Infiltrative tuberculosis, herpes zoster, and melanoma as comorbidities in systemic lupus erythematosus and antiphospholipid syndrome: a case report

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No additional data are available.

Cover letter. The study demonstrates clinical cases of the presence of various comorbid conditions in patients with SLE and APS, the complexity of diagnosis and their management. Our described cases show the need for alertness with respect to cancer and tuberculosis in patients with SLE, especially during long-term immunosuppressive therapy. Severe HZ can complicate the cutaneous manifestations of SLE and make the choice of immunosuppressive drugs difficult. Studying the complex disease in patients with RDs can improve the early diagnosis of concomitant diseases, thereby expanding therapeutic approaches and, possibly, decreasing the risk of a recurrence of the underlying disease. Author confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.

Author Biography

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Abstact

Background. Neoplastic diseases and infections have become the leading causes of death in SLE in recent decades. Cancers and infections were also precipitating factors in the development of catastrophic APS.

Case summary. We describe two patients: one of them had definite antiphospholipid syndrome (APS) and melanoma and the other had definite systemic lupus erythematosus (SLE) with APS, melanoma, infiltrative tuberculosis and severe Herpes Zoster (HZ). Management of patients with SLE concurrent with APS is a rather difficult task in rheumatology practice. In addition to kidney damage and cardiovascular disease, infections and malignancies are a significant cause of death in this cohort. The risk of malignancy in SLE is of considerable interest, since the immune and genetic pathways underlying the pathogenesis of this disease, as well as the immunosuppressive therapy, can significantly alter the risk. Both patients still had reliable APS, confirmed by triple-positive aPL. Both were at high risk of thrombosis. Patients ' adherence to treatment with direct oral anticoagulants and relapse of thrombosis on the background of rivaroxaban were noted.

Conclusion. The cases where cancer or tuberculosis develops in the presence of rheumatic diseases are not so common and complicate the possibilities of therapeutic approaches, limiting the use of drugs that are not regulated by clinical recommendations.

Keywords: antiphospholipid syndrome; systemic lupus erythematosus; melanoma; pulmonary tuberculosis; herpes zoster; case report.

Core tip: Systemic Lupus Erythematosus (SLE), Tuberculosis (TB), Herpes Zoster (HZ) and malignancy are intricately related with an increase in the risk of TB in SLE. Primary mechanisms pertaining to the increased susceptibility for TB are the inherent immunodeficient state of SLE and use of immunosuppressant agents in the treatment of SLE. The activity of SLE, the presence of antiphospholipid antibodies (aPL) and other concomitant diseases are risk factors for thrombosis.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that embraces a wide range of symptom complexes leading to varying severity of the condition. It is characterized by the impaired activation of T and B lymphocytes, the uncontrolled overproduction of a broad spectrum of organ-specific autoantibodies to nuclear antigens (such as native double stranded DNA (dsDNA) and ribonucleoproteins (RNP), Ro complex, La RNA-binding protein, RNA molecule/Sm protein complex, the C1q subunit of complement component C1, and phospholipids) and by the formation of immune complexes that cause immune-mediated inflammatory damage to tissues and internal organs [1, 2].

Antiphospholipid syndrome (APS) is an acquired thrombophilic disease associated with the production of autoantibodies to cell membrane phospholipids or phospholipid-binding blood proteins. The clinical manifestations of APS are recurrent thromboses, fetal losses, and the presence of blood serological markers - antiphospholipid antibodies (aPL). In more than 40% of cases, SLE is associated with the presence of highly positive aPL, whereas 50-70% of patients develop definite APS over the next 10 years of the disease [3, 4].

In recent decades, death causes, such cancers and infections, in SLE have come to the fore [5]. The difficulty in managing patients with infections, such as infiltrative tuberculosis and herpes zoster, is in the inability to fully use immunosuppressive drugs. Cancers and infections have also been noted to be precipitating factors for the development of catastrophic APS [6]. The incidence of cancers in SLE ranges from 2.5% to 7.3% [7]. Since the role of aPL in oncology is still a matter of debate, more investigations should be conducted to study the relationship between aPL and malignant neoplasms in order to potentially affect the mechanism and treatment when cancer and APS coexist [8]. There is more and more evidence to support the triggering mechanism for infections in aPL positivity in the development of thrombosis by the mechanism of molecular mimicry [9].

