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Original Contribution

Oral manifestations of Langerhans cell histiocytosis with unusual histomorphologic features

Badr AbdullGaffar[a,*], Farzad Awadhi[b]

[a] Pathology Section, Rashid Hospital, Dubai, United Arab Emirates
[b] Oral and Dental Surgery Unit, Rashid Hospital, Dubai, United Arab Emirates

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a bone marrow-derived immature myeloid dendritic cell proliferative disorder with diverse clinical manifestations commonly involves bone, skin, lymph node and lung. Oral involvement is uncommon. Intraoral lesions can be the first sign of either a localized LCH or clinically undiagnosed systemic LCH, predates systemic manifestations of LCH, or an early indicator of recurrence in known cases. Clinically, it can be mistaken for primary oral and dental inflammatory, infectious and neoplastic lesions. Histologically, diagnostic challenges may arise because of the nature of oral and dental specimens, different tissue reaction patterns and variations in histomorphology of LCH. We performed a retrospective review study over 10 years. We searched for diagnosed cases of LCH. We retrieved and reviewed cases of LCH with oral involvement. We found 54 cases of LCH, four (7.4%) with oral involvement. The age range was between 1 and 27 years with an average age of 13.7 years. They were males. They were clinically confused with abscess, cysts, infection, granulation tissue and other neoplastic lesions. Histologically, they showed different histopathologic features including different patterns of necrosis, granulomas, allergic-like inflammation, superimposed infection, stomatitis, cyst and sinus formation, foreign body giant cell reaction, and foci mimicking lymphomas and metastasis. Certain cytologic features were helpful hints. In doubtful cases, immunohistochemistry helped confirm the diagnosis. Because of the multiple fragmented nature of oral specimens with different tissue reaction patterns, the diagnostic Langerhans cells may be missed or misinterpreted. Oral LCH may be confused with infectious, inflammatory, benign and malignant neoplastic lesions because of its variable clinical presentations and its heterogeneous histomorphologic features. Pathologists have an important role in guiding clinicians to the correct diagnosis and patients' management. They should be familiar with the different histomorphologic patterns to avoid pitfalls. Attention to certain morphologic features and immunohistochemistry should help resolve challenging cases.

1. Introduction

Langerhans cell histiocytosis (LCH) is a bone marrow-derived immature myeloid dendritic cell proliferative disorder with diverse clinical manifestations commonly involves bone, skin, lymph node and lung [1]. Oral involvement is uncommon. It can be the first and only sign of a localized isolated oral lesion, an early sign of a clinically occult disease, reactivation or more commonly an expression of a multisystemic LCH disease [2-5]. Clinically, it can be mistaken for primary oral and dental inflammatory, infectious and neoplastic lesions [2,5-8]. Because oral and dental specimens are usually submitted in fragmented pieces with different tissue reaction patterns, and because of the variable clinical presentations and heterogeneous histomorphologic features of oral LCH, the diagnostic cells may be missed or misinterpreted. We performed a retrospective review study to investigate the different histomorphologic patterns, diagnostic challenges and potential histologic clues of oral LCH. Our aim is to highlight these unusual histomorphologic features particularly in clinically unsuspected cases of oral LCH, their potential pitfalls, to find certain helpful clues and emphasize the importance of a proper use of a panel of immunomarkers.

2. Materials and methods

We used a computer-based search to retrieve all of the cases of LCH that were diagnosed in our institution over the past 10 years from 2019 to 2009. We reviewed the microscopic descriptions, final diagnoses and comments from all the pathology reports. We retrieved cases with the diagnosis of LCH. We searched for oral, gingival, palate, tongue and

* Corresponding author at: Pathology Section, Rashid Hospital, Oud Metha Road 4545, Dubai, United Arab Emirates.
E-mail address: badr.agaffar@gmail.com (B. AbdullGaffar).

