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RESEARCH ARTICLE

MULTISYSTEM MULTIFOCAL LANGERHANS CELL HISTIOCYTOSIS IN AN ADULT PRESENTING WITH CLASSICAL TRIAD: LYTIC BONE LESIONS, EXOPHTHALMOS, AND DIABETES INSIPIDUS - A RARE CASE REPORT

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ABSTRACT

Langerhans Cell Histiocytosis (LCH) is a rare clonal disorder of antigen-presenting dendritic cells expressing CD1a, S-100, and Langerin (CD207). It may involve a single organ or multiple organ systems with variable severity. Adult-onset multisystem LCH is uncommon and easily misdiagnosed. We report a 28-year-old male presenting with the classical Hand-Schuller- Christian triad of osteolytic bone lesions, exophthalmos, and central diabetes insipidus . A skeletal survey and CT imaging revealed multifocal lytic lesions of skull, pelvis, and long bones with pulmonary and abdominal organ involvement. Histopathology confirmed LCH as CD1a+, S-100+ and Langerin(CD207) +. Management included systemic corticosteroids, vinblastine- based chemotherapy, and desmopressin, with counseling on smoking cessation and follow-up. This case underscores the need to recognize adult multisystem LCH to enable timely biopsy, risk stratification, and targeted therapy.

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INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is a rare clonal proliferative disorder of Langerhans-type dendritic cells, characterized by activation of the mitogen-activated protein kinase (MAPK) pathway, most commonly due to BRAF-V600E or MAP2K1 mutations. These pathologic cells express CD1a, S-100, and Langerin (CD207) and infiltrate various tissues, forming granulomatous lesions that can cause organ dysfunction. On the basis of accumulating molecular and clinical data, LCH is now regarded as an inflammatory myeloid neoplasm in the recent WHO 2022 classification rather than a purely reactive histiocytic disorder.[1–3] The incidence of LCH in adults is approximately 1–2 per million per year, and adult disease often shows heterogeneous and multisystem involvement, making timely diagnosis challenging.[4] Clinical manifestations reflect the extent and site of disease and may range from isolated unifocal osseous lesions (eosinophilic granuloma) to disseminated multisystem disease with involvement of bone, skin, pituitary, liver, spleen, lungs, and bone marrow.[5–7] The classical Hand-Schüller-Christian triad of osteolytic skull lesions, exophthalmos, and central diabetes insipidus is well described in pediatric populations but is distinctly uncommon in adults, in whom only partial components are usually encountered.[5] Multisystem LCH with "risk organ" involvement carries a worse prognosis, but the advent of standardized chemotherapy protocols and targeted therapies directed against MAPK pathway mutations has significantly improved outcomes.[6–9] In this context, we report a 28-year-old male with multisystem multifocal LCH presenting with the complete Hand-Schüller-Christian triad, extensive skeletal involvement, pulmonary and abdominal organ disease.

Unifocal LCH: Also termed eosinophilic granuloma, this localized disease involves a single lesion (most often skull or long bones). Prognosis is excellent with curettage and/or local steroids.

Multifocal Unisystem LCH: Multiple lesions within a single organ system (classically bone) with systemic symptoms in some patients. In children, a triad of bone lesions, exophthalmos, and diabetes insipidus is described; adults may show partial or complete triads.

Multifocal Multisystem LCH: A disseminated form with involvement of two or more organ systems including bone, skin, pituitary, liver, spleen, lungs, and marrow. Prognosis depends on 'risk organ' involvement and early initiation of systemic therapy.

Pulmonary LCH: Predominantly an adult smoking-associated disease featuring cystic and nodular changes on HRCT, recurrent pneumothorax, and potential progression to fibrosis. Smoking cessation is a cornerstone of management.

CASE PRESENTATION

A 28-year-old male presented with a 3-month history of progressive polyuria, polydipsia, and dull aching bone pain involving the skull and pelvic region. He also reported intermittent headaches, easy fatiguability, and unquantified weight loss. There was no history of visual loss, seizures, prior malignancy, or chronic systemic illness. The patient was a chronic smoker but denied alcohol or illicit drug use. There was no relevant family history of endocrine or haematological disorders. On examination, the patient was hemodynamically stable. General physical examination revealed bilateral, non-pulsatile proptosis and pallor. There was bony tenderness over the frontal and parietal skull bones and over the iliac crests. Mild hepatosplenomegaly was noted on abdominal examination; there were no focal neurological deficits or cutaneous lesions. Laboratory investigations showed haemoglobin 6.5 g/dL, platelet count 66,000/µL, and LDH 349 IU/L. Serum sodium was 149 mmol/L with serum osmolality 313 mOsm/kg and urine osmolality 55 mOsm/kg, consistent with central diabetes insipidus. Renal and liver function tests were otherwise within normal limits.

