ORIGINAL INVESTIGATIONS

Comorbidity in patients with lobular panniculitis-lipodermatosclerosis

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Lipodermatosclerosis (LDS) is one of the variants of lobular panniculitis. The onset of LDS falls on the age of 50–60 years, when many patients already have comorbid pathology requiring complex therapy, which affects the course, the choice of treatment and prognosis of LDS, as well as the quality of life.

Objective: *to study the structure and frequency of comorbid conditions in patients with LDS.*

Patients and methods. *53 patients (3 men and 50 women), 18–80 years old, with a verified diagnosis of LDS were included, all of them had an average follow up of 10 years (they were observed in the V.A. Nasonova Research Institute of Rheumatology). The duration of the disease ranged from 2 weeks to 20 years. During clinical examination, the localization, prevalence, color and number of affected skin areas and subcutaneous fat were determined. The intensity of pain on palpation of the node was assessed using a visual analogue scale (VAS). Laboratory and instrumental research included: blood and urine tests, computed tomography of the chest and ultrasound Doppler of the lower extremities with registration of the linear blood flow velocity in the affected veins (femoral, popliteal, posterior tibial, foot veins). Clinical, laboratory and instrumental examination of patients was carried out 2 times a year. The CIRS and Charlson indices were used to assess the relationship between comorbid pathology and LDS.*

Results and discussion. *Most patients (60.3%) were women with increased body weight (91.5±21.8 kg). Depending on the duration of the disease, the main variants of the LDS course were: acute (<3 months), subacute (3–6 months), and chronic (>6 months). Skin changes were associated with polyarthralgia (34%) and/or myalgia (22.6%), mainly on the side of the affected limb. In 16 patients, an increase in ESR, on average 23.8±7.8 mm per hour, was detected, in 7 patients, including 4 with an acute course of LDS, – more than a threefold increase in the level of CRP. No comorbid diseases had 17 patients, 64.7% of them were under 50 years and had an acute course of LDS (p=0.02). In 68% of patients, mainly with chronic LDS, the following concomitant diseases was recorded: chronic venous insufficiency (CVI; in 67.9%); exogenous constitutional obesity (in 60.3%); rheumatic diseases (45.2%), including osteoarthritis (75%), rheumatoid arthritis (17%), antiphospholipid syndrome (8%), and arterial hypertension (39.6%). Most patients had 1 concomitant disease, and almost one fifth of patients had 2 concomitant diseases. The proportion of patients with 3 comorbid pathologies was 11.1%, with 4 – 8.3% and with 5 – 5.5%. When assessing the Charlson index, a 10-year survival rate of >90% (index values from 0 to 2 points) was observed in 66% of patients, 53–77% (3–4 points) – in 26.4% and <21% (⩾5 points) – in 7.5%. There was correlation between the comorbidity index and the age of patients (r=0.8, p<0.05); no association with the duration of LDS was found (r=0.3, p=0.2). Patients over 61 years had ⩾1 comorbid disease. The average CIRS index for this group was 4.2±0.3 points (0–10), in most patients (45.2%) it was <5 points. Analysis of the Charlson and CIRS scales confirmed their statistically significant relationship (r=0.5, p=0.0000001).*

Conclusion. *In patients with LDS, a high incidence of comorbid pathology was noted. Interdisciplinary approach with interaction between doctors of different specialties is required for treatment of these patients.*

Key words: *panniculitis; lipodermatosclerosis; comorbidity; Charlson index; scale for assessing comorbidity CIRS.*

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Comorbidity is a fundamental problem in modern medicine. Currently, comorbidity is understood as a combination of i2 chronic diseases in one patient, interrelated etiopathogenetically or coinciding in time of occurrence, regardless of the activity of each of them [1–3].