We present a description of clinical cases of two patients with rheumatic disease concurrent with cancer and, in one case, two more infectious diseases such

as tuberculosis and herpes zoster. A similar combination was found in these two of the 116 patients in our cohort of patients observed since January 2019.

Case reports

Patient A., aged 35 years, has been followed up at the V.A. Nasonova Research Institute of Rheumatology since March 2019.

Medical history: in August 2014, the patient aged 29 years experienced acute right lower extremity iliofemoral thrombosis complicated by pulmonary embolism (PE) in the left lower lobe artery. Doppler ultrasonography (USD) of the lower extremity veins revealed right lower extremity deep vein thrombosis (non-occlusive parietal thrombi in the popliteal vein, occlusive thrombi in the deep vein of the thigh, common femoral vein (CFV), and external iliac vein; the upper level of distribution of thrombotic masses in the inferior vena cava corresponds to the site of its confluence with the internal iliac vein). The patient is a carrier of thrombophilic gene mutation: heterozygous genetic polymorphism in the plasminogen activator inhibitor-1 (PAI-1), integrin subunit α2: specialized receptors of platelets Ia/IIa (integrin ITGA-α2), methylenetetrahydrofolate reductase (MTHFR 667, 1298), and methionine synthase reductase (MTRR 66). The level of homocysteine did not exceed the norm. He received enoxaparin sodium 0.4 ml subcutaneously and acetylsalicylic acid 100 mg/day with initial recanalization, as shown by USD.

In September 2014, the patient had an occlusive thrombosis in the right saphenofemoral fistula, otherwise without negative changes. He took warfarin at a dose of 3.75 mg/day under international normalized ratio (INR) control for 3 months; due to increased hair loss, he was switched to rivaroxaban 15 mg/day on January 2015.

At 30 years of age in May 2015, the patient was surgically treated for melanoma in situ (detected in February 2015) in the area of the inner surface of the left thigh, which had previously been regarded as a nevus. Histological examination revealed non-ulcerated lentigo melanoma in situ with mild small focal lymphoid infiltration in the upper layers of the dermis; the melanoma was removed

within intact tissues. He was followed up by an oncologist; the patient's condition remained stable.

In 2016, the 31-year-old patient discontinued rivaroxaban on his own. At 32 years of age in 2017, he had right leg deep vein relapse of thrombosis and left lower leg deep vein thrombosis. Rivaroxaban 15 mg/day was restarted; in the summer of 2018, the patient reduced its dose to 10 mg/day; his health status was satisfactory.

At the age of 33 years in November 2018, the patient was found for the first time to have a positive lupus anticoagulant (LA), total IgG (>100 IU/ml) and IgM (5.22 IU/ml) aPL and total (IgA, IgM, IgG) antibodies to β2 glycoprotein 1 (anti-β2GP1) (143.6 IU/ml). Rivaroxaban was temporarily discontinued; the patient received enoxaparin sodium 1.6 mg/day subcutaneously for a month, then rivaroxaban therapy was restarted at the previous dose. USD of the lower extremity veins showed signs of postthrombophlebitic disease in the right iliofemoral segment with signs of a recanalization rate of 60-65%, in the left popliteal vein and the anterior tibial veins with signs of complete recanalization.

At 34 years of age in March 2019, the patient was admitted for the first time to Rheumatology Department Four, V.A. Nasonova Research Institute of Rheumatology. His examination demonstrated mild fine-meshed livedo on the skin of the lower extremities.

The immunological markers of SLE and APS are given in Table 1.

Table 1. Immunological criteria for SLE and APS

Immunological parameters					
SLE-associated antibodies			APS-associated antibodies		
Parameter, references value	2019	2020	Index	2019	2020
ANF HEP2	**1/640h+sp**	**1/320 sp**	LA	+ (in the medical past history)	
Cc3, g/l	**0.814**	**0.780**	IgG aCL, GPL	**>120.0**	**>120.0**
C4, g/l	0.119	0.130	IgM aCL, MPL	7.1	4.3

anti-Sm Ab, U/ml	0.1	0.1	IgG anti-β2GP1, U/ml	**69.4**	**93.5**
dsDNA, U/ml	**25.7**	**24.0**	IgM anti-β2GP1, U/ml	2.9	1.7

Note: the deviations from the reference values are highlighted in bold.

