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CASE REPORT

ADULT STILL'S DISEASE – A MULTIDISCIPLINARY DISEASE

Leonid I. DVORETSKY[1], Daria V. NOVIKOVA[2], Anna V. TORGASHNA[3], Alla M. KOVRIGINA[2], Tatiana N. MOISEEVA[2], Roza M. VAKOLYUK[1], Maria A. KARNAUSHKINA[4]✉

[1] "I.M. Sechenov" First Moscow State Medical University (Sechenov University), Moscow, Russian Federation
[2] Municipal Hospital named after S.S. Yudin of the Moscow Healthcare Department, Moscow, Russian Federation
[3] Federal Research Institute of Rheumatology named after V.A. Nasonova, Moscow, Russian Federation
[4] Federal State Autonomous Educational Institution of Higher Education "Peoples' Friendship University of Russia" (RUDN University), Russian Federation

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Abstract

Introduction. Adult-onset Still's disease is a rare systemic autoinflammatory disorder of unknown etiology, characterized by persistent fever, maculopapular skin rash, and arthritis or arthralgia. This triad of symptoms is usually accompanied by lymphadenopathy, hepatosplenomegaly, and various systemic manifestations. In the absence of adequate therapy, the disease course might become life-threatening, with complications such as macrophage activation syndrome, hemorrhagic alveolitis, disseminated intravascular coagulation syndrome.
Case report. We present a case of adult-onset Still's disease, misdiagnosed and treated initially as Hodgkin's lymphoma. The further examination revealed a complex of lymphadenopathy, skin changes, articular syndrome, making possible to reject the diagnosis of Hodgkin's lymphoma and to diagnose adult Still's disease. In the context of this case, we present potential difficulties in the analysis of clinical and

Résumé

Maladie Still de l'adulte – une maladie multidisciplinaire

Introduction. La maladie Still de l'adulte est une maladie auto-inflammatoire systémique rare d'étiologie inconnue, caractérisée par une fièvre persistante, une éruption cutanée maculopapuleuse et une arthrite ou une arthralgie. Cette triade de symptômes est généralement accompagnée d'une lymphadénopathie, d'une hépatosplénomégalie et de diverses manifestations systémiques. En l'absence de traitement adéquat, l'évolution de la maladie peut mettre la vie en danger, développant des complications telles que le syndrome d'activation des macrophages, l'alvéolite hémorragique, le syndrome de coagulation intravasculaire disséminée.
Rapport de cas. Cet article décrit un cas de maladie Still de l'adulte, mal diagnostiqué et traité au début comme un lymphome de Hodgkin. L'examen plus précis, révélant un complexe de lymphadénopathie, de changements cutanés, de syndrome articulaire a

✉ Address for correspondence: Maria A. KARNAUSHKINA
Federal State Autonomous Educational Institution of Higher Education
"Peoples' Friendship University of Russia" (RUDN University)
Address: 117198, Miklukho-Maklaya str, no. 6, Moscow, Russian Federation
Email: kar3745@yandex.ru

laboratory data, histology results, and the differential diagnosis difficulties of this disease.

Conclusions. The diagnosis of adult Still's disease requires a vast spectrum of clinical and morphological manifestations of the disease, that will make possible the correct interpretation of the clinical symptoms and laboratory tests, avoiding unnecessary examinations, and will speed up the diagnosis time.

Keywords: adult Still's disease, lymphadenopathy, lymphoma.

List of abbreviations:
ABVD – (A)driamycin, (B)leomycin, (V)inblastine, (D) acarbazine)
ANA – antinuclear antibodies
ASD – adult Still's disease
DIC – disseminated intravascular coagulation
ESR – erythrocyte sedimentation rate
PET-CT – positron emission tomography
RF – rheumatoid factor
GGT – gamma-glutamyl transpeptidase
SUVmax – maximum standardized uptake value

permis de rejeter le lymphome de Hodgkin et de diagnostiquer la maladie Still de l'adulte. Dans le cadre de ce cas, nous discutons des difficultés potentielles dans l'analyse des données cliniques et de laboratoire, les résultats histologiques et la recherche diagnostique différentielle chez ces patients.

