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Chapter

The Case of Langerhans Cell Histiocytosis (Abt-Letterer-Siwe Disease) in Twin Girls

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Abstract

Abt-Letterer-Siwe disease is a form of Langerhans cell histiocytosis and occurs in 2–10 cases per 1 million of the child population per year. The Russian and foreign literature provide descriptions of this disease in children of different ages. Family cases of this pathology are described in a small number. The chapter presents a rare clinical observation of the Abt-Letterer-Siwe disease in twin girls.

Keywords: langerhans cell histiocytosis, Abt-Letterer-Siwe disease, children, twins, family case

1. Introduction

Langerhans cell histiocytosis (LCH) is a disease associated with abnormal proliferation and accumulation in the organs and tissues of pathological Langerhans cells, leading to local damage and violation of the affected organ function [1]. The term LCH includes eosinophilic granuloma, Hand-Schuller-Christian, and Abt-Letterer-Siwe diseases. The latter is considered the most difficult option with a mortality rate of at least 50% [2]. The study of Abt-Letterer-Siwe disease was started in 1924 by a German pathologist Erich Letterer [3]. In 1933, a Swedish pediatrician Sture Siwe published the first clinical description of the disease and proposed criteria for diagnosis [4]. In 1936, American authors Arthur Abt and Edward Denenholz in their publication proposed the adoption of the term “Letterer-Siwe disease” [5]. The disease is also mentioned in the literature as “Abt-Letterer-Siwe disease.”

The LCH frequency is 2–10 cases per 1 million children in a year [1, 6–10]. Boys have this disease 1.5–2 times more often than girls, mainly in early childhood [1]. The skeleton (60–80%), skin (22–50%), lymph nodes (10–15%), liver (10–15%), bone marrow (10–15%), lungs (10–15%), endocrine glands (25%), central nervous system (2–4%), etc. [1, 11–13] may be involved in pathological process. These lesions are specific for Hand-Schuller-Christian and Abt-Letterer-Siwe diseases, but the latter is characterized by severity of the course, generalization of the process, and onset in the first years of life [7, 14, 15].

The involvement of skin in the process in 10% may be the only symptom [7, 13]. LCH foci on the skin are represented by yellowish-red, dense, highly itchy papules and nodules with a slight hemorrhagic hue, cracking is specific. Elements are localized in the retroauricular region, in large folds of the body. The scalp is affected like a seborrheic eczema type. With the development of the disease, the dissemination of rash occurs. For skin rash in case of LCH, a poor response to treatment with topical glucocorticosteroids is typical. In case of damage to the oral mucosa, ulcers with fibrinous plaque are formed [7]. The involvement of many organs and systems in the pathological process leads to the appearance of defects in the bones (mainly in flat bones), impaired hemostasis, lymphadenopathy, hepatosplenomegaly, and suppression of bone marrow function. Damage to the lungs is manifested by the spontaneous pneumothorax occurrence. Long, recurrent course of otitis is specific [1, 7, 14].

A probable clinical diagnosis is confirmed by histopathological and immunohistochemical methods. A biopsy of skin, osteolytic foci, and lymph nodes is preferred. Liver or lung biopsy is performed in the absence of other materials [1]. Light microscopy does not allow an unambiguous diagnosis. The “gold standard” of diagnosis is the identification of Birbeck granules by electron microscopy. A more sensitive and specific diagnostics is immunohistochemical staining with langerin (CD 207), which is a monoclonal antibody against type II transmembrane protein bound to the Birbeck granules [13].

According to the data of Moskacheva et al., until 1931, about 65 cases of Hand-Schuller-Christian disease and 4 cases of Abt-Letterer-Siwe disease were described. According to other authors to 1955 described about 350 and 68 cases of the disease it [15]. In the Russian Scientific Electronic Library in the period from 2004 till 2017, about 8 clinical observations of this disease in children were described. PubMed’s English language text database for the same period represents more than 300 sources, including cases of Abt-Letterer-Siwe.

Until the middle of the twentieth century, the relationship of Abt-Letterer-Siwe disease with genetic disorders was questioned [5, 15]. The described family cases in siblings and, moreover, cases of the disease in twins were of particular interest. The Russian language descriptive works of the LCH family cases, including the disease Abt-Letterer-Siwe, in the Russian Scientific Electronic Library for the last 10–15 years are absent. Over the past 50–60 years, we have found about 40 LCH familial cases (half of Abt-Letterer-Siwe disease) in the PubMed database, of which 12 are twins with a description of the disease.

Due to the pathology rarity, we represent a description of the Abt-Letterer-Siwe disease case in two monozygotic twin girls A and E, who were admitted to our clinic at the age of 12 months.

2. Description of the Abt-Letterer-Siwe disease case

Children are from monozygotic twins from one pregnancy. Parents are young and healthy. Delivery occurred at a period of 34 weeks. Both children were switched to artificial feeding during the first month. The development of children throughout the observation period corresponded to the age.

