CLINICAL OBSERVATIONS

Scleroderma-panniculitis: view of the rheumatologist

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Difficulties in diagnosis and therapy of scleroderma-panniculitis (S-PN), one of the variants of the septal PN, are discussed. Feasibility of ultrasonography, magnetic resonance imaging of soft tissues and histological examination of the lesions in order to set the diagnosis of PN in time is considered. The clinical case of S-PN combined with antiphospholipid syndrome is presented.

Keywords: *panniculitis; scleroderma-panniculitis; antiphospholipid syndrome; diagnostics; treatment.*

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Panniculitides (Pn) are a group of heterogeneous inflammatory diseases characterized by damage to subcutaneous fatty tissue (SFT) and often involving the musculoskeletal system and internal organs [1]. Pn is one of the most complex diagnostic tasks for rheumatologists, dermatologists and doctors of other specialties.

There is no single concept of etiology and pathogenesis of Pn. A certain role is assigned to infectious factor (viruses, bacteria), injury, medical drugs, immuno-inflammatory and autoinflammatory diseases [2–5].

Currently, no generally accepted classification of Pn has been developed. However, some authors propose to verify the diagnosis of Pn on the basis of its etiology and histomorphological picture. Depending on the predominance of inflammatory changes in the connective tissue septa or fat lobules, Pn is divided into septal (SPn) and lobular (LPn). Both types of Pn can develop with or without signs of vasculitis, which is reflected in the clinical picture of the disease (see Table) [2–4].

Clinical picture of Pn is characterized by areas of skin thickening having different coloring (from flesh-colored to purple) and pain intensity on palpation, which are predominantly localized on the lower limbs, and less often – on the upper limbs, the trunk and the face.

Successful diagnostics of Pn depends on a carefully taken history, as well as on adequate assessment of clinical manifestations, laboratory and instrumental findings and identifying typical morphological signs. Changes in acute-phase inflammation indicators are non-specific, mostly reflect the presence and severity of an inflammatory process, and are not diagnostic [1]. Histological examination is of great importance and is considered to be the "gold standard" for diagnosis of Pn [3, 6].

At the onset of the disease, in the absence of changes in blood indices and due to the complexity of the morphological examination, the use of ultrasound and magnetic resonance imaging (MPI) of soft tissues allows to determine the structure of the tissue, the depth and area of the lesion, which is important for the choice of therapy. However, currently there is no unified assessment of ultrasound and MRI results.

Of interest is nosological diversity of SPn variants (see Table), since the typical symptom of "blooming bruise" and regress of skin indurations without formation of ulcers and scars present a diagnostic challenge for a physician. Scleroderma-Pn (S-Pn) is a rare variant of SPn, which also refers to a localized form of scleroderma (SD), namely, to the subtype of deep SD, or morphea profunda [7]. It is reported that the annual incidence of S-Pn is 2.7 per 100 thousand, with female predominance [8]. R. Lafyatis and V. Farina [9] assume that in women a certain role in the development of S-Pn can be played by microchimerism – persistence of embryonic cells after pregnancy.

Different triggers are involved in the development of S-Pn: autoimmunity, genetic predisposition (HLA class I and II alleles) and external environmental factors (infections, injuries, toxins, drugs and radiation), which may cause inflammation of the skin and subcutaneous fat tissue (SFT) with the subsequent accelerated process of collagen formation. The emerging secondary fibrosis is due to the penetration of mononuclear cells into the dermis and, as a result, damage to blood vessels (especially subepidermal). In the presence of epidermal growth factor and interleukin 4 (IL-4), transforming growth factor α (TGFα) plays an important role in the regulation of pro-fibrosis aspects of congenital

Table 1.

