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CASE REPORTS

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FEATURES OF DIAGNOSIS AND ADVERSE COURSE OF NEONATAL JUVENILE XANTHOGRANULOMA: CASE REPORT

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The work describes a case of rare neonatal systemic juvenile xanthogranuloma with an initial damage of the scalp, limbs, back and abdomen, multiple damages of the parenchyma of both lungs, spleen and liver with the development of a severe form of congenital cholestatic hepatitis. The diagnosis was established on the basis of histopathological and immunohistochemical examination of the skin nodules. The child on the background of therapy under the Langerhans cell histiocytosis III program achieved a partial response, which was manifested by a reduction of granulomatous formations on the skin, elimination of liver failure, but retained hepatosplenomegaly, specific lesions of the lung parenchyma, liver, and left kidney. Against the background of cytostatic therapy, the patient developed secondary pancytopenia, perianal ulcerative-necrotic dermatitis with lesions on buttocks, stomatitis, protein-energy deficiency, acute liver failure. coagulopathy, disseminated intravascular coagulation syndrome, acute renal failure, respiratory failure of III degree, cardiovascular insufficiency of III degree, pulmonary edema, cerebral edema, cerebral coma of II–III degree, enterocolitis, intestinal paresis. Despite multicomponent intensive care, the child's condition progressively deteriorated, and the patient died. The aspects of differential diagnosis of neonatal systemic juvenile xanthogranuloma are discussed.

***Key Words*: neonatal systemic juvenile xanthogranuloma, histopathological, immunohistochemical method.**

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Neonatal systemic juvenile xanthogranuloma (NSJXG) is a rare non-Langerhans cell histiocytosis (LCH) with multisystemic lesions that occurs predominantly in infancy [1]. The disease often affects the skin manifesting itself in skin papules or nodules [2], or specific infiltrates in extradermal organs with or without skin lesions [3]. In 3.9–5.0% of patients, there are extradermal infiltrates in liver, spleen, lungs, kidneys, eyes, subcutaneous soft tissue, bones and central nervous system [1, 3, 4].

We present the rare clinical case in a newborn child with a multisystem NSJXG lesions demonstrating the difficulties and problems faced by doctors due to ignorance of the clinical presentation and the peculiarities of verification of this nosological unit. We also focus on the characteristics of the response to the applied therapy, the unfavorable prognosis of the course of the disease.

A boy was born from the first normal pregnancy, with a body weight of 3,400 g, height 52 cm at gestational age of 39 weeks by urgent cesarean section due to fetal distress, Apgar 6/8 points. Premature aging of the placenta from 25 weeks of gestation. At 13–14 weeks of pregnancy, mother had an acute respiratory disease. During pregnancy (3 months), the mother was in contact with a husband with COVID-19, at this time she was not examined, there were no symptoms of the disease.

On the 4th day of life, a rash of dark cherry color up to 3 mm from the seal appear on the skin of the head, limbs, back and abdomen. At the age of 5 days, the child was transferred to the department of anesthesiology and intensive care at the Lviv City Children's Hospital. On examination, the general condition was serious. The skin was pale icteric, marble with multiple polymorphic rash elements all over the body (Fig. 1, *a–c*), dense on palpation, liver + 4.0 cm from under the edge of the costal arch dense, spleen not enlarged, there were manifestations of bilateral pneumonia (confirmed on X-ray). Blood count: red blood cells — 5.8 • 10^{12}/l, hemoglobin — 10.2 g/dl, white blood cells— 18.4 • 10^{9}/l, blasts — 0%, eosinophil count — 1%, bands — 4%, segm — 34%,

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Abbreviations used: LCH – Langerhans cell histiocytosis; NSJXG – neonatal systemic juvenile xanthogranuloma.

