A clinical case of B-cell lymphoma in a patient with overlap, primary Sjogren's syndrome and scleredema adultorum of Buschke

Abstract. This is a presentation of case report on B-cell lymphoma in a patient with overlapping primary Sjogren's syndrome (PSS) and scleredema adultorum of Buschke. Scleredema adultorum of Buschke (SB) is a rare disorder characterized by a diffuse indurative edema and skin tightening. A putative classification of this disease is based on the etiological factors and encompasses three types: Type 1 is associated with an infectious disease; Type 2 with paraproteinemia; Type 3 – with diabetes mellitus. There are very rare cases involving malignant neoplasms or autoimmune diseases. This clinical case describes a rare combination of SB with an autoimmune disease – PSS. It highlights the importance of studying other SB associations, in particular with autoimmune diseases, to ensure proper management and treatment of these patients. For a 51-year-old patient, the disease onset featured a dense facial edema, dry skin, dry eye syndrome and a feeling of sand in the eyes, subfebrile fever and dense skin formations in the low neckline, mammary glands and interscapular region, which was pathohistologically regarded as scleredema Buschke. Lymphadenopathy, xerophthalmia, sialadenitis, Raynaud's syndrome were revealed, lung damage (alveolitis and bronchiolitis), positive ANA, anti-SSa/La, antiSSb/Ro were diagnosed. Based on this symptom complex, the patient was diagnosed with an overlap syndrome of SB with PSS. The use of combined therapy with methotrexate and methylprednisolone allowed to reduce the disease activity, clinical and laboratory appearance of the disease. However, 9 months after the onset of the first skin symptoms, there was a bulging of the left eye, widespread lymphadenopathy. Histopathological examination revealed the diagnosis of non-Hodgkin B-cell lymphoma. The use of rituximab therapy resulted in a significant regression of the orbital tumor. The relevance of this clinical observation is not only due to the rarity of combined pathology, but also to the need for an early diagnostics of lymphoma developing against the background of PSS, based on the risk factors, which include low levels of C₄ and/or C₃, enlargement of the parotid salivary glands, cryoglobulinemia, persistent splenomegaly’s systemic activity and lymphadenopathy, since the frequency of this disease is quite high in this patient population.

Keywords: scleredema adultorum of Buschke; Sjogren's syndrome; lymphoma; overlap syndrome; clinical case

Introduction

The overall progress achieved in the studies of systemic scleroderma and scleroderma-like conditions with various clinical forms being distinguished, along with differentiation and specification of nosologies in line with the new forms of induced scleroderma, resulted in a concept of scleroderma disease group. According to the recent beliefs, the term of “scleroderma” unites a wide circle of scleroderma diseases: systemic and focal scleroderma, diffuse eosinophilic fasciitis, induced scleroderma – chemical, iatrogenic, paraneoplastic and tumor-associated scleroderma and pseudoscleroderma.

The group of scleroderma-like conditions involves a rare disease: scleroderma adultorum of Buschke (edema-attend ed scleroderma, progressive benign subcutaneous induration, adult scleroderma) [1].

Scleroderma adultorum of Buschke (SB) is a rare disease characterized by a diffuse indurated edema and induration...
of the skin, commonly involving the face, neck, shoulder girdle and upper body, with a pathological process focused in the hypoderm. It may resolve itself spontaneously in the next 2 years or have a progressive or durable course with a potentially lethal outcome [2]. This disease is traditionally classified into three types depending on the etiological factor present: Type 1 is usually preceded by a contagious fever; Type 2 is associated with paraproteinemia; Type 3 — with diabetes mellitus [2]. There are very few cases associated with malignant neoplasm (biliary cancer or autoimmune disease) [3-5]. The SB-associated autoimmune diseases involve rheumatoid arthritis (RA), spondyloarthritis and primary Sjogren’s syndrome (PSS).