The need to objectify the patient's polymorbid status in order to develop individual approaches to therapy has led to the development of 17 universally recognized international indices for evaluating comorbidity. The most common instruments used abroad are: Cumulative Illness Rating Scale PCIRS [4], Chronic Disease Score – CDS [5], Adjusted Clinical Groups PACG [6], the Geriatric Index of Comorbidity (GIC) [7], the Kaplan–Feinstein-KF index, reflecting comorbidity according to the severity of diseases [8], the Duke Severity of Illness Checklist – DUSOI), which assesses the severity of diseases according to four parameters: symptoms, complications, prognosis within 6 months without treatment and curability [9] and the Charlson Comorbidity Index proposed in 1987 by ME Charlson to predict mortality [10]. Comparative characteristics of 11 comorbidity indexes showed that the GIC index most accurately predicted mortality during hospitalization, and the CIRS index predicted the length of hospital stay [11–14]. In the provision of primary health care, the ACG, Charlson and CDS indices are considered the most convenient, while the ACG index is also preferable for calculating the cost of medical care [11, 15].

Early diagnosis of comorbid pathology and treatment of patients with rheumatic diseases (RD) is a complex task, the solution of which lies in interdisciplinary interaction and the development of a general algorithm for patients' management [16–20].

In this respect, panniculitis (Pn), a group of heterogeneous inflammatory diseases characterized by damage to the subcutaneous fatty tissue (SCF), the musculoskeletal system and inter-

Table 1. Cumulative disease assessment scale (CIRS) [4]

Content and interpretation	Points				
	0	1	2	3	4
Diseases of the heart					
Diseases of the blood vessels (blood and lymphatics)					
Diseases of the blood (bone marrow, spleen and peripheral blood)					
Diseases of the respiratory system (trachea, bronchi and lungs)					
Diseases of the sense organs (eyes, nose, ears, pharynx and larynx)					
Diseases of the organs of the upper digestive tract (esophagus, stomach, duodenum, pancreas, excluding diabetes mellitus, and gallbladder)					
Diseases of the organs of the lower parts of the digestive tract (small and large intestine)					
Liver diseases					
Kidney diseases					
Diseases of the genitourinary system (ureters, bladder, urethra, prostate and genitals)					
Diseases of the organs of the musculoskeletal system (muscles, joints, bones) and skin					
Diseases of the central and peripheral nervous system (brain, spinal cord and nerves)					
Diseases of the endocrine system and metabolic disorders (including diabetes mellitus)					
Mental disorders					
Total points					

Note. Assessment of organs and systems: 0 points – absence of diseases in this organ system or presence of pathology that does not interfere with normal life, does not affect the prognosis and does not require treatment; 1 point – slight deviations from the norm or past diseases; 2 points – a disease in which drug therapy is necessary; 3 points – a disease that caused disability; 4 points – life-threatening disease requiring emergency treatment.

Table 2. The Charlson Comorbidity Index [10]

Concomitant disease	Points
Myocardial infarction	1
Heart failure	1
Damage to peripheral vessels (presence of intermittent claudication, aortic aneurysm> 6 cm, acute arterial insufficiency, gangrene)	1
Transient cerebrovascular accident	1
Acute disorder of cerebral circulation with minimal residual effects	1
Dementia	1
Bronchial asthma	1
Chronic nonspecific lung diseases	1
Collagenoses	1
Peptic ulcer and / or duodenal ulcer	1
Liver cirrhosis without portal hypertension	1
Diabetes mellitus without end-organ lesions	1
Acute cerebrovascular accident with hemiplegia or paraplegia	2
Chronic renal insufficiency with creatinine levels > 3 mg%	2
Diabetes mellitus with end-organ lesions	2
Malignant tumors without metastases	2
Acute and chronic lymphocytic or myeloid leukemia	2
Lymphomas	2
Cirrhosis of the liver with portal hypertension	3
Malignant tumors with metastases	3
Acquired immunodeficiency syndrome	6

Note. When calculating the index, the points corresponding to concomitant diseases are summed up (see Table 2), and 1 point is added for each decade of life if the patient exceeds the age of 40 (that is, 50 years – 1 point, 60 years – 2 points, and etc.).

nal organs, are of particular interest. There are two types of Pn: predominantly septal (inflammatory changes predominate in the connective tissue septa) and predominantly lobular (affection of fatty lobules), which may be accompanied by signs of vasculitis, which affects clinical symptoms [21]. Lipodermatosclerosis (LDS) is a variant of lobular Pn, manifested by degenerative-dystrophic changes in the SCF, that mainly occurs in middle-aged women with chronic venous insufficiency (CVI). The frequency of edematous syndrome and trophic disorders in CVI, including hyperpigmentation, LDS and eczema, varies from 3% to 11% [22].