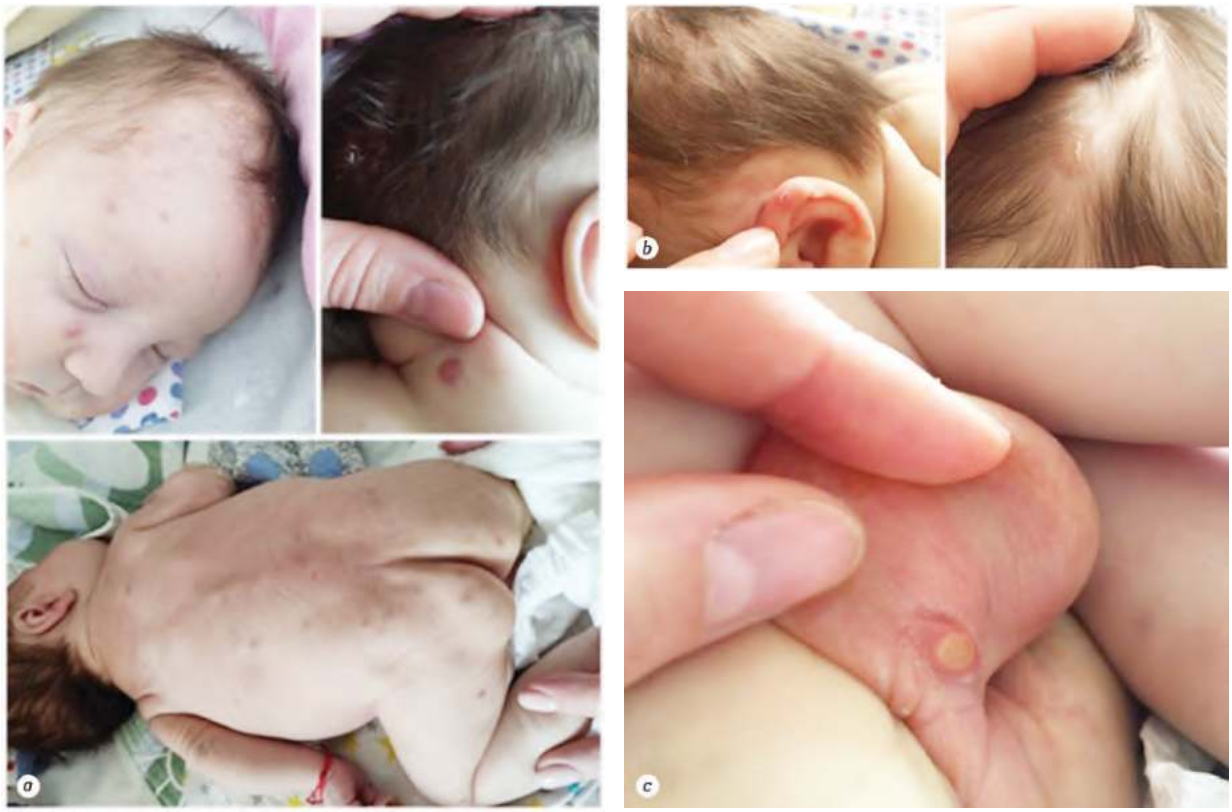

Fig 1. Changes in the skin of the lower extremity in the onset of the disease: *a* — multiple dark cherry color, rash like blueberry muffin spots; *b* — papulo-pustular elements with a clear contour with scales protruding above the surface; *c* — in the area of the scrotum there is a dense element of vesicular nature, dark red, protruding above the skin

lymphocytes — 56%, monocytes — 6%, platelet count — 20 • 10^9/l, erythrocyte sedimentation rate 6 mm/h. Blood biochemistry: alanine transaminase 8.4 IU/l, aspartate transaminase 6.0 IU/l, bilirubin total 120.0 µmol/l, bilirubin direct 69.0 µmol/l, amylase 32.5 IU/l, total protein 38.0 g/l, albumin 25.0 g/l, K 5.2 mmol/l, Na 135.0 mmol/l, urea 4.74 mmol/l, creatinine 11 µmol/l, ferritin 808.0 ng/ml, Fe 2.9 µmol/l, alpha-1-antitrypsin 1.92 g/l, thyroid stimulating hormone 6.3 mIU/l, phenylalanine 1.5 mg/dL, 17-OH-progesterone 14.0 ng/ml, antistreptolysin "O" 200 IU/ml; rheumatoid factor negative. Analysis of cerebrospinal fluid was normal. Hepatitis B, C, Epstein — Barr virus, cytomegalovirus, SARS-CoV-2, human immunodeficiency virus-1, -2, rubella, parvovirus B19, toxoplasmosis, syphilis, HIV, primary congenital immunodeficiency and galactosemia were excluded.