Conclusions. Un diagnostic de la maladie Still de l'adulte nécessite la prise en compte d'un vaste spectre de manifestations cliniques et morphologiques de la maladie. Cela permettra une interprétation correcte des symptômes cliniques et des signes de laboratoire, évitant les examens inutiles, et accélérera le diagnostic.

Mots-clés: maladie Still de l'adulte, lymphadénopathie, lymphoma.

Introduction

Adult-onset Still's disease (ASD) is a rare systemic autoinflammatory disorder of unknown etiology, characterized by persistent fever, maculopapular skin rash, and arthritis or arthralgia. This triad of symptoms is usually accompanied by lymphadenopathy, hepatosplenomegaly, and various systemic manifestations. In the absence of adequate therapy, the disease course might become life-threatening, with complications such as macrophage activation syndrome, hemorrhagic alveolitis, and disseminated intravascular coagulation syndrome[1].

This disease is named after George Frederick Still, who in 1897 described a group of children with symptoms, now referred to as juvenile chronic arthritis[2]. In 1933, 36 years after Still's observation of "a special form of joint disease in children", Moltke published his article "Still's disease in adults"[3]. The author observed four young men, aged between 15 to 28 years, with acute polyarthritis, fever, profuse sweating, lymphadenopathy, pharyngitis, muscle atrophy, anemia, and accelerated erythrocyte sedimentation rate. Until the middle 60s, several descriptions of such cases were published in the French and English literature, without designating them as Still's disease. In 1966, the famous English rheumatologist Bywaters, in his report "What is Still's disease?" on Heberden oration[4], proposed the name of "adult Still's disease" to previously described cases of fever, rash, lymphadenopathy, and splenomegaly in adults. Five years later, in his article describing 14 cases of adults' disease[5], Bywaters pointed out a special nature of ASD, not "age-related" form of adult polyarthritis, but an independent disease with a unique complex of symptoms. Gradually, Still's disease ceased being only a pediatric problem, being named "adult Still's disease" in all cases beyond the scope of childhood and adolescence. This was reflected in the ICD-10 under the heading "other rheumatoid arthritis" and code M06.1.

The difficulties in the diagnosis of ASD are conditioned by numerous symptoms and low specificity of laboratory tests. Each patient has particular symptoms, which causes the necessity of an individual, and always multidisciplinary, approach. Depending on the dominant symptom, diagnosis and further treatment should be provided by the appropriate specialist: rheumatologist in case of arthritis, hematologist in case of lymphadenopathy and splenomegaly, dermatologist or allergologist in case of skin manifestations. In fact, a thorough examination of patients does not always solve the diagnostic problems, because of frequent misinterpretation of unremarkable organ-specific manifestations.

ASD is diagnosed by the presence of Yamaguchi criteria, with a sensitivity and specificity of 90%. Major criteria include fever up to 39°C for at least one week, presence of arthritis or arthralgias for at least two weeks, nonpruritic salmon colored rash

on trunk/extremities and granulocytic leukocytosis (10,000/microL or greater). Minor criteria include sore throat, lymphadenopathy, enlarged liver and spleen, abnormal liver function tests and negative tests for rheumatoid factor and antinuclear antibodies. The diagnosis of ASD requires at least five features, at least two of these being major diagnostic criteria[6]. Yamaguchi criteria yet do not remove the necessity of differentiation the patient's condition from different infectious pathologies, lymphomas, or other autoimmune diseases.

There are three main courses of evolution of the disease:

- monocyclic course (30%), in which a complete remission can be achieved within a year after the first clinical manifestations;
- intermittent or polycyclic course (30%), characterized by alternating periods of remission, which can last more than a year, and exacerbations that are usually milder than the initial episode;
- chronic course (40%), with predominance of severe joint destructive changes[7].