Clinical and morphological classification of Pn [2-4]

View Pn	Pn without vasculitis	Pn with vasculitis
Septal Pn	Erythema nodosum, scleroderma-Pn, lipoidica necrobiosis, eosinophilic fasciitis, eosinophilia-myalgia syndrome	Surface migrating thrombophlebitis in the Behcet's Disease, nodule polyarteritis, skin nodule polyarteritis
Lobular Pn	Idiopathic lobular Pn, cytophagic histiocyte Pn, lipodermatosclerosis, physical Pn (cold, infectious, traumatic, etc.), neonatal Pn, Pn after glucocorticoids , Pn, associated with systemic disease (pancreatic, lupus-Pn, Pn during dermatomyositis, gout , Pn with psoriatic arthritis, Pn with systemic scleroderma, subcutaneous sarcoid), calcification, Pn-like T-cell lymphoma, infectious Pn, α1- antitripsein Pn.	Nodule vasculitis, erythema induratum of Bazin, leprous Pn, Lucio phenomenon (diffuse lepromatous leprosy), neutrophilic LPn associated with RA

immune activation; IL4 produced by CD4 + TH2 lymphocytes, regulates the production of TGFα [10–11], which entails lesion of the skin and SFT, expanding on fascia, muscles and bones. With free radical oxidation of neutrophils in patients with deep SD, dysfunction of T-lymphocytes CD3 +, CD4 +, CD11B + is revealed, simultaneously with an increase in the number of T-lymphocytes CD8 +, CD16 +, as well as activation markers CD19 +, CD25 +, CD95 + and HLA-DR + cells [9, 12]. A number of researchers report increased regulation of intercellular adhesion molecules of the 1st type and adhesion molecules of vascular cells in response to such cytokines, as interferon γ, IL-1 and tumor necrosis factor α (TNF-α). Despite the data obtained, the role of autoantibodies in the development of deep SD requires further clarification.

Approximately 20% of patients can develop arthritis, uveitis and cramps.

Literature analysis shows scientific and practical interest in the problem of SPn, which warranted describing our clinical observation.

***Patient I.**, a 35-year-old woman, Circassian, in October 2020 was admitted to V.A. Nasonova Research Institute of Rheumatology with complaints of diffuse itching purple indurations on the upper limbs, buttocks, thighs and lower back. From the history it is known that since the age of 10 she was observed by a hematologist for idiopathic thrombocytopenic purpura. Therapy with glucocorticoids (GCs) at a dose of up to 40 mg / day in 1995–1996 led to normalization of platelet levels, and in 1996 the treatment was discontinued. In 1997 recurrence of thrombocytopenia (95×10^9 / L) occurred, and splenectomy was performed, which was followed by remission of the disease. The patient is still observed by a hematologist. Over the last 6 years, the patient had four adverse outcomes of pregnancy, three of which ended with miscarriages in early gestation periods (up to 10 weeks) and one – with an abortion for medical indications. In July 2019, she noted an unprovoked moderately painful skin induration of light pink color on the right upper arm. She did not seek medical aid and did not receive treatment. By the autumn of the same year, the thickened area spread to the upper and lower limbs, lumbar and gluteal regions. A local dermatologist diagnosed dermatitis and recommended ascorutin, one tablet twice a day. The treatment had no effect. In December 2019, an increase in body temperature up to 38.3 °C, dry cough, myalgia suddenly occurred. Examination findings: Hb – 118 g / L (norm 120–140 g / L), Tr. – 110×10^9 / L (norm 180–320×10^9 / L), l. – 9.8×10^9 / L (norm 4–9×10^9 / L), ESR – 19 mm / h (norm 2–15 mm / h), CRP – 10 mg / L (norm 0–5 mg / L). The diagnosis of left-sided lower-grade pneumonia was suspected, which was confirmed by computed tomography (CT) of the chest organs. Antibacterial therapy was prescribed (amoxiclav 725 mg 2 times a day for 7 days) with a positive effect. After the treatment of pneumonia, the patient noted an increase in the intensity of the color of the skin indurations. Local therapy with radevit was prescribed, but without any effect. The platelet level was not controlled. In March 2020 – appearance of new indurations on the skin of the forearm.*

In April 2020, the patient was consulted in V.A. Nasonova Research Institute of Rheumatology. Physical examination revealed multiple painful (according to the Visual Analog Scale-VAS – 25 mm), purple-brown (stage II) skin indurations on the upper and lower limbs, on the gluteal and lumbar area. Positive "saucer" symptom. On examination changes in the following indicators were revealed: Hb – 118 g / L (norm 120–140 g / L), Tr. – 90×10^9 / L (norm 180–320×10^9 / L), ESR – 16 mm / h (norm 2–15 mm / h), antinuclear factor (ANF) HEp2 – 1/640 Sp (norm <1/160), anticardiolipin antibodies (aCL) IgM – 7.3 MPL (norm 0.0–7.0 MPL), lupus anticoagulant (LA) – 1.24 (norm 0.79–1.20), other immunological indicators were within the normal range.