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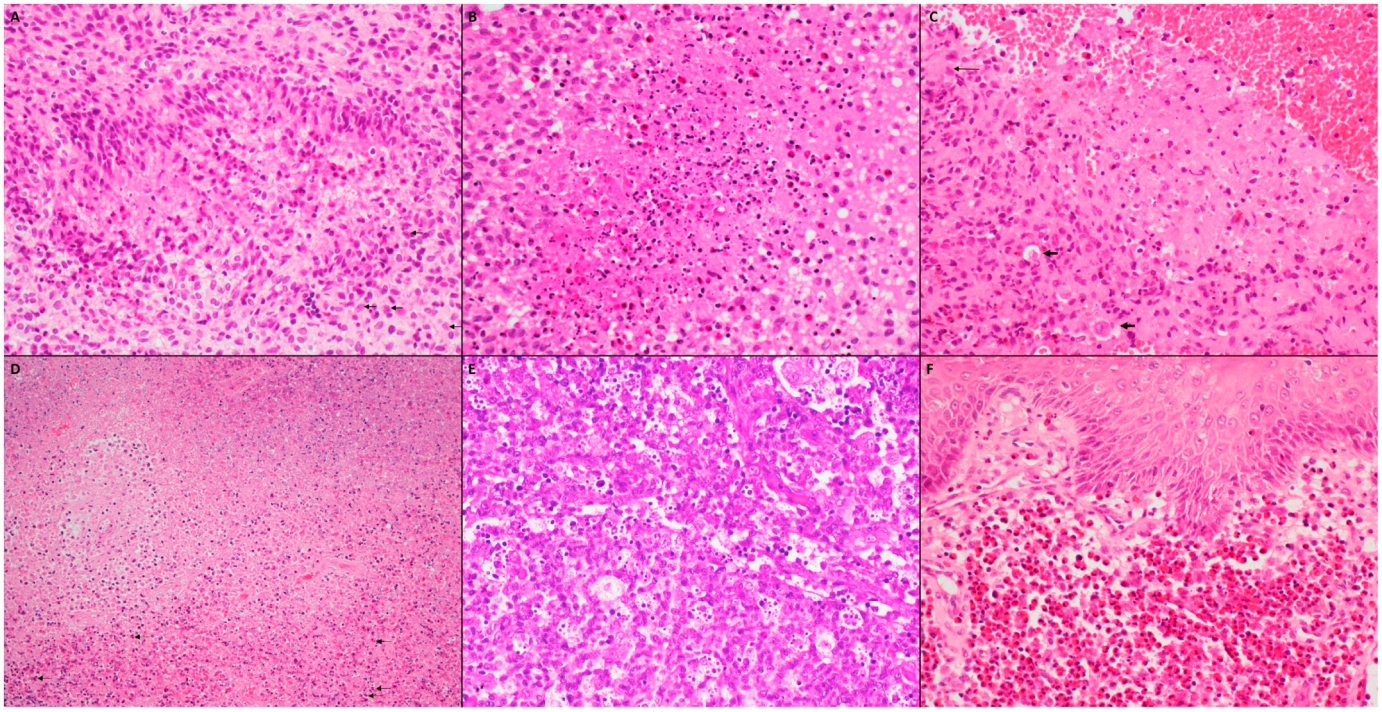

