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Authors

Stadnikova, Antonina Sergeevna
Abbas, Walaa Fadhil
Tamrazova, Olga Borisovna
et al.

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Letterer-Siwe disease presenting with gastrointestinal and cutaneous manifestations

Antonina Sergeevna Stadnikova[1] PhD, Walaa Fadhil Abbas[2] MD, Olga Borisovna Tamrazova[1] PhD, Ekaterina Andreevna Pristanskova[3] PhD, Irina Nikolaevna Zakharova[4] PhD, Irina Vladimirovna Berezhnaya[4] PhD, Dmitry Alexandrovich Skobeev[5] PhD, Lyudmila Viktorovna Goncharova[6] MD

Affiliations: [1]Federal State Autonomous Educational Institution of Higher Education "Peoples' Friendship University of Russia" of the Ministry of Education and Science of the Russian Federation, Children's City Clinical Hospital named after PER, Bashlyaeva, Moscow Department of Health, Moscow, Russia, [2]Department of Dermatovenerology with Course Cosmetology, RUDN university, Moscow, Russia, [3]Russian Children's Clinical Hospital of the Federal State Autonomous Educational Institution of Higher Education "Russian National Research Medical University named after NI Pirogov" of the Ministry of Health of the Russian Federation, Moscow, Russia, [4]Department of Pediatrics named after Academician GN Speransky FGBOU DPO RMANPO of the Ministry of Health of Russia, Moscow, Russia, [5]Pathoanatomical Department of the Morozov Children's Clinical Hospital, Moscow, Russia

Corresponding Author: Walaa Fadhil Abbas MD, Miklukho-Maklaya Street, 6, 117198, Moscow, Russia, Tel: 7-9875396330, Email: walaafadil1@gmail.com

Abstract

Histiocytosis is a set of distinct proliferative illnesses defined by the proliferation and infiltration of varied numbers of dendritic cells, macrophages, and monocytes in the afflicted tissues. The skin and other organs may be impacted by the inflammatory infiltration. It can occur at any age. The severity of the symptoms can range from mild to severe, depending on the degree and type of organ involvement. Although certain forms of histiocytosis can be fatal, others can be treated successfully without sequelae. Langerhans cell histiocytosis manifests itself clinically in both children and adults. A combination of clinical, histological, and radiological tests is required to achieve a diagnosis. A severe, multisystemic, acute form of Langerhans cell histiocytosis is called Letterer-Siewe illness, which usually affects infants in their first year of life. In this article, we provide a brief literature review and a case study of a 9-month-old girl who presented with recurring gastrointestinal problems as the first sign of Letterer-Siwe disease.

Keywords: gastrointestinal, histiocytosis, Langerhans cell, Letterer-Siwe disease, seborrheic dermatitis, skin rash

Introduction

Histiocytosis is a heterogeneous group of multisystem diseases defined by the accumulation of proliferative cells presumed to have originated from macrophages or dendritic cells. The Working Group of the Histiocyte Society produced the first categorization of histiocytosis in 1987, which comprised three categories: Langerhans cell, non-Langerhans cell histiocytosis, as well as malignant histiocytosis [1]. Although Dr. Thomas Smith first recorded instances of histiocytosis in 1865, it has only been in recent years that the pathogenesis of these illnesses has begun to be explained via the use of molecular analysis [2]. Pluripotent stem cells present in bone marrow give rise to histiocytes. Histiocytes can become dedicated, developing into certain groupings of specialized cells in response to various cytokines such as granulocyte-macrophage colony-stimulating factor, interleukin IL3, IL4, tumor necrosis factor, and others. One of two lineages can form from dedicated histiocytes: Macrophages and monocytes are examples of antigen-processing cells. Interdigitating reticulum cells, Langerhans cells, and dendritic cells are examples of antigen-presenting cells, with Langerhans cells being dendritic cells located in the epidermis [3]. These dendritic cells express CD1a/CD207 [3]. Eosinophilic granuloma (most commonly bone), Hand-Schuller Christian disease, Letterer-Siwe disease, and Hashimoto-Pritzker disease are some of the clinical manifestations of LCH that have historically been characterized as separate entities. Over time, it