Case presentation

In October 2019, a 43-year-old woman, complaining about fever, joint pain, skin rash, and weakness, was admitted to the National Medical Research Center of Hematology of the Ministry of Health of Russia, Moscow. The first symptoms of the disease – itchy rash on shoulders, thighs, back – had appeared in January 2018, with no improvement after antihistamine treatment. Subsequently, she started to notice pain in the large joints with restriction of movement, and fever up to 38°C. In the regional hospital, a diagnosis of rheumatoid arthritis was made. Despite a successful anti-inflammatory therapy, in March 2018 her condition became worse (fever up to 40°C, increasing joint pain). Further examination revealed enlarged intrathoracic, intra-abdominal and peripheral lymph nodes. Lymph node biopsy was performed. The histological examination ascertained the presence of Hodgkin's lymphoma, nodular sclerosis subtype. From May 2018 to January 2019, 8 courses of chemotherapy were performed with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD). The patient refused radiation therapy. In May 2019, the hematologist found no evidence of disease progression and recommended dynamic observation. At the end of June 2019, the episodes of fever (38-39°C) returned and, despite antibacterial, antifungal, and antiviral therapy, the fever maintained. In October 2019, she noted for the first time pigmented spots on the skin. Positron emission tomography (PET-CT) revealed generalized lymphadenopathy: enlargement of cervical, supraclavicular lymph nodes up to 0.85 cm, axillary lymph nodes up to 0.68 cm, and inguinal lymph nodes up to 0.87 cm, maximum standardized uptake value (SUVmax) 3.31. Because of the suspicion of a recurrent lymphoma, she was hospitalized in the National Medical Research Center of Hematology, Moscow. At the time of hospitalization, her general condition was of moderate severity. On the background of moderately pale skin on the shoulders, arms, anterior abdominal wall, back, front of the thighs, there were hyperpigmentation areas of a dark brown color (Fig. 1, 2). During the peak of the fever, unstable macular pink-colored erythema emerged (Fig. 3). Also, there were multiple bilateral, painless, small (up to 0.8-1 cm in diameter) supraclavicular, axillar, inguinal lymph nodes. No signs of arthritic changes were noticed, all the movements were preserved. No other symptoms were revealed: normal breathing, normal heart sounds and blood pressure, abdomen soft and painless, liver and spleen not palpable.

Laboratory studies revealed elevated erythrocyte sedimentation rate (ESR) up to 108 mm/h, hyperproteinemia (91 g/L), increased C-reactive protein (CRP) up to 234 mg/L and ferritin > 1500 μg/L.

The ultrasound of peripheral lymph nodes revealed generalized enlargement of submandibular, cervical, supraclavicular, axillar, and inguinal lymph nodes. All lymph nodes were hypoechoic, with a small echo-positive center with active perinodular blood flow. The abdominal ultrasound showed slightly enlarged liver, with smooth contours and diffuse moderate increase of echogenicity, and mild enlargement of the spleen. The main trunk of the portal vein was normal. Retroperitoneal lymph nodes were up to 21x10 mm. Echocardiography did not show any abnormalities of the heart (normal cavities, intact heart valves, left ventricular ejection fraction 67%, according to Simpson, no impairment of the diastolic function) and major vessels (no signs of pulmonary hypertension).

The cytological examination of bone marrow trephine biopsy corresponded with reactive changes. No cytomegalovirus, Epstein-Barr virus, human herpesvirus type 6 were identified using PCR method.

The examination of skin biopsy material revealed only signs of vasculitis, possibly of autoimmune genesis, or associated with infection, but no features of malignancy. The axillary lymph node biopsy showed preserved histoarchitectonics of the lymphatic tissue, presence of follicles of different sizes with light zones of reproduction and distinct mantle zones (Fig. 4). It was noticed the focal widening of the paracortex, containing lymphoid cells of varying degrees of maturity, with numerous plasma cells. Parafollicularly and