At the time of examination, there was no evidence in favor of SLE, there was definite primary APS: recurrent lower extremity vein thromboses, left lower lobe artery PE, and triple aPL positivity. Taking into account the presence of a positive ANF, a slight increase in anti-dsDNA antibodies, hydroxychloroquine 200 mg/day was initiated to the patient as a basic drug; there were no indications for glucocorticoids. Positive anti-dsDNA antibodies, C3 hypocomplementemia, and ANF positivity can be considered within the framework of both lupus-like syndrome and APS activity values. Recurrent venous thromboses and the persistence of a high risk of recurrence in terms of aPL, as well as the carriage of thrombophilic gene polymorphisms, are indications for lifelong anticoagulation. Due to the higher soluble fibrin monomer complex (SFMC) level, rivaroxaban therapy was completed; apixaban 10 mg/day was initiated. During one-year (2019-2020) follow-up, the condition of the patient is stable; no recurrent inhibitions are noted; he continues therapy with apixaban 10 mg/day, immunological disorders persist without a considerable increase in the level of anti-dsDNA antibodies and in the absence of clinical manifestations of SLE. The patient is diagnosed with primary APS: acute right lower extremity iliofemoral thrombosis (non-occlusive parietal thrombi in the popliteal vein; occlusive thrombi in the deep femoral vein, CFV, and external iliac vein); right femoral vein thrombosis with extension to the right external iliac vein (in 2014); right leg deep vein rethrombosis without thrombus floatation; left leg deep vein thrombosis (in 2017), left lower lobe artery PE (in 2014), and highly positive IgG-anti- β2GP1and IgG-aCL. The patient remains in the group at high risk for recurrent thromboses and developing systemic connective tissue disease, which provides a rationale for a rheumatologist's follow-up.

Clinical Case Two

A 40-year-old female patient Yu. has been following up at the V.A. Nasonova Research Institute of Rheumatology since February 2012.

It is known from her medical history that false-positive Wassermann reactions for syphilis have been detected since 1994 (at 16 years of age), photosensitization since 1996, and positive aCL since 1998. In 2000 (the patient was 22 years old), a chest X-ray diagnosed focal tuberculosis of the right lung; she took anti-tuberculosis drugs; during therapy, leukopenia up to $3.0x10^9$/L was first detected (in August 2001), which was regarded as drug-induced one. In 2001, the patient made a complete clinical and laboratory recovery. Her condition has been satisfactory for 8 years.

At the age of 31 years in 2009, her first pregnancy ended with delivery at term; the pregnancy and postpartum periods were normal. After childbirth, there was a nasal mucosal ulcer. At 32 years of age in 2010, erythematous skin rashes and arthralgia first appeared.

In 2011, when the patient was 33 years, she got pregnant the second time. USD of the lower extremity veins revealed thrombosis in the small saphenous vein (SSV) of the left lower extremity. In December 2011, she was found to have anemia (a hemoglobin count of up to 108 g/l), leukopenia (a white blood cell count of $2.9x10^9$/l, accelerated ESR up to 60 mm/h, hyperbilirubinemia, highly positive aCL, and anti- β2GP1; abdominal ultrasound showed signs of portal hypertension. The patient was examined by a hematologist; blood diseases (the bone marrow pattern characteristic of chronic anemia) were excluded according to trephine biopsy findings.

In February and March 2012, the patient was admitted for the first time to Rheumatology Department Four, V.A. Nasonova Research Institute of Rheumatology. Hemolytic anemia was confirmed by a positive Coombs' test; there were positive anti-Sm antibodies, antinuclear factor (ANF), and inherited thrombophilia: homozygous polymorphisms in the genes of PAI-1 and vitamin K epoxide reductase; cytochrome P450 (CYP2C9), heterozygous polymorphisms in

