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Primary Breast Langerhans Cell Histiocytosis in an Adolescent Girl: A Rare Diagnostic Case with Clinicopathologic and Immunohistochemical Insights

Hanadi A. Mohamed,[1] MBBS ; Yousef M Ali Hasen MD, FCRPATH[1,2] ; Asaid A. Zeiton,[3] MBBCH, FRCS ; Mahmoud A. Aloriby,[2*] BSc-BMS, ASCPi CTgyn

Abstract

Background: Langerhans Cell Histiocytosis (LCH) is a rare clonal myeloid neoplasm characterized by the proliferation of CD1a-positive dendritic cells driven by activation of the MAPK pathway. Breast involvement is exceptionally uncommon, particularly in adolescents, where it may mimic more prevalent benign and malignant breast lesions, posing a significant diagnostic challenge.

Case Presentation: A 16-year-old female presented with a progressively enlarging left breast mass. Radiologic assessment revealed a large heterogeneous lesion extending from the axilla into the breast, with cystic components, skin thickening, and vascular encasement, categorized as BI-RADS 4C. The patient underwent surgical excision. Histopathologic examination demonstrated sheets of large histiocytic cells with oval to grooved nuclei and abundant eosinophilic cytoplasm, accompanied by a prominent inflammatory infiltrate rich in eosinophils, lymphocytes, plasma cells, and multinucleated giant cells. Immunohistochemical analysis showed diffuse positivity for CD1a, S100, and CD68, confirming the diagnosis of LCH. Comprehensive staging revealed no evidence of multisystem involvement, consistent with single-system disease. The patient was treated with complete surgical excision without systemic therapy and remains clinically stable, 3 months postoperatively.

Conclusion: This case highlights an exceedingly rare presentation of LCH as a primary breast mass in an adolescent. It underscores the importance of considering LCH in the differential diagnosis of atypical breast lesions in young patients. Definitive diagnosis relies on histopathologic and immunophenotypic evaluation, which is critical for appropriate management and avoidance of misdiagnosis.

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1. Department of Histopathology, Saray Salam Diagnostic Center, Tripoli, Libya
2. Department of Pathology, University Medical center, Benghazi, Libya
3. Department of Breast Surgery, Medical Care Clinic, Tripoli, Libya

*Corresponding Author:

mahmoud.aloriby@limu.edu.ly

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Introduction

Langerhans cell histiocytosis (LCH) is a rare clonal myeloid neoplasm characterized by the proliferation of dendritic cells that phenotypically resemble epidermal Langerhans cells. Diagnosis relies on histomorphological evaluation supported by immunohistochemistry, with lesional cells typically expressing CD1a, CD207 (Langerin), and S100, and demonstrating Birbeck granules ultrastructurally.[1] Recent advances have redefined LCH as a MAPK pathway–driven neoplasm, with activating mutations such as BRAF V600E identified in a substantial proportion of cases.[2]

Historically referred to as histiocytosis X, LCH encompasses a broad clinical spectrum ranging from localized, self-limited disease to aggressive multisystem involvement affecting risk organs, including the liver, spleen, and hematopoietic system, which is associated with increased morbidity and mortality.[1,3,4] The disease most commonly involves bone and skin but may also affect the lung, pituitary gland, and lymph nodes.[5,6] Its clinical heterogeneity reflects both its neoplastic and inflammatory components, contributing to variable presentation and outcomes.[7] LCH predominantly affects children, with an estimated incidence of 2–9 cases per million annually.[4] However, adolescents represent a distinct subgroup, demonstrating clinicopathologic features that partially overlap with adult disease. Compared to younger children, adolescents more frequently exhibit involvement of the pituitary gland, lungs, and lymph nodes, with relatively

less frequent skin and hematopoietic system involvement. Molecularly, differences in MAPK pathway alterations have also been observed across age groups.[5]

Breast involvement in LCH is exceedingly rare and is most often reported in adults, frequently in association with multisystem disease, overlap syndromes such as Erdheim–Chester disease, or concomitant malignancies including breast carcinoma.[8–11] Isolated breast involvement is exceptionally uncommon, with very few cases reported in the literature, often presenting diagnostic uncertainty due to radiologic and clinical overlap with more common benign and malignant breast lesions.[11,12] Herein, we report a rare case of LCH presenting as a primary breast mass in a 16-year-old girl.

