 0.083 g/L; antibodies to cardiolipins G and M, antibodies to cytoplasm neutrophils (ANCA screen), anti-SS-Ro/La, anti-Scl-70, anti-RNP-70 and RF were not detected. No hepatitis markers (HBS Ag, anti-HCV) or human immunodeficiency virus were detected, the Wasserman test was negative. Urine analysis: proteinuria – 1.1 g/L, red blood cells – 2–3 in the field of view, hyaline cylinders – 2 in the field of view. Urinalysis: daily urine volume – 2000 ml, proteinuria – 0.6 g/day, urine creatinine – 6.90 mmol/L, glomerular filtration – 126.2 ml/min. Mantoux test – 2 mm.

Electrocardiography: sinus rhythm, 86 beats / min, vertical position of the electrical axis of the heart. Computer tomography of the chest without pathology. Sialography: signs of parenchymal sialadenitis. Ultrasound of the compaction of the right gluteal and lumbar regions: decreased thickness of the SFT and changes in its structure – the absence of differentiation into the skin and SFT; the surface layers are significantly diffusely densified with fistulous passages to inhomogeneous liquid contents lying in the deep layers; in some areas – minimal vascularization enhancement. The obtained data allowed to exclude ILP and systemic scleroderma. Diagnosis: SLE with a chronic course, activity 4 (SLEDAI 2K –

Figure 1. *Patient F., 33 years old. Alopecia*

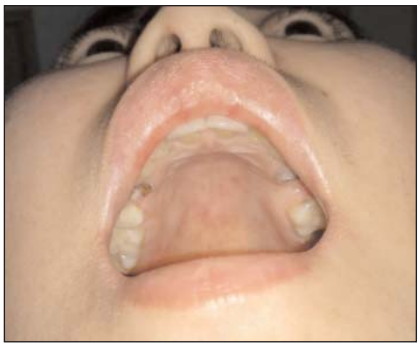

Figure 2. *Same patient. Enanthema on hard palate and cheilitis*

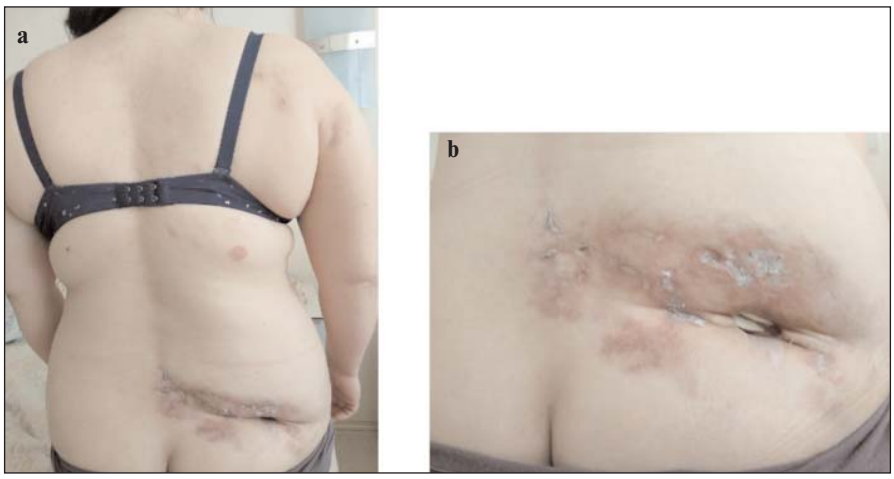

Figure 3. *The same patient: a - common erythema on the back; b – diffuse crimson painful (VAS 80 mm) seal size 30×20 cm in the lumbar and gluteal regions on the right and ulcerative necrotic defect 10×6 cm in the right gluteal region*

20 points, SLICC / ACR damage index – 2): nephrotic syndrome, lupus-Pn, maculopapular rash on the face, extended erythema, alopecia, cheilitis, enanthema of the hard palate, immunological disorders (anti-DNA, hypocomplementemia), ANF +.

Given the torpid course of the disease, three extracorporeal hemocorrection sessions were carried out followed by intravenous administration of glucocorticoids (GK) in the total dose of 2250 mg in combination with cyclophosphamide (CF) 1000 mg, the oral dose of GK was increased to 25 mg/day. Treatment of necrotic ulcer on the right gluteal area was carried out using anticoagulants and hydrocolloid dressings. The therapy contributed to a significant improvement: there was a regression of rashes on the face and in the decollete zone, regression of the enanthema of the hard palate, a decrease in pain (40 mm according to VAS) and the size (25×15 cm) and color of the compaction area in the right lumbar and gluteal regions; a decrease in ulcerative necrotic defect of the right gluteal region (7×4 cm); a decrease in SLEDAI 2K to 4 points (Fig. 4).

The patient was discharged to be followed up by a rheumatologist in the place of residence with a recommendation to continue monthly single extracorporeal treatment with intravenous administration of GK 1000 mg and CF 1000 mg, taking prednisone 25 mg/day and local therapy.