In the patient's hemogram: severe normochromic anemia (Hb 7.4 g/dL, RBC 2.37 • 10^{12}/l, MCV 88.6 fl, MCH 31.7 pg), thrombocytopenia, monocytosis 17%, and erythroblasts 6:100. In the myelogram on the 13th day of life: hypocellular punctate, all lineages of hematopoiesis are present, not affected by neoplastic process, erythroblasts 37.5%, lymph 26.0%, myelo 7.0%, metamyelo 1.5%, bands 15.5%, segm 4.5%, eos 0.5%, bazo 0%, mono 5.0%, blasts 2.5%. Megakaryocytes are partially active without platelet detachment.

On the 17th day of life, a skin biopsy was performed. Histological conclusion: a fragment of skin with horny scales on the surface. Intradermally diffusely, a significant lympho-histiocytic infiltrate with a significant number of multinucleated giant cells (Touton cells), foamy macrophages (xanthoma cells) and epithelioid cell proliferates is detected (Fig. 2 *a, b*). Immunohistochemical study of tumor cells: Cytokeratin (AE1/AE3), CD56/NCAM-1, Ab-4, CD117/c-kit, CD43 Ab-3, CD20cy, CD30 Ab-1, CD45, CD79 alpha, myeloperoxidase Ab-1, TdT (terminal deoxynucleotidyl transferase), CD1a Ab5 (Fig. 3, a), CD34, Pax-5, CD3 — negative reactions; S100 (Fig. 3, *b*), CD68 (Fig. 3, *c*), CD4 (Fig 3, *d*) — positive reactions. The immunophenotype corresponds to juvenile xanthogranuloma. The patient received intensive treatment (broad-spectrum antibiotics, antifungal drugs, red cells concentrate and almost daily transfusion of thromboconcentrate, human intravenous immunoglobulin).

Within three weeks of differential diagnosis, the following changes were noted: increased hepato- (+ 5.0 cm) and splenomegaly (+ 2.0 cm), increased number of rashes all over the body, sonographic signs of ascites, portal hypertension, colloidal inclusion in the thyroid gland, increased of level of direct hyperbilirubinemia (total 271.37/direct 121.1 µmol/l), coagulation disorders (prothrombin time 31 s; prothrombin index 48%; recalcification time – the clot was not formed within

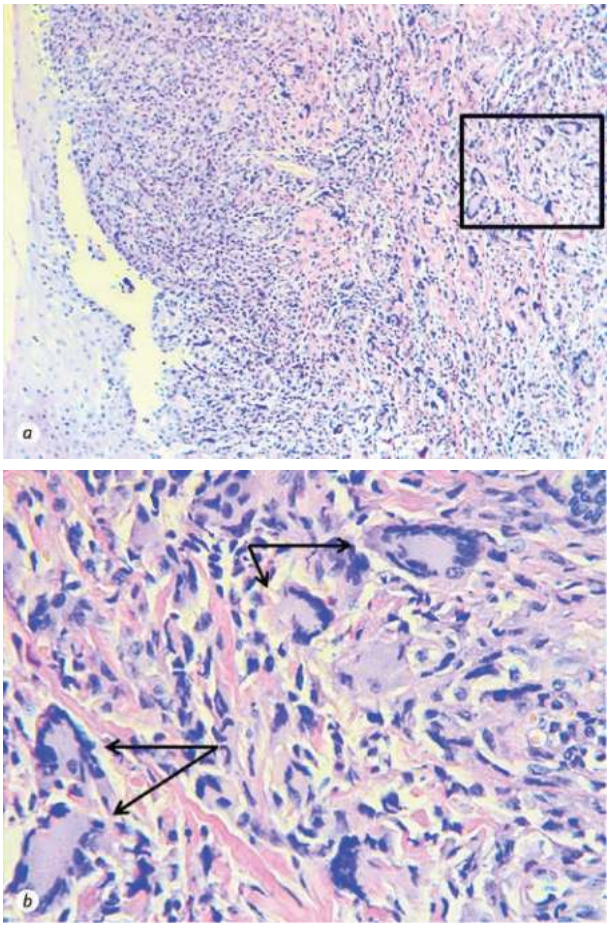

Fig. 2. Microscopic structure of the tumor. H&E stain: *a* — ×100; *b* — ×400. Numerous Touton giant cells (arrows)

10 min; total fibrinogen 1.6 g/l). Hypoproteinemia was maintained (total protein 33.0 g/l, albumin 25.94 g/l), alpha-fetoprotein 7727.0 ng/ml.