Fig. 1. A) A focus of necrotizing palisading epithelioid granuloma-like collection of plump oval to epithelioid-like histiocytes surrounding a central fibrinous necrotic area with neutrophils and round bubbly vacuolated spheres mimicking fungal microorganisms. Note the prominent presence of eosinophils in the central necrosis and among the sheets of histiocytes surrounding the granuloma. Few scattered histiocytes show nuclear grooves and folds (arrows) [hematoxylin and eosin (H&E), original magnification ×400] B) A necrotizing Kikuchi-like area shows karyorrhectic debris without neutrophils or plasma cells, with some of the surrounding histiocytes showing curved crescent-like nuclei. The presence of eosinophils and grooved nuclei in some of the surrounding histiocytes are helpful clues (H&E ×400). C) An area with necrotizing caseating epithelioid granuloma-like formation edged by epithelioid histiocytes with a multinucleated giant cell (thin arrow), mimicking mycobacterial granulomas. Some large atypical Hodgkin cell-like histiocytes (thick arrows) are also seen intermixed with eosinophils and scattered plasma cells, mimicking necrosis associated with Hodgkin lymphoma (H&E ×400). D) Massive necrosis of sheets and nested groups of medium to large necrotic ghost cells mimicking lymphoma, sarcoma or carcinoma tumor-necrosis. Some degenerate but discernable viable binucleated eosinophils (arrows) are present (H&E ×200). E) Another pattern of necrosis characterized by a solid sheet of viable lymphoid-like cells punctuated by starry-sky pattern, which is due to numerous tingible body macrophages and apoptotic bodies. The background shows intermediate to large eosinophilic cells with vesicular nuclei and conspicuous nucleoli. Some nuclei show grooves and folds. Note the absence of eosinophils (H&E ×400). F) A portion of oral mucosa shows a heavy dense subepithelial eosinophilic infiltrate with edema, dilated capillaries and venules with high endothelial cells. Note the absence of atypical histiocytes. The squamous epithelium shows basal spongiosis with intraepithelial eosinophils and lymphocytes as well as foci of interface inflammation and subepithelial cleft formation (H&E ×400).

dental specimens with the microscopic description, diagnoses and comments of Langerhans cell histiocytosis, atypical histiocytes, histiocytic infiltration, eosinophilic granuloma and Langerhans cells. We retrieved the archived hematoxylin and eosin (H&E) stained slides and the available immunohistochemical slides of these cases. We reviewed the slides to confirm the diagnosis of LCH in the retrieved oral and dental specimens. In addition, for the well-documented cases of oral LCH, we searched for the previous clinical impressions and initial pathologic diagnoses. We reviewed the H&E slides of these previous oral LCH cases to identify any missed initial diagnosis of LCH. We have included cases of LCH with intraoral involvement that fulfilled the diagnostic criteria of typical Langerhans cells (LC) with nuclear grooves that were positive for CD1a, langerin and S-100 protein. We have excluded cases that showed S-100 and CD68 positive histiocytic lesions without evidence of CD1a and langerin coexpression. Immunohistochemistry and molecular studies for BRAF V600E oncogenes and Merkel cell polyomavirus (MCPyV) are not available in our laboratory. We looked for any associated non-LCH lesions and any unusual morphologic variations of LCH in the submitted oral and dental specimens. We collected the relevant clinical information for each patient.

3. Results

We found four cases (7.4%) with a confirmed diagnosis of LCH with oral involvement out of 54 total cases of LCH. The age range was between 1 and 27 years with an average age of 13.7 years. All of the patients were males. The first patient was a 27-year old man who complained of pain and swelling of the left mandible after having a tooth extraction three months ago. Clinical impression was an inflamed cyst, non-healing granulation tissue, an abscess as well as myxoma or neurogenic tumor because of the lesion's proximity to mental nerve. The second patient was a 25-year-old man who presented with a painful non-healing left mandibular ulcer and swelling for two months. Clinical impression was malignant ulcer or an infected radicular cyst. These two patients did not have a previous or current history of systemic diseases. The third patient was a 1-year-old baby boy with a recent oral biopsy in a private hospital suspicious for LCH. He presented with right maxillary swelling and was referred to our institution for a second opinion. Clinical impression was eosinophilic granuloma, pyogenic granuloma, ranula and cyst. The fourth patient was a 1.7-year-old baby boy who is a known case of multisystemic LCH on chemotherapy presented with a persistent bleeding intraoral gingival swelling after tonsillectomy one month ago. Clinical impression was recurrent LCH, abscess, infection and cyst. All of the cases were referred to our oral and dental surgery unit for further evaluation and diagnostic biopsy. Upon prospective follow up, the first adult patient developed bilateral apical lung lesions and femur bone lesions and the second adult developed right lung and pleural lesions. They were subsequently confirmed to be LCH lesions by tissue biopsies. The two babies had multisystemic LCH diseases.