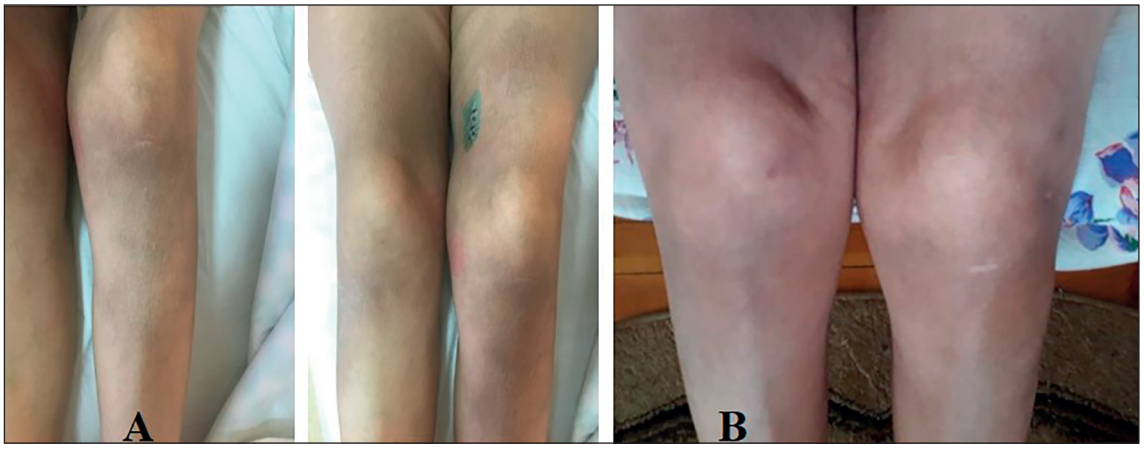

Figure 1. Hyperpigmentation on thighs and shins (A) and its reduction (B) after two months of therapy.

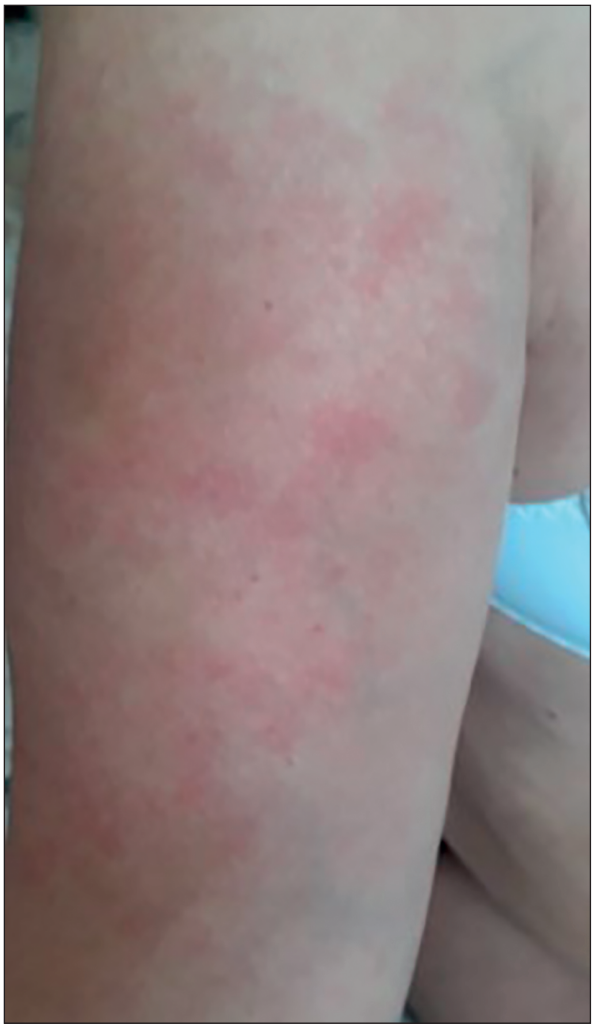

Figure 2. Macular rash on the right shoulder.

in the paracortex zone, there were scattered activated large lymphoid cells, morphologically representing centroblasts and immunoblasts (Fig. 4). The walls of small blood vessels were with fibrinoid swelling (Fig. 4). The immunohistochemical study revealed large activated lymphoid B-cells $CD20^+$, $CD30^+$ (Fig. 5), which were located separately parafollicularly, in the paracortex. These findings reflected reactive changes with extrafollicular B-cell activation, which could be a sign of immune-mediated lymphadenopathy.