Case Presentation

Clinical Data: A 16-year-old female presented with a progressively enlarging mass in the left breast over a 6-month period. She denied systemic symptoms, including fever, weight loss, or endocrine abnormalities. There was no significant personal or family history of breast disease. Clinical examination revealed a palpable firm, mobile mass occupying the upper outer quadrant of the left breast without overlying skin ulceration, erythema, nipple discharge, or fixation to underlying structures. The contralateral breast was unremarkable, with no clinically significant axillary lymphadenopathy.

Radiologic Findings: Ultrasound examination is shown in Figure 1. Breast MRI further characterized the lesion as a large heterogeneous enhancing mass originating from the left axilla and extending into the breast parenchyma. It was associated with areas of non-mass enhancement and diffuse skin thickening. The lesion encased adjacent musculature without definite invasion, demonstrated diffusion restriction, and showed a washout kinetic pattern.

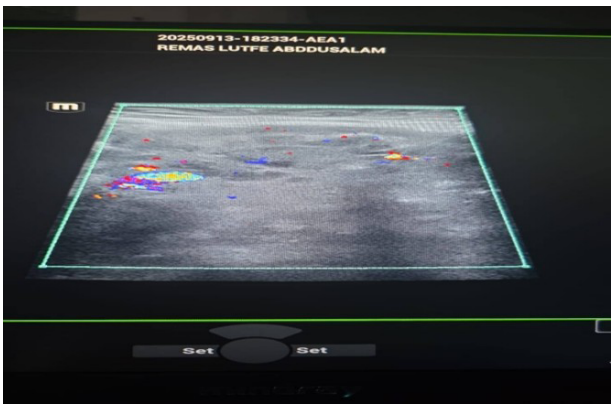

Figure 1: A heterogeneous enhancing mass is seen in the left axilla extending into the left breast, with associated non-mass enhancement and skin thickening. The lesion shows diffusion restriction and washout kinetics, raising suspicion for malignancy (BI-RADS 4C).

Pathologic Findings: An initial core needle biopsy was interpreted as fat necrosis on external review. Due to radiologic–pathologic discordance, a repeat core biopsy was performed, suggesting a benign fibroepithelial lesion, and surgical excision was advised. Intraoperative frozen section analysis suggested benign breast tissue without evidence of malignancy.

Gross examination of the excised specimens revealed multiple irregular fragments measuring collectively 6 × 6 cm, pink-tan, soft, and irregular. The separately excised axillary mass consisted of multiple fragments ranging from 1 × 0.4 cm to 5.5 × 4 × 2.3 cm, gray-white to brown, firm, and irregular. Microscopically, both breast and axillary specimens showed sheets of large histiocytic cells with oval to grooved nuclei and abundant eosinophilic cytoplasm, with minimal atypia and low mitotic activity. These were accompanied by a dense inflammatory infiltrate rich in eosinophils, lymphocytes, plasma cells, and scattered multinucleated giant cells. Focal necrosis was identified. No evidence of malignancy or sarcomatous transformation was seen. Mitotic figures were infrequent (Figure 2).