Magnetic resonance imaging of the brain revealed small focal hyperintense changes in the T1 mode in the parenchyma of the hemispheres – most likely due to hemorrhagic infiltration (Fig. 4, *a, b*). Computed tomography displays bilateral pneumonia with emphasis in the lower lobes of both lungs, paravertebral formation at the level of Th6–Th7 on the right (Fig. 5, *a, b*), hepatomegaly (Fig. 5, *c*), ascites, intestinal hyperpneumatosis. On magnetic resonance imaging of the thoracic spine, pathological changes were not detected. Against the background of inflammatory changes, there are subpleurally visualized hyperintense formations in the dorsal parts of both lungs (Fig. 5, *a*).

Regarding the underlying disease, cytostatic therapy was started with LCH III induction I for the high-risk group. The right femoral vein was catheterized. Against the background of cytostatic therapy (the first 4 injections of vinblastine) the course of the disease was complicated by bilateral focal pneumonia, right-sided aspiration pneumonia, bilateral pleurisy, ulcerative-necrotic perianal dermatitis of both buttocks stomatitis, thrombophlebitis of the right femoral vein. However, despite cytostatic therapy, complete remission

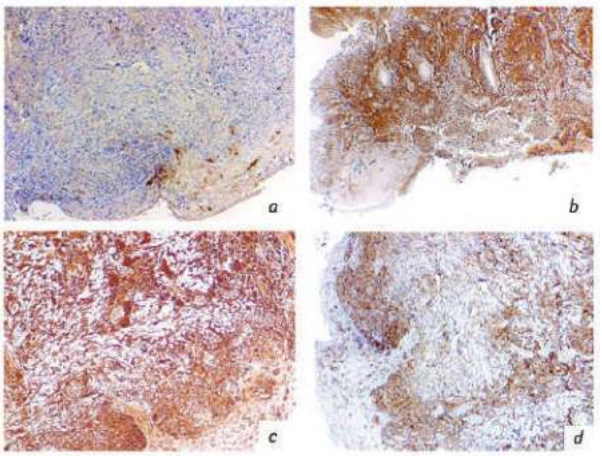

Fig. 3. Immunohistochemical profile of the tumor: *a* — absence of expression of CD1a by tumor cells; *b* — expression of S100 in tumor cells; *c* — expression of CD68 by tumor cells; *d* — expression of CD4 in tumor cells