For the first time, parents noted the appearance of moderately itchy skin rash and ulcerative stomatitis in children at the age of 1.5–2 months. Hyperemia, papules, crusts were present in the area of large skin folds (cervical, axillary, inguinal). The boundaries of skin changes were legibly delineated (**Figure 1**). Quickly enough, the scalp (hyperemia, severe desquamation, yellowish crusts, papules) and the parotid area (hyperemia, crusts, papules, weeping) were involved in the process. Rare small



(a)



(b)

Figure 1.
Skin changes: inguinal fold (a) and neck fold (b).

papules and pustules occasionally appeared on the skin of the limbs and trunk (outside the folds), which was considered as pyoderma. Secondary changes, such as small scars, remained in place of some papules and pustules. In a retrospective assessment, it is possible that there were small nodules on the skin. Children received antihistamines, care cosmetics, and topical corticosteroids; milk mixtures were changed. No improvement was observed. The application of topical corticosteroids to the affected areas exacerbated itching and hyperemia, and anxiety appeared in children.

Over the next 4–5 months, against the background of the treatment variety, skin manifestations persisted in a stable condition of children and sufficient weight gain. On the scalp (“seborrheic area”) and the parotid region, yellowish crusts, erythema, peeling, papules, and weeping were observed.

The main changes were localized in large folds, which were manifested by hyperemia, papules, crusts, and cracks. Soles, palms, and interdigital spaces were involved in the process, where hyperemia, peeling, yellowish crusts, and cracks were observed. The skin of the limbs, trunk, and face was intact, with the exception

of rare episodes of pustular rash. Despite extensive and persistent skin lesions, itching was moderate. During the periods of exacerbation, children became restless due to pain.

The dermatologist examined the children at the age of 7 months for the first time. Bright erythema-squamous rash with weeping and mucous discharge in the area of large folds were described, scars after previous pustulosis. Erythematous diaper rash and atopic dermatitis were diagnosed. Antihistamines, topical glucocorticoids, and antibiotics were administered as treatment. After 2 weeks, no significant dynamics were observed.

At the age of 9 months, the dermatologists in the clinic diagnosed an infant form of atopic dermatitis. Skin symptoms were the same. On the part of the internal organs and in blood tests, no significant pathology was detected. In bacteriological studies from the inguinal, axillary, and neck folds, *Staphylococcus aureus* was identified. Girls received a dairy-free diet, a solution of potassium permanganate on the affected skin folds, nystatin, hydrocortisone + oxytetracycline, and papaverine ointment. Children were discharged without improvement at the age of 9 months 3 weeks with recommendations for treatment of intestinal dysbiosis, a hypoallergenic diet and continued local therapy.

At the age of 11 months, the children were examined by a pediatrician in the consultation center. During physical examination, the attention was paid to the course of the disease, which was atypical for atopic dermatitis—localization of rash was mainly in skin folds of the “diaper dermatitis” type of dark-red color with a relatively intact remaining surface, damage of the palms, soles, interdigital spaces of the feet, ulceration of the oral mucosa in the onset, episodes of pustular rash with an outcome in small scars, repeated worsening of symptoms (increased hyperemia, increased itching, and the appearance of pain) when using topical glucocorticosteroids, the absence of any improvement after the exclusion of cow’s milk protein from the diet (at the time of the consultation, the children received a high-hydrolysis formula for a long time and scanty complementary foods). The girls showed periodic weeping in the ears area, damage of the entire scalp like a seborrhea type, which had an unusually stubborn course. An anamnesis of the disease, clinical picture, absence of the effect of glucocorticosteroids, and a therapeutic diet excluded the atopic dermatitis diagnosis.

At the age of 12 months, the condition worsened and the children were admitted to our clinic. Children had fever up to 39–40°C, intoxication, and moderate hepatosplenomegaly. Skin symptoms significantly increased (**Figure 2**). In the clinical blood analysis of girls A and E, anemia (erythrocytes 3.32 and $3.58 \cdot 10^{12}/L$, and hemoglobin 75 and 84 g/L, respectively), leukocytes at level $5.8 \cdot 10^9/L$ and $9.3 \cdot 10^9/L$, respectively, thrombocytopenia (platelets 66 and $108 \cdot 10^9/L$, respectively), and ESR 20 mm/h in both girls were observed. The range of differential diagnosis included primary immunodeficiency, psoriasis, and LCH. During one day, the children received intravenous immunoglobulin based on the course dose of 1 g/kg due to the severity of the condition and a probable diagnosis of immunodeficiency.