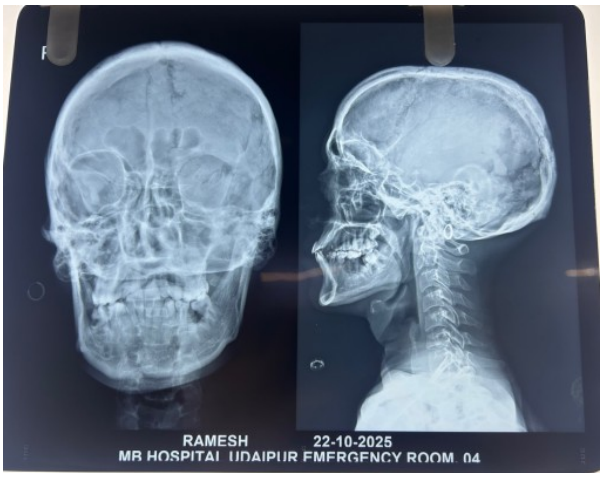

Figure 1. Skull X-ray: multiple lytic lesions in frontal and parietal bones

A skeletal survey and cross-sectional imaging revealed multiple lytic lesions in the frontal and parietal bones (Figure 1), mixed lytic-sclerotic lesions of the iliac bones (Figure 4), hepatosplenomegaly with para-aortic lymphadenopathy (Figure 2), and multiple pulmonary nodules with mediastinal lymphadenopathy (Figure 3), along with clavicular and humeral involvement on chest radiography (Figure 6). Biopsy from a skull lesion showed sheets of Langerhans cells with nuclear grooves in an eosinophil-rich background, and immunohistochemistry was positive for CD1a, S-100, and Langerin (CD207),confirming the diagnosis of multi-system Langerhans cell histiocytosis with the classical Hand-Schüller-Christian triad. Histopathology showed Langerhans cells with nuclear grooves. IHC was positive for CD1a, S-100, and Langerin (CD207), confirming LCH. Management included oral prednisolone (1 mg/kg), vinblastine (6 mg/m2 weekly x 6 weeks), desmopressin for diabetes insipidus, and supportive care.

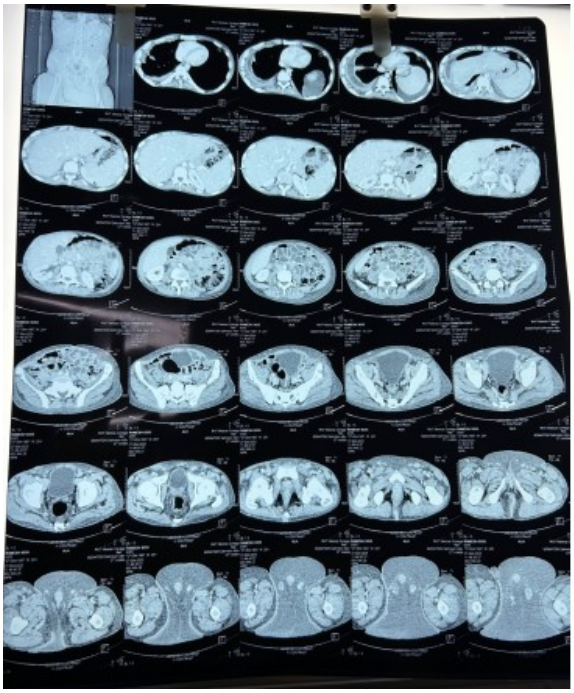

Figure 2. CT Abdomen: hepatosplenomegaly and para-aortic lymphadenopathy.