the genes of thrombospondin-4, glycoprotein, and angiotensin-converting enzyme. The presence of discoid erythematous lupus, photosensitization, arthralgias, hemolytic Coombs positive anemia, leukopenia, positive anti-Sm antibodies, and ANF provided the basis for the diagnosis of SLE. Whereas SSV thrombosis, a false-positive Wassermann reaction, and highly positive aPL, detectable at the age of 16 years, were regarded as a manifestation of APS. Hospitalization at 16-17 weeks' gestation, which along with the preservation of highly positive aPLs and signs of hypercoagulability, was an indication for anticoagulant therapy, nadroparin calcium 0.6 ml/day was subcutaneously administered. Methylprednisolone 12 mg/day and hydroxychloroquine 200 mg/day were initiated in the hospital. During the therapy, the patient's condition was satisfactory, there were positive changes: a decrease in ESR, LDH, and fibrinogen; however, the increased SFMC level remained, which was acceptable for this gestational age. After discharge, the patient was followed up in an outpatient setting; her condition remained stable; the dose of methylprednisolone was decreased to 8 mg/day; hydroxychloroquine 200 mg/day and subcutaneous nadroparin calcium 0.6 ml/ day were continued. The patient delivered a baby via cesarean section in July 2012. The postpartum period was normal; erythematous skin lesions occasionally appeared; she used topical steroids; the therapy was not corrected.

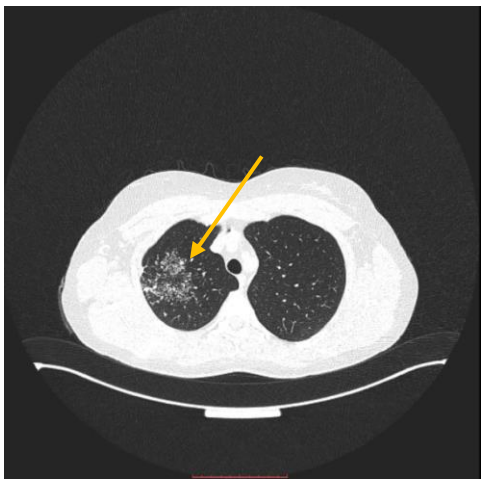
The patient's condition was satisfactory until January 2017 (she was 39 years old) when cutaneous manifestations gradually appeared and began to progress; these included alopecia, bright red painful erythematous rashes on the skin of the hands, face, back, and shoulders, as well as ulcers of the mucous membrane. In May 2017, she was admitted to the V.A. Nasonova Research Institute of Research; leukopenia ($3.23x10^9$/l), anemia (92 g/l), a positive direct Coombs' test, highly positive anti-dsDNA antibodies, aPLs, and hypocomplementemia persisted. SLE activity was high with a preponderance of skin and mucosal lesions with necrotic ulcerative changes and hematological disorders. Pulse intravenous dropwise methylprednisolone 500 mg therapy was performed during 3 days. The dose of oral methylprednisolone was increased up to 16 mg/day and that of

hydroxychloroquine up to 400 mg/day; anticoagulant therapy with fondaparinux was done, after discharge the patient took rivaroxaban 15 mg/day. The performed therapy relieved mucocutaneous syndrome. In November 2017, therapy with mycophenolate mofetil (MMF) was initiated due to a recurrence of necrotic skin symptoms; pulse intravenous dropwise methylprednisolone 500 mg therapy was performed during 3 days; and rivaroxaban therapy was continued. The skin lesion was arrested.

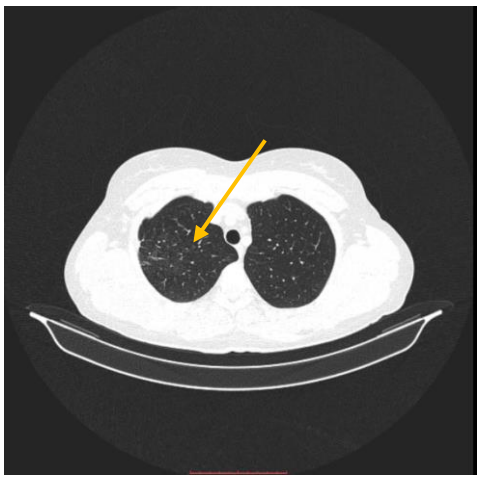
In June 2018, a nevus in the lumbar region was removed. Histological examination revealed nodular malignant pigmented melanoma of the skin in the lumbar region, Stage IB ($T_2N_0M_0$) (Clark's Level IV of invasion; a Breslow thickness of 1.2 mm), without epidermal ulceration; no tumor growth at the resection margins; a mitotic rate of 1x1 mm^2. MMF was discontinued; the methylprednisolone dose was reduced to 8 mg/day; the intake of hydroxychloroquine 400 mg/day was continued.