Histological examination of the skin and SFT biopsy samples taken from the most painful skin lesions on the upper third of the left thigh revealed multiple productive-destructive vasculitis of subcutaneous fat tissue with the development of mixed septal-lobular Pn. The results obtained suggested the diagnosis of S-Pn, and hydroxychloroquine (HC) 200 mg / day for 2 weeks was prescribed with a further dose increase up to 400 mg / day, as well as dipyridamole 25 mg 2 times a day. On the therapy, the intensity of colored indurations decreased, new foci did not appear. However, 5 weeks after the start of HC therapy, itching and hyperemia of the skin appeared on the face and hands, redness of the eyes developed. In October 2020, the patient was consulted by an ophthalmologist, who revealed a rupture of the retina in the left eye and recommended to discontinue HC therapy. Due to the disease progression and the need for correction of the therapy, the patient was hospitalized to V.A. Nasonova Research Institute of Rheumatology.

Examination findings: height – 167 cm, body weight – 57 kg, body mass index – 20.44 kg / m^2. On the skin of the upper and lower extremities, gluteal region – multiple symmetrical diffuse moderately painful (30–60 mm according to VAS) purple (stage II) indurations. No folding of the skin and SFT in the thickened areas, positive "saucer" symptom (Fig. 1, a–d). The area of lesion – 14 palms. Full movements in the joints. The muscular system without pathology. Vesicular breathing, no wheezes. The heart sounds are sonorous, rhythmic. Arterial pressure – 110/70 mm Hg. The abdomen is soft, painless. The liver is at the edge of the costal arch, the spleen is not enlarged. Pasternatsky's symptom (costovertebral arch tenderness) in the lumbar region is negative. Laboratory findings: Tr. (according to FONIO) – 57.0×10^9 / L (norm 180–320×10^9 / L), ESR – 16 mm / h (norm 2–15 mm / h), lactate dehydrogenase – 253 U / L (norm 135–225 U / L), ANF (HEP2) – 1 / 640 Sp (norm <1/160), LA – 1.34 (norm 0.79–1.20), other indicators within the reference values. Hepatitis markers (HBS Ag, anti-HCV), syphilis, human immunodeficiency virus are not detected. Urinalysis without pathology. Mantoux test – 2 mm. The results of instrumental examination (electrocardiogram, echocardiogram, CT of the chest organs, abdominal ultrasound) – no pathology detected. Ultrasound examination of the soft tissues of the upper and lower extremities, showed areas of diffuse increase in echogenicity of FST with its thinning, compared with unchanged zones, with thickened anechogenic septa between fat lobules, poorly compressed with a sensor compression, without signs of enhancement of vascularization in a power mode Doppler mapping (Fig. 2, a, b). MRI of soft tissues of the thighs (STIR mode) (adipose tissue signal suppression) detected multiple pronounced infiltration zones, as well as sections and zones of edema in the form of a non-homogeneous increase in the intensity of MR signal in STIR T2 mode and corresponding hypointensity in T1 mode, characterized by attenuation of the septal structure of SFT, separation and decrease in the volume of fatty lobules (Fig. 3, a, b). Changes were localized on the ventral and dorsal surfaces of both thighs throughout the visibility area, starting with the level of the gluteus maximus, and were most pronounced in the proximal third of the left thigh. The data obtained confirmed deep edematous-infiltrative and fibrous changes of SFT of the thighs. Analysis of clinical, laboratory and instrumental findings allowed us to exclude systemic lupus erythematosus, systemic SD, idiopathic LPn and other Pn variants.