The condition of children remained serious due to an increase in hematological disorders (anemia—hemoglobin up to 70–90 g/L, thrombocytopenia up to single cells, and leukopenia up to 3–4 $M09/L$), hemorrhagic (bleeding of elements in large-folds) and hepatolienal syndromes, fever up to 39–40°C, and infection of the skin—primarily with “wild,” and then with hospital strains of bacteria. An intensive, replacement therapy and an antibiotic therapy were applied.

During treatment, a temporary improvement was observed in the form of drying, reduction of purulent crusts, and improvement of well-being. On the 10th day of hospitalization, child A developed a septic shock. In the intensive care unit,



(a)



(b)

Figure 2.
Dynamics of skin changes: foot skin lesion (a) and inguinal areas (b).

the girl was on the mechanical ventilation of lungs for 10 days. The condition of the second child remained stably severe.

Both girls excluded HIV infection, primary immunodeficiencies of the humoral, cellular, and phagocytic parts of the immune system, and violation of complement. Specific lesions of bones and lungs were excluded according to X-ray and computed tomography (CT) results. In child E, according to spiral CT, a left-sided otitis media was observed without destructive changes. According to bone marrow puncture, in

child A, the process disorders differentiation and the maturation of cells were not determined, the erythroid germ was expanded, and a moderate delay in maturation at the level of myelocytes was observed in the granulocytic germ. Megakaryocytes were not found during the study. Free platelets were isolated.

In a cytological study of smear impressions from the creases in child A, in addition to inflammatory elements and eosinophils, cells with hyperchromic sharply enlarged nuclei, with signs of nuclear polymorphism and atypia, and binuclear cells were found. Atypical large cells with an oval nucleus, fine-grained chromatin, containing 1–2 nucleoli, and an abundant pale-stained cytoplasm were visualized in a significant amount. Some cells contained vacuoles.

The child A underwent a skin biopsy from a pathological focus. Light microscopy in the papillary layer at the border with the epidermis revealed single foci of proliferation of large oval and process cells with an eosinophilic cytoplasm, hyperchromic nuclei, and single binuclear cells. The described that the morphology was specific for histiocytosis. In the Federal State Budgetary Institution “National Medical Research Center named after Dmitry Rogachev” (Moscow), an immunohistochemical study was performed. According to this analysis, large cells express Langerin, CD13, and single cells express CD68. Reactions with other antibodies to them are negative. Conclusion: LCH.

Two weeks after admission to the hospital, an intravenous administration of glucocorticosteroids at a dose 20 mg/kg was started in pulse mode 3 times a week with further switch to oral administration of prednisolone at a dose 2 mg/kg. Confirmation of the LCH diagnosis (Abt-Letterer-Siwe disease) made it possible to continue therapy according to the LCH III protocol in the Pediatric Oncohematology Department. Against the background of some stabilization of the condition, episodes of fever, hepatosplenomegaly, pancytopenia in the clinical blood analysis, and bleeding persisted. Rash in large skin folds was without significant dynamics. Taking it into account, a lack of response to therapy was reported. Children were directed to the Federal State Budgetary Institution “National Medical Research Center named after Dmitry Rogachev” (Moscow) for further treatment.

Our clinical case of Abt-Letterer-Siwe disease is one of the most severe LCH variants. In children, there was a multisystem lesion, involving the liver, hemato-poietic system, and spleen, which is prognostically unfavorable. A feature of the described case is the simultaneous onset of the disease in two twin girls, which is an extremely rare observation. This clinical case shows the difficulty in diagnosing LCH (Abt-Letterer-Siwe disease) at an early age. Difficulties in making a diagnosis arise when there is still no developed clinical symptomatology of the disease or the clinical picture is inapparent [15]. The prevalence of damage to one organ or system, especially at the beginning of the disease, leads to erroneous diagnoses. In our clinical case, the main symptom of the disease during 10–11 months in both girls was skin damage. During this period of time, they were observed by pediatricians and dermatologists with a diagnosis of atopic dermatitis and diaper rash.

3. Conclusions

In our opinion, the attending physician should have been alerted by a number of symptoms that are not specific for atopic dermatitis: ulcerative stomatitis in the onset; absolutely unspecific localization of the rash—large folds without damage to the skin areas typical for atopic dermatitis at this age; unusual coloring of elements (dark-red); damage of the palms, soles, and interdigital spaces; episodes of an abscess rash that left small scars—this symptom indicates a deeper lesion of the skin than with ordinary pyoderma; and one of the significant symptoms is the deterioration

of skin symptoms with the “gold standard” topical application treatment of atopic dermatitis—topical glucocorticosteroids. The latter manifestation is typical for the Abt-Letterer-Siwe disease, but is absolutely not specific for allergic rash.

Thus, at present, the diagnosis of orphan diseases remains difficult at the early stages. This is due to the polymorphism of manifestations, the rarity of cases, and the similarity with other nosologies.

Conflict of interest

The authors of the chapter confirmed the absence of financial support for the study that needs to be reported and declare no conflict of interest.

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