To exclude metastasis, positron-emission computed tomography (PET/CT) was carried out, which detected changes in the right upper lobe (Fig. 1, a). Mycobacterium tuberculosis (MBT) was revealed by bronchoscopy in the bronchoalveolar lavage material. The patient diagnosed with infiltrative tuberculosis in the right upper lobe was hospitalized at the Central Tuberculosis Research Institute from September 12, 2018 to May 13, 2019. Antituberculosis therapy was initiated with pyrazinamide 1500 mg/day, cycloserine 0.5 mg/day, sparfloxacin 0.4 mg/day, linezolid 0.6 mg/day, protionamide 0.75 mg/day, one glutamic acid tablet thrice daily, and one methionine tablet thrice daily). In the hospital, the patient experienced an exacerbation of SLE: arthritis in the small joints of the hands; morning joint stiffness lasting up to 2 hours; foci of subacute cutaneous lupus erythematosus on the face, neck, décolleté area, back, and upper extremities. In April 2019, she discontinued rivaroxaban on her own.

*Fig. 1. Infiltrative tuberculosis of the right upper lobe, as evidenced by PET/CT dated August 2018 (**a**), changes dated March 2020 (**b**) (arrow)* ↙



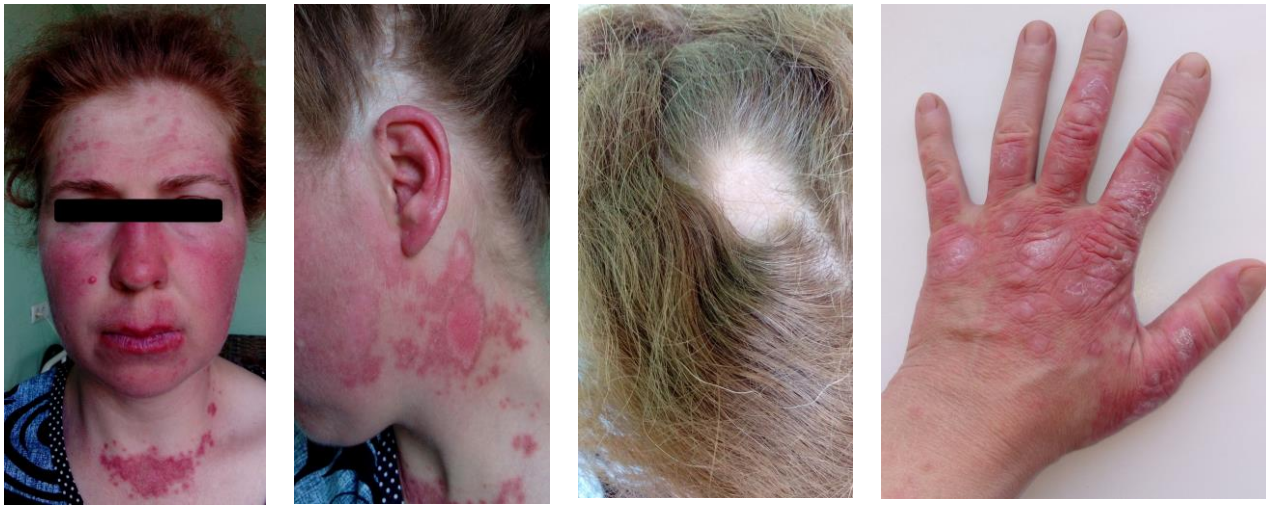
a) PET/CT dated August 2018



B) CT changes dated March 2020

Another hospitalization of the patient to the V.A. Nasonova Research Institute of Rheumatology occurred in May 2019. Her examination showed low aPL levels, hypocomplementemia (Complement C3, 0.52 g/l; C4, 0.02 g/l). The signs of an SLE exacerbation were confined to a mucocutaneous system lesion (CLASI for activity scores of 32 and that for damage scores of 9 are given in Fig. 2) and to musculoskeletal types.