became clear that not all instances fell neatly into the initial, rigorous categories and that many of them had overlapping characteristics [4]. Langerhans cell histiocytosis has the potential to affect the central nervous system, thymus, lymph nodes, liver, skin, bones, and lungs. Children usually have an estimated incidence of 8-9 per million per year [5]. In addition, 1% of patients have been shown to have familial clustering and twin studies have revealed that monozygotic twins have a greater incidence of concordance than dizygotic twins (92% compared to 10%), [5]. The median age of diagnosis is 3.5 years. The male-to-female ratio is 2:3 [4]. With a mortality rate of at least 50%, Abt-Letterer-Siwe disease (LSD) is considered to be the most serious variant of LCH and is usually seen before one year of age. German doctor Erich Letterer began researching the Abt-Letterer-Siwe illness in 1924. The earliest clinical report of the illness was published in 1933 by Swedish doctor Sture Siwe [6]. Due to the prognostic significance of the particular damaged organ in LSD, high-risk organs, including the bone marrow, liver, and spleen, can cause death during intrauterine life or just a few weeks after delivery. Skin, lymph nodes, digestive tracts, and central nervous system involvement are regarded as low-risk organs [7]. Involvement of the digestive tract in LCH is uncommon (1-5%). Due to the vagueness of gastrointestinal tract (GIT) symptoms, like those of a food allergy, its occurrence is likely underreported [8]. According to a review of the literature, 62% of children were female and under the age of two in virtually all cases of GIT involvement [9]. Targeted treatment may take precedence over chemotherapy in light of recent findings of driver mutations in the *BRAF* and mitogen-activated protein kinase pathway (*MAP2K1*) genes in LCH [10].

Case Synopsis

A 9-month-old girl was admitted to the Children's Clinical Hospital ZA Bashlyaeva, Moscow, Russia, with a history of loose stools with mucus and streaks of blood and a reduced rate of weight gain since three months of age. The infant was on mixed feeding with an adapted milk formula. There were no food restrictions in the mother's diet. Switching to a hypoallergenic formula had a temporary positive effect. At four months, a seborrheic scaly rash appeared on the scalp and diaper area. From the words of the mother, the infant did not gain weight well on the background of complementary foods due to chronic diarrhea. Nifuroxazide syrup was tried along with oral rehydration with some improvement.

