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Langerhans Cell Histiocytosis beyond Childhood

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Abstract

Introduction: Langerhans cell histiocytosis (LCH), is an uncommon hematological disorder affecting infants and young children, with male predominance. It is considered a rare disease, and its real incidence is unknown. With an annual incidence of approximately 2 - 5 cases per million individuals, it occurrs more frequently in children (4 - 8 per million per year) than in adults (1 - 2 per million per year). The disease hallmarks are round and have characteristic "coffee-bean" cleaved nuclei and eosinophilic cytoplasm. **Case Presentation:** We describe the case of a 19-year-old female who is known as the case of Langerhans cell histiocytosis. Presented to our department at the age of 11, when she started to develop skin rash in her chest with redness and papules, which then became an ulcer after that started in her scalp. Microscopic description of biopsy sections shows a cellular infiltrate composed predominantly of large mononuclear cells with abundant pale eosinophilic cytoplasm and irregular, grooved ("coffee-bean") nuclei. The background contains a mixed inflammatory infiltrate rich in eosinophils, along with scattered lymphocytes, plasma cells, and occasional multinucleated giant cells. **Conclusions:** The definitive diagnostic approach for Langerhans Cell Histiocytosis (LCH) is histopathological examination. Once diagnosed, the treatment plan is determined based on the severity of the disease. In adults with LCH, treatment strategies vary depending on the organs involved, the clinical stage of the disease, the patient's age, and the extent of organ dysfunction.

Keywords

Langerhans Cell Histiocytosis, Adult, Histology, Clinical Evaluation

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare hematological disorder characterized by abnormal proliferation of Langerhans cells and presents with a wide range of clinical features [1]. Although primarily affecting infants and young children, LCH can occur at any age, and its presentation varies significantly among patients [2]. The disease is considered rare, and determining its exact incidence remains challenging due to its diverse manifestations [3]. Estimates suggest an annual incidence of 2 - 5 cases per million children and 1 - 2 cases per million adults worldwide [4].

LCH can affect multiple organs, including the skin, bones, lymph nodes, and visceral organs, with clinical severity ranging from isolated, self-limiting lesions to life-threatening multisystem disease [5]. Histologically, the disorder is characterized by clonal proliferation of dendritic cells exhibiting characteristic "coffee-bean" nuclei and eosinophilic cytoplasm [6]. Diagnosis is confirmed using immunohistochemical markers such as CD1a and CD207 (langerin) [7].

Advances in the understanding of LCH pathogenesis reveal dysregulation in the MAPK pathway, especially mutations such as BRAF V600E, which have significant diagnostic and therapeutic implications [8]. Clinically, the disease most frequently affects bone, particularly in the skull and jaw, with head and neck involvement reported in up to 80% of pediatric cases [5]. Cutaneous manifestations, often appearing as erythematous or crusted papules, may be the first sign of disease, particularly in infants [9].

Oral involvement is common and may present as ulcers, bleeding gingiva, tooth mobility, or bone destruction—symptoms that often precede systemic manifestations, highlighting the importance of early dental evaluation [10]. Accurate staging of LCH requires thorough imaging, such as skeletal surveys, CT, or MRI, to determine disease extent [11]. Systemic symptoms, including polyuria, polydipsia, lymphadenopathy, and neurological changes, may occur in multisystem disease [12].

Current classification systems categorize LCH into single-system, lung LCH, and multisystem disease, with or without risk-organ involvement, including the liver, spleen, and bone marrow [13]. Management strategies vary based on the severity and extent of disease and may involve surgery, corticosteroids, chemotherapy, or targeted therapies aimed at molecular mutations [14].

2. Case Presentation

A 19-year-old female, known case of Langerhans cell histiocytosis. Presented to our department at age of 11, when she starts to develop skin rash started in her chest with redness and papules then become like ulcer after that started in her scalp. Upon examination, erythematous popular rash on the high fraction areas (the central of the chest, armpits and midline back) associated with pain, pruritus and bleeding progression to ulcerations and erosions as secondary lesions (**Figure 1**). Additionally, she developed yellow scaly crusted plaques in the external ear,