The primary Sjogren’s syndrome (PSS) is a systemic autoimmune disease with a lot of clinical manifestations ranged from the “dry syndrome” to systemic extraludular afflications [6]. While the “dry syndrome” is primarily affecting the life quality by reducing it and may result in topical lesions involving mucous membranes, the systemic affection determines the overall prognosis of the disease outcome. The risk of PSS patients’ developing lymphoma grows from 3 % in the first 5 years to 9.8 % after 15 years, i.e. up to 40 times over the population risk [7]. The present lymphadenopathy, constant enlargement of parotid gland, palpable purpura, low serum C\(_\text{r}\) rates and cryoglobulinemia predict an elevated risk of this complication’s developing and may even increase the risk of lymphoma 5 times over [8]. The mean age of disease onset is about 50 years; the SS diagnosis usually precedes the lymphoma by 7 years on average [8]. The most common localizations are parotid gland and other saliva glands, followed by orbits, stomach, thyroid gland, lungs and upper respiratory pathways, rarely other foci [7].

**Clinical case**

There is a clinical case presented of the B-lymphoma developing in a patient afflicted with an overlap syndrome of SB and PSS.

The 51-year-old patient was admitted to the Clinic of Modern Rheumatology on 25.10.2019, complaining at a moderate expansion of subarachnoid spaces, being the signs of the minor focal cerebral lesions which have a vascular genesis and are associated with cerebral microangiopathy, cervicocranialgia. As of 19.10.2019, there was a consultation by a pulmonologist, phthisiologist, and oncologist. There is a clinical case presented of the B-lymphoma developing in a patient afflicted with an overlap syndrome of SB and PSS.

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On 23.10.2019, the X-ray of thoracic cage organs revealed an intrathoracic lymphadenopathy (bifurcating lymph nodes of 14 mm, other groups of up to 10 mm). On 25.10.2019, the computer tomography (CT) of thoracic cage organs (TCOs) and abdominal cavity organs (ACOs) demonstrated numerous bilateral minor foci with diffuse contours of up to 1 mm in the lungs (primarily S\(_{1,3,4}\), they were surrounded by the “mat glass” type changes. On the right side, on the subpleural level (S\(_{13,4}\)), there were singular nodular inductions of up to 3 mm, while along the interlobular pleura there were bilateral nodular inductions of up to 3.5 mm. There are singular air cavities found of up to 9 mm large. Singular paratracheal, para-aortal and bifurcating lymph nodes were up to 4-9 mm in size. Adipose tissue induction was observed in the axillary areas, with the lymph nodes being 7-13-15 mm large. In the upper lateral quadrant of the right and left mammary gland there are areas of consolidation with a more intensive contrast accumulation of up to 13-10 mm. The cutaneous inductions at the level of mammary glands are bilateral and symmetrical. At the sternum level, T\(_{1,3}\) on the right side of the spinous processes is characterized by the subcutaneous adipose induction of the anterior and posterior chest wall. The enlarged size of the spleen (104-154-140 mm), in a para-aortal/vena cava perspective there are numerous lymph nodes with diffuse contours of up to 8-12 mm. The CT signs point to bronchiolitis/alveolitis. Conclusions. The focal pulmonary pathology of a non-specific character. Splenomegaly. Adenopathy of lymph nodes is observed in the retroperitoneal space. Mammary glands have neoplasms. Multinodular goiter. On 18.10.2019, magnetic resonance imaging (MRI) examination of the brain revealed signs of the minor focal cerebral lesions which have a vascular genesis and are associated with a moderate expansion of subarachnoid spaces, being the initial signs of dyscirculatory (cerebral microangiopathy-attribute) encephalopathy. As of 19.10.2019, there was a consultation by a neurologist who diagnosed an unspecified cerebral microangiopathy, cervicocranialgia.

During the rheumatologist’s consultation on 25.10.2019, an objective examination demonstrated: visual examination reveals a dense edema of facial skin, swelling of parotid salivary glands, dense hyperemic foci of up to 3 cm in diameter around mammary glands, cleavage and interscapular area, thyroid gland enlargement of Grade 1 (Fig. 1, 2). The submandibular and cervical lymph glands are enlarged to 1.5 cm. While auscultating the lungs and heart, the rheumatologist did not reveal any pathology. The stomach palpation does not produce any pain, the liver is not enlarged, and the lower pole of the spleen and intestine are palpated and provide the regular palpatory signs.

