

Perianal Langerhans Cell Histiocytosis

Journal of Clinical Case Reports,
Medical Images and Health
Sciences

Volume 4 Issue 5, 2023

Article Information

Received date: 01/05/2023

Published date: 04/07/2023

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*Key Words:

Perianal lesion, Langerhans cell histiocytosis, Diabetes insipidus, Pituitary insufficiency.

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Abstract

Background: Langerhans cell histiocytosis (LCH) is a rare disease with an unknown pathogenesis. It is thought that environmental factors, infections, immunological and genetic factors play a role in its etiology. LCH is a disorder of antigen presenting cells. It is the most common disease of the monocytic phagocytic system. In his histopathology; Inflammatory cells such as T-cells, eosinophils, macrophages as well as Langerhans cells, multinucleated giant cells attract attention. The disease has a wide clinical spectrum. The clinical course varies according to the tissues and organs involved. Sometimes spontaneous recovery may occur in the clinic, as well as the disease may be progressive and fatal.

Case report: A 28-year-old male patient from Kazakhstan applied to us with the complaints of diarrhea and perianal wound. His complaints have been ongoing since 2021. In 2018, she suddenly started to complain of being very thirsty and drinking water. Diabetes insipidus was diagnosed in the examinations, and desmopressin 120 mg tablet was used as drug treatment. His treatment was discontinued in 2019 and the patient's complaints regressed. In March 2021, perianal lesions began to form. For the perianal lesions, it was suggested that he might have Crohn's disease, but he did not receive medication. Our patient also had tooth loss, muscle and bone pain, and infertility. Since her complaint continued, she applied to us from Kazakhstan for examination and treatment. In physical examination, the patient had a decrease in hair growth, severe erosion, ulceration and discharge on the skin in the perianal region (Figure 1), redness on the scalp and a lesion that bled from place to place (dermatitis?). Crushed lesion (involvement) in the right outer ear, missing teeth in the mouth, shed, distorted dysmorphic appearance (Figure 2), 2 cm opening in the anterior part of the neck (due to involvement) (Figure 3), testicles were bilaterally atrophic. CNS was normal, CVS was normal, there was no comfortable defense rebound in the abdomen, there was no pretibial edema. A biopsy was performed from the patient's ulcerated lesion in the perianal region. In the biopsy, Langerhans cell histiocytosis was diagnosed. The patient, whose treatment was arranged, was discharged to continue his treatment in his country.

Conclusions: Perianal LCH is a rare disease. In young patients with diabetes insipidus, Langerhans cell histiocytosis should be considered in the differential diagnosis if there is perianal ulceration that does not respond to local treatments.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease with an unknown pathogenesis that begins in LCH cells. LCH cells are a type of dendritic cell that normally helps the body fight infection. Sometimes mutations (changes) develop in genes that control how dendritic cells function. These include mutations of the BRAF, MAP2K1, RAS, and ARAF genes.

Its incidence is at the level of 1-2/million people. It is thought that environmental factors, infections, immunological and genetic factors play a role in its etiology. LCH is a disorder of antigen presenting cells. It is the most common disease of the monocytic phagocytic system. In its histopathology, multinucleated giant cells are noted besides Langerhans cells as well as inflammation cells such as T-cells, eosinophils, macrophages. The disease has a wide clinical spectrum. The clinical course varies according to the tissues and organs involved. Sometimes spontaneous recovery may occur in the clinic, as well as the disease may be progressive and fatal (1).

Case Report

A 28-year-old male patient applied to us from Kazakhstan with the complaints of diarrhea and perianal wound. His complaints have been ongoing since 2021. In 2018, he suddenly started to complain of being very thirsty and drinking water. Diabetes insipidus was diagnosed in the examinations, and desmopressin 120 mg/day tablet was used as drug treatment. His treatment was discontinued in 2019. The patient's complaints regressed. In March 2021, perianal lesions began to form. For the perianal lesions, it was suggested that he might have Crohn's disease, but he did not receive medication. Our patient also had tooth loss, muscle and bone pain, and infertility. Since her complaint continued, she applied to us from Kazakhstan for examination and treatment.