Moreover, a reexamination of lymph node samples from 2018 demonstrated the same immunohistochemical characteristics (reactive changes with the phenomenon of extrafollicular B-cell activation, probably of autoimmune nature) with no evidence of tumor growth, including lymphoma.

All the patient's clinical data, with detection of a combination of persisting fever for six months, arthralgia, skin hyperpigmentation and skin rash, pharyngitis, lymphadenopathy, enlargement of the spleen, and changes in laboratory tests raised the suspicion of ASD. In fact, the patient had more than enough Yamaguchi criteria for a definite diagnosis of ASD.

The patient was transferred to the Institute of Rheumatology, where the diagnosis of ASD, polycyclic clinical variant with a high degree of activity with systemic manifestations, was confirmed. Due to the severity of patient's condition, the progressive course of the disease (the presence of small hand joints arthritis, hyperferritinemia of more than 1500 μg/L, hemoglobin concentration 6.6 g/dL), therapy with tocilizumab, methylprednisolone, methotrexate was initiated. After treatment, the indicators of disease activity decreased. The patient was discharged without fever, arthralgia, skin rash, with lower inflammatory markers, with a recommendation to reduce the dose of methylprednisolone gradually and continue taking methotrexate. According to the follow-up data (May 2020), the patient was stable. She had no fever or signs of arthritis, skin rash resolved completely, and hyperpigmented foci significantly turned pale (Fig. 1, 3).

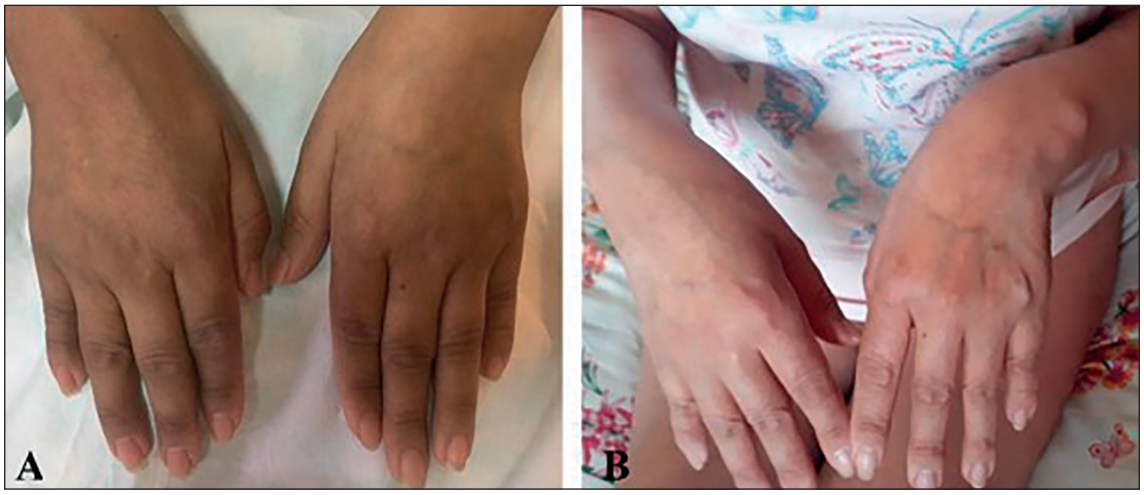

Figure 3. Hyperpigmentation on the wrists (A) and its reduction (B) after two months of therapy.