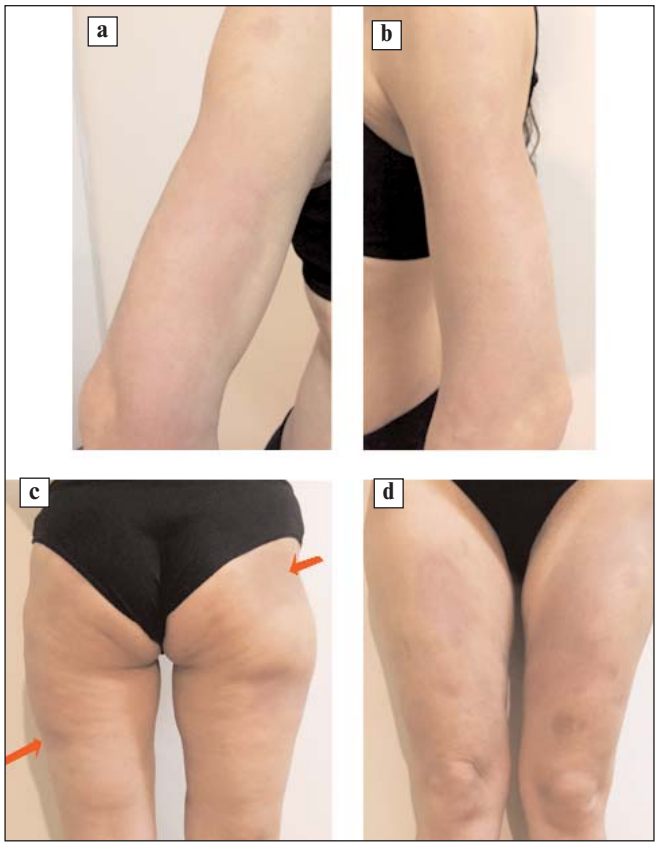

Fig. 1. *Patient I., 35 years. S-Pn: a, b – hyperemic (stage II) diffuse indurated lesions on the front surface of the right and left upper arms; c – diffuse indurated lesions on the back surface of thighs and gluteal region with skin retraction symptom (arrows); d – hyperemic (stage II) diffuse indurated lesions on the front thigh surface*

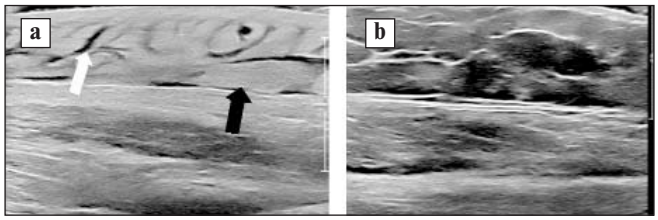

Fig. 2. *Ultrasound of soft tissues: a – diffuse increase in the echogenicity of the subcutaneous fat (black arrow) with its thinning compared with the contralateral side, thickened anechogenic partitions – septa (white arrow) – between fat lobules; b – contralateral side (normal fat, B-mode)*

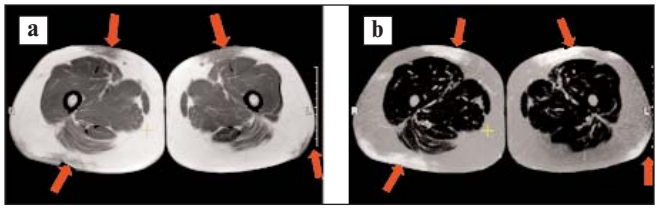

Fig. 3. *MRI of the thigh soft tissues: a – in T1-mode, the hypointensity (arrows) is detected, exhaustion of subcutaneous fat septal structure; b – In STIR T2-mode, nonhomogeneous increase in the intensity of the MR-signal is detected – areas of edema (arrows)*

SPn was diagnosed: generalized S-Pn, stage II and antiphospholipid syndrome – APS (three consecutive cases of spontaneous abortions within 10 weeks of gestation, two positive LA tests).

