# ATYPICAL PRESENTATION IN LANGERHANS CELL HISTIOCYTOSIS: Hearing Loss, Diabetes Insipidus, & Extensive Cutaneous Lesions with Nail Distrophy

# LANGERHANS HÜCRELİ HİSTİOSİTOZDA ATİPİK PRESENTASYON: İşitme Kaybı, Diabetes İnsipitus & Tırnak Distrofisi ile Beraber Geniş Kutanöz Lezyonlar

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**ÖZET**

Langerhans hücreli histiositoz (LCH) CD-1a boyanması gösteren klonal proliferatif lenfohistiositik bir hastalıktır. Hastalık unifokal veya multifokal tek bir sitemi veya birçok sitemi tutacak şekilde geniş bir klinik seyir gösterebilir. Tutulan alana göre diabetes insipitus, işitme kaybı veya tırnak değişiklikleri oluşabilir. Burada atipik presentasyon gösteren iki vakayı litaretür derlemesi ile beraber sunduk.

**Anahtar Kelimeler:** Langerhans hücreli histiositoz, diabetes insipitus, işitme kaybı, tırnak distrofisi

**ABSTRACT**

Langerhans cell histiocytosis (LCH) is a clonal proliferative lymphohistiocytic disorder with mainly CD-1a positive staining. It has a wide spectrum of unifocal or multifocal mono or multisystemic disease. Rare symptoms like diabetes insipidus, hearing loss or nail distrophy might also occur according to the involved sites. In here, two cases of LCH with atypical presentation are reported with review of the literature.

**Keywords:** Langerhans cell histiocytosis, diabetes insipidus, hearing loss, nail distrophy

## Background

Langerhans cell histiocytosis (LCH) which was known as histiocytosis-X formerly is a rare clonal proliferative lymphohistiocytic disorder accompanying with skeletal (osteolytic bone metastasis) or extraskeletal lesions such as visseral, skin or central nervous system (CNS) involments (1-3). It occurs with an estimated incidence of 4-4,6 per million in childhood and 1-2 per million in adults (4). Aberrant immunmodulation with a predominance of large, mononuclear CD1a-positive dendritic cells infiltration has a key role in pathogenesis. S-100, CD1a & CD207 positivity on immunhistochemical (IHC) staining is a cornerstone in histopathological diagnosis (5,6).

The clinical presentation and severity depend on the involved regions (2-4,7). Billiary cirrhosis, diabetes insipidus (DI) or hearing loss in mastoid infiltration might also occur in rare involvements of liver, CNS or mastoid (8-10). The prognosis and treatment modalities (local / systemic) depend on the sites and extent of the disease. Spontaneous regressions might also occur in those with limited involvement (11).

Langerhans cell histiocytosis in two cases with atypical presentations is discussed in this report with review of the literature.

## Case 1

A 24-year old female was admitted to the hospital with disseminated skin lesions and icterus, hyperbilirubinemia with transaminase elevation besides constitutional symptoms such as weight loss, malasie and disseminated pain.

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She had non-wealing wounds on her face, neck, armpits and groins. She has had skin lesions and dystrophic nail changes for 9 years and intermittent polydipsia for a year on history. Her skin & nail lesions worsened during last year. She was referred to our center after she has progressed with vincristine and predinisone upon an unclassified lymphoproliferative disorder on pathology at another center. She had hypothyroidism with no remarkable family history. On physical examination, she had generalized bilaterally cervical, occipital & axillary lymphadenopathy (LAP) besides hepatomegaly. In addition, she had left abducens nerve palsy on ophtalmological evaluation. Upon dermatologic examination, we observed numerous erythematous-brownish papules with serous to thick hemorhagic crusts with confluence to form plaques distributed over face, scalp, flexural areas, nipples and areolas (Figure 1a, 1b, 1c); exophytic, vegetative tumours with multilobulated surface on perioral, nasolabial regions and chin (Figure 1a); moist red eroded and ulcerated areas in axillary and inguinal regions (Figure 1b, 1c) and anonychia of all finger nails (Figure 1d). Her repeated skin biopsy revealed LCH with epidermal ulceration and subepidermal atypical histiocytoid cell infiltration with giant nuclei and pale cytoplasm. These cells had *'coffe bean-like'* nuclei in papillary dermis extending into the epidermis with an admixture of inflammatory cells like eosinophils, neutrophils, lymphocytes and plasm cells in the dermis (figure 2a). Histiocyte markers (S100, CD1a) were positive on IHC staining (figure 2b, 2c). Laboratory tests were suggestive of hyperbilirubinemia (total/direct bilirubin: 7,3/6,2 mg/dL) and elevation of transaminases [aspartate aminotransferase (AST): 221IU/L, alanine aminotransferase (ALT): 423 IU/L)], alkaline phosphatase (ALP): 2873 IU/L, gamma-glutamyl transpeptidase (GGT): 3020 IU/L and lactate dehydrogenase (LDH): 4726 IU/L, respectively. She had hyponatremia (128; N=135-145 mEq/L), with high levels of prolactin (28,79; N=4,23-23, 3 ng/mL) & thyroid-stimulating hormone (7,5; N=0,27-4,2 µIU/mL). She had no bone marrow involvement. She had heterogenity and hyperechogenic thickenning around portal vein on liver ultrasonography (US) while she had a 38x32x29 mm solid lesion with cystic and necrotic components in the pons extending to the cerebellary pedincules and indentation to the fourth ventricule on magnetic resonanse imaging (MRI) (figure 3a, 3b, 3c). There were disseminated cervical, supraclavicular, axillary and intraabdominal LAPs with a greatest diameter of 40x11 mm close to the left carotid artery on toracoabdominal computerized tomography (CT). She had also disseminated milimetric cystic nodular pulmonary lesions with cystic hepatic involvement which were considered as LCH involvement after other causes were ruled out. She had central hypothyroidism without an additional thyroidal involvement. She had prominent regression in the LAPs, skin & nail lesions after one cycle of Ara-C and steroid. Hypothyroidism & DI were under control with thyroxin & vasopressine. However, radiotherapy (RT; 30 Gy) had to be applied for worsening left hemiparesis after the first cycle. She had radiation recall phenomena (RCP) though RCP is not so common with Ara-C (12). Second cycle of chemotherapy had to be delayed for 10 days after RT. Hyperbilirubinemia (total/direct bilirubin: 30,4/15 mg/dL, & transaminase elevation (AST: 218 IU/L, ALT: 518 IU/L) worsened rapidly in the following days. She was given dose-adjusted Ara-C & steroid with closer follow-up. She had clinical benefit especially in the skin lesions after two cycles, however hyperbilirubinemia persisted almost in less high levels (total/direct bilirubin: 16/8,2 mg/dL). She got worsened in the following weeks and lost-of follow-up after five weeks of best supportive care.

## Case 2

A 37- year old male referred to our center with hearing loss. On physical examination, he had a 5x5mm polypoid lesion on external ear canal and a mobile 6,5x5 cm mass on his right scapula. He had a mass on his right mastoid on the posterior wall of the external ear canal involving petrous component and semicircular canals, extending to the sigmoid sinus with loss of right mastoid aeration on magnetic resonanse imaging (figure 4a, 4b, 4c). He had also multiple axillary lymphadenopathies (LAP) and pelvic lytic lesions. There was a 6x4,5x4 cm mass expanding to the surrounding muscle with cortical destruction on the glenoid and spinous components of his right scapula on magnetic

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resonanse imaging (figure 5a, 5b, 5c). The biopsy of the scapular mass revealed LCH with positive CD1a staining (figure 6a, 6b). He had partial response with 2 cycles of vinblastine and steroid & still goes on chemotherapy .

## Discussion

Langerhans cell histiocytosis is a rare disorder which might have atypical presentations & outcomes according to the involved sites (1-3). Histopathological evaluation needs IHC stains for histiocyte markers, like CD1a and S-100 (5,6). Both of our patients had positive staining on histopathology with atypical presentations.

The patients are classified as high or low risk according to visseral or nonvisseral involvement (13). Disseminated disease, organ dysfunction and younger age at presentation are generally poor prognostic factors while liver dysfunction was defined as the worst prognostic factor (13,14). Our first patient did well with slowly disseminating skin involvement for years and mild hypothyroidism with polydipsia due to CNS involvement for a year. However, she had worsened with liver involvement. Liver metastasis is a poor prognostic factor in LCH as mentioned above. It might mimic primary sclerosing cholangitis or nonsupurative destructive cholangitis with cyctic lesions as in our first patient. She had transaminase elevation and hyperbilirubinemia with heterogenity & cyctic lesions on liver imaging. However, she had mild regression in the liver despite prominent regression in the skin lesions after chemotherapy.

Thyroid involvement might also occur in LCH. Though skin lesions in LCH are common, scalp involvement without skull metastasis and dystrophic nail changes are remarkable. The first patient had smoldering skin lesions, but her scalp lesions with nail distrophy seem to differ from other common skin involvements in the literature. Hypothyroidism and DI associated with CNS involvement were under control with thyroxin & vasopressine besides chemotherapy, but RT had to be given since she had additional left hemiparesis related to the involvement of the pons.

Otologic involvement rate was 15%-61% whereas mastoid was reported as an involvement site in 4% of head and neck LCH patients (9,15). He had also scapular metastasis besides pelvic lesions. He had lateralization for mastoidal, scapular & pelvic bone lesions (i.e. all of the lesions were on the right). Bone metastasis is not rare in LCH but scapula is an uncommon site for metastasis, especially in those without disseminated bone involvement. We consider that lateralization of the involved sites, almost atypical sites for LCH seem to remarkable.

## Conclusion

LCH has a widespread involvement and presentation according to the involved sites. Atypical bone metastasis and CNS involvement might accompany with other LCH involvements. Skin involvement is common, however nail distrophy is rare. Prognosis is poor in visseral involvement, especially in liver metastasis. So, the patients with atypical presentations and/or visseral metastasis like liver involvement should be followed-up more carefully.

**Conflict of interest:** None

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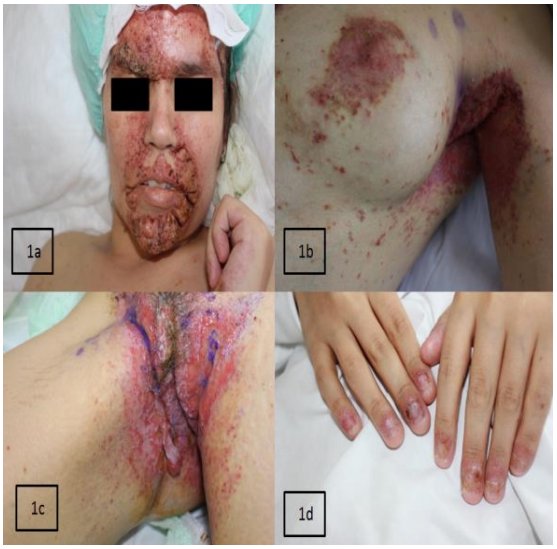
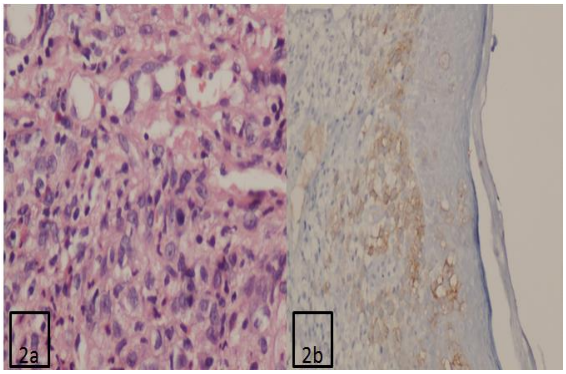



**Figure 1a:** Multiple erythematous-brownish papules with crusts merging to form plaques on forehead, nasolabial folds and multilobulated vegetating tumours on perioral region, left nasolabial sulcus and chin

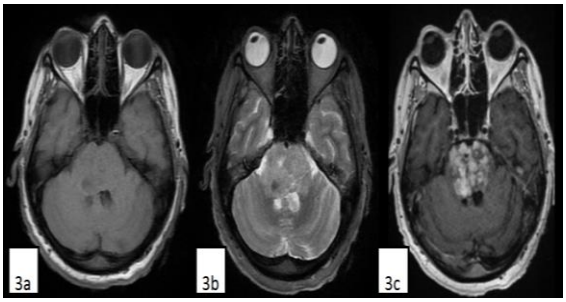
**Figure 1b:** Erythematous-brownish papules scattered over trunk and coalesced to form plaques on left nipple, areola and axillary region, eosion on left axillary fold

**Figure 1c:** Moist, red, eroded areas on vulva and inguinal folds and a whitish, erythematous, pedunculated, fleshy mass on right inguinal fold

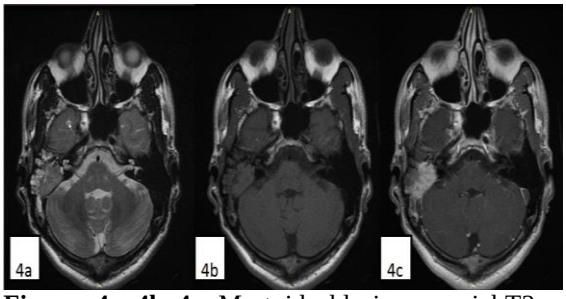
**Figure 1d:** Anonychia of all finger nails with centrally atrophic erythematous plaques with brownish to hemorhagic crusts on distal parts of fingers.



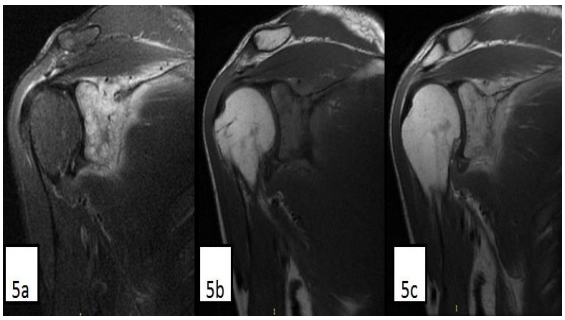

**Figures 2a, 2b:** Superficial dermal infiltration of atypical, eosinophilic large cells with pale cytoplasm, indented nuclei and large nucleus; atypical cell infiltration with positive CD1a (HE,x40 and IHC, x 200)



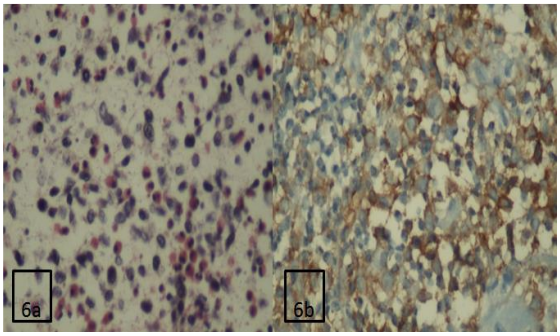

**Figures 3a, 3b, 3c:** Pons involvement on axial non-contrast T1- weighted, T2-weighted & contrasted T1-weighted magnetic resonanse imaging, respectively




**Figures 4a, 4b, 4c:** Mastoideal lesion on axial T2-weighted, non-contrast T1-weighted & contrast T1-weighted magnetic resonanse imaging, respectively




**Figures 5a, 5b, 5c:** Scapular involvement on coronal fat-saturated T2-weighted, non-contrast T1-weighted & contrast T1-weighted magnetic resonanse imaging, respectively




**Figures 6a, 6b:** Atypical cell infiltration with eosinophils on hematoxilin-eosin & CD1a staining (HE, x40 and IHC, x40)

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