Fig. 2. Mucocutaneous syndrome in Patient Yu. in May 2019

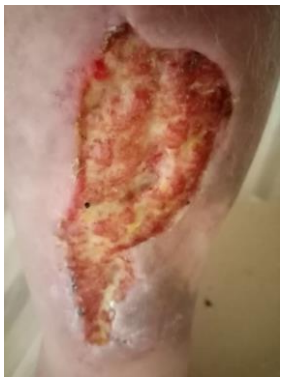


Due to high disease activity and obvious cutaneous manifestations (subacute cutaneous lupus erythematosus foci occupying about 48% of the body surface), methylprednisolone 500 mg was intravenously injected during 5 days, with an effect in rash reversal; arthralgia was relieved. Cytostatic drug therapy cannot be intensified due to the presence of active tuberculosis. The activity of SLE and

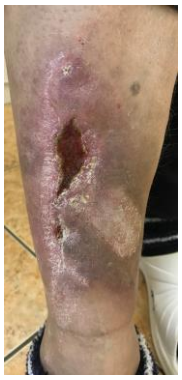
iatrogenic (drug) genesis in the etiology of leukopenia were discussed. It was decided to prescribe anticoagulant therapy with low-molecular-weight heparins (enoxaparin sodium 0.5 ml twice daily for 2 months, with a further switch to apixaban 10 mg/day. She was discharged in a satisfactory condition.

On August 15, 2019, she sustained a scalp wound in the lower and middle third of the anterior surface of the right leg (Fig. 3); primary surgical debridement was performed; however, some of the sutures turned out to be incompetent; the wound healed by secondary intention (Fig. 3), which was a risk factor for thrombosis and infection.

In August 2019, in the presence of stress, she again noticed the appearance and rapid progression of erythematous rashes on the face, neck, auricles, hands, elbow bends, upper third of the shoulders, as well as obvious cheilitis. By September 2019, she discontinued apixaban on her own and restarted rivaroxaban 15 mg/day again. She applied akriderm topically to the erythematous foci, which produced an incomplete effect.



a) September 2019



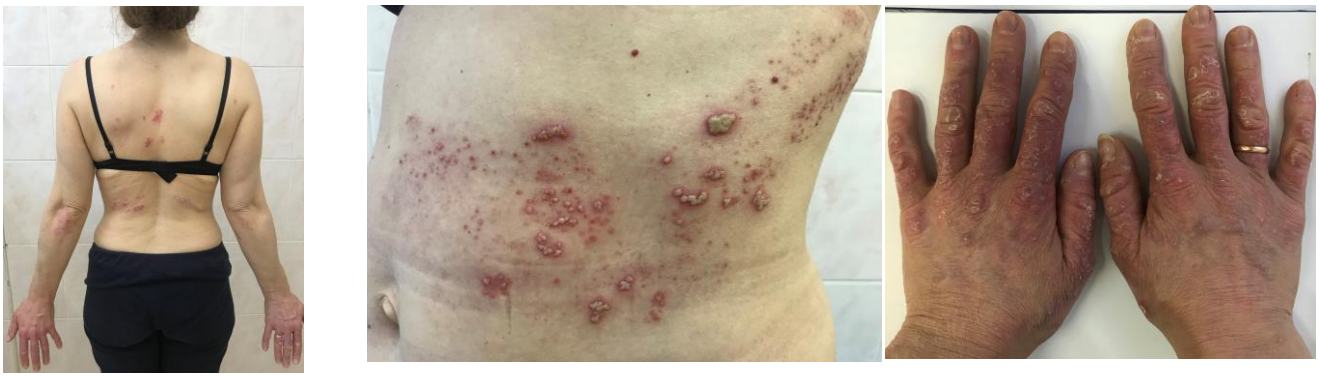
b) December 2019

Fig. 3. Scalp wound in the right leg.

In August 2019, a control examination made at the Central Tuberculosis Research Institute could diagnose infiltrative tuberculosis in the right upper in the phase of resorption and consolidation, MBT (-). She had a history of previous extensive drug resistance. Stage 2 respiratory failure. Moderate respiratory dysfunction. There were recommendations on continuing antituberculosis therapy for 1 year. In December 2019, she experienced herpes zoster.