Considering the CT-manifested TCO and ACO changes, lymphadenopathy, skin lesions, we’ve concluded that sarcoidosis attended by the skin and lung lesions should be ruled out, as well as the paraneoplastic pathology. The consultation by a pulmonologist, phthisiologist, and oncologist is recommended, along with the skin lesion biopsy.
On 11.11.2019, the pathohistological skin examination revealed that all the dermal tissue is in the state of edema, the collagen fibers levels closest to the epidermis present the considerable degenerative-dystrophic changes and a partial destruction of fibers. In the deeper dermal layers, there are coarse collagen fibers with degeneration, depleted skin processes. The perivascular infiltration occurs via lymphoid nodule-like cells, collagen and mucin are deposited in the derma. Similar infiltrates surround the hair structures. Conclusions: skin changes correspond to the sclerodema adultorum of Buschke (SB). There is a syndrome of mucocutaneous-lymphoid manifestations of systemic connective disease.

The pulmonologist found no evidence of sarcoidosis, tuberculosis. The hematologist- oncologist found no evidence of oncopathology. The conclusions were based on the clinical, laboratory and instrumental data.

There was a repeat rheumatologist’s consultation on 20.11.2019. Additional examination was recommended: assay of antinuclear antibodies and anti-SSa/Ro and anti-SSb/La, examination of thyroid gland function, assay of anti-thyroid peroxidase autoantibodies (anti-TPO antibodies), ophthalmologist’s consultation with Schirmer’s test being taken, capillaroscopy.

The capillaroscopy of 24.11.2019 resulted in the following findings: while analyzing the capillary blood flow, there were signs of minor-diameter capillary loop spasm, the capillaries being predominantly of short and medium length account for 70 %; there are short, undercurled spirals, paragraphs registered, along with capillary loops of mostly minor and medium caliber – 30 %. There are multiple avascular fields in 1 and 2 echelons, on the 2-5 digits of both hands (sclerodermic pattern predominantly present on the left hand). Specific gravity weight of capillaries is mostly minor and medium caliber – 30 %. There are multiple avascular fields in 1 and 2 echelons, on the 2-5 digits of both hands (sclerodermic pattern predominantly present on the left hand). Specific gravity weight of capillaries is significantly reduced on the 2nd finger of left hand and 5 fingers of both hands (4-5 capillary loops per 1 mm²), the rate of capillary blood flow is insignificantly reduced. The capillary curvature index is 30 %. Raynaud syndrome of 1-2 degree is diagnosed. Microcirculation is of a spastic type. There are signs of slowly-progressing systemic scleroderma-type disease.

On 21.11.2019, the antinuclear antibodies (ANA) amounted to 1:1200; the anti-SSa/Ro (50 IU/ml) and anti-SSb/La (46 IU/ml) were found at the high titre. The thyroid gland function is not compromised. Anti-TPO are at an elevated titre (150 IU/ml). The rheumatoid factor is 12 IU/ml. The ophthalmologist’s consultation brought in the following diagnoses: the “dry eye” syndrome, Schirmer’s test: 1 mm per 5 minutes.

Considering the data being received at the repeat examination of 18.12.2019, the following diagnosis was made: overlap syndrome of scleredema adultorum of Buschke (SB) (dense facial edema, focal indurations at the back, cleavage, mammary glands) with primary Sjogren’s syndrome (PSS) affecting the saliva glands (sialadenitis), lungs (alveolitis), vessels (Raynaud syndrome), reticuloendothelial system (lymphadenopathy; splenomegaly), dryness syndrome (xerophthalmia), thyroid gland (autoimmune thyroiditis, euthyroidism), immunological (ANA, anti-SSa/La, anti-SSb/Ro) and hematological (thrombocytopenia, leukopenia) syndromes.

It is recommended to take methylprednisolone at a daily dose of 12 mg, methotrexate at a weekly dose of 10 mg with a predicted elevation after 2 weeks to a weekly dose of 15 mg, folic acid at a dose of 5 mg 24 hours after the methotrexate being taken once a week, Calcium (1200 mg) and Vitamin D (800 mg) supplements once every 24 hours, to apply topical mometasone ointment on the cutaneous foci, to use “artificial tear” drops locally.

The choice of methylprednisolone and methotrexate therapy was based on the performed clinical studies and a series of cases in the PubMED database which were traced according to the keywords «Sjogren’s syndrome and scleroderma adultorum of Buschke» and the EULAR 2019 guidelines on SS management [9]. The Table presents the dynamics of patient’s laboratory values.