postauricular region and scalp (Figure 2). Systemic review: evidence of diabetes insipidus (polyuria and polydipsia) symptoms improved after starting desmopressin, other systems unremarkable no involvement of nails, hair and mucous membranes, no personal and family history of skin disease or atopy. A pinch biopsy specimen of the chest showed a cellular infiltrate composed predominantly of large mononuclear cells with abundant pale eosinophilic cytoplasm and irregular, grooved ("coffee-bean") nuclei. The background contains a mixed inflammatory infiltrate rich in eosinophils, along with scattered lymphocytes, plasma cells, and occasional multinucleated giant cells (Figure 3). Immunohistochemical staining demonstrated strong positivity for CD1a and CD207 (Langerin)—both definitive diagnostic markers that confirm the presence of Langerhans cells, thereby establishing the diagnosis of LCH. S100 was positive, and HMB-45 was negative. Baseline laboratory tests, including CBC, ferritin, thyroid profile, and liver and renal function, were within normal ranges. MRI Brain and Pituitary gland (Sella Turcica): The lack of T1-weighted high-signal intensity of the posterior pituitary with associated thickening of the infundibulum more than 3 mm is highly suggestive of Langerhans cell histiocytosis especially in clinical context of Diabetes Insipidus. Drug history on antihistamine for itching, topical treatment with no significant improvement, immunosuppressants (Hydrocortisone, Mometasone, Betamethasone, Tacrolimus. Keratolytic (Tretinoin). Currently, the patient responded to the management with systemic thereby (Trametinib 0.5 mg od day on day off). Residual disease and clinical wound dehiscence of the left axilla improved. Referred to radiation clinic and wound care clinic. Clinically improved by 30% - 40% by repeated dressing. Interval resolution of the skin lesions at the back and anterior chest wall.

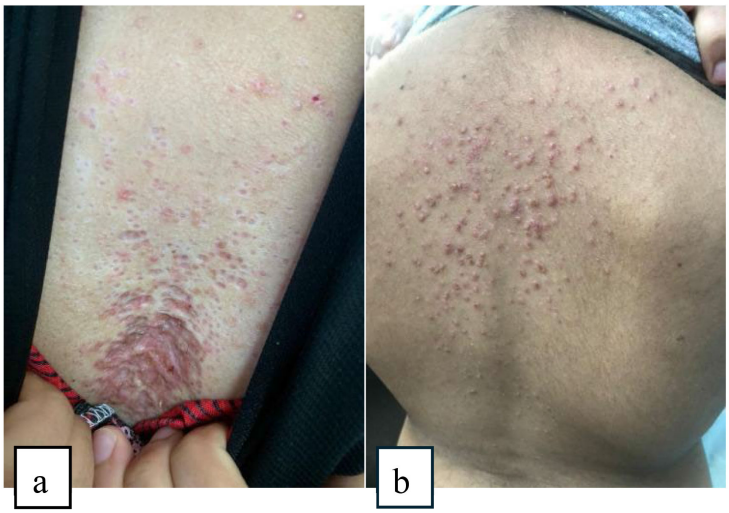

Figure 1. (a) shows hypopigmented macules and scars on the chest, and (b) shows papules on back.

Disease Course and Treatment Progression (Ages 11 - 19):

-Ages 11 - 17: The patient was managed with topical corticosteroids (hydrocor-

tisone, mometasone, betamethasone), tacrolimus, keratolytics, and antihistamines. Despite these therapies, she experienced minimal improvement, with persistent and recurrent lesions.

-Ages 17 - 18: Several systemic immunosuppressants were trialed, resulting in only partial disease control.

-Age 19 (Current Status): At her most recent evaluation, the patient was started on Trametinib 0.5 mg once daily, day-on-day-off, a MEK inhibitor increasingly used in LCH with suspected MAPK-pathway activation. She was also referred to wound-care services and radiation oncology.

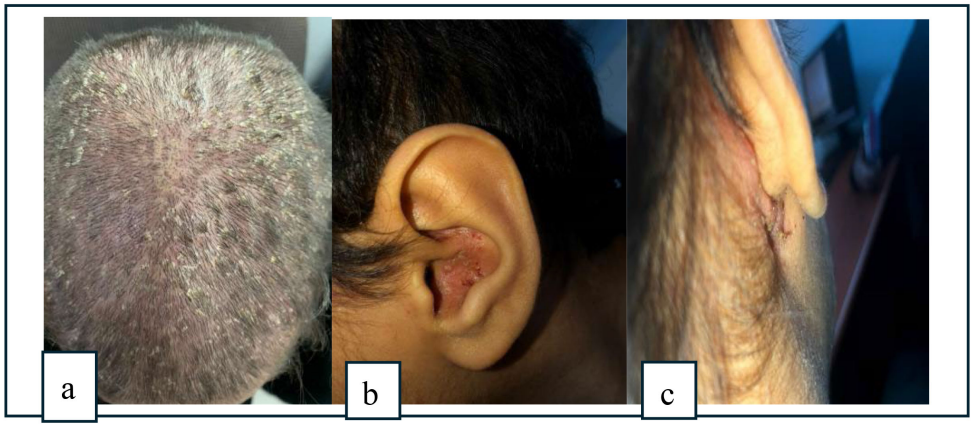

Figure 2. (a) (b) (c) show yellow scaly crusted plaques in the external ear, postauricular region and scalp.