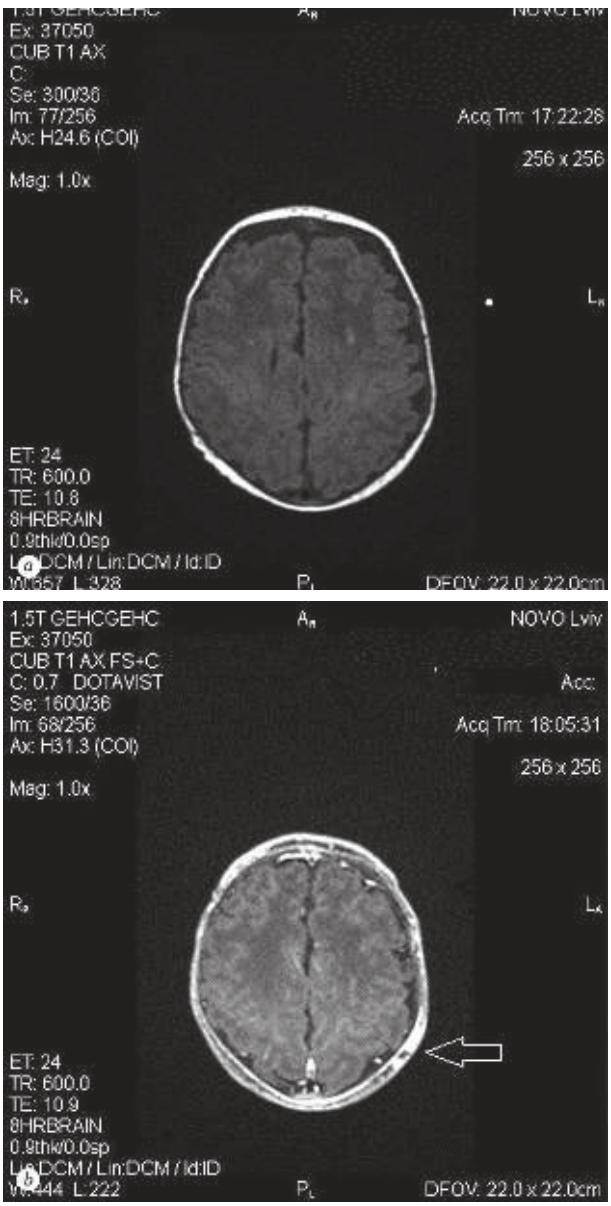

Fig. 4. Magnetic resonance imaging of the brain: *a* — T1 small hyperintensive foci in the brain parenchyma (most likely due to hemorrhages); *b* — T1-C nodular structures in the soft tissues of the parietal area on the left, which accumulate contrast