Table. Dynamics of the patient’s laboratory values at the pre-examination and treatment stage

<table>
<thead>
<tr>
<th>Values</th>
<th>Date</th>
<th>21.10.2019</th>
<th>17.12.2019</th>
<th>09.01.2020</th>
<th>11.02.2020</th>
<th>17.03.2020</th>
<th>19.05.2020</th>
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<td>Leukocytes, 10⁹/l</td>
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<td>56</td>
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<td>Eosinophils, %</td>
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<td>132</td>
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<tr>
<td>Platelets, 10⁹ /l</td>
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<td>ESR, mm/hour</td>
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<td>Aspartate aminotransferase, IU</td>
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<td>70</td>
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Notes: ESR - erythrocyte sedimentation rate, IU – international units.

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The background therapy of methotrexate, methylprednisolone during the first 2 months resulted in a reduced facial edema, saliva gland edema, cutaneous neoplasm regression (Fig. 3), and ESR and leukocyte rate normalization. Considering a significant improvement of clinical picture, absence of complaints, the healthcare providers initiated a methylprednisolone reduction of 2 mg every 2 weeks starting from February 2020, and of 2 mg a month from April until a complete cessation in May, 2020. The methotrexate treatment of 15 mg a week continues.

The add-up doses of methotrexate and methylprednisolone received by the patient during 7 months before the lymphoma’s onset in July 2020 were 420 mg and 1900 mg, respectively.

While observing the patient, the healthcare providers registered a tendency towards neutropenia and lymphocytosis in the total blood count since March, 2020. Since June, 2020, the patient observed an out swelling of left eye (Fig. 4). There were no general symptoms (fever, general weakness, increased sweating) observed. The skin rash has no dynamics. On 17.07.2020, there was CT performed on the orbits, thoracic cage and abdominal cavity organs: in the left orbit between the lateral and upper rectus muscles there was an extra soft-tissue mass of 6-16-14 mm detected adjacent to the upper lateral area of eyeball; being inseparable from the upper saliva gland. According to the similarly accumulated contrast, the above-mentioned muscles manifest a reduced contour differentiation. There are multiple lymph nodes detected on both sides of the neck, the biggest one in the submental group reaching 4 mm, in the submaxillary group — up to 7 mm, upper jugular group — up to 7 mm, lower jugular group — up to 7 mm, dorsal group — up to 5 mm, supraclavicular group — up to 5 mm. There are perivascular, aortopulmonary, bronchopulmonary, bifurcating lymph nodes visualized in the mediastinum of up to 9 mm large. On the pulmonary side, there is a positive dynamic: no infiltrating changes. There is a positive dynamic on the bilateral axillary side: the adipose tissue swelling and size is reduced, thickness of anterior chest wall is reduced as well. In the upper lateral quadrant of the right mammary gland there is a persistent nodular induration of 6-10 mm, characterized by a positive dynamic due to its reduced size and density. The nodular changes of thyroid gland persist. The hepatosplenomegaly is observed (right hepatic lobe is 201 mm long; spleen size is 49-130-141 mm). There are mul-

Fig. 1. Dense facial edema. Parotid gland edema (November 2019)

Fig. 2. Dense hyperemic neoplasm, subcutaneous neoplasm of the cleavage and left mammary gland (November 2019)
tiple lymph nodes in the hepatoduodenal junction of up to 10 mm large, in the retroperitoneal area of up to 7 mm large, in the pelvis minor area (general and exterior iliac) of up to 8 mm large.