Her last hospitalization to the V.A. Nasonova Research Institute of Rheumatology occurred in December 2019. She was diagnosed with chronic SLE, SLEDAI-2 K scores of 7, with a skin lesion: subacute cutaneous lupus erythematous (Fig. 5): non-indurated psoriasiform rash, alopecia areata, and cheilitis (CLASI for activity score of 16 and that for damage score of 4 are given in Fig. 4), adhesive pericarditis, hematological (leukopenia) and immunological (hypocomplementemia) disorders; she had a history of articular (arthralgia) and mucosal (oral and nasal ulcers) damages, hematological disorders (Coombs-positive anemia, highly positive anti-dsDNA antibodies), ANF (+). SLICC DI = 1 (cataract). APS: thrombosis in the SSV of the left lower extremity, portal hypertension, and positive aPLs. Leukopenia persisted; hypocomplementemia, IgM aCL and IgM aβ2-GP in average titers were revealed. Having an exacerbation of mucocutaneous manifestations of SLE, the patient had residual herpes zoster phenomena (Fig. 4).

Fig. 4. Mucocutaneous manifestations of SLE and active herpes zoster in Patient Yu. in December 2019



Taking into account disease activity and a mixed skin lesion (subacute cutaneous lupus erythematosus foci and a secondary viral infection), replacement therapy using intravenous human immunoglobulin 20 g and premedication with a total of 1500 mg of methylprednisolone administered in an intravenous dropwise manner resulted in a reversal of rash and herpetic eruptions. The doses of methylprednisolone (GC) and hydroxychloroquine (HCQ) were the previous. The total cumulative dose of HCQ is 729,800 mg, and that of GC is 34,168 mg.

The condition of the patient was satisfactory. In March 2020, she was stricken off the tuberculosis register because of her clinical recovery from tuberculosis (Fig. 1, b).

Discussion

Melanoma is a potentially deadly skin cancer that develops from melanocytes (the pigment cells producing melanin). It is localized mainly in the skin, less frequently in the retina and mucous membranes (oral cavity, vagina, and rectum). Although at the time of diagnosis most patients have a localized mass requiring only surgical treatment, metastasis often develops, which correlates with the depth of penetration into the dermis [10]. Since the 1960s, the incidence of melanoma has been on the rise, especially in Caucasians; and according to D.S. Rigel et al, in the United States only, it increased by 270% from 1973 to 2002 [11]. The most important and potentially modifiable risk factor for this disease is exposure to ultraviolet (UV) rays. A history of sunburn is associated with a high risk of melanoma, whereas chronic continuous sunlight exposure is more associated with actinic keratosis and non-melanoma skin cancer. Artificial UV radiation and photochemotherapy are related to an increased risk for melanoma [12]. Epidemiological studies have shown that chronic inflammatory diseases, such as rheumatoid arthritis (RA) and SLE, are linked with an increased risk of hematologic, cutaneous, and solid malignancies [13, 14]. The higher risk of developing malignant neoplasms in patients with autoimmune diseases may be associated with systemic immune dysregulation [15] or, alternatively, as a consequence of immunosuppressive therapy used to treat these diseases, which can modify the risks of developing cancer [16].

In 1865, Armand Trousseau suggested that the presence of a tumor at any site was associated with the body’s prothrombotic readiness [17]. Venous and arterial thromboses are one of the most common complications in patients with malignant neoplasms. And although the frequency of other genetic markers for thrombophilia, such as Factor V Leiden and prothrombin gene mutations, did not differ in cancer patients and healthy individuals, controversies about the primacy

of this or that process remain [18]. Even before the identification of APS, the false-positive Wassermann reaction and LA were noted to be associated with some malignant neoplasms [19-20]. Later, cancers were described not only in patients with aCL, LA, or anti-β2GP1, but also in those with antibodies against phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol, phosphatidylserine, etc., which are non-criteria markers for APS [21-22].

In 1995, Zuckerman E. et al. proposed several mechanisms underlying the relationship between aPL positivity and cancer development:

1) production of autoantibodies by the immune system as a response to tumor antigens;

2) production of monoclonal antibodies by LA and aCL immunoglobulins;

3) secretion of aCL from tumor cells [23].