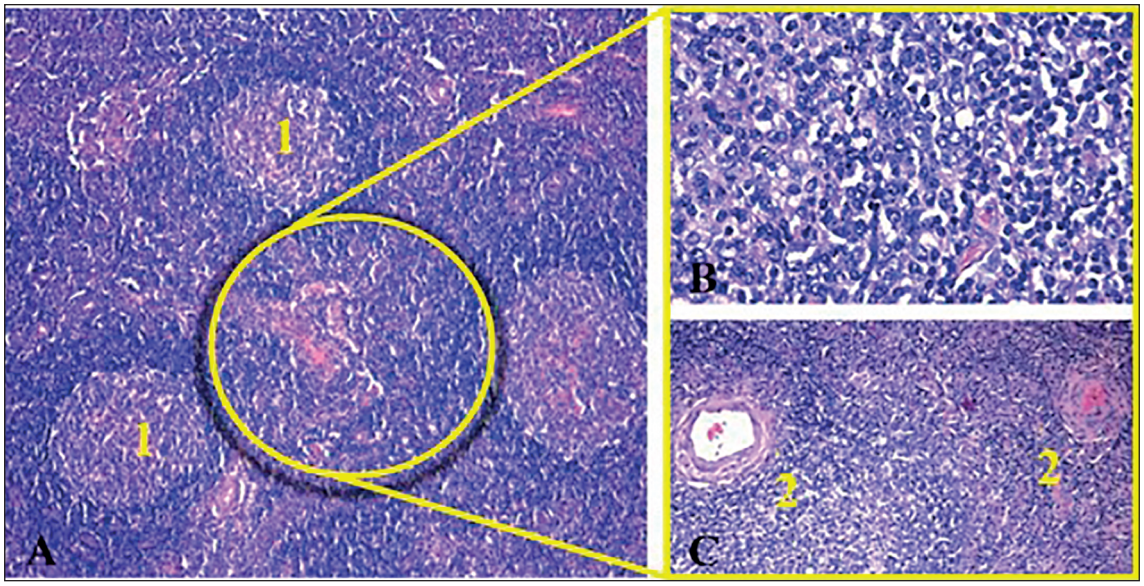

Figure 4. Biopsy of lymph node demonstrated multiple follicles (A) with light zones (1), focally widened paracortex (yellow circle, B,C). In the paracortex there are multiple lymphoid cells in different stages of maturity; also, it contains centrocytes and immunoblasts (B). Small vessel walls (2) demonstrate features of fibrinoid swelling. Magnification x100 (A,C), x400 (B); H&E stain.

Discussion

In this patient, ASD was diagnosed two years after the onset of the first symptoms of the disease. The presence of lymphadenopathy in ASD patients, especially with concomitant fever, often raises suspicion of lymphoproliferative diseases (lymphoma or Hodgkin's lymphoma). This differential list usually results in a lymph node biopsy. Being generalized (peripheral, intrathoracic, and intra-abdominal lymph nodes), lymphadenopathy in our patient did not exclude the likelihood of lymphoproliferative disease, yet induced to continue the diagnosis search, taking into account the presence of articular syndrome and changes in the skin.

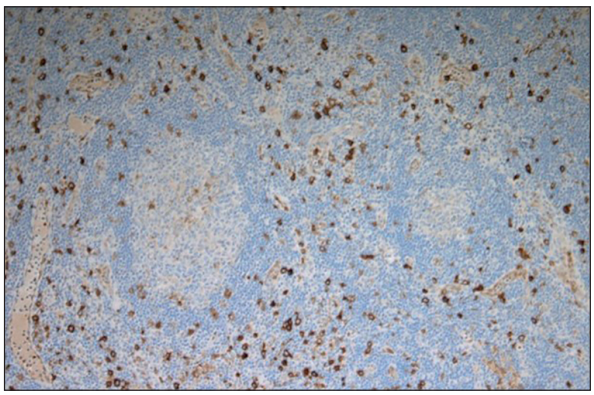

Figure 5. Immunohistochemical staining for $CD30^+$ and hematoxylin stain. In the mantle zone and paracortex there are giant activated lymphoid cells, $CD30^+$ and plasmatic cells, some of which are located intrafollicular.