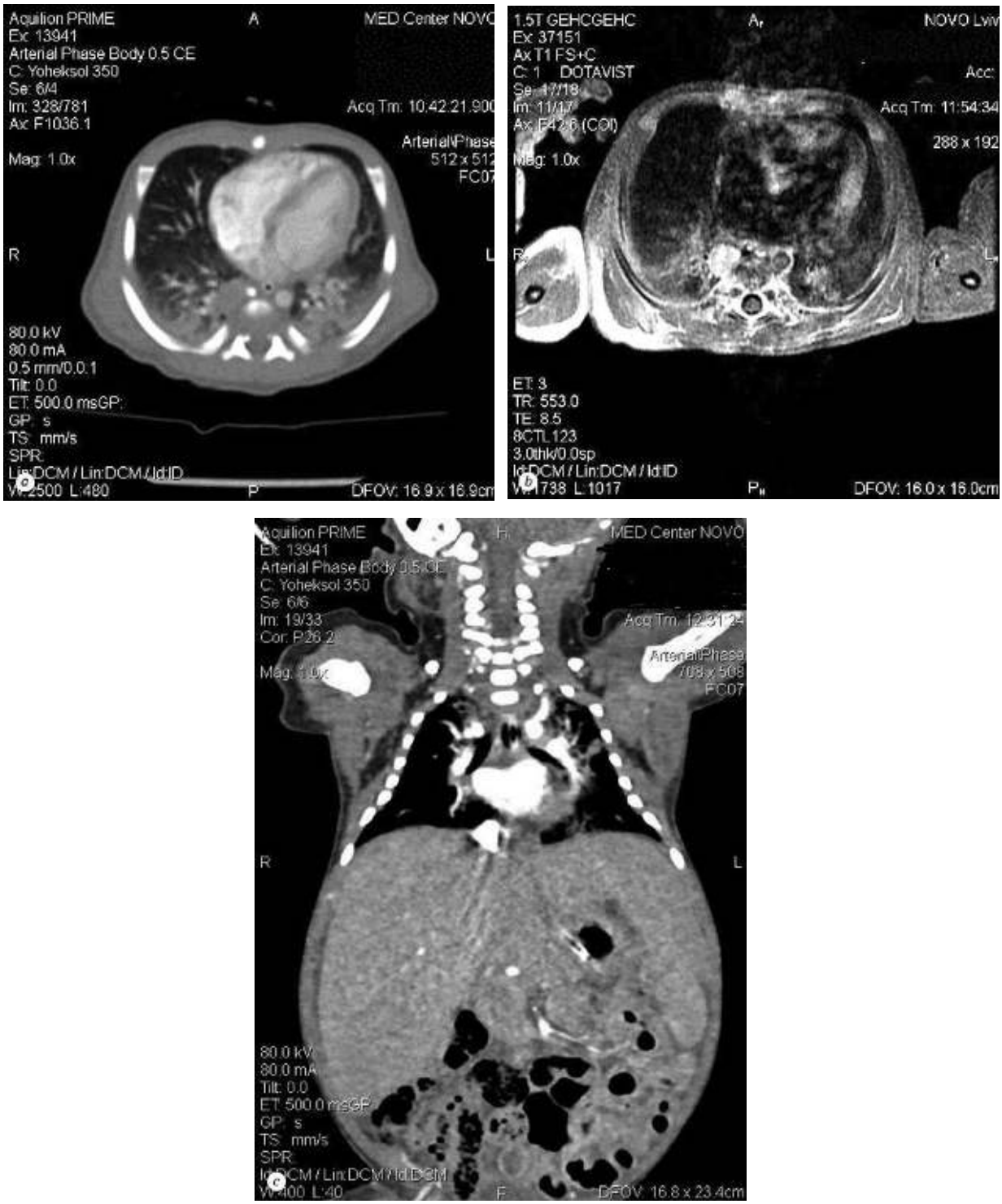

Fig. 5. Computed tomography of chest and abdominal organs: *a* — Infiltrative-inflammatory changes in the dorsal parts of the lungs; prevertebral formation in the right chest; *b* — T1-C prevertebral formation in the right chest; *c* — hepatosplenomegaly

of the underlying disease could not be achieved, blood transfusion dependence retained, frequent transfusions of the red cells concentrate and almost daily transfusion of the thromboconcentrate were required. After the 5th administration of vinblastine in 2 days there were manifestations of enterocolitis (*Klebsiella pneumoniae*), the next day intestinal paresis developed, bile secretion on the nasogastric tube appeared, child refused to eat, hyperthermia, deep pancytopenia, bacteremia *Klebsiella pneumoniae*, manifestations of hepatic insufficiency (growing hepatosplenomegaly and palpatory density of the liver and spleen, increasing cytolysis, hypoproteinemia, hypoalbuminemia, secondary coagulopathy) also joined. Subsequently the child died. The findings on autopsy: diffuse portal xanthogranulomatosis with pronounced fibrosis of the portal tracts, numerous subcapsule granulomas of the liver (Fig. 6, *a*, *b*), subpleural and interstitial xanthogranulomas of both lungs (Fig. 7, *a*,

b), subcapsular granuloma of the left kidney, hepatosplenomegaly. It should be noted that in the lungs xanthogranulomas were of varying degrees of maturity. The "young" consisted mainly of histiocytes, mainly with foamy cytoplasm and a small number of Tuton cells (in contrast to the findings in the skin, where there were no histiocytes with foamy cytoplasm, but there was a large number of Touton cells). In the composition of these granulomas, lymphocytes were also present in some places. A feature of pulmonary xanthogranulomas was the frequent presence of a significant amount of mucus in their composition.

NSJXG in newborns is a rare disease that occurs in 0.52% of children [5]. It is possible that the incidence of NSJXG may be higher, as the cases with a single, small NSJXG locus are usually not recorded. The average age at diagnosis is 3 months [1]. According to various authors, boys suffer from systemic xanthogranuloma more often and are more likely to develop multiple lesions [1, 6]. Most often, NSJXG lesions have a cutaneous form as single or multiple elements, but sometimes other organs (including lungs, liver, spleen, bone marrow or eyeball) are involved [7–9]. In most newborns, skin changes with NSJXG are manifested in the form of papules and nodules from yellow to pinkish-brown; typical yellow and erythematous color [3, 10–14]. Some individuals with NSJXG may have atypical skin changes such as purpura [15], and other children may have bluish nodules, ecchymoses, petechiae, and blueberry muffin spots [4, 5, 15–18]. Therefore, diagnosis by visual examination of the patient is difficult, because skin changes vary in color, shape and may change over time. In our clinical case, the manifestations of specific dermatitis were very diverse: most elements all over the body size 1–3 mm were dark cherry color, rash like "blueberry muffin" spots. Dense on palpation, some papulopustular elements with a clear outline are protruded above the surface of the skin, in the area of the scrotum – vesicular in nature, dark red, also protruded above the level of the skin. Subsequently, on the background of cytostatic therapy, the rash changed to papules and nodules of light yellow color.