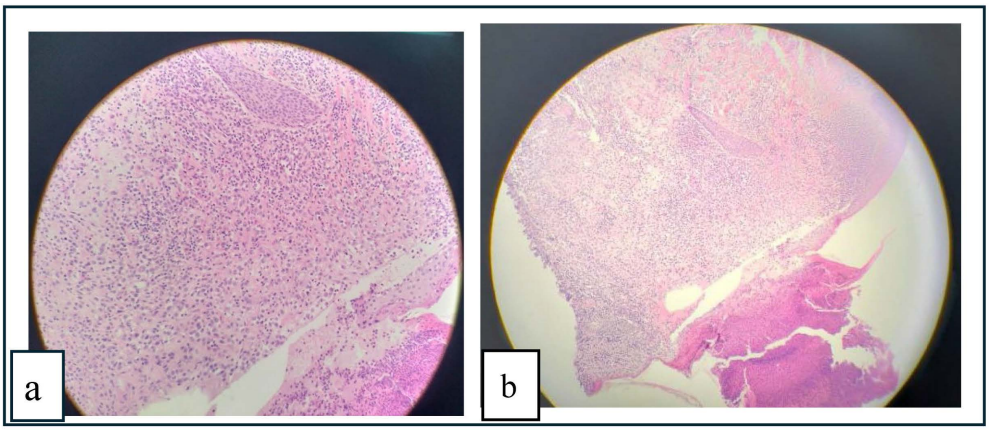

Figure 3. (a) (b) show biopsy sections a cellular infiltrate composed predominantly of large mononuclear cells with abundant pale eosinophilic cytoplasm and irregular, grooved ("coffee-bean") nuclei. The background contains a mixed inflammatory infiltrate rich in eosinophils, along with scattered lymphocytes, plasma cells, and occasional multinucleated giant cells.

3. Discussion

Previously known as histiocytosis X, with presentations ranging from the fulminant, to those that spontaneously involute without any lasting sequelae [2] [12]. Our understanding of the pathogenesis of the disease has evolved from a reactive

clonal proliferation of Langerhans cells (LCs) to an inflammatory myeloid neoplasia; this evolution from a disorder of immune dysregulation to a bona fide neoplastic disorder has reclassified the disease and opened the door for the development of targeted therapies [14]. For the treatment of adults struggling with LCH, different treatment plans are available based on the organs this disease has involved, its clinical stage, age of the patient, and dysfunction of the affected organs. Treatment options are such as watchful waiting, surgical excision and curettage, intralesional corticosteroid injection, Mechlorethamine, Hydrochloride aqueous solution, Thalidomide, irradiation, chemotherapy, immunomodulation, and transplantation (in advanced stages of the disease) [11]. Low doses of radiation may be used for less accessible lesions although the chance of malignancy secondary to this treatment is a concern in younger patients. Intralesional corticosteroid agents may be effective in some patients with localized lesions (e.g., prednisolone 20 - 30 mg/day for 2 - 4 weeks and then followed by tapering of the dose). Multisystemic disease needs systemic chemotherapy. The most common agents used in different combination regimens and several cycles are corticosteroids, vinblastine, etoposide, cytarabine, 6-mercapto purine, methotrexate, 2-chlorodeoxyadenosine, cyclosporine, thalidomide and others. A combination of vincristine and prednisone seems to reduce the risk of recurrence [10]. LCH frequently carries activating mutations in the MAPK pathway, which make the disease responsive to pathway-directed therapy. MEK inhibitors like trametinib work by blocking downstream signaling in this pathway, reducing Langerhans cell proliferation and disease activity. in this case, trametinib was selected because of the patient's persistent symptoms despite standard therapy and the presence of diabetes insipidus, indicating more extensive involvement. The patient's improvement of approximately 30% - 40% is consistent with the reported benefits of mek inhibition in refractory LCH. The patient was initially treated with antihistamine for itching, topical treatment with no significant improvement, immunosuppressants (Hydrocortisone, Mometasone, Betamethasone, Tacrolimus. Keratolytic (Tretinoin). Currently, the patient responded well to the management with systemic thereby (Trametinib 0.5 mg od day on day off). Residual disease and clinical wound dehiscence of the left axilla improved. Referred to radiation clinic and wound care clinic. Clinically improved by 30% - 40% by repeated dressing. Interval resolution of the skin lesions at the back and anterior chest wall.

4. Conclusion

This case underscores the unique challenges of managing Langerhans Cell Histiocytosis across the transition from adolescence into adulthood, particularly when the disease remains active despite years of conventional therapy. The patient's favorable response to trametinib highlights the growing role of targeted MAPK-pathway inhibition as an effective option for refractory LCH. Early recognition of persistent or multisystem involvement and timely escalation to pathway-directed therapy may improve long-term outcomes in similar cases.

Statement of Ethics

A study approval statement was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Author Contributions

Sarah Alamer: acquisition of data and writing of the paper, Turki Alkahtani: acquisition of data and writing of the paper, Lamees Elhussein: acquisition of data and writing of the paper, Salha Alhakami: acquisition of data and critically revising the work, Asker Bin Asker: acquisition of data, Abdulaziz Alhuwaish critically revising the work. All authors have given the final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participant but are available from S.A. (corresponding author) upon reasonable request.

Conflicts of Interest

All authors declare that they have no conflicts of interest relevant to this manuscript.

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