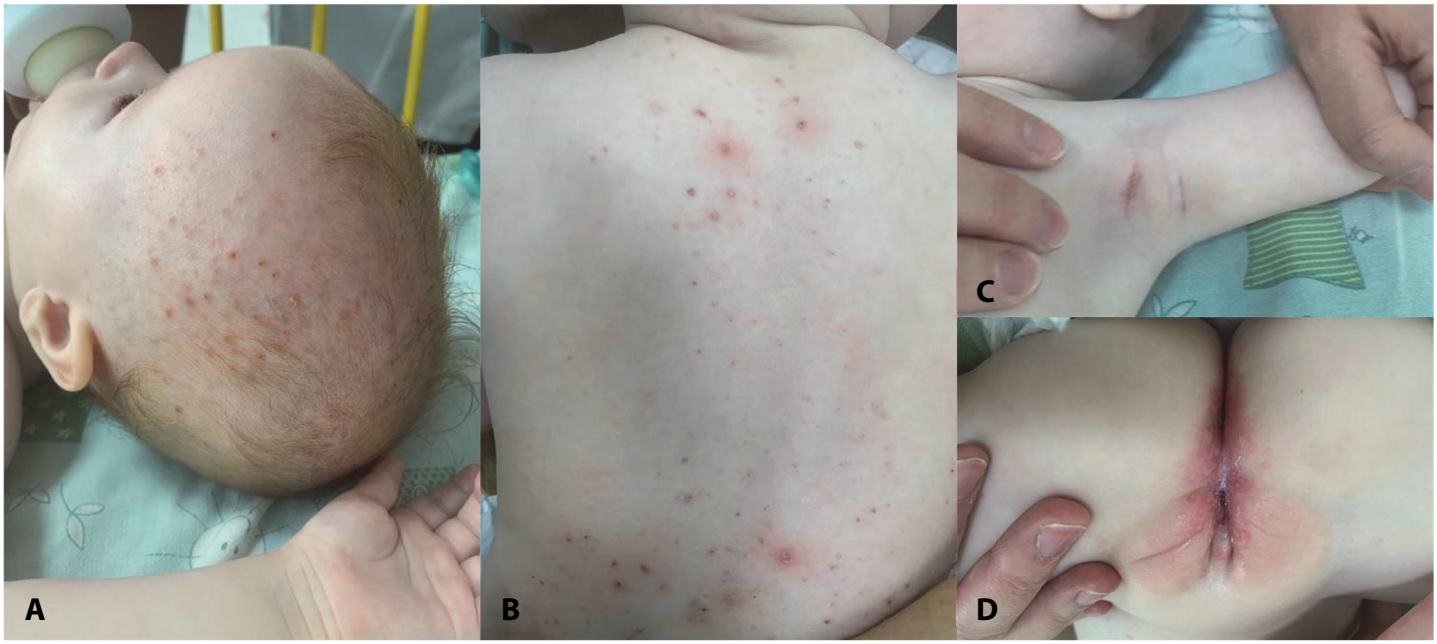

Figure 1. ***A)*** *Yellowish, scaly, and erythematous papular eruption on the scalp.* ***B)*** *Crusted papules on erythematous base with yellow exudates on the back.* ***C)*** *Intertrigo like rash in the axillary folds, with distinct boundaries and deep fissures.* ***D)*** *Against the background of erythema, multiple ulcers in the anogenital area, covered with fibrinous plaque without signs of epithelization.*

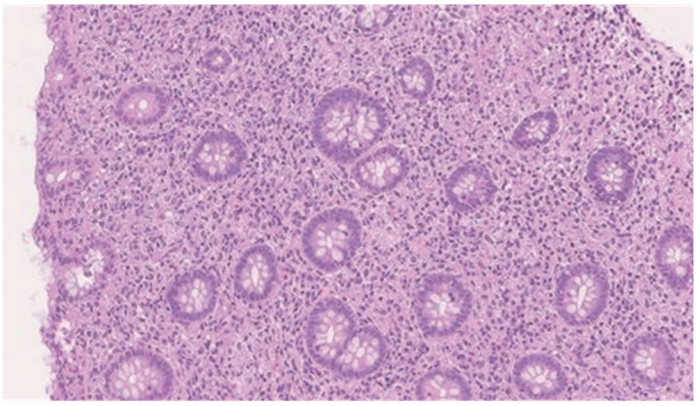

Figure 2. *A biopsy of the gastrointestinal tract and colonic mucosa showed granulomatous lesions with a characteristic inflammatory infiltrate composed mainly of histocytes (medium-sized cells with eosinophilic cytoplasm and a bean-shaped nucleus with a central nuclear notch) mixed with eosinophils and neutrophils. H&E, 20×.*