For professional care of a patient with NSJXG, first of all it is necessary to establish the diagnosis. Histopathological and immunohistochemical examination should be performed. The name "xanthogranuloma" is explained by its histopathological morphological picture, it is the presence of histiocytes loaded with lipids, with vacuolated

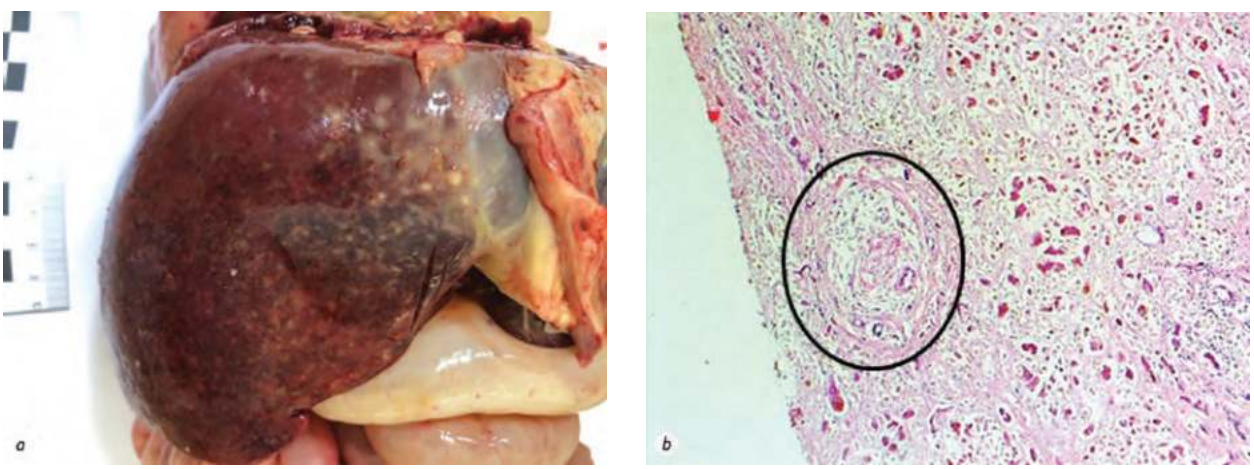

Fig. 6. Subcapsule granulomas in liver: *a* — numerous subcapsule granulomas in right lobule of the liver; *b* — microscopic structure; H&E stain, ×100

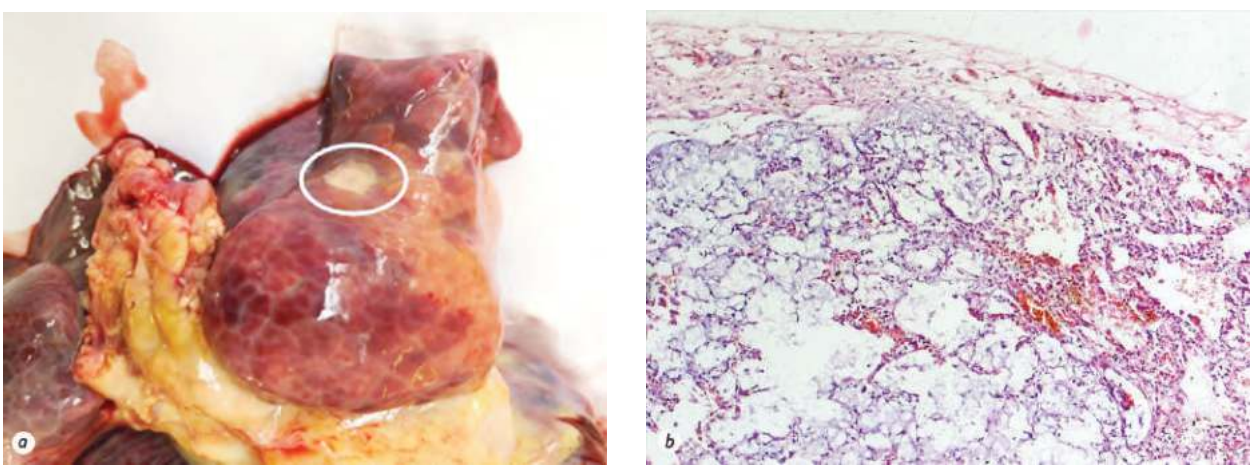

Fig. 7. Subpleural gigantic granuloma in lung: *a* — gigantic granuloma in the lower lobe of left lung; *b* — microscopic structure of subpleural gigantic granuloma in lung with abundant mucus accumulation; H&E stain, ×100