Given the nature of the course and the common form of S-Pn, mycophenolate mofetil (MMF) 250 mg / day, apixaban 5 mg / day, and local therapy on the indurated areas (50% dimethyl sulfoxide with betamethasone of 40 mg 2 times a day) were prescribed. After 3 weeks, the patient's condition improved significantly: the lesion area shrank (up to 10 palms), the density and intensity of color of the nodes decreased. The patient was discharged to be followed up by a rheumatologist at the place of residence, it was recommended to continue MMF 250 mg / day, apixaban 5 mg / day and local therapy.

Discussion. Lesions of FST are almost universal manifestations of Pn. In differential diagnosis, clinical features of each of its types and characteristic manifestations of nosological variants should be taken into account, which determine the choice of laboratory and instrumental methods of examination and therapeutic approaches. The presented clinical case demonstrates the development of S-Pn in a 34-year-old Circassian woman. A number of authors note that in adulthood this pathology is more common in women than in men (ratio 2–4 : 1), with a peak incidence in the 5th decade of life, while the average age of the disease onset in children is 6.4–8.7 years [13–15]. Data on the ethnic features of the disease are ambiguous. Some researchers note that S-Pn is more common among Europeans [13, 16]. L.S. Peterson et al. [8] found a high frequency of the S-Pn among residents of Minnesota, most of whom (88%) were Europeoids, which confirms our observation.

The characteristic feature of the described case is a combination of S-Pn with APS. In the available literature there are few reports of the association of these two diseases, while opinions of researchers about the effects of antiphospholipid antibodies on the course of Pn are ambiguous. Thus, A. Lis-Swiety et al. [17], examined 45 patients with various forms of deep SD for the presence of IgG / IgM antiphospholipid antibodies, aCL and LA, and in 15 of them identified immunological disorders, and in 2 patients – secondary APS. The authors believe that immunological APS markers did not affect the course of deep SD. The opposite point of view on the role of APS in SPn was expressed by R.D. Hunt et al. [18], who described a 60-year-old man with development of isolated painful erythematous indurations on the lower limbs in combination with arthralgia, elevated levels of aCL (IgG and IgM), antibodies to β2-glycoprotein (IgM and IgG), LA and an increase in activated partial thromboplastin time. The patient received 81 mg of aspirin daily, and on this therapy, a decrease in the intensity of pain and density of the nodes was noted. The biopsy of one of the induration areas found typical signs of SPn and LPn with neutrophils, histiocytes, numerous eosinophils, foci of fibrosis and fat necrosis, but without vasculitis, while APS with lesions of the skin and SFT is characterized by lymphocytic vasculitis and vascular thrombi without signs of Pn [19]. Thus, despite the fact, that histologically APS was not confirmed, the course of Pn on the background of positive antiphospholipid antibodies was severe. The histological picture of biopsy samples of the skin indurations taken from our patient was characterized by multiple productive-destructive vasculitis of subcutaneous fat tissue with signs of both SPn and LPn. A similar case of painful thickened areas on the thighs in combination with positive LA and increased levels of IgG antibodies to aCL in the blood serum

(126 GPL U/ mL; norm <22 GPL U/ mL) was described by J. Jimenez-Mazuecos et al. [20]. Prednisolone therapy was effective for the clinical symptoms of Pn and the level of aCL, which decreased to 66 GPL-units / mL. Thus, though the pathophysiological association between antiphospholipid antibodies and Pn remains unclear, manifestations of Pn in these patients responded to APS therapy. Further studies are needed to determine the relationship between Pn and APS.

Clinical picture of S-Pn is often associated with other subtypes of a localized SD – morphea profunda, linear SD on the trunk, limbs, head («sable blow»), face (Parry-Romberg's progressive hemiatrophy of the face), pansclerotic and mixed SD (combination of two or more subtypes) [21]. Limited and generalized SD often debuts in adults, which we observed in our patient, while linear SD – in childhood [22–23]. The most significant non-cutaneous manifestations of SD are arthralgia, arthritis, joint contractures, myositis, fasciitis, reduction of muscle function and atrophy, as well as neurological, ophthalmic and dental symptoms [24–25]. Probably, the eye pathology detected in our patient can be viewed within the framework of S-Pn.