In FM, the patient has a decrease in hair growth, severe erosion of the skin in the anal region, ulceration and discharge (Figure 1), redness of the scalp and a lesion that bleeds in places (dermatitis?). Crushed lesion (involvement) in the right outer ear, missing teeth in the mouth, shed, distorted dysmorphic appearance (Figure 2), 2 cm opening in the anterior part of the neck (due to involvement) (Figure 3), testicles were bilaterally atrophic. CNS was normal, CVS was normal, there was no comfortable defense rebound in the abdomen, there was no pretibial edema.

In the laboratory examinations of the patient; TB (Quantiferon TB-Gold test) was negative, CRP was high, HBV and HCV, HIV, Covid-19 test were negative. The patient had anemia, leukopenia (due to bone marrow involvement), mildly elevated prolactin level, low IGF-1, low testosterone, low ACTH level, T3, T4, FSH and LH. The findings in the

patient were evaluated as hypopituitarism. The serum sodium level ranged between 150-185. The fact that the patient did not feel thirsty compared to hypernatremia was explained by the hypothalamic bag. Urine density was 1003. Liver enzymes, pancreas and kidney function tests were normal. IL-6 level was 47 pg/ml ($n < 7$ pg/ml), and serum alpha-1, alpha-2 and light chain levels were slightly increased in protein electrophoresis. In the 24-hour urine immunofixation test, kappa light chains and lambda light chain levels were normal.

In brain MRI examination; There were hypothalamic mass, atrophy in the stalk and pituitary gland, loss of neurohypophysis signal in favor of Diabetes insipidus, hypothalamic involvement, edema in the mesencephalon, anterior commissure, optic chiasm due to vasogenic edema of the hypothalamic mass. Findings in favor of primary disease involvement in the external ear canal, infiltrative soft tissues in the masticator space, pterygopalatine space, right petrous bone, sphenoid bone pterygoid plates, right maxillary sinus extending to the root of the tooth and hard palate and evaluated in favor of primary disease involvement were detected.

Abdominal USG and chest X-ray were normal. Oncological PET/CT: Intense pathological increased FDG uptake was observed in the nodular soft tissue structuring defined in the hypothalamus. Pathologically increased FDG uptake in the right external auditory canal, pathologically increased FDG uptake in the upper part of the right maxillary bone, hard palate, right masticator space, and bilateral pterygoid bone, extending from the tongue and tongue root to the skin in the anterior neck, with air and soft tissue densities in it. Pathologically increased FDG uptake in the paratracheal region, pathological hypermetabolic lesions with air densities in a wide area that also destroys the bilateral thyroid cartilage, pathologically increased FDG uptake in the soft tissue structure extending from the jugular notch to the posterior of the manubrium sterni, in the left gluteal region, starting from the gluteus maximus muscle, the skin Heterogeneous pathological increased FDG uptake was observed in the lesion with fluid density extending below. Increased FDG uptake in the fistula tract, starting from the lower part of the rectum and extending to the perineum and the left paratesticular area, Anterior part of the diaphragm, anterior abdominal wall in the left lower quadrant, posterior abdominal wall on the right, left biceps femoris muscle, between the left obturator internus and externus muscles, and left gluteus maximus Pathologically increased FDG uptake was observed in lesions involving the muscles defined in the muscle, and diffusely increased FDG uptake in the bone marrow was observed.