and xanthomatous cytoplasm. Histopathology indicates typical signs of histiocytosis with frequent infiltrative lesions of the dermis, the presence of multinucleated giant cells with variable numbers and inflammatory cells. Lymphocytes, eosinophilic granulocytes and plasma cells are present in the infiltrate. In 85% of cases, giant Tuton cells are found in histological specimens. Immunohistochemical study is performed to differentiate with LCH. In the juvenile xanthogranuloma, tumor cells are positive for factor XIIIa, CD68, CD163, fascein, and CD14, and in less than 20% of cases positive for S100 and negative for CD1a, the latter marker being specific for LCH [19]. In our patient, the diagnosis was verified by histological and immunohistochemical examination of the skin.

NSJXG is usually mild and often does not require treatment. A number of studies indicate an increase in the frequency of spontaneous regression of individual histiocytic lesions in newborns [20]. The lesions may disappear completely on their own, but can sometimes lead to discoloration or residual atrophic tissue changes. Often the only form of NSJXG treatment is surgery (for single lesions). The treatment protocols recommended for patients with symptoms who have unresectable lesions are the protocols used for LCH [18]. However, the systemic type of NSJXG is difficult to treat in newborns, and fatalities are possible.

In conclusion, NSJXG is a rare histiocytic systemic disease and may have an unfavorable prognosis. NSJXG should be excluded in case of multiple dark cherry rashes on the skin, hepatosplenomegaly and signs of cholestatic hepatitis in newborns. To verify the entire spectrum of lesions in NSJXG, it is necessary to carry out a comprehensive imaging study. For the purpose of differential diagnosis, histological and immunohistochemical study is required.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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ОСОБЛИВОСТІ ДІАГНОСТИКИ ТА НЕСПРИЯТЛИВОГО ПЕРЕБІГУ ЮВЕНІЛЬНОЇ КСАНТОГРАНУЛЬОМИ НОВОНАРОДЖЕНИХ. КЛІНІЧНИЙ ВИПАДОК

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Описано рідкісну неонатальну системну ювенільну ксантогранульому з початковим ураженням волосистої частини голови, кінцівок, спини та живота, множинним ураженням паренхіми обох легень, селезінки та печінки з розвитком тяжкої форми вродженого холестатичного гепатиту. Діагноз встановлено на підставі патогістологічного та імуногістохімічного дослідження шкіри. У дитини на фоні терапії за програмою LCH III досягнуто часткової відповіді, що проявлялося зменшенням гранулематозних утворень на шкірі, усуненням печінкової недостатності, але зберігалася гепатоспленомегалія, специфічні ураження паренхіми легень, печінки, лівої нирки. На тлі цитостатичної терапії у хворого виникла вторинна панцитопенія (анемія, тромбоцитопенія, лейкопенія та агранулоцитоз), періанальний виразково-некротичний дерматит з ураженням обох сідниць, стоматит, білково-енергетична недостатність, що розвинулася при гострому захворюванні печінки, коагулопатія, ДВЗ-синдром, гостра ниркова недостатність, дихальна недостатність III ст., серцево-судинна недостатність III ст., набряк легенів, набряк мозку, церебральна кома II–III ст., ентероколіт, парез кишечнику. Незважаючи на багатокомпонентну інтенсивну терапію, стан дитини прогресивно погіршувався. Після повторної зупинки серця, незважаючи на всі реанімаційні заходи, хворий помер. Неонатальна системна ювенільна ксантогранульома є рідкісним гістіоцитарним системним захворюванням. З метою диференціальної діагностики необхідно проводити імуногістохімічне дослідження.

***Ключові слова*:** неонатальна системна ювенільна ксантогранульома, патогістологія, імуногістохімічний метод.