Langerhans cell histiocytosis with histopathological features, single center experience

Histopatolojik özellikleriyle langerhans hücreli histiyositoz, tek merkez deneyimi

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Aim:
Langerhans cell histiocytosis (LCH) is a rare histiocytic disease, occurring in 2-10 children per million and 1-2 adults per million, and may have a wide variety of clinical manifestations. Infiltration can develop in almost any organ (the most commonly reported organs are bone, skin, lymph nodes, lungs, thymus, liver, spleen, bone marrow and central nervous system). We aimed to evaluate the histopathological features of the lesions and review the literature in pediatric patients referred to our department for pathological examination and diagnosed as LCH.

Materials and Methods:
Retrospectively, childhood cases diagnosed with LCH in 2012-2019 were screened by hospital automation system. Age, gender, lesion localizations of the cases were recorded and histopathological features were reviewed.

Results:
5 male and 5 female total of 10 cases were detected. The youngest 3 were under the age of 1, the oldest was 16 years old. Localization; 6 of the cases were bone (2 femur, 3 skull bone, 1 scapula), 2 skin, 1 bone and lymph node, 1 lung and lymph node. Histopathology revealed histiocytic cells with grooved nuclei, eosinophilic cytoplasm with eosinophils, and neutrophils in some cases. Immunohistochemical CD1a staining was positive in all cases and positivities were present with S100 in applied 9 cases, CD68 in 4. Ki67 proliferation index was studied in 2 patients with bone localization, 15% and 20%.

Conclusion:
The term LCH is due to the morphological and immunophenotypic similarity of the infiltrating cells of this disease to Langerhans cells specialized as dendritic cells in the skin and mucous membranes. But these cells do not originate from the Langerhans cells of the skin, but from the myeloid progenitor cells of the bone marrow. Several studies have shown the BRAF-V600E mutation in LCH. The term LCH is currently recommended; histiocytosis-X, Letterer-Siwe disease, Hand-Schüller-Christian disease and diffuse reticuloendotheliosis were abandoned. The term eosinophilic granuloma may be used in the presence of a single lesion, especially in lytic bone lesions. As in our cases, it usually occurs with single or multiple osteolytic bone lesions and to a lesser extent with other organ involvement. It is characterized by infiltration of grooved nuclei histiocytes, accompanied by lymphocytes, neutrophils, macrophages and eosinophils, and areas of fibrosis and necrosis may develop. Immunohistochemical S100, CD1a, Langerin are positive, CD68 is variable. In the differential diagnosis, acute myelomonocytic leukemia, lymphoma, mastocytosis, osteomyelitis, sinus histiocytosis with massive lymphadenopathy should be considered.

Keywords: *Langerhans cell histiocytosis, Childhood, Histopathology*

Özet

Amaç: LHH (Langerhans hücreli histiyositoz) nadir histiyositik bir hastalıktır, her yıl milyonda 2-10 çocukta ve milyonda 1-2 erişkinde karşılaşılır, oldukça çeşitli klinik tablolarla hemen her organda infiltrasyon gelişebilir (en sık bildirilen organlar; kemik, deri, lenf nodları, akciğerler, timus, karaciğer, dalak, kemik iliği ve santral sinir sistemidir). Bölümümüze patolojik inceleme için gönderilen ve LHH tanısı alan pediatrik olgularda lezyonların histopatolojik özelliklerini değerlendirmeyi ve literatür bilgilerini gözden geçirmeyi amaçladık.

Gereç ve Yöntem:
Retrospektif olarak, 2012-2019 yıllarında LHH tanısı alan çocukluk çağındaki olgular hastane otomasyon sistemiyle taranarak tespit edildi. Olguların yaş, cinsiyet, lezyon lokalizasyonları, histopatolojik özellikleri gözden geçirildi.

Bulgular:
5'i erkek, 5'i kız 10 olgu tespit edildi. En küçük 3'ü 1 yaşından küçüktü, en büyüğü 16 yaşındaydı. Lokalizasyon; olguların 6'sında kemik (2'sinde femur, 3'ünde kafa kemiği, 1'inde skapula), 2'sinde deri, 1'inde kemik ve lenf nodu, 1'inde akciğer ve lenf noduydu. Histopatolojilerinde tümünde çentikli nükleuslu, eozinofilik sitoplazmalı histiyositik hücreler ve eozinofiller, bazı olgularda nötrofiller mevcuttu. Tüm olgularda immünohistokimyasal CD1a pozitifti ve S100 uygulanan 9 olguda, CD68 uygulanan 4 olguda pozitiflik mevcuttu. Ki67 proliferasyon indeksi kemik yerleşimli 2 olguda çalışılmıştı, %15 ve %20 oranlarındaydı.

Sonuç:
LHH terimi bu hastalıktaki infiltrasyonu oluşturan hücrelerin deri ve mukozalarda dendritik hücreler olarak özelleşmiş Langerhans hücrelerine morfolojik ve immünfenotipik olarak benzemeleri nedeniyledir. Fakat bu hücreler derinin Langerhans hücrelerinden değil kemik iliğinin myeloid progenitör hücrelerinden köken alır. Çeşitli çalışmalarda LHH'da BRAF-V600E mutasyonu gösterilmiştir. Günümüzde LHH terimi önerilmektedir; geçmişte kullanılan histiyositozis-X, Letterer-Siwe hastalığı, Hand-Schüller-Christian hastalığı ve diffüz retiküloendoteliozis terkedilmiştir. Tek lezyon varlığında, özellikle litik kemik lezyonunda eozinofilik granülom terimi kullanılabilmektedir. Olgularımızdaki gibi, çoğunlukla tek veya multipl osteolitik kemik lezyonlarıyla, daha az oranda diğer organ tutulumlarıyla ortaya çıkar. Çentikli nükleuslu histiyositlerin infiltrasyonuyla karakterlidir, lenfositler, nötrofiller, makrofajlar ve eozinofiller eşlik eder, fibrozis, nekroz gelişebilir. İmmünohistokimyasal S100, CD1a, Langerin pozitiftir, CD68 değişkendir. Ayırıcı tanıda lokalizasyona göre akut myelomonositik lösemi, lenfoma, mastositoz, osteomyelit, masif lenfadenopatili sinüs histiyositoz düşünülmelidir.

Anahtar Kelimeler: *Langerhans hücreli histiyositoz, Çocukluk çağı, Histopatoloji*

Introduction
Langerhans cell histiocytosis (LCH) is a rare histiocytic disease that can affect many organ systems. Lesions may vary from solitary bone involvement to aggressive disease with multisystem involvement (1). Although the etiology is not clear, it is thought to be a neoplastic process as a result of some studies showing the presence of monoclonality in histiocytes (1,2).

Materials and Methods

Retrospectively, childhood cases diagnosed with LCH in 2012-2019 were detected by hospital automation system. Age, sex, lesion localization and histopathological features of the cases were reviewed.

Results

5 cases were male and 5 cases were female. The youngest was 4 months, the oldest was 16 years old. Localization; 6 of the cases were bone (femur in 2, skull bone in 3, scapula in 1), skin in 2, bone and lymph node in 1, lung and lymph node in 1. Histopathology revealed histiocytic cells and eosinophils with grooved, folded or lobed nuclei, eosinophilic cytoplasm in all, and neutrophils in some cases. Mitotic figures without atypical forms, necrosis foci and eosinophil abscesses were observed. Immunohistochemical CD1a was positive in all cases and there were S100 positivity in applied 9 cases and CD68 positivity in applied 4 cases. Ki67 proliferation index was studied in 2 patients with bone localization, and it was in the ratio of 15% and 20% (Figure 1, figure 2 and table).

Discussion

In 1953 Lichtenstein described three conditions associated with the proliferation of histiocytes: eosinophilic granuloma of the bone, Hand-Schüller-Christian disease and Letterer-Siwe disease. Letterer-Siwe disease was recommended acute diffuse form with skeletal, skin and visceral involvement, Hand-Schüller-Christian disease was chronic diffuse form including skeletal involvement, exophthalmus and diapedes insipitus triad, and eosinophilic granuloma was usually as unifocal and limited form with skeletal involvement (3). Today, the term LCH is preferred, histiocytosis-X, Letterer-Siwe disease, Hand-Schüller-Christian disease and disseminated reticuloendotheliosis remained as historical terms, the term eosinophilic granuloma is sometimes used in solitary bone involvement (2). LCH is under the heading of tumors originating from langerhans cells in the histiocytic and dendritic cell neoplasms group in 2017 WHO classification of tumors of hematopoietic and lymphoid tissue (4).

LCH is the neoplastic clonal proliferation of langerhans cell type cells (4). Due to the monoclonality of histiocytic cells, this disease is thought to be neoplastic (3). Pathological langerhans cells carrying BRAF V600E mutation have been identified in CD34 + stem cells and more mature myeloid dendritic cells in LCH patients, thus showing a clonal myeloid neoplasia (5). Recurrent BRAF V600E mutation has been identified in patients with multisystem involvement (1). IL1 cycle model is recommended in pathogenesis. IL17 levels in the lesion and blood, and tyrosine phosphatase SH1 levels in the lesion are high especially in patients with multiple organ involvement (4). Loss of heterozygosity for some tumor suppressor genes has been reported in bone lesions and in some lung lesions (6). Pulmonary LCH is more common in adults and almost always associated with smoking (6,7), pulmoner involvement occurs in 25% of all pediatric cases usually as part of multisystem involvement. Isolated pulmonary LCH is seen 1% of pediatric cases (7).

LCH can be seen in all age groups, most common in children aged 1-3 years (8). Male predominance is reported (M/F approximately 3.7/1) (4), but no male dominance in all series (8). M/F ratio is 1 in adults (6). Five of our cases were male and 5 were female (M/F:1), 3 were younger than 1 year of age (3/10), 4 older than 3 years of age (4/10), and 3 were 1-3 years of age (3/10).

The disease is usually localized in a single region. It may be multiple foci within a single system (such as bone) or may develop more common and multisystem involvement. In general, bone and adjacent soft tissue are predominantly affected (skull, femur, vertebra, pelvic bones, ribs), and lymph node, skin and lung involvement are less common. Multifocal lesions are mostly in

bone and adjacent soft tissue. In multisystem involvement, skin, bone, liver, spleen and bone marrow are affected. Gonads and kidneys are preserved (4). Skull, especially the calvaria and temporal bone are the most predominant regions in the bone involvement, while the other bones are vertebra, jaws, ribs, pelvic bone and proximal long bones (6). In our cases, the predominant localization was bone (7/10) in accordance with the literature, and one of them had associated lymph node involvement. Bone involvement was located in femur in 3 cases, frontal bone in 2 cases, calvarium in 1 case and scapula in 1 case.

Acute disseminated multisystem involvement is most commonly seen in children younger than three years, while a milder form with a single organ is more common in older children and adults (2). A rare adult case with multisystem involvement has been reported (9). Our case with bone and lymph node involvement was 10 months old and the patient with lung and lymph node involvement was 5 years old.

LCH microscopy shows diagnostic Langerhans cell type cells (3,4). These cells have an oval nucleus, similar to coffee beans due to their longitudinal grooves (3). Nucleus can be folded, cleaved, lobulated, chromatin is thin, nucleol is not prominent, nuclear membrane is thin (4). Cytoplasm is slightly eosinophilic, moderately abundant, may contain infrequent vacuoles and very little phagocytic material, without dendritic processes unlike dermal langerhans cells (2). Nuclear atypia is minimal, mitosis is variable (1,3,4), it may be significant, but there is no atypical mitosis (4). These cells contain ultrastructural Birbeck granules (1,4). Birbeck granules are intracytoplasmic rod-shaped organelles with central striation. Occasionally there is terminal vesicular dilatation that gives the Birbeck granule the appearance of a "tennis racket" (2).

LCH lesions have a polymorphic ground with eosinophils, polymorphic leukocytes, histiocytes, lymphocytes and multinucleated giant cells, and a lesser proportion of plasmocytes (1). Benign giant cells are almost always found (3). Eosinophils can sometimes be prominent and produce abscess foci (1,4,6). Necrosis foci are common. Histiocytes generally form loose aggregates, do not form sheets (3). Langerhans cells may be predominant with eosinophils and neutrophils in the early period, Langerhans cells decrease in the late period, foamy macrophages and fibrosis increase (4). Some authors have described four phases of the disease: proliferative, granulomatous, xanthomatous and scar phases (1). In our cases, langerhans cells with pale eosinophilic cytoplasm cleaved, folded nuclei with small nucleoli and eosinophils, neutrophils, histiocytes were observed. The foci of necrosis were observed and the areas where mitosis was high were observed. It was observed that eosinophils became prominent and formed abscesses. Multinucleated giant cells were found also.

Immunohistochemically, langerhans cells express CD1a, Langerin (CD207) and vimentin (1,4). CD1a stains the cell surface with a perinuclear dot (4). S100 protein shows nuclear and cytoplasmic positivity (4,6). CD68 positivity is variable (1). CD45 and lysozyme expression is low. B cell and T cell markers (except CD4), CD30 and follicular dendritic cell markers were negative. Ki67 proliferation index is variable (4). In immunohistochemical profile of our cases, CD1a was positive in all cases (10/10), S100 was positive in applied 9 cases (9/9), CD68 was positive in applied 4 cases (4/4), Ki67 index was studied in 2 cases and it was 15% and 20%.

It is said that pathological findings may vary according to the involved region (2). Mass lesion is seen in bone, skin, cerebrum, hypothalamus and pituitary involvement, while demyelination of the cerebellum may cause destruction (2). Intrahepatic biliary involvement is prominent in liver and progressive sclerosing cholangitis develops. In the lymph nodes, sinusoids are primarily affected, and paracortex in the second plane. Nodular red pulp involvement is seen in the spleen (4).

In differential diagnosis; other histiocytic and dendritic cell diseases, metastatic solid and hematopoietic neoplasms, hemophagocytic lymphohistiocytic and macrophage activation syndromes should be considered. Since LCH can affect many organ systems, differential

diagnosis in the bone, lymph node, thymus, liver, spleen involvement with lymphomas, solid tumors, central nervous system tumors may be necessary (2).

In Rosai-Dorfman Disease, usually increased histiocytes with broad cytoplasm, and some are multinuclear are found, emperipolesis is prominent. Histiocytes are S100, CD68 positive, CD1a and langerin negative (10).

Erdheim-Chester disease is a multisystem histiocyte disease, usually seen in adults (2,11). Lipid-containing foamy cytoplasm histiocytes, lymphoid cells, and occasionally fibrosis are seen. Histiocytes are CD68 positive, CD1a, S100 and Langerin negative (1). Cases with mixed LCH and Erdheim-Chester disease (mixed histiocytosis) have been reported (2).

In osteomyelitis, granulation tissue appearance and capillary proliferation are typical (1,3), S100 and CD1a help in difficult cases (3).

Lymphomas can enter the differential diagnosis (3), showing T and B markers helps (1). No grouping and loose arrangement of histiocytic cells (3). Neoplastic cells are CD15 and CD30 positive in Hodgkin's lymphoma (1).

Juvenile xanthogranuloma is an early childhood disease caused by benign proliferation of dermal histiocytic cells in the non-langerhans cell histiocytosis group. It appears as a papule or nodule on the skin. Histology contains foamy or Tuton type giant cells (2).

Mastocytosis includes cells with granulated cytoplasm and with coarse chromatin nucleus. CD68 and CD117 are positive (1).

Multiple myeloma may enter the differential diagnosis as osteolytic bone lesions. It is distinguished by histological, immunophenotypic findings and the presence of monoclonal protein in the serum (2).

In hemophagocytic lymphohistiocytosis and macrophage activation syndrome, infiltration of non-neoplastic histiocytes occurs. Significant hemophagocytic activity is seen in the bone marrow (2). In common LCH, the bone marrow may be filled with CD68-positive macrophages, langerhans cells may not be seen, but hemophagocytosis and macrophage activation are not seen (6).

Conclusion

LCH is a histiocytic disease that can be seen at any age with single or multisystem involvement. This rare disease was reviewed with our cases in terms of histological features and entities that can be included in the differential diagnosis.

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Figure Legends:

Figure 1: Langerhans cell histiocytosis. **A.** Langerhans cells with folded, grooved nuclei, eosinophils and lymphocytes in the ground (200x, H/E) **B.** A mitotic figure at the center of the field (400x, H/E) **C.** CD1a staining with cell surface and perinuclear dot (200x) **D.** S100 staining with nuclear and cytoplasmic (400x).

Figure 2: Another case of langerhans cell histiocytosis. **A.** Langerhans cells, eosinophils and necrotic area at the bottom right corner (100x, H/E) **B.** CD1a staining (200x) **C.** CD68 staining (200x).

Table: Age, gender, localization and immunohistochemistry results of the cases

No	Age	Gender	Localization	Immunohistochemistry
1	3	Male	Femoral diaphysis	CD1a(+), CD68(+)
2	1	Female	Frontal bone	CD1a(+), S100(+), Ki67 %20
3	16	Female	Frontal bone	CD1a(+), S100(+)
4	0 (10 months)	Male	Femur and lymph node	CD1a(+), S100(+)
5	0 (4 months)	Female	Lomber skin	CD1a(+), S100(+), CD68(+)
6	0 (9 months)	Female	Ankle skin	CD1a(+), S100(+), CD68(+)
7	5	Male	Lung and lymph node	CD1a(+), S100(+)
8	1	Male	Scapula	CD1a(+), S100(+), Ki67 %15
9	7	Male	Femur	CD1a(+), S100(+)
10	10	Female	Calvarium	CD1a(+), S100(+), CD68(+)

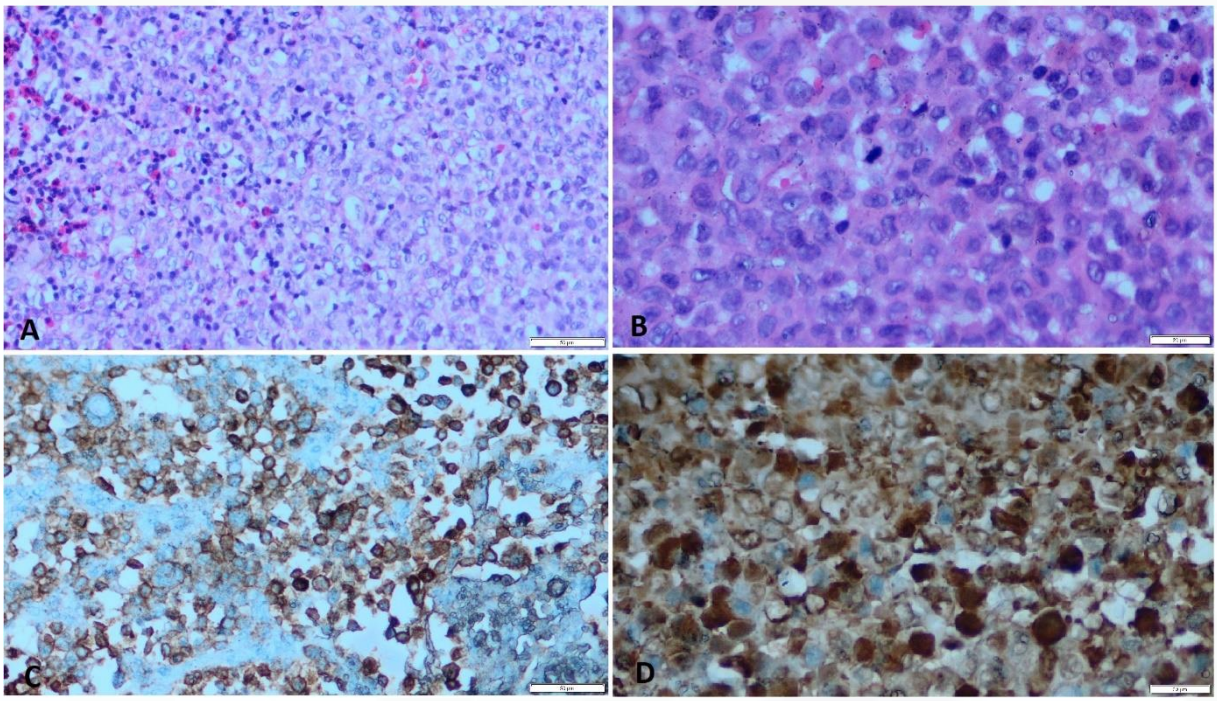

Figure 1

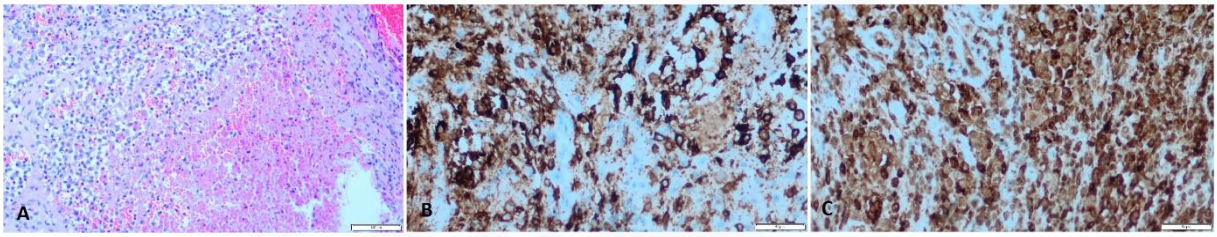

Figure 2