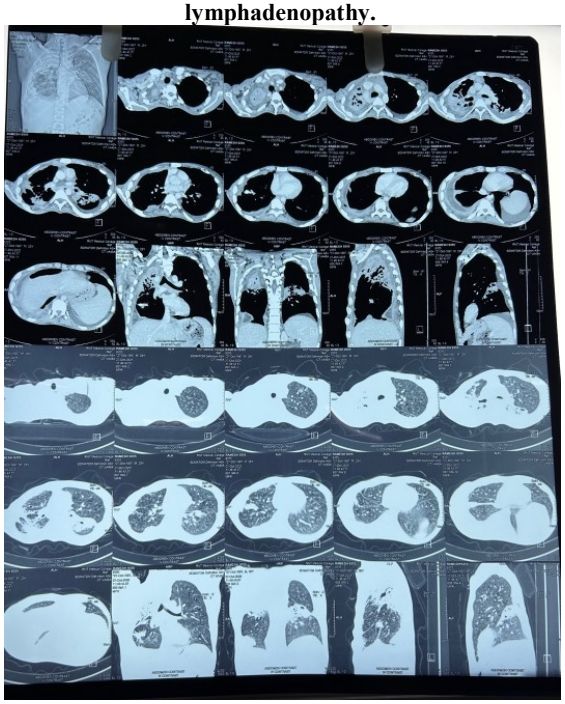

Figure 3. CT Thorax: multiple pulmonary nodules and mediastinal lymphadenopathy

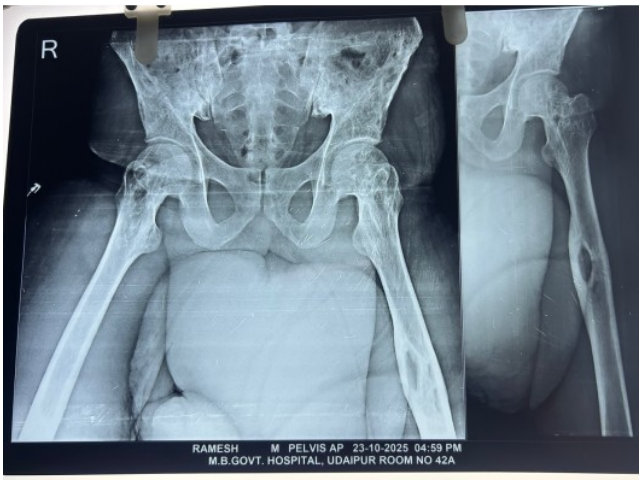

Figure 4. Pelvic radiograph: mixed lytic-sclerotic changes in iliac bones

Figure 5. Clinical photograph: Unilateral exophthalmos (Hand-Schuller-Christian triad)

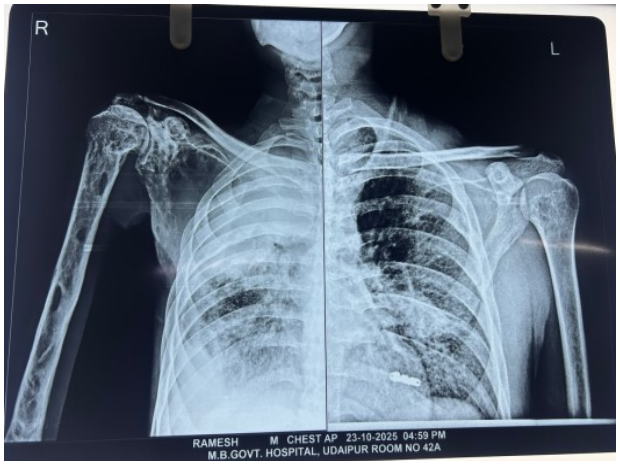

Figure 6. Chest X-ray: bilateral clavicular and humeral involvement

DISCUSSION

LCH is now classified as an inflammatory myeloid neoplasm driven predominantly by dysregulated MAPK pathway signaling, most commonly involving BRAF-V600E or MAP2K1 mutations. These mutations promote constitutive activation of ERK, leading to uncontrolled proliferation and survival of Langerhans-type dendritic cells.[4–6] In adults, multisystem involvement is less common than in children but is frequently associated with high-risk organ dysfunction, especially when liver, spleen, or bone marrow are affected. Pulmonary LCH, largely linked to smoking, may coexist with osseous or endocrine involvement. The classic Hand-Schüller-Christian triad—diabetes insipidus, lytic skull lesions, and exophthalmos—is rare in adults but strongly signifies hypothalamic–pituitary axis infiltration, as seen in this patient.[7–9] Diagnosis relies on clinicoradiological correlation, tissue biopsy, and immunohistochemistry showing CD1a, S100Langerin (CD207). PET-CT provides superior sensitivity in detecting active lesions and monitoring therapeutic response. Treatment strategies depend on disease burden: localized lesions may respond to curettage or steroids, whereas multisystem disease requires systemic chemotherapy.

Vinblastine-prednisolone remains first-line therapy; however, targeted agents (BRAF or MEK inhibitors) are increasingly used in mutation-positive or refractory cases. Endocrine sequelae such as diabetes insipidus often persist despite disease control.[10–13] . In the present case (Sharma et al., 2025), the coexistence of multifocal lytic skull lesions, orbital involvement leading to proptosis, and central diabetes insipidus underscores the typical but rare Hand-Schüller-Christian triad. These findings align with prior reports describing adult-onset multisystem LCH with craniofacial and pituitary axis involvement (Allen et al., 2018; Abla & Weitzman, 2015; Rodriguez-Galindo & Allen, 2020). Diagnosis relies on histopathology and IHC (CD1a, S-100, Langerin). Electron microscopy may show Birbeck granules. Imaging defines burden and distribution (skeletal survey, CT, or PET- CT). Localized disease may be treated with local modalities; multisystem disease requires systemic therapy (vinblastine with steroids). Refractory or mutation-positive cases can benefit from BRAF or MEK inhibition. Endocrine deficits, notably diabetes insipidus, may persist.

CONCLUSION

Adult multisystem LCH is an uncommon but clinically significant entity that requires a high index of suspicion, particularly in patients with lytic bone lesions, craniofacial involvement, or unexplained endocrine dysfunction. Early histopathological confirmation facilitates appropriate staging and risk stratification. Systemic therapy remains the cornerstone of treatment for multisystem disease, while novel targeted therapies offer promising outcomes in mutation-positive cases. Lifelong multidisciplinary follow-up is essential, as endocrine complications, including diabetes insipidus, may remain irreversible despite adequate disease control. This case highlights the importance of correlating radiological clues with endocrine abnormalities to expedite diagnosis. Similar cases in literature emphasize early biopsy and molecular testing for MAPK pathway mutations, which significantly guide prognosis and treatment decisions (Diamond et al., 2019; Emile et al., 2016).

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