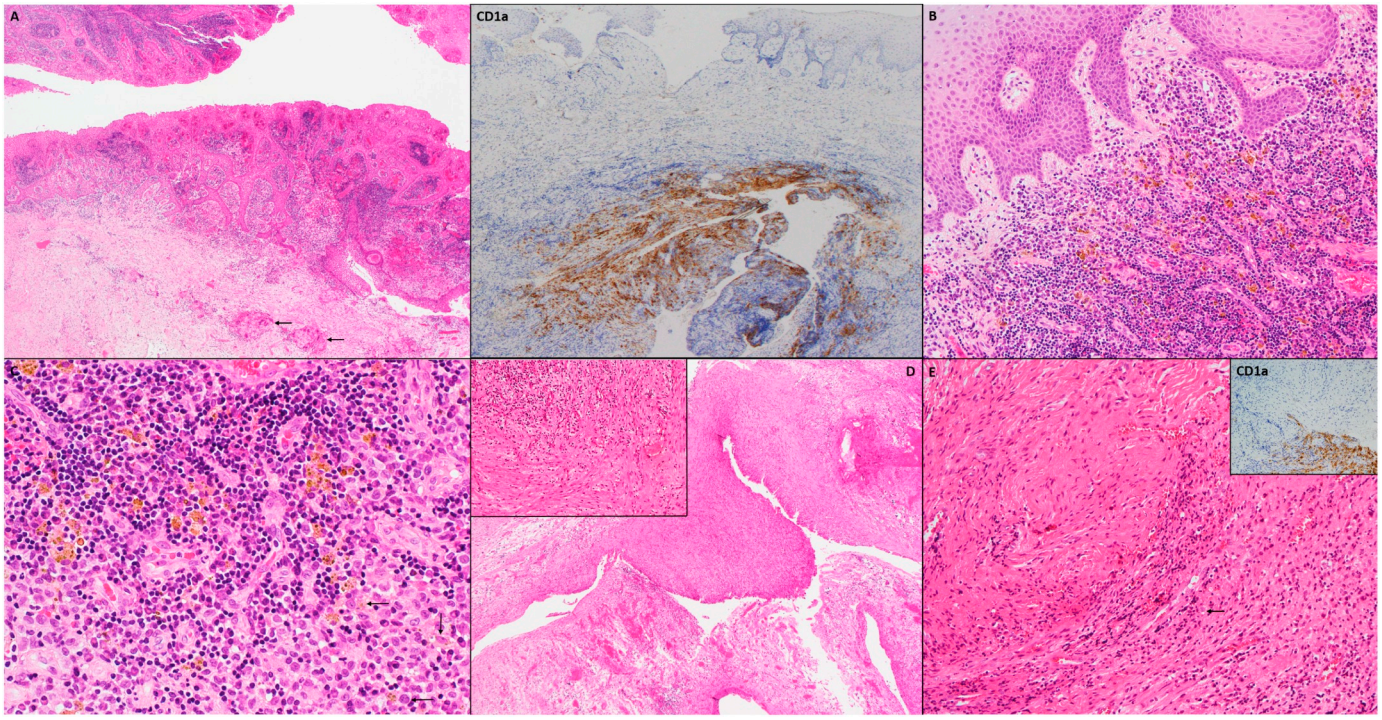

Fig. 2. A) A portion of an inflamed gingival mucosa with pseudoepitheliomatous hyperplasia of the squamous epithelium, dense subepithelial lymphocytic infiltrate and stromal edema, and foci of foreign body pulse granulomas (arrows). This tissue is not involved by histiocytic infiltrates. (H&E ×40). In other portion of the gingival mucosa, CD1a highlights the deep partly crushed granulation tissue involved by Langerhans cells. The remaining inflammatory and subepithelial stromal tissues are negative (Dako CD1a ×40). B) Other areas of the inflamed oral mucosa shows a hyperplastic squamous epithelium with a dense subepithelial stromal lymphoplasmacytic infiltrate punctuated by siderophages and blood vessels. No atypical histiocytes are present (H&E ×100). C) The deeper portion reveals Langerhans histiocytes intermixed with a dense lymphoplasmacytic inflammatory infiltrate without eosinophils. Apart from the siderophages, some of Langerhans cells (arrows) demonstrate intracellular hemosiderin granules (H&E ×400). D) A cavity shows an irregular cyst wall with sloughed lining epithelium, thick fibrous edematous inflamed wall and granulation tissue (H&E ×40). Inset: Some areas of the cyst wall show a fibrotic wall and inflammatory granulation tissue without a lesion (H&E ×200). E) Other areas of the cavity wall shows a transition from the fibrotic wall to an inflammatory cellular granulation tissue with scattered atypical histiocytes (arrow) (H&E ×200). CD1a highlights the Langerhans cells infiltrating the inflammatory granulation tissue in contrast to the lesion-free fibrotic cyst wall (Dako, CD1a ×200).

Grossly, we received all of the specimens as multiple fragmented soft tissue pieces. Histologically, the specimens were composed of multiple fragmented pieces of oral and gingival squamous mucosa and soft-tissue stromal tissues without bone tissues. All of the specimens showed granulation tissue, ulceration and inflamed fibrotic mucosal tissue with focal fibromyxoid stromal degeneration. In some cases, the LCH lesions were obvious. In other cases, the diagnostic samples were small, few, or crushed, while the remaining larger tissue fragments showed uninvolved reactive and inflamed tissue pieces. In the two adult males, the differential diagnosis included LCH, Hodgkin lymphoma, T-cell lymphoma, metastatic carcinoma, melanoma, allergic inflammatory reaction and other histiocytic lesions because the diagnostic tissues were small and few with some unusual histomorphologic features (Figs. 1–4). In the two babies, LCH was correctly diagnosed because the diagnostic tissue was representative and adequate. In addition, unlike the adult cases, they were clinically suspected for LCH. They also showed some additional unusual histomorphologic features upon retrospective review (Figs. 1–4). Fungal, mycobacterial and spirochetal infections in the granulomas, histiocytic infiltrates and allergic mucin materials were excluded by negative periodic acid-Schiff, Grocott-Methenamine, Ziehl-Neelsen and Warthin-Starry stains. Initially, we performed an immunohistochemistry (IHC) panel of CD20, CD3, cytokeratin (AE1/AE3), Melan-1, CD68 and CD1a. The neoplastic cells were positive for CD1a and negative for the remaining markers. We extended our panel by adding S-100 protein and langerin (CD207). In the suspected areas with unusual histomorphologic features, these markers confirmed involvement by LCH, uncovered concealed areas, disclosed involved crushed areas, excluded look-a-like malignant cells, and ruled out other potential differential diagnoses (Figs. 2–4).