There was a pathohistological study made of the orbital tumor. The histological puncture of left orbital neoplasm (30.07.2020) revealed a mass of polymorph cells with disparate hyperchrome nuclei which are lymphoma-pathognomonic. The bone marrow puncture was performed and immunohistochemical assay of the orbital tumor cells. The tumor cells revealed a positive membrane reaction to CD20, CD23, bd2. Part of the tumor cells revealed a positive membrane reaction to CD11c. The tumor cells are negative to CD123, DBA44, annexin F1, CD10, CD30, SOX-11, cyclin D1, CD3, CD5. Considering the results of histological and immunohistochemical studies, there are bone marrow cells damaged by the B-cell lymphoma whose phenotype is characterized by the nodal lymphoma from the marginal zone cells. The patient had a hematologist-oncologist consultation resulting in a non-Hodgkin’s B-cell lymphoma of the nodal marginal zone lymphoma (NMZL), IVa stage with bone marrow damage. According to the hematologist-oncologist’s recommendations, the methotrexate therapy suspended, Rituximab therapy of 1 g twice every 2 weeks was initiated. On 1.08.2020 and 25.08.2020, 2 injections were performed, followed by a significant regression of orbital tumor. The patient is observed by hematologist-oncologist and rheumatologist.

The PSS patients may develop numerous systemic signs, both as clinical manifestations functioning as the initial disease signs and those associated with the progressing disease [10]. Among the systemic manifestations resulting in an early and elevated mortality of PSS patients, there are cryoglobulinemic vasculitis, interstitial pulmonary disease and lymphoma [11]. It is worthy of noting that the PSS patients have a higher lymphoma risk than patients with other autoimmune diseases: 7 and 4 times as often as the systemic lupus erythematosus (SLE) and RA, respectively, and 10 times as often as the healthy subjects [12]. The recent studies dealing with the prognostic marker role in the PSS-associated lymphoma offer a synergetic risk model as the more prognostic factors there are, the higher risk of developing lym-
Conclusions

To sum up, the above-mentioned clinical case featured a rare combination of SB and PSS, an autoimmune disease. The reference sources describe only one clinical observation of SB associated with secondary SS (RA-attended) [4] and one associated with primary SS [5]. The importance of other SB associations, namely with autoimmune diseases, is relevant for the adequate management and treatment. Furthermore, the risk of lymphoma developing on the PSS backdrop is rather high, implying an elevated onco-awareness of the practitioners in terms of likely development and target ruling-out of lymphoma in the PSS patients along with risk factor evaluation.

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References


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Клінічний випадок розвитку В-клітинної лімфоми у пацієнтки з оверлап-синдромом первинного синдрому Шегрена і склередеми Бушке

Резюме. Наведений випадок клинічного випадку розвитку В-клітинної лімфоми в пацієнтки з оверлап-синдромом первинного синдрому Шегрена (ПСШ) і склередеми Бушке (СБ). Склередема Бушке — рідкісне захворювання, що характеризується дифузним індуративним набряком і ущільненням шкіри. Прийнята умовна класифікація цього захворювання залежно від епідеміологічного чинника: тип 1 — асоційований з інфекційним захворюванням; тип 2 — з парапротеїномією і тип 3 — з цукровим діабетом. Існують дуже рідкісні випадки, пов'язані з іншими новоутвореннями або автоімунними захворюваннями. Даний клінічний випадок описує рідкісне поєднання СБ з антитілами до цукрового діабету. Існують дуже рідкісні випадки, пов’язані з іншими новоутвореннями або автоімунними захворюваннями. Даний клінічний випадок описує рідкісне поєднання СБ з антитілами до цукрового діабету.

Ключові слова: склередема Бушке; синдром Шегрена; лімфома; оверлап-синдром; клиничний випадок

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Клінічний случай развития В-клеточной лимфомы у пациентки с оверлап-синдромом первичного синдрома Шегрена и склередемы Бушке

Резюме. Представлено описание клинического случая развития В-клеточной лимфомы у пациенки с оверлап-синдромом первичного синдрома Шегрена (ПСШ) и склередемы Бушке (СБ). Склередема Бушке — редкое заболевание, характеризующееся диффузным индуративным отеком и уплотнением кожи. Принятая условная классификация этого заболевания в зависимости от этиологического фактора: тип 1 — ассоциированный с инфекционным заражением; тип 2 — с парапротеинемией; тип 3 — с сахарным диабетом. Имеются очень редкие случаи, связанные со злокачественными новообразованиями или автоиммунными заболеваниями. Данный клинический случай описывает редкое сочетание СБ с сахарным диабетом. Имеются очень редкие случаи, связанные со злокачественными новообразованиями или автоиммунными заболеваниями.

Ключевые слова: склередема Бушке; синдром Шегрена; лимфома; оверлап-синдром; клинический случай

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