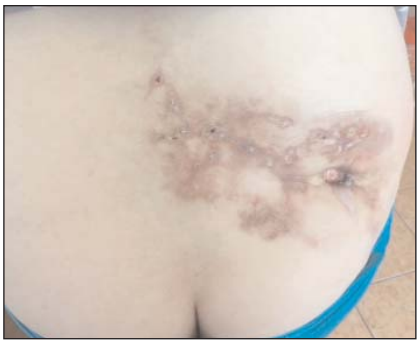

Figure 4. *Same patient. After the course extracorporeal treatment followed by intravenous administration of GK 2250 mg and 1000 mg CF while taking per os prednisolone at 25 mg/day and local therapy showed a decrease in size (25×15 cm) and the intensity of coloration of lump in the lumbar and gluteal regions on the right and ulcerative necrotic defect on the right gluteal region (7×4 cm)*

Discussion. Despite a generally recognized association of skin and SFT lesions in Rd [4, 8–10, 12, 13], the true clinical and prognostic value of Pn in these diseases remains underestimated. It is necessary to study Rd from the point of view of skin changes and damage to SFT. Correct interpretation of these changes is important for differential diagnosis, and may contribute to reliable and timely recognition of the disease. Differential diagnosis of Pn in Rd is associated with significant difficulties, especially at the initial stage of the underlying disease. Of course, awareness of the typical manifestations of Pn variants in Rd is important for verification of the main diagnosis.

In our patient the diagnoses of ILP and lupus-Pn in SLE were considered. What are the common and specific features of these diseases?

In 1892, V. Pfeifer first described the syndrome of focal dystrophy of SFT with localization of nodes on the cheeks, breast, upper and lower extremities, accompanied by progressive weakness. In 1928, N. Christian drew attention to the presence of fever in this disease, and in 1936 I. Brill proposed a new term – «Pfeiffer-Weber-Christian disease». According to modern terminology, this pathology is regarded as ILP – a rare poorly studied systemic recurrent disease, which represents lobular Pn without vasculitis [1–5]. ILP more often occurs in women 20–50 years old, is characterized by a rapid development of limited subcutaneous nodes located in the SFT at different depths, usually multiple, with localization predominantly on the lower and upper limbs, in the gluteal region, less often – on the chest and abdomen. Usually within a few weeks, the nodes dissolve, leaving behind saucer-like skin retractions, in which calcium salts are sometimes deposited (table). Clinical symptoms depend on the form of ILP. So, in the nodular form, the nodes are clearly demarcated from the surrounding tissue, and depending on the depth, their color can vary from the color of normal skin to bright pink, and the diameter – from a few millimeters to 5 cm and more. The plaque form is a result of merging of individual nodes into a dense elastic tuberous conglomerate, with the skin color above it varying from pink to cyanotic. The infiltrative form is characterized by fluctuations in the area of individual nodes or conglomerates of bright red or crimson color; lancing the focus leads to a release of yellow oily mass [1, 5, 6, 13]. The mesenteric form is characterized by pain in the umbilical region and inflammation of the adipose tissue of the intestinal

Differential diagnosis of ILP and lupus-Pn

Sign	**Idiopathic lobular panniculitis**	**Lupus panniculitis when SLE**
Lobular Pn	Yes	Yes
Disease debut	SFT seal	SFT seal
Current of Pn	Recurrent	Recurrent
Form of Pn	Nodular, plaque, infiltrative, mesenteric	Nodular, plaque, infiltrative
Seal localization	Upper and lower limbs, trunk, gluteal area	Upper limbs, trunk, gluteal area, face and scalp.
Symptom "saucers"	Yes	Yes
Cicatricial changes	Sometimes	Sometimes
Low-grade fever	Yes	Sometimes
Alopecia	No	Sometimes
Erythema on the face and body, cheilitis, enanthema, capillaritis, Raynaud's syndrome, etc.	No	Yes
ESR> 20 mm / h	Yes	Yes
CRP> 5.0 mg / L	Increase in 3 or more times	Increase in 1.5-3 times
DNA> 20 U / ml, ANF-Hep2> 1/160, C3 / C4	No	Yes
Nephrotic or urinary syndrome	No	Yes

mesentery, omentum, pre- and retroperitoneal adipose tissue detected by computer tomography of the abdominal organs [13].

Another characteristic form of lobular Pn is lupus-Pn, or deep LE, first described by M. Kaposi in 1883 [15]. The disease occurs more often in women, mainly at the age of 40 years [7, 11, 14]. In lupus-Pn deep subcutaneous nodes or plaques are formed, often painful, accompanied by ulceration. They are located on the upper extremities, trunk, gluteal regions, sometimes on the head, face and neck. Involvement of lower limbs is not characteristic and can serve as a distinctive symptom in differential diagnosis with other Pn options (table). An atypical arrangement of nodes in the region of the mammary glands (lupus mastitis), the thyroid gland, and in the periocular zone has been described [15]. Lupus-Pn is characterized by a relapsing course, the inflammatory process often results in the formation of atrophic scars. Pn is included in modern diagnostic criteria for SLE (SLICC, 2012) [16]. Of great importance in the diagnosis of lupus-Pn is identification of the laboratory changes characteristic of SLE [14] (table).

Thus, the common features of the considered nosologies are the clinical signs of Pn, recurring nature of the underlying disease and increased laboratory indicators of inflammatory activity. However, lupus-Pn has specific manifestations: localization of compaction areas on the face and scalp, absence of skin and SFT lesions on the lower extremities, presence of immunological changes characteristic of SLE (table).

As our observation shows, successful diagnosis of Pn variants depends primarily on a carefully collected history, including information about previous diseases, and adequate assessment of clinical and laboratory symptoms. Therefore, accumulation of clinical experience (probably, based on multicenter studies with a uniform design) will allow to come closer to understanding the nature of these diseases and developing pathogenetic methods of their treatment.

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