The variety of clinical symptoms [1–3], correct biopsy sampling, as well as changes in the cell composition of inflammatory infiltrates during the disease [6] create prerequisites for complex instrumental examination of patients with Pn. Promising methods of primary instrumental diagnostics, in our opinion, are ultrasound and MRI of soft tissues. In foreign literature, the use of these methods for diagnosis of Pn is described in few studies [26–29]. J. Romani et al. [28] analyzed the data of histological and ultrasound examination of skin indurations of 64 patients with Pn. The sensitivity and specificity of ultrasound for the diagnosis of LPn are 85.2% and 88.6%, respectively, positive likelihood ratio – 7.45, and negative likelihood ratio – 0.16. Other researchers presented cases of Lupus-Pn of the face, Pn with dermatomyositis and gout, which were verified using ultrasound and MRI of soft tissues [26–27, 29].

Treatment of Pn is not developed and is carried out mainly taking into account the therapy of the underlying disease. Most of the drugs that are used in rheumatology in systemic inflammatory diseases are also effective in many variants of Pn [30]. In S-Pn local therapy with GCs [31], calcipotriol [32] and other drugs is used. Systemic treatment with GCs, methotrexate [33], MMF [34], HC [35], cyclosporine [36] and genetically engineered biologic drugs (GEBDs) [37–38], as well as phototherapy [31] are widely prescribed. Clinical observations are gradually accumulated, confirming the difficultiesof laboratory and instrumental examination and the choice of treatment tactics in various variants of LPn.

Thus, S-Pn is a rare disease which is difficult to diagnose. The presented data emphasize the need for interdisciplinary cooperation of rheumatologists, dermatologists and other specialists in order to improve the methods of diagnostics and treatment of rare variants of Pn.