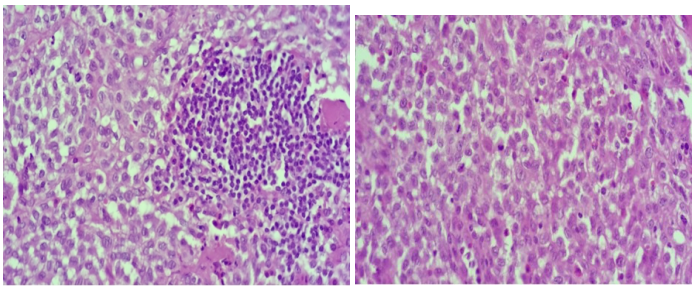

Figure 2: Histopathological examination showing sheets of large histiocytic cells with grooved (coffee-bean) nuclei and abundant eosinophilic cytoplasm accompanied by dense eosinophilic inflammatory infiltrate (H&E, x40 and x400).

Immunohistochemical studies demonstrated diffuse positivity of the lesional cells for CD1a, CD68, and S100, confirming the diagnosis of Langerhans cell histiocytosis (Figures 3–5). Although Langerin (CD207) is considered a highly specific marker for LCH, the diagnosis in this case was established based on the characteristic morphologic findings together with diffuse CD1a and S100 positivity.

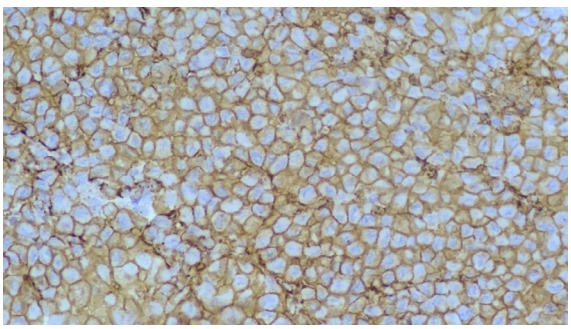

Figure 3: CD1a immunohistochemical staining demonstrating strong diffuse membranous positivity in lesional cells (×200).

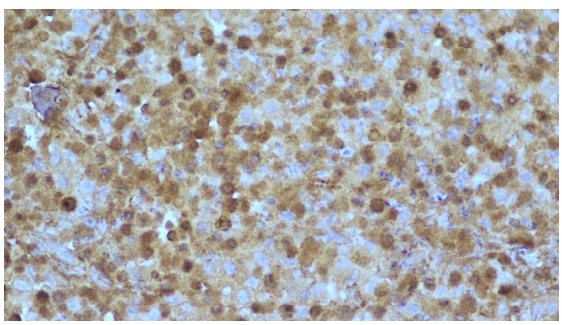

Figure 4: CD68 immunostaining highlighting histiocytic differentiation of the lesional cells (×200).

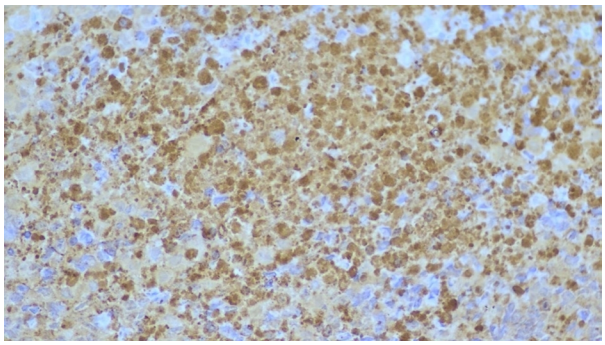

Figure 5: Diffuse nuclear and cytoplasmic positivity for S100 protein in lesional cells supporting the diagnosis of Langerhans cell histiocytosis (×200).

Testing for BRAF V600E mutation was not performed due to limited resources.

Staging Workup: Comprehensive staging, including skeletal survey, chest imaging, and laboratory investigations, revealed no evidence of disease beyond the left breast and axilla, consistent with single-system LCH. Although PET/CT was recommended radiologically, it was not performed because conventional staging investigations showed no evidence of multisystem disease.

Treatment and Follow-Up: The patient underwent complete surgical excision without initiation of systemic therapy. She has remained clinically stable with no evidence of recurrence during a follow-up period of (3 months). Follow-up surveillance includes periodic clinical assessment and imaging studies through a multidisciplinary approach involving pathology, breast surgery, radiology, and oncology teams.