In the pathological examination of the biopsy performed



Figure 1: Ulcerated, eroded and runny appearance in the perianal region



Figure 2: Involvement-related appearance in the front of the neck

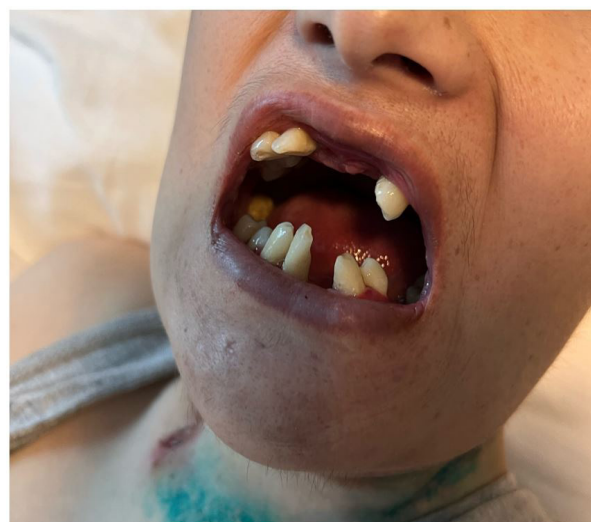


Figure 3: Floating tooth image, missing and erupted teeth

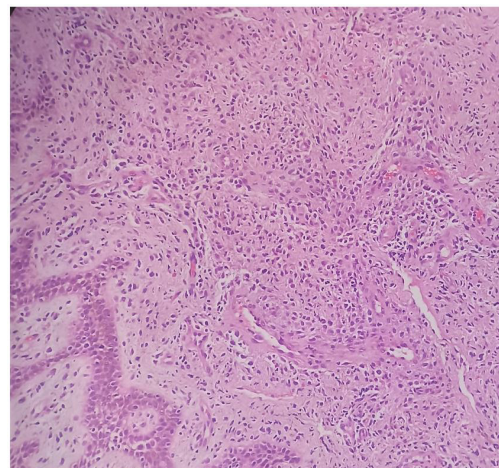


Figure 4a: H&E: Diffuse histiocytic infiltration filling the papillary and superficial reticular dermis (x200).

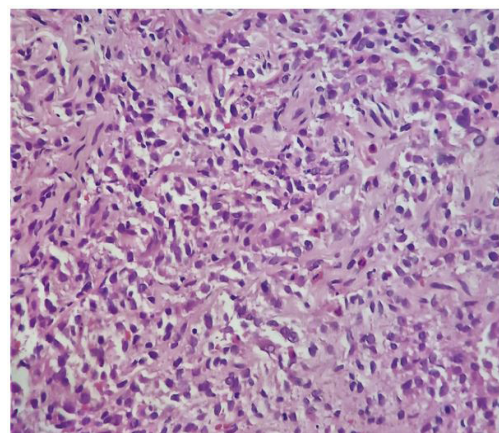


Figure 4b: H&E: Inflammatory infiltrate of Langerhans cells accompanied with abundant eosinophils (x400).

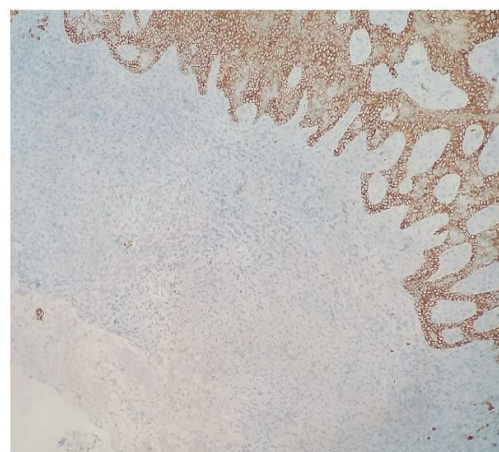


Figure 4c: CD138: Positive in rare plasma cells, negative in the infiltration (x100).

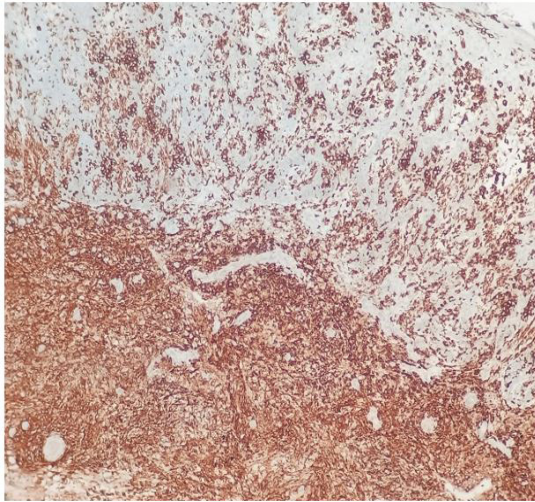


Figure 4d: CD1a: Langerhans cells are also positive for CD1a (x100)

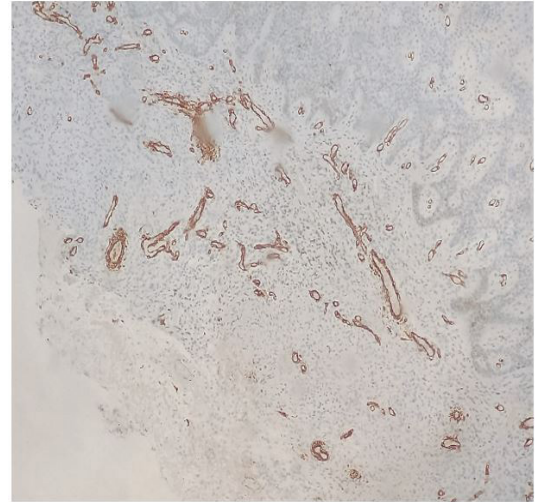


Figure 4g: SMA: Positive in vascular smooth muscle, negative in the neoplastic infiltration (x100).