The hallmarks of LDS are painful hyperemic indurations on the skin of the lower third of the leg, more often on its medial surface. With the progression of sclerosis and atrophy of the SCF in the lesion, hyperpigmentation and induration of the skin develop, up to the formation of a woody compaction with a clear demarcation line. This leads to a characteristic Tinverted champaign bottleУ appearance of the lower third of the leg. Later, in the absence of CVI treatment, trophic ulcers are formed [21–23].

There are no data on the combination of LDS with other diseases, as well as on the effect of comorbidity on the development of complications and the outcome of Pn, which promoted this study.

Purpose: to study the structure and frequency of comorbid conditions in patients with LDS.

Materials and methods. The study involved 53 patients (3 men and 50 women) aged 18 to 80 years with a verified diagnosis of LDS, who were followed up at V.A. Nasonova Research Institute of Rheumatology on average for 10 years. The duration of the disease ranged from 2 weeks to 20 years.

Clinical examination determined the localization, prevalence, color and quantity of the affected skin and SCF. The intensity of pain on palpation of the node was assessed using the visual analogue scale (VAS) when pressing on the center of the node until the researcher's nail phalanx became white. Laboratory and instrumental investigations included: blood and urine tests, computed tomography of the chest organs and ultrasound Doppler of the lower extremities with registration of the linear blood flow velocity in the veins concerned (femoral, popliteal, posterior tibial, veins of the foot). Clinical, laboratory and instrumental examination of patients was carried out 2 times a year.

To assess the relationship between comorbid pathology and LDS, the CIRS and Charlson indices were used (Tables 1, 2) [4, 10].

Statistical data processing was carried out on a personal computer using the methods of parametric and nonparametric statistics of the Statistica 10 software for Windows (StatSoft Inc., USA). For independent samples, the significance of differences was analyzed by nonparametric methods using the Mann – Whitney test. To analyze the dependencies, the method of correlation analysis was used with the calculation of the Spearman's rank correlation coefficient. Differences were considered significant at $p \leqslant 0.05$.

Results. The majority of patients (60.3%) were women with excess body weight (91.5±21.8 kg). Twenty patients (38%) had positive family history of CVI. In 70% of cases, the nodes were located asymmetrically, mainly on the medial surface of the leg (74.4%), their size was 3–6 cm, the intensity of pain on palpation (according to VAS) was up to 80 mm.

Depending on the duration of the disease, the main variants of the course of LDS were identified: acute (<3 months), subacute (3–6 months), and chronic (>6 months). The acute course of the disease was detected in 20 (38%) patients (mean age 51.2±4.6 years). The subacute course of LDS was found in 12 (22.6%) patients (mean age 54.1±6.1 years, mean duration of the disease 4.7±1.3 months); in the overwhelming majority of cases

(91.7%) indurations of red-purple color and a positive symptom of Tinverted champaign bottleУ were detected. The chronic course of LDS was present in 21 (39.6%) patients (mean age 58.3±5.7 years, mean duration of the disease 43.3±24.0 months) and was characterized by the presence of clearly demarcated purple-brown indurations and the symptom of «inverted champaign bottle» in 81% of cases.

Skin changes were associated with polyarthralgias (34%) and / or myalgias (22.6%), mainly on the side of the affected limb. In 16 patients, an increase in ESR was recorded, on average up to 23.8±7.8 mm / h; in 7 patients (including 4 with acute LDS) more than a threefold increase in the level of CRP was found; 4 patients had positive titers of rheumatoid factor, and 2 patients – antibodies to cardiolipins and lupus anticoagulant. Thirty four (64.2%) patients showed signs of CVI according to the International Classification of Chronic Venous Diseases [24]: the clinical class of the disease is LDS (C4b), and according to the classification proposed by V.S. Savelyeva [25] – CVI IIIA degree. In 28 patients, including 19 (67.9%) with chronic LDS, CVI was recurrent, its average duration reached 10.2±1.3 years.