REFERENCES

1. Егорова ОН, Белов БС. Панникулиты в практике дерматовенеролога и интерниста. Consilium Medicum. 2020;22(7):78-83. [Egorova ON, Belov BS. Panniculitis in the practice of a dermatovenerologist and internist. *Consilium Medicum*. 2020;22(7):78-83. (In Russ.)].
2. Wick MR. Panniculitis: a summary. *Semin Diagn Pathol*. 2017 May;34(3):261-72. doi: 10.1053/j.semdp.2016.12.004. Epub 2016 Dec 27.
3. Caputo V, Rongioletti F. Panniculitis in the setting of dermato/rheumatologic diseases. *G Ital Dermatol Venereol*. 2018 Apr;153(2):194-207. doi: 10.23736/S0392-0488.17.05845-X. Epub 2017 Dec 15.
4. Requena L, Yus ES. Panniculitis. Part I. Mostly septal panniculitis. *J Am Acad Dermatol*. 2001 Aug;45(2):163-83; quiz 184-6. doi: 10.1067/mjd.2001.114736.
5. Requena L, Yus ES. Panniculitis. Part II. Mostly lobular panniculitis. *J Am Acad Dermatol*. 2001 Sep;45(3):325-61; quiz 362-4. doi: 10.1067/mjd.2001.114735.
6. Раденска-Лоповок СГ, Егорова ОН, Белов БС и др. Идиопатический лобулярный панникулит: клинико-морфологические корреляции. Архив патологии. 2019;81(3):37-44. [Radenska-Lopovok SG, Egorova ON, Belov BS, et al. Idiopathic lobular panniculitis: clinical and morphological correlations. *Arkhiv patologii*. 2019;81(3):37-44. (In Russ.)].
7. Bö er-Auer A. Differenzialdiagnostik der Pannikulitis. *Hautarzt*. 2016 Jul;67(7):555-69. doi: 10.1007/s00105-016-3794-2.
8. Peterson LS, Nelson AM, Su WP, et al. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-93. *J Rheumatol*. 1997 Jan;24(1):73-80.
9. Lafyatis R., Farina V. New understanding of the mechanisms of innate immunity receptor signaling in fibrosis. *Open Rheumatol J*. 2012;6:72-9. doi: 10.2174/1874312901206010072. Epub 2012 Jun 15.
10. Badea I, Taylor M, Rosenberg A, Foldvari M. Pathogenesis and therapeutic approaches for improved topical treatment in localized scleroderma and systemic sclerosis. *Rheumatology (Oxford)*. 2009 Mar;48(3):213-21. doi: 10.1093/rheumatology/ken405. Epub 2008 Nov 20.
11. Zulian F, Vallongo C, Woo P, et al. Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum*. 2005 Sep;52(9):2873-81. doi: 10.1002/art.21264.
12. Романова НВ. Иммунопатологические нарушения и цитокиновый профиль при системной и ограниченной склеродермии. Терапевтический архив. 2012;(5):28-31. [Romanova NV. Immunopathological disorders and cytokine profile in systemic and limited scleroderma. *Terapevticheskii arkhiv*. 2012;(5):28-31. (In Russ.)].
13. Li SC. Scleroderma in children and adolescents: localized scleroderma and systemic sclerosis. *Pediatr Clin North Am*. 2018 Aug;65(4):757-81. doi: 10.1016/j.pcl.2018.04.002.
14. Scalapino K, Arkaschaisri T, Lucas M, et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. *J Rheumatol*. 2006 May;33(5):1004-13. Epub 2006 Apr 1.
15. George R, George A, Kumar TS. Update on management of Morphea (Localized Scleroderma) in childrenIndian. *Indian Dermatol Online J*. 2020 Mar 9;11(2):135-45. doi: 10.4103/idoj.IDOJ_284_19. eCollection Mar-Apr 2020.
16. Careta MF, Romiti R. Localized scleroderma: Clinical spectrum and therapeutic update. *An Bras Dermatol*. Jan-Feb 2015;90(1):62-73. doi: 10.1590/abd1806-4841.20152890.
17. Lis-Swiety A, Brzezinska-Wcislo L, Arasiewicz H, Bergler-Czop B. Antiphospholipid antibodies in localized scleroderma: the potential role of screening tests for the detection of antiphospholipid syndrome. *Postepy Dermatol Alergol*. 2014 May;31(2):65-70. doi: 10.5114/pdia.2014.40978. Epub 2014 Apr 22.
18. Hunt RD, Robinson M, Patel R, Franks AG. Antiphospholipid-antibody-associated panniculitis. *Dermatol Online J*. 2012 Dec 15;18(12):18.
19. Renfro L, Franks AG, Grodberg M, Kamino H. Painful nodules in a young female: antiphospholipid syndrome. *Arch Dermatol*. 1992 Jun;128(6):847-8, 850-1. doi: 10.1001/archderm.1992.01680160133022.
20. Jimenez-Mazuecos J, Yebra-Bango M, Sanchez-Ruiz A, Villarreal-Garcia-Lomas M. Weber-Christian disease associated with lupus