PET-CT demonstrated the presence of generalized lymphadenopathy, SUVmax 3.3, which did not contradict the ASD diagnosis. PET-CT has recently been increasingly used for the differential diagnosis of ASD and lymphomas, since lymphadenopathy on the background of autoimmune diseases is accompanied by increased metabolic activity[8]. ASD, as previously mentioned, is characterized by multiple enlarged lymph nodes (especially in the cervical and axillary regions), with normal structure and increased metabolic activity[9]. An additional characteristic feature in cases of ASD is the diffuse accumulation of radiopharmaceutical (RP) in spleen and bone marrow. An increased accumulation of RP can occasionally be noted in the joints, salivary glands, pericardium and pleura[10]. There is an opinion that PET-CT scans in ASD and lymphoma may be similar, so this imaging method is especially useful for determining the localization of the most suspicious lymph node for biopsy[11].

In our case, the patient had several variants of skin changes: papular itchy rash on the back and thighs at the onset of the disease, unstable macular rash on the thighs, back, and abdomen one year after. Also, the patient had confluent hyperpigmentation on the skin of the abdomen, forearms, dorsum of the hands, in the area of the knee joints (Fig. 1, 3). Skin lesions in patients with ASD appear as itchy, unstable, rapidly disappearing macular or macular-papular elements of pink color (salmon color). They are usually localized on the trunk, limbs, or areas of the skin friction (Kebner phenomenon). Notably, often the rash is found only during fever and disappears when the temperature returns to normal[12]. Skin changes cannot always be detected by a superficial examination and require a targeted search. Regardless, in cases of detection of rash, it is usually considered as a manifestation of a drug allergy while taking antipyretic drugs or antibiotics for fever. Thus, dermatological examination without a critical assessment of other presented symptoms does not always reveal the nature of skin rashes. Along with these typical skin changes called "Still's rash", rarer changes are described, in particular the presence of pigmented areas of varying intensity[13], as in our patient. Such pigmented lesions, due to their rarity for this pathology, delay the diagnostic search.

Even typical for ASD, skin lesions were not immediately recognized by specialists and were considered quite rare. More than half a century after the publication by Still et al, cutaneous manifestations of ASD had not been studied in-depth[14]. Several atypical ASD types of skin rashes associated with fever have been recently described: urticarial, vesiculopustular, eczematous, persistent hyperpigmentation or migratory erythema[15]. At the same time, only typical rashes are included in the major Yamaguchi criteria, while other types are regarded as insignificant. Even though the relationship between atypical skin lesions and ASD pathogenesis is unclear, their simultaneity with development of systemic symptoms and disappearance after immunosuppressive therapy suggest they are of ASD nature. The morphological picture of skin lesions in ASD is diverse and not very specific yet[12].

Deterioration of the patient's condition (recurrence of the fever, lymphadenopathy) was assumed as a relapse of the lymphoproliferative disease. This initiated the transfer of the patient to a specialized institution. The precise clinical examination and laboratory tests called into question the previous diagnosis of Hodgkin's lymphoma. Moreover, the previous diagnosis mistake was proved by the histological examination of the lymph node, and revision of earlier histological data revealed a similar morphology: extrafollicular B-cell activation. The clinical effect on the background of several courses of polychemotherapy can be explained by the immunosuppressive effect of cytostatic drugs.

Conclusions

The absence of pathognomonic morphological signs of ASD does not allow the use of histological examination as a reliable diagnostic criteria. Still, it allows to exclude hematological disease, so morphological studies of lymph nodes and skin in patients with suspected ASD are carried out not to confirm this disease, but to exclude malignancy. However, morphological examination is determined by professional competence, as well. Regarding our patient, histology revealed morphological and immunohistochemical signs of extrafollicular B-cell activation, characterized by reactive changes, which could be of an autoimmune or viral/bacterial nature.

The diagnosis of ASD requires to take into account a vast spectrum of clinical and morphological manifestations of the disease, making possible the correct interpretation of the clinical symptoms and laboratory tests, avoiding unnecessary examinations, and speeding up the diagnosis.

Author Contributions:

L.I.D., D.V.N., A.V.T. and R.M.V. were responsible for the diagnostic procedures, clinical diagnosis, and treatment decisions. A.M.K., T.N.M. made the histopathological diagnosis. L.I.D., M.A.K. analyzed the literature and wrote the manuscript. All the authors have read the manuscript and agreed on the final form.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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