4. Discussion

LCH is a dendritic cell disorder characterized by proliferation of cleaved histiocytes often accompanied with eosinophils. LCs cells express S-100 protein, CD1a and langerin with a variable CD68 staining [1]. The diagnostic cells are medium to large cells with abundant eosinophilic to pale cytoplasm, irregular enlarged nuclei with prominent nuclear grooves and folds, fine chromatin and indistinct nucleoli. Background usually shows eosinophilia and may show occasional multinucleated cells, foam cells, fibrosis with or without neutrophils and plasma cells. Foci of necrosis in LCH are common often surrounded by a rim of eosinophils, the so-called eosinophilic microabscesses [9,10]. Oral manifestations of LCH whether isolated or part of a multisystemic disease are uncommon. More commonly, they involve the underlying jawbones. Primary intraoral soft-tissue lesions can be the first sign of either a localized LCH or clinically undiagnosed systemic LCH, predates systemic manifestations of LCH, or an early indicator of recurrence in known cases [2,5]. Mostly, they involve the gingiva and hard palate soft tissues [2,5]. Infrequency of intraoral mucosal and soft-tissue LCH lesions, absence of jawbone involvement, different histology of different parts of oral cavity tissues and their different reaction patterns to underlying lesions with superimposed complications make the diagnosis of LCH challenging for clinicians and pathologists. Clinically, intraoral LCH lesions may manifest as a mass, gingivitis, ulcer, loose teeth, bleeding gum, pain, cysts, sinuses, leukoplakia, periodontitis-like pockets, post-surgical procedure or tooth extraction