anticoagulant and anticardiolipin antibodies. *Rheumatology (Oxford)*. 1999 Aug; 38(8):796-7. doi: 10.1093/rheumatology/38.8.796.
21. Torok KS, Li SC, Jacobe HM, et al. Immunopathogenesis of Pediatric Localized Scleroderma. *Front Immunol*. 2019 Apr 30; 10:908. doi: 10.3389/fimmu.2019.00908. eCollection 2019.
22. Weibel L, Laguda B, Atherton D, Harper JI. Misdiagnosis and delay in referral of children with localized scleroderma. *Br J Dermatol*. 2011 Dec;165(6):1308-13. doi: 10.1111/j.1365-2133.2011.10600.x. Epub 2011 Nov 2.
23. Wu EY, Li SC, Torok KS, et al. Baseline description of the juvenile localized scleroderma subgroup from the childhood arthritis and rheumatology research alliance legacy registry. *ACR Open Rheumatol*. 2019 Apr 10; 1(2):119-24. doi: 10.1002/acr2.1019. eCollection 2019 Apr.
24. Li SC, Li X, Pope E, et al. New Features for Measuring Disease Activity in Pediatric Localized Scleroderma. *J Rheumatol*. 2018 Dec;45(12):1680-8. doi: 10.3899/jrheum.171381. Epub 2018 Sep 15.
25. Schoch J, Schoch B, Davis D. Orthopedic complications of linear morphea: Implications for early interdisciplinary care. *Pediatr Dermatol*. 2018 Jan;35(1):43-6. doi: 10.1111/pde.13336. Epub 2017 Nov 9.
26. Kimball H, Kimball D, Siroy A, et al. Novel diagnostic imaging features of facial lupus panniculitis: ultrasound, CT, and MR imaging with histopathology correlate. *Clin Imaging*. Nov-Dec 2019;58:177-81. doi: 10.1016/j.clinimag.2019.07.006. Epub 2019 Jul 23.
27. Hemmi S, Kushida R, Nishimura H, et al. Magnetic resonance imaging diagnosis of panniculitis in dermatomyositis. *Muscle Nerve*. 2010 Jan;41(1):151-3. doi: 10.1002/mus.21537.
28. Romani J, Giavedoni P, Roe E, et al. Inter- and Intra-rater Agreement of Dermatologic Ultrasound for the Diagnosis of Lobular and Septal Panniculitis. *J Ultrasound Med*. 2020 Jan;39(1):107-12. doi: 10.1002/jum.15080. Epub 2019 Jun 27.
29. Cid PM, Flores CR, Caelles IP, et al. High-frequency ultrasound features in a case of gouty panniculitis. *Dermatol Online J*. 2017 Jun 15;23(6):13030/qt33j2z14m.
30. Егорова ОН, Белов БС. Панникулиты: ревматологические аспекты. Современная ревматология. 2018;12(2):73-8. [Egorova ON, Belov BS. Panniculitis: rheumatological aspects. *Sovremennaya revmatologiya = Modern Rheumatology Journal*. 2018;12(2):73-8. (In Russ.)]. doi: 10/14412/1996-7012-2018-2-73-78.
31. Narbutt J, Holdrowicz A, Lesiak A. Morphea – Selected local treatment methods and their effectiveness. *Reumatologia*. 2017; 55(6):305-13. doi: 10.5114/reum.2017.72628. Epub 2017 Dec 30.
32. Dytoc MT, Kossintseva I, Ting PT. First case series on the use of calcipotriol-betamethasone dipropionate for morphoea. *Br J Dermatol*. 2007 Sep;157(3):615-8. doi: 10.1111/j.1365-2133.2007.07971.x. Epub 2007 Jun 6.
33. Koch SB, Cerci FB, Jorizzo JL, Krowchuk DP. Linear morphea: A case series with long-term follow-up of young, methotrexate-treated patients. *J Dermatolog Treat*. 2013 Dec;24(6):435-8. doi: 10.3109/09546634.2013.806769. Epub 2013 Jul 15.
34. Martini G, Ramanan AV, Falcini F, et al. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology (Oxford)*. 2009 Nov;48(11):1410-3. doi: 10.1093/rheumatology/kep244. Epub 2009 Aug 27.
35. Kumar AB, Blixt EK, Drage LA, et al. Treatment of morphea with hydroxychloroquine: A retrospective review of 84 patients at Mayo Clinic, 1996-2013. *J Am Acad Dermatol*. 2019 Jun;80(6):1658-63. doi: 10.1016/j.jaad.2019.01.040. Epub 2019 Jan 29.
36. Bali G1, Früh auf J, Wutte N, Aberer E. Cyclosporine reduces sclerosis in morphea: A retrospective study in 12 patients and a literature review. *Dermatology*. 2016;232(4): 503-10. doi: 10.1159/000448171. Epub 2016 Aug 30.
37. Zhang A, Nocton J, Chiu Y. A case of pansclerotic morphea treated with tocilizumab. *JAMA Dermatol*. 2019 Mar 1;155(3): 388-9. doi: 10.1001/jamadermatol.2018.5040.
38. Kim SR, Charos A, Damsky W, et al. Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. *JAAD Case Rep*. 2018 Apr 30;4(5):443-5. doi: 10.1016/j.jdcr.2017.12.003. eCollection 2018 Jun.

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