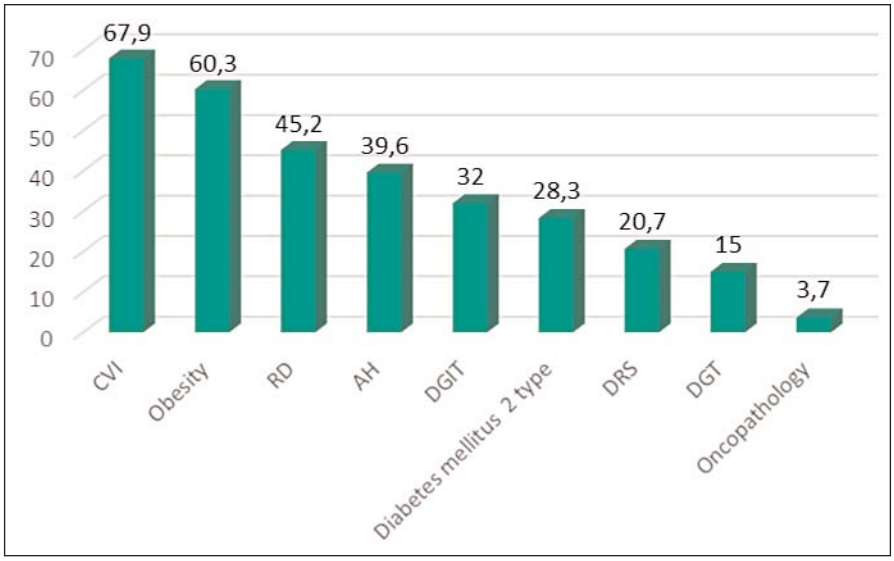

Fig. 1. *The incidence of comorbid pathology in patients with LDS (n = 53): DGIT – diseases of the gastrointestinal tract, DRS – diseases of the respiratory system, DGT – diseases of the genitourinary tract*

In 17 (32%) patients, no concomitant diseases were detected, 64.7% of them were under 50 years of age and had an acute course of LDS (p=0.02). Comorbid pathology was observed in 68% of patients, mainly with chronic LDS. In 67.9% of cases CVI was observed, in 60.3% – exogenous constitutional obesity, in 45.2% – rheumatic diseases (RD): osteoarthritis (in 75%), rheumatoid arthritis (RA; in 17%), antiphospholipid syndrome (in 8 %), as well as arterial hypertension (39.6%; see Figure 1). Most patients (55.5%) had 1 concomitant disease, 19.4% – 2; 11.1% – 3; 8.3% – 4 and 5.5% – 5 concomitant diseases.

According to the correlation analysis, a moderate positive relationship (r=0.3, p=0.0002) of the age of patients with the number of concomitant diseases was noted. In the age group of 51–60 years old, the proportion of patients with comorbid diseases was 58%, in the age group of 61–70 – 71%, and over 70 years old – 100%.

When assessing the Charlson index, the 10-year survival rate > 90% (index value 0–2 points) was noted in 66% of patients, 53% – 77% (3–4 points) – in 26.4%; and <21% (i5 points) – in 7.5% of patients. Correlation analysis revealed an association between the Charlson index and the age of patients (r=0.8; p <0.05), as well as with the frequency of hospitalizations (r=0.4; p <0.05); no relationship with the duration of LDS was found (p=0.2). Analysis of the incidence of concomitant diseases according to the CIRS index (14 organs and systems) showed that patients over 61 had i1 comorbid pathology. The median CIRS index for this age group was 4.2±0.3 (0–10 points), in most patients (45.2%) the CIRS index did not exceed 5 points. Analysis of the Charlson and CIRS scales confirmed their moderate correlation (r=0.5, p=0.0000001).