Discussion

Langerhans cell histiocytosis (LCH) is a rare clonal myeloid neoplasm with an incidence of approximately 4–5 cases per million children and 1–2 per million adults annually.[6,7] It most commonly involves bone, skin, and the pituitary gland.[1] Breast involvement is exceptionally rare, particularly as a primary presentation in adolescents, making this case highly unusual within the disease spectrum. The pathogenesis of LCH has evolved from a reactive disorder to a neoplastic process driven by activating mutations in the MAPK pathway.[13,14] The most frequent alteration is the BRAF V600E mutation, identified in a significant proportion of cases, with additional mutations such as MAP2K1 described in BRAF–wild-type disease.[15,16] These molecular alterations result in constitutive ERK activation, promoting cellular proliferation, resistance to apoptosis, and impaired migration, ultimately leading to accumulation of pathological Langerhans-like cells and granuloma formation.[13]

The coexistence of clonal proliferation and a prominent inflammatory infiltrate supports the concept of LCH as an inflammatory myeloid neoplasm. The differential diagnosis of LCH in the breast includes other histiocytic disorders and epithelial malignancies. Erdheim–Chester disease is characterized by foamy histiocytes and fibrosis, lacking CD1a and Langerin expression.[7,11] Rosai–Dorfman disease demonstrates emperipolesis and is CD1a-negative but S100-positive.[7] Langerhans cell sarcoma shows marked cytologic atypia and a high proliferative index.[17] In contrast, histiocytoid breast carcinoma expresses cytokeratins and demonstrates malignant epithelial features, aiding in distinction from LCH.[18] Recognition of these morphologic and immunophenotypic differences is essential to avoid misdiagnosis. Breast involvement in LCH has been reported mainly in adults, often in association with multisystem disease or concurrent malignancies.[8–11] Reports of isolated breast LCH are exceedingly limited. Previously described cases include a 32-year-old woman with breast involvement mimicking fibroadenoma reported by Rodrigues et al., as well as an 18-year-old patient with involvement of an intramammary lymph node, both confirmed by CD1a and Langerin positivity.[12,19] These reports, together with the present case, emphasize that LCH can rarely present as a solitary breast lesion, posing a significant diagnostic challenge.

Management of LCH is determined by disease extent.[1,16] Single-system disease is typically treated with local approaches, including surgical excision, whereas multisystem disease may require systemic therapy. In cases of isolated breast involvement, surgical excision appears to be both diagnostic and therapeutic.[12,16] Emerging targeted therapies against MAPK pathway mutations may further refine treatment strategies in the future.[15] Prognosis in LCH is strongly dependent on disease distribution. Single-system disease carries an excellent prognosis, whereas multisystem involvement, particularly with risk-organ dysfunction, is associated with increased morbidity and mortality.[16] Adolescents with single-system LCH generally have favorable outcomes, with reported 5-year survival rates exceeding 90%.[5] However, disease recurrence and long-term sequelae remain important considerations.

Conclusion

Langerhans cell histiocytosis involving the breast in adolescents is exceedingly rare and may clinically and radiologically mimic malignant breast lesions. This case highlights the importance of maintaining a broad differential diagnosis for atypical breast masses in young patients. Accurate diagnosis relies on careful histopathologic evaluation supported by immunohistochemistry, allowing appropriate management and avoidance of overtreatment. Early recognition is essential to prevent misdiagnosis and guide appropriate conservative management.

Disclosure Statement

The authors declare no conflicts of interest.

Ethical Approval

This case report was conducted in accordance with institutional ethical standards and approved by the Department of Histopathology at Saray Salam Diagnostic Center, Tripoli, Libya. Written informed consent for publication of the clinical data and accompanying images was obtained from the patient's legal guardian

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