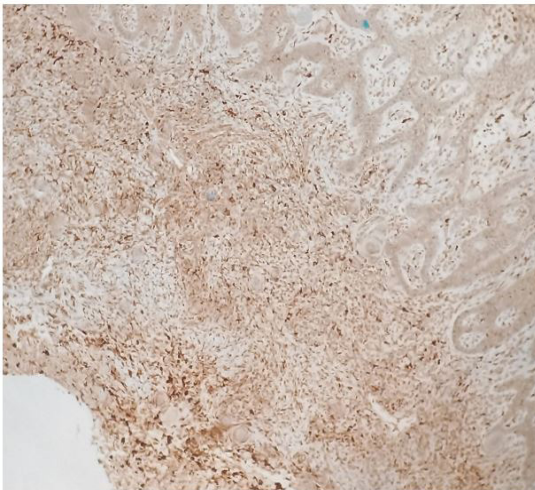


Figure 4e: CD68: Patchy positivity in the infiltration (x100).

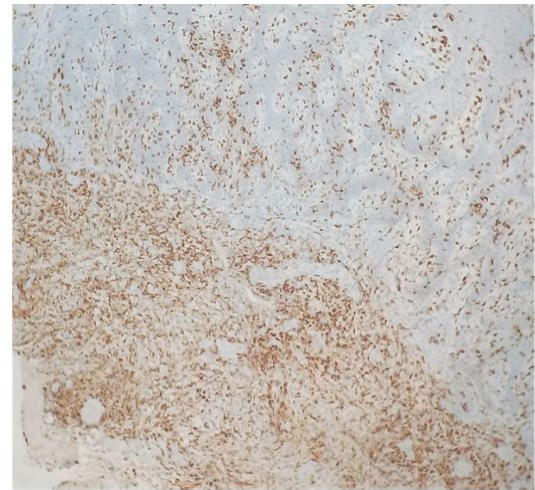


Figure 4h: Langerinx100.jpg

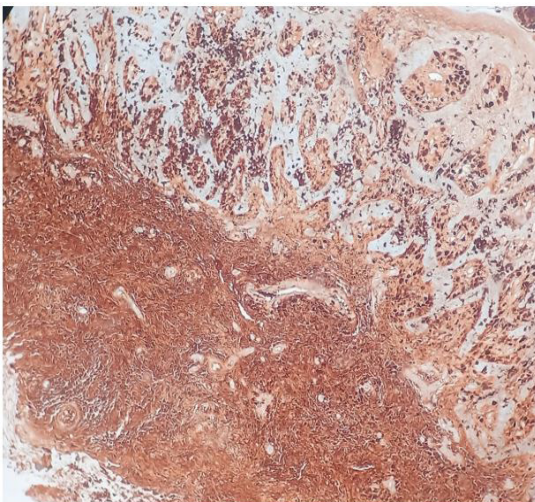


Figure 4f: S100: Diffuse positivity in the dermal infiltration (x100).

from the perianal lesion, Langerhans cell histiocytosis (CD1a positive, S100 positive, Langerin positive, CD 68 positive, CD 138 positive in a small number of Langerhans cells, negative in the lesion, SMA negative) was detected (Figure 4a, 4b, 4c, 4d, 4e, 4f, 4g).

As a treatment; desmopressin dose spray 0.1 mg intranasal, hydrocortisone 20 mg (total) tab, pantoprazole 40 mg 1x1 before breakfast, 10 mg cladribin I.V, levothyroxine 50 µgr/day, 1x1, testosterone treatment was planned. Oxacillin-sensitive *Staphylococcus aureus* was grown in the aerobic culture in the wound swab culture and ampicillin/sulbactam treatment was started. Hematology/Oncology service physician was consulted and drug treatment was planned. The patient was discharged because he would continue his treatment in his own country.