More than a half (54.7%) of patients with LDS received multiple drug therapy due to comorbid pathology. These were mainly non-steroidal anti-inflammatory drugs (NSAIDs), which were taken by 74% of patients, venotonic drugs (hesperidin and diosmin 1.0 g/day) – by 40%, glucocorticoids (on average 7.9±2.5 mg/day in terms of prednisolone) – by 28.3%, hydroxychloroquine – by 18%, methotrexate (average 18.3±0.8 mg/day) – by 5.6%, azathioprine (50 mg/day) and leflunomide (20 mg/day) – by 2.7% each, respectively.

Discussion. In recent years more and more attention has been paid to the problems of comorbidity in rheumatic diseases. In everyday practice, rheumatologists supervise patients with several comorbidities, so comorbidity for them is a rule, not an exception. Thus, in RA, a high coefficient of comorbid conditions (1.6) was noted, increasing with age, duration and / or activity of the disease [2, 16–18]. For other RD, such as psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), or ankylosing spondylitis (AS), data are scarce [16, 19, 20, 26]. There is no information about concomitant pathology in Pn, which promoted this study.

In our work, LDS was more often observed in middle-aged women (male: female ratio 1:18), the average age of disease onset was 52.6±9.4 years. Correlation analysis revealed the relationship between the age of patients and the number of concomitant diseases (r=0.3, p=0.0002). According to the results of numerous studies in which comorbidity in different diseases was studied, a significant increase in overall survival (OS) was observed in patients under 50 years of age – from 45% to 57% over 5 years. With increasing age of patients, OS significantly decreased: from 39% to 48% at 50–59 years old [27], from 31% to 36% at 60 to 69 years old, and from 27% to 29% after 70 years old [18, 26, 28, 29]. Thus, age, being an independent risk factor, can have a negative impact on the course of the disease and the results of treatment, and this must be taken into account when choosing the tactics of therapy in patients with RD. At the same time, according to the latest data, elderly patients with a satisfactory somatic status can tolerate more intensive therapy rather well, gaining an advantage in OS [2, 16, 20].

As shown by the analysis of the comorbid status of patients with LDS, only one third of them had no concomitant pathology. The data obtained are consistent with the results of studies in RA, PsA and SLE [16, 18, 26, 29, 30].

In our patients, CVI and exogenous constitutional obesity were the most frequent comorbid conditions, which can be considered as pathogenetic factors in the development of LDS [22, 23, 31]. For comparison: patients with RA have the highest prevalence of cardiovascular diseases, depression and osteoporosis [18, 29, 30]; young women with SLE have a high risk and a more than 50 times higher probability of developing myocardial infarction compared with the population control [19, 32], in patients with AS the frequency of cardiovascular pathology is not precisely established, but it is higher than in the general population, which may be due to long-term use of NSAIDs [20, 33].

In patients with RD, 2–3 comorbidities are most often encountered, in isolated cases – up to 6–8 diseases simultaneously [16, 18, 29, 30]. In our study, 86% of patients were diagnosed with up to 3 comorbid conditions, and in 14%, in addition to LDS, 4–5 more diseases were diagnosed.

The Charlson and CIRS scales were used to assess comorbid status. Despite a different range of nosologies used to calculate these indices, a significant correlation was found between the scales, which makes it possible to recommend their further study in other variants of Pn.

An increase in the number of concomitant diseases per 1 patient in our study significantly more frequently (p=0.002) was observed in the chronic course of LDS, which complicated treatment and aggravated the prognosis of the disease.

Conclusion. Thus, regardless of the selected assessment tool, the majority of LDS patients have concomitant pathology with the involvement of various systems and organs in the pathological process, which necessitates an interdisciplinary approach and interaction between doctors of different specialties in the treatment of such patients. It seems relevant to further study the effect of comorbidity on the course of Pn in order to develop algorithms for monitoring and treating this disease.

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Conflict of Interest Statement

The study has been conducted within investigative research (№ ИКБРС 0397-2020-0006).

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