A lactose-free formula was used for 2-3 weeks without problems. From the detailed history that was taken on admission, the mother's previous pregnancy ended with intrauterine fetal death at 20 weeks of gestation. The present infant's prenatal history included a threatened abortion in the first trimester, gestational diabetes in the second trimester, and early term labor at 38 weeks gestation. The following parameters were met at birth: body weight 2650g, height 50cm, and Apgar score 8-9. On admission to the hospital, the infant was afebrile, weighed 7.1kg, conscious, active, and had normal vital parameters. The cervical lymph nodes were palpable. The abdomen was soft and non-tender. The cardiac and respiratory examinations were unremarkable. Skin examination revealed multiple cutaneous eruptions on the scalp, axilla, back, and perineum (**Figure1**). The eruption was yellowish, scaly, and erythematous on the scalp. Crusted papules with yellow exudates were seen on the back. In the axillary folds, the rash was similar to intertrigo, but with distinct boundaries and deep fissures. In the anogenital area, against the background of erythema, multiple ulcers were noted, covered with fibrinous plaque without signs of epithelization. A yellowish white plaque was seen on the tongue. A routine blood examination showed white blood cells at 12.9×10^9/L (normal $6.5\text{-}12.5\times10^9$/L) with a moderate elevation of lymphocyte percentage, hemoglobin 98g/L (normal 100-145g/L), serum iron 4.4μmol/L (normal 8-28μmol/L), total protein level 45g/L (normal 57-78g/L), and albumin 32 g/L (normal 29-51g/L). The liver function tests, renal function tests, blood glucose, IgE level, and other parameters were normal. Viral serology, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV TORCH screen, and syphilis tests were negative except for cytomegalovirus (IgM and IgG positive). Blood and stool cultures were negative. An abdominal ultrasound revealed mesenchymal lymphadenopathy with no organomegaly. On ultrasound, a decrease in the size of the thymus gland was seen. The skull X-ray and skeletal survey were normal. Esophagogastroduodenoscopy and colonoscopy revealed erosive gastritis, atrophic ulcerative duodenitis, and erosive colitis, respectively. A biopsy of colonic mucosa showed granulomatous lesions with a characteristic inflammatory infiltrate composed mainly of histocytes mixed with eosinophils and neutrophils (**Figure 2**). CD1a, S100, and CD207 (Langerin) immunohistochemistry were strongly positive (**Figure 3**). Once the diagnosis of multisystemic Langerhans cell histiocytosis (MS-LCH) was confirmed, treatment was started with mesalazine 250mg twice a day for 7 days; diphenhydramine intramuscular 0.1ml; metronidazole 50mg; and ceftriaxone 0.35g twice a day for 5 days. Topical

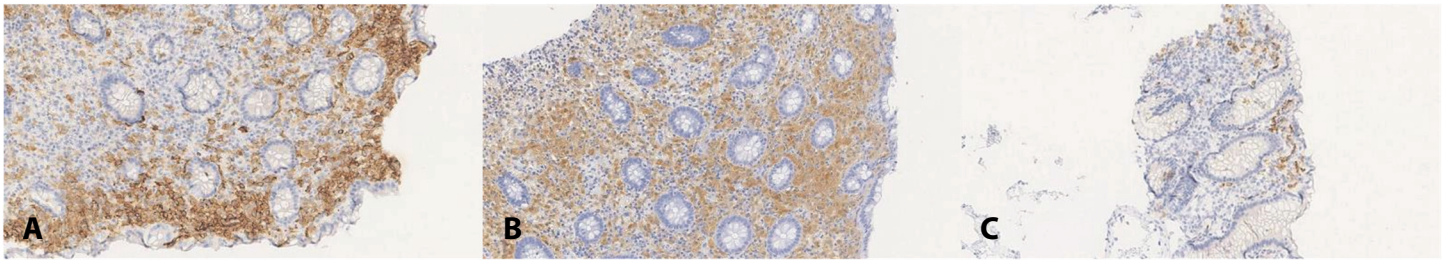

Figure 3. *In an immunohistochemical study, the cells of the infiltrate are positive in reactions with antibodies to* ***A)*** *S100, 10×;* ***B)*** *CD1a, 10×; and* ***C)*** *CD207 (Langerin), 20×.*

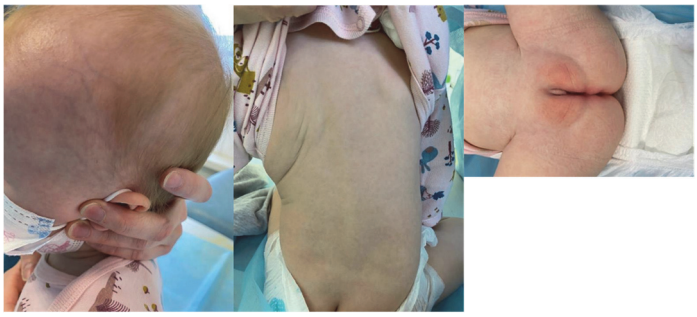

Figure 4. *Significant improvement in the scalp, back, and perineum skin rash, followed by slight residual pigmentation.*

treatments included hydrocortisone ointment with natamycin and neomycin, zinc, and dexpanthenol cream, applied twice daily to skin folds for 5 days. The infant was then transferred to the pediatric oncology department, where oral prednisone (1.3mg/kg/day, 40mg/m2, in three divided doses for four weeks, tapering over a period of two weeks) and vinblastin (0.2mg/kg/dose, 6mg/m2/dose, i.v. bolus on day one of weeks 1, 2, 3, 4, 5, and 6) were planned. Improvement was seen after four months of follow-up following the chemotherapy block as determined by CT scan of the organs of the abdominal cavity, retroperitoneal space, and pelvis). The nature of the stools improved and the skin eruption resolved, leaving residual pigmentation (**Figure 4**).

Case Discussion

Langerhans Cell Histiocytosis, also known as "class I histiocytosis" or "histiocytosis X," is a rare type of hyperplastic cellular disorder characterized by an increased number of Langerhans cells in the skin and other organs.

Etiology and pathophysiology

It has been argued for years whether the origin of disease is due to an immunological reactionary inflammatory process, a benign proliferative illness, or a malignancy. Despite the fact that the causes of inflammation are poorly understood, a prominent immune infiltration, comprised of dendritic cells and activated T cells as well as an excess of inflammatory cytokines (including IL1and IL17), is a hallmark of Langerhans cell histiocytosis lesions. High quantities of programmed cell death ligands are expressed in Langerhans cell histiocytosis lesions, and invading T lymphocytes express the programmed cell death proteins. The long-running controversy about Langerhans cell histiocytosis began as it was considered a case of inflammatory activation of Langerhans cells through these histological alterations [11,12]. These reactive histiocytes have a benign appearance and modest mitotic activity. Therefore, LCH is viewed in this context as an immunological reaction disease in which normal cells multiply in response to numerous environmental stimuli (like infections) and usually resolve spontaneously or after treatment with anti-inflammatory agents.

Rollins and colleagues examined CD1a+ cells extracted from LCH lesion biopsies using better sequencing technology and discovered recurring *BRAF* V600E mutations in more than 50% of the patients [13]. Later research revealed that LCH almost always contains the *BRAF* V600E (65-70%) or alternative activating MAPK pathway (20%) gene alterations, as well as other *BRAF* mutations and *MAP2K1* mutations [14]. These changes result in aberrant activation of the *ERK* gene, which regulates intercellular signals. These mutations are not inherited and are *genetic accidents* that happen during DNA copying in dendritic cells [14]. The stage of differentiation of the cell at which the activating somatic *MAPK* mutation arises determines the severity of the illness. *MAPK* gene mutations of stem cells from bone marrow cause high-risk multisystem LCH (liver, spleen, bone marrow); somatic *MAPK* mutations of committed dendritic precursor cells in the blood cause low-risk multisystem Langerhans cell histiocytosis (skin, gastrointestinal tract, central nervous system, lymph node, and lung). However, somatic *MAPK* mutations of more mature dendritic cells in the blood cause low-risk single-system LCH [15]. These findings point to a neoplastic genesis of the illness due to the disruption of the intracellular processes that regulate cell growth, proliferation, and differentiation. However, genetic susceptibility has also been proposed because of greater familial occurrence, increased appearance in identical twins, and the link to human leukocyte antigens such as HLADRB1*03, CW7, and DR4 [16]. Murakami et al. reported that *BRAF* mutations can promote a

protracted inflammatory response following infection [17]. On the other hand, there are data that support the neoplastic concept since it was shown that LCH lesions had higher expression of Ki67, p53, Hras, cmyc, and Bcl2 [5].

Classification

According to the International Histiocytosis Society's proposed classification of histiocytic alterations in 2016, patients are divided into five groups based on clinical, histological, and molecular characteristics. These groups are: group I-Langerhans; group C-cutaneous and mucocutaneous; group M-malignant histiocytosis; group R-Rosai Dorfman disease; and group H-hemophagocytic lymphohistiocytosis [18]. Langerhans cell histiocytosis is classified based on how many systems are involved (single versus multisystem) and whether risk organs are affected. Many kinds of this illness reflect its vast clinical spectrum, including eosinophilic granuloma (focal chronic), Hands-Shuller-Christian disease (disseminated chronic), and Letterer-Siwe disease (disseminated acute), [19].

Clinical manifestations

The age ranges that are impacted differ depending on the presentation. The multisystemic form often occurs relatively early (less than two years), whereas the unifocal form is typically seen in late childhood. Although numerous adult cases have been documented in the literature, the disease affects adults less commonly. The organs that are most frequently impacted include the bone (80%), skin (33%), pituitary (25%), liver (jaundice, elevated liver enzymes, or decreased albumin), spleen, and lung (cough, chest pain, and tachypnea), (15%), and lymph nodes (5-10%), [4].

Because isolated skin lesions are seen in less than 2% of cases, skin involvement is usually associated with multi-systemic disease [20]. When skin manifestations are presented as an early finding of Langerhans cell histiocytosis, they are frequently misdiagnosed as seborrheic dermatitis, diaper dermatitis, candidiasis, or atopic dermatitis. Like in the infant in this case report, it usually affects skin folds (the neck, axilla, and perineum) and presents as red, pink, or skin-colored pruritic papules and plaques with central ulceration and yellow crusts. On the scalp, scaly white-to-yellow erythematous lesions mimicking seborrheic dermatitis can be seen. Vesicular, pustular, lichenoid, eczematous, hemorrhagic, and polymorphic eruptions have been described [21]. Mucosal lesions like ulcers in the genital area or oral mucosa are also encountered. Non-specific nail changes like paronychia or onycholysis have also been reported [22].

Patients with either single-system or multisystem diseases may experience systemic symptoms such as fever, weight loss, malaise, and lymphadenopathy. The involvement of the gastrointestinal tract in LCH is highly uncommon, with very diverse and non-specific symptoms that can be misinterpreted initially as food allergies, as in our case and others [23]. In 37 cases of LCH with gastrointestinal tract involvement, Yadav and colleagues conducted a literature analysis and found that 62% of the children were female and nearly 95% of the patients were under the age of two [24]. Bloody diarrhea, protein-losing enteropathy (PLE), anemia, vomiting, abdominal discomfort, constipation, and intestinal perforation were the most frequent presenting symptoms. More than half of the patients in this study died within 18 months of diagnosis. Determining whether the digestive system is a high-risk organ or not may be difficult since it is frequently accompanied by the involvement of other organs.

Eosinophilic granuloma is the most frequent type of LCH in children aged 5 to 10 years old, and it commonly manifests as a painful bone mass (osteolytic lesion). Hand-Schüller-Christian illness is a kind of endocrinopathy that is characterized by diabetes insipidus (involvement of the hypothalamus-pituitary axis), lytic bone lesions, and exophthalmos. Finally, Abt-Letterer-Siwe illness is the most severe multisystemic type of LCH and is frequently diagnosed in infancy. It is characterized by cutaneous signs, liver involvement, lymph node involvement, and a poor prognosis.

Diagnosis and treatment

The diagnosis is made primarily by correlating the history, clinical picture, radiology, laboratory tests, and histopathological results. Excisional biopsy usually shows tissue infiltration by histiocytes that

are surface-positive for CD1a, CD207, and S100 in immunohistochemistry. In addition, T lymphocytes (FOXP31 and CD41), multinucleated giant cells, eosinophils, and macrophages were also present in the mixed inflammatory infiltrate. Langerhans cell histiocytosis cells exhibit spherical shapes, eosinophilic cytoplasm, and "coffee-bean" cleft nuclei. Pleomorphism and aberrant mitosis are often not found, and if they are, Langerhans sarcoma should be suspected [25]. To differentiate LCH from other diagnoses, Tzanck preparations, bacterial, viral, and fungal cultures, and serology can be utilized. The maternal history of infections, use of medications, and smoking during pregnancy may increase the risk of the disease. In addition to that, in vitro fertilization, blood transfusions during infancy, neonatal infections, low socioeconomic status, inadequate feeding, and a family history of thyroid disease are all possible risk factors for the development of LCH [26,27]. The disease was found to be less common in Black patients and more common in Hispanic patients [28]. Langerhans histiocytosis has been linked to various neoplasms in 2.6% of children and 32% of adults, including Hodgkin lymphoma, non-Hodgkin lymphoma, and acute myeloid leukemia [29].

Treatment is determined by disease extent and affected organs. First-line therapy for limited disease is surgical resection and/or high-potency topical corticosteroids. Topical imiquimod, nitrogen mustard, and phototherapy have all been used with variable responses [25,30,31]. Isolated skin lesions may disappear on their own, as in the case of congenital self-healing reticulo-histiocytosis. For severe multisystemic illness, a combination of systemic corticosteroids and vinblastine for 6-12 months is advised. Methotrexate, thalidomide, 6-mercaptopurine, cytarabine, and azathioprine are further therapy choices [32]. Targeted therapeutics targeting the MAPK pathway were developed as a result of the discovery of *BRAF* and *MAP2K1* mutations in LCH. Vemurafenib and dabrafenib are first-generation BRAF inhibitors that have been investigated for the treatment of high-risk or refractory LCH with off-label clinical usage. In many cases, there was a significant dramatic improvement and excellent but short-term results (reactivation following the discontinuance), [33,-36]. Target treatment has a number of limitations because BRAF inhibitors were unsuccessful for a large number of additional *BRAF* mutations, including insertion or deletion of exon 12, *BRAF* fusion with a partner gene, and mutations of genes encoding proteins functioning upstream of RAF (such as RAS). This lack of efficacy has the potential to cause a paradoxical transactivation mechanism, which can lead to major cutaneous side effects such as keratoacanthomas and squamous cell carcinomas [37].

The prognosis is primarily determined by organ involvement, with a survival rate of 100% in single organ disease but a mortality rate of 50% in infants with multiple high-risk organ disease. The most frequent sequelae of LCH include diabetes insipidus, growth hormone deficiency, orthopedic disabilities, skin problems, hearing loss, neurologic/cerebellar sequelae, and secondary cancers [38].

Regarding our case, there are many unique characteristics that add interest to the findings and associations because risk factors for LCH might be present in this case scenario. The maternal history was vague, with hazy details like the lack of obstetric information regarding the mother's previous pregnancy, which ended in intrauterine fetal death, the threatened abortion in the first trimester of this patient's gestation, and the development of gestational diabetes, which may have caused an early term delivery at 38 weeks gestation. All of these events, in addition to this infant's positive cytomegalovirus serology, raise the possibility of various maternal infections and congenital fetal infections. As we previously mentioned in the etiology section, cytomegalovirus infection may also play a role in one of the pathophysiological mechanisms of disease development. Furthermore, because the severe form of the disease can result in intrauterine death or death may occur just a few weeks after delivery, there is a possibility that the fetus from the previous pregnancy had a severe multisystemic form that ended in intrauterine death. Our patient presented with an uncommon clinical picture of multi-systemic Langerhans histiocytosis, which can be termed an atypical Letterer-Siwe

disease due to the involvement of the digestive tract, skin, and possibly lymph nodes (biopsy required for confirmation). In this case, because a normal skeletal survey doesn't rule out bone involvement, bone marrow aspiration and biopsy were considered necessary.

Conclusion

In our case, Langerhans cell histiocytosis manifested as gastrointestinal disturbance and a non-specific skin rash, which can explain why it is frequently misinterpreted. Because it is challenging to make the right diagnosis without clear clinical findings and correlation between a thorough medical history, laboratory findings, and biopsy results, skin conditions such as seborrhea, acrodermatitis enteropathy, congenital candidiasis, eosinophilic pustular folliculitis, and others might have symptoms that are quite similar to LCH. The signs and symptoms of gastrointestinal damage caused by LCH and its variant LSD are broad and non-specific, and an early diagnosis is usually food allergy or gastroenteritis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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