Whether there is an increased risk for developing cancer, including melanoma, in primary APS, as observed in other systemic autoimmune diseases, remains open.

In his study, J.A. Gómez-Puerta detected melanoma in 6 (5%) of 120 aPL-positive patients [24]. The standardized incidence rate was reported to be increased for non-melanoma skin cancer (basal and squamous cell skin cancers), whereas the risk of melanoma did not change significantly [14, 25]. The meta-analysis conducted by Song L. et al. showed that the risk of melanoma and prostate cancer was much lower than the population risk in patients with SLE. The results indicated that SLE was correlated with a reduced risk of skin melanoma [26]. Among the risk factors for non-melanoma skin cancer, there was the use of glucocorticoids (GCs), especially at their cumulative dosage of >5 g in patients with SLE and >1 g of hydroxychloroquine (HCQ). Long-term GC therapy can induce an immunosuppressive status in patients with autoimmune diseases. HCQ has anti-inflammatory and immunomodulatory effects that were found in increasing apoptosis and in reducing autoimmunity through elimination of autoreactive lymphocytes [27]. The high cumulative doses of HCQ in the genesis

of melanoma may be discussed in both patients with SLE. Patient A. is taking HCQ at a dose of 200 mg/day (the total cumulative dose is 83,000 mg). In Patient Yu., the total cumulative dose of HCQ is 729,800 mg, and that of GC is 34,168 mg.

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis complex [28]. The higher prevalence of tuberculosis in SLE is attributed to multiple immune abnormalities observed in these patients, as well as to the immunosuppressive therapy used [29]. There are scarce actual data on treatment safety and pulmonary tuberculosis outcomes in patients with rheumatic diseases (RDs). The treatment of tuberculosis in patients with and without RDs is practically identical; however, comorbidities, drug-related toxic effects, and metabolic interactions between immunosuppressants and anti-TB drugs can create therapeutic problems, which may affect both therapy adherence and efficiency [30]. The study conducted by Park D.W. et al. enrolled 37 patients with pulmonary tuberculosis and RDs, among whom 4 patients had SLE; a control group included 191 tuberculosis patients without RDs. The incidence of severe adverse drug reactions and their related changes in first-line anti-tuberculosis therapy were significantly higher in the RD group than in the control one. There were no substantial differences between the groups for long-term adverse outcomes (including recurrence and death) [31]. Herpes zoster (HZ) in SLE is another infectious problem. Recent immunosuppressive medication use is associated with an increased risk of HZ in patients with SLE, particularly in those receiving high-dose oral corticosteroids and multiagent immunosuppressive therapy.

There is currently insufficient evidence for the treatment of just several diseases complicating the course of each other. The use of cytostatics and biological therapy in patients with an oncological history is limited, which makes it difficult to treat the underlying RD. Belimumab is presently the only biologic agent approved for the treatment of SLE; nonetheless, rituximab has been approved by the EULAR as a treatment of refractory lupus nephritis [32]. The data available in the literature suggest that belimumab does not increase the risk of

developing tuberculosis in SLE [33]. The BIOGEAS registry evaluated 344 patients with systemic autoimmune diseases (including 140 patients with SLE); 77% on rituximab, 91% on corticosteroids. Only two cases of tuberculosis were recorded in the rituximab group [34], which corresponds to the average population risk.

Conclusion. The given clinical cases demonstrate the presence of various comorbid conditions in patients with SLE and APS, the complexity of diagnosis and their management. Our described cases show the need for alertness with respect to cancer and tuberculosis in patients with SLE, especially during long-term immunosuppressive therapy. Severe HZ can complicate the cutaneous manifestations of SLE and make the choice of immunosuppressive drugs difficult. Studying the complex disease in patients with RDs can improve the early diagnosis of concomitant diseases, thereby expanding therapeutic approaches and, possibly, decreasing the risk of a recurrence of the underlying disease. Both patients still had reliable AFS, confirmed by triple-positive afl profile. Both were at high risk of thrombosis. Patients ' adherence to treatment with direct anticoagulants and relapse of thrombosis on the background of rivaroxaban were noted

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