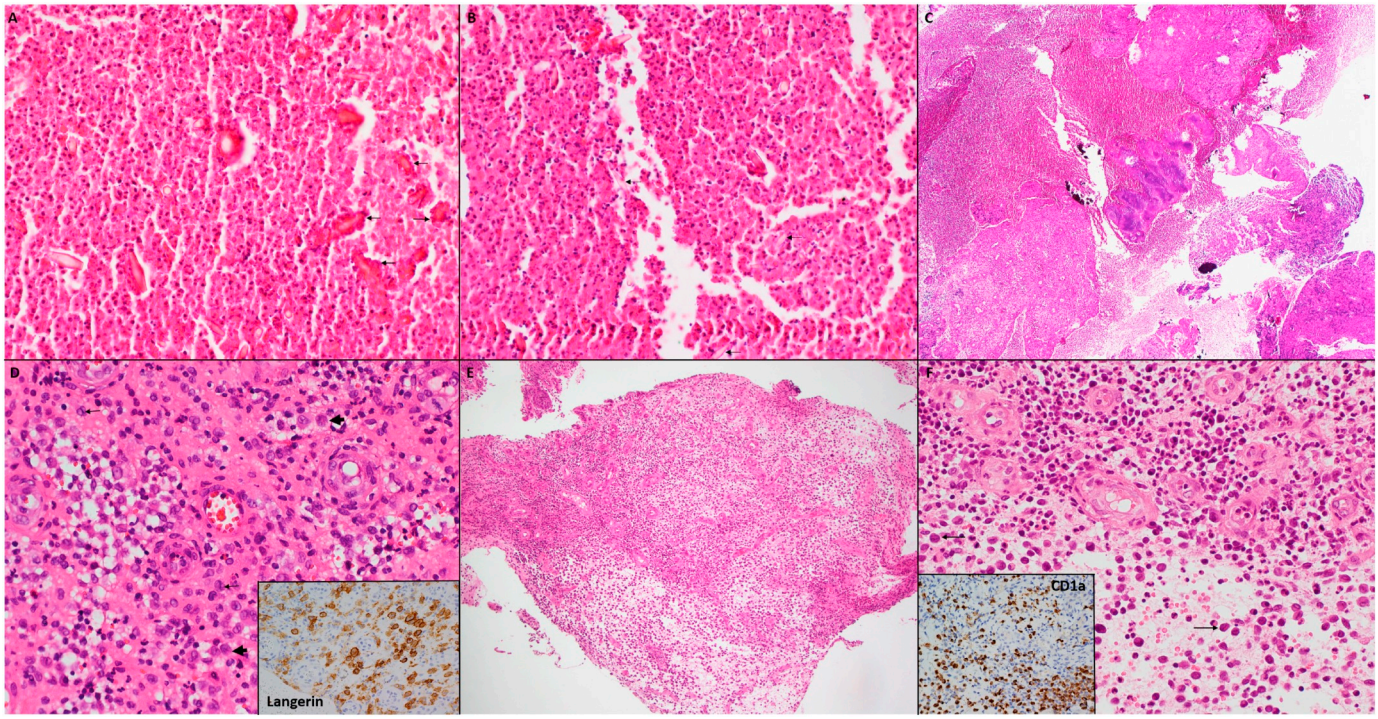

Fig. 3. A) Other areas show solid eosinophilic allergic mucin-like degenerate materials with numerous mostly degenerate degranulated eosinophils without histiocytes. Splendore-Hoeppli-like bodies (arrows) are present (H&E ×400). B) Charcot-Leyden crystals (arrows) partly chattered and masked by the eosinophilic material (H&E ×400). C) Pieces of a hemorrhagic sinus tract lined by fragments of granulation tissue and squamous epithelium. The sinus cavity contains a collection of dark blue to purple Actinomyces-like filamentous organisms with calcifications (H&E ×40). D) The sinus tract granulation tissue shows atypical histiocytes arranged singly (arrows) or in small clusters (arrowheads), difficult to distinguish from the inflammatory cells (H&E ×400). Hints are irregular oval elongated hyperchromatic nuclei with grooves and folds. Langerin helps demonstrate the single and grouped Langerhans cells within the granulation tissue (Dako, CD207 ×400). E) Other areas showed polypoid pyogenic granuloma-like granulation tissue nodules. The base shows a more diffuse cellular area with less blood vessels compared to the vascularized lobular capillary-like granulation tissue (H&E ×40). F) The top part of the polypoid granulation tissue shows a mixed plasma cell-rich inflammation with prominent capillaries. The base shows a nonvascularized edematous tissue with a homogenous population of atypical hyperchromatic cells some with nuclear grooves (arrows). Note the absence of eosinophils (H&E ×400). CD1a highlights the individually scattered Langerhans cells among the granulation tissue inflammatory cells, and the densely populated sheets of Langerhans cells beneath the granulation tissue (Dako, CD1a ×400). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nonhealing wounds [2,3,5,6,8]. They may mimic abscess, cysts, as well infectious, inflammatory and neoplastic oral and dental lesions, lymphoma and even metastasis [2,4,5]. Variations in symptoms and signs may lead to a mistaken diagnosis. A definite diagnosis depends on correct histologic recognition in oral biopsy.