Discussion and Conclusions

Langerhans cell histiocytosis (LCH) is a rare disease with an unknown pathogenesis (1-10). It is thought that environmental factors, infections, immunological and

genetic factors play a role in its etiology. LCH is a disorder of antigen presenting cells. It is a rare disease and its frequency is 1-2/million people. It is the most common disease of the monocytic phagocytic system (8, 9, 10). In its histopathology, multinucleated giant cells are noted besides Langerhans cells as well as inflammation cells such as T-cells, eosinophils, macrophages. The disease has a wide clinical spectrum. LCH can make a single clinical presentation as well as involve multiple systems (11-25). It shows different clinical course according to the tissues and organs involved. Sometimes spontaneous recovery may occur in the clinic, the disease may also be progressive and fatal.

Adult cutaneous LCH lesions are most commonly found on the scalp, face, and external genitalia, and most commonly occur as pruritic skin lesions that closely resemble seborrheic dermatitis and usually affect the flexural and intertriginous region. Cutaneous lesions may also appear as red or purple nodules, erythematous papules, ulcerations, and abscesses. Severe acute forms may present as necrotizing plaques with pruritic and erosive lesions. Acute forms may present as painful, itchy, scaly, or erosive lesions in addition to hemorrhagic or even necrotizing plaques. LCH is typically; On biopsy, CD1a is associated with S100 protein and langerin expression.

LCH is seen in a wide spectrum from solitary lesion to multisystem involvement (1-7). Clinical findings in LCH are very variable. The clinical Figure can vary from one organ involvement to multiple organ involvement. Clinical signs and symptoms in LCH differ according to the organ involved and the degree of involvement. The disease is named as localized or systemic form according to the number of organs and systems involved. In older children, the localized form is usually seen, accompanied by bone involvement and local swelling, pain, and dysfunction. The most common sites of involvement are bone, skin, CNS, liver, spleen, ear, lung, endocrine system, gastrointestinal mucosa, and eyes, respectively (18). Other observed symptoms are anemia, thrombocytopenia, exophthalmos, and gingival lesions. While the time between diagnosis and the onset of symptoms may be 1-4 years, in some cases this period may be up to 20 years. LCH should be suspected in the presence of treatment-resistant purulent otitis media and accompanying skin lesions in the external ear canal.

CNS involvement is present in 10-20% of patients with multisystem involvement (11,12). Langerhans cell histiocytosis most commonly involves the hypothalamic/pituitary axis in the central nervous system. Involvement

can take three forms: space-occupying lesion, neurodegenerative changes, and endocrine system involvement. Space-occupying lesions usually form an edematous appearance in the cerebral cortex on MRI. In neurodegenerative involvement, there is progressive cerebellar dysfunction (such as nystagmus, dysarthria, hypotonia, spastic tetraparesis, pseudobulbar palsy, cranial nerve involvement). In this case, increased signal intensity is seen in the dentate nucleus region of the cerebellum on MRI. Later, cerebellar atrophy often develops. There may also be similar changes in the basal ganglia, pons, and midbrain. In addition, cerebral hemispheres, choroid plexus, spinal cord, optic tract and nerves may also be affected (11, 12). The lesion may be in the pituitary gland or at the level of the hypothalamus. The frequency of development of diabetes insipidus (DI) is given in a wide range (2-40%) in different series. DI can occur months or years before the diagnosis of LCH is made. DI, risk factors can be listed as the systemic form of the disease, especially the presence of craniofacial bone lesions such as frontal, orbital, middle ear and mastoid bone.

D. insipidus that occurs in the disease can sometimes be the first sign of the disease and shows histiocytic infiltration of the pituitary. In general, skin lesions and especially perianal involvement occur years after D. insipidus. Involvement of the perianal region may clinically mimic condyloma acuminata or latae, and the differential diagnosis on microscopy should be considered for lymphoma, signet ring carcinoma, and melanoma. Definitive diagnosis is confirmed by diffuse positivity for CD1a, S100 protein, and langerin (CD 207). Biopsies are usually performed because of the failure of repeated topical therapeutic interventions. Most reported cases go into remission after use of vincristine, vinblastine, prednisolone, etoposide, cyclophosphamide, doxorubicin, and methotrexate. Sometimes, aggressive treatments such as abdominoperineal rectal resection and colostomy have been reported (26-30).

In conclusion, LCH is a rare disease. In young patients with diabetes insipidus, Langerhans cell histiocytosis should be considered in the differential diagnosis if there is perianal ulceration that does not respond to local treatments.

All of the data and materials will be available upon a reasonable request to the corresponding author.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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