Histologically, diagnostic challenges may arise. Oral specimens usually consist of multiple fragmented pieces of variable sizes and from different parts of the intraoral and gingival mucosa and underlying soft-tissues. The involved diagnostic pieces could be small, few, crushed and ulcerated, while the remaining larger pieces may contain reactive inflammatory tissues that do not contain the diagnostic LC cells. LCH show variations in histomorphology. Different patterns of necrosis may be present. Foci of necrosis in LCH are common often surrounded by a rim of eosinophils, so-called eosinophilic microabscesses. Formation of palisading necrotizing granulomas rimmed by epithelioid histiocytes (Fig. 1A) has been described [9,10]. They could be confused with other granulomatous lesions such as infections, for example mycobacterial, fungal, Cat-Scratch disease, parasites, or connective tissues diseases such as Wegner's granulomatosis and Churg-Strauss syndrome (Table 1) [2,9,10]. Another form is necrotizing lymphadenitis-like pattern mimicking Kikuchi and lupus inflammation (Fig. 1B). Caseous-like necrosis with epithelioid histiocytes can mimic tuberculosis, particularly in the presence of multinucleated giant cells or may mimic Hodgkin lymphoma-related necrosis particularly with the presence of atypical large Hodgkin cell-like histiocytes and mixed inflammatory background (Fig. 1C). Massive tumor necrosis may simulate necrotic carcinoma or lymphoma cells (Fig. 1D). The hint is the presence of background eosinophils and nuclear grooves in some of the histiocytes (Fig 1A–D). A starry-sky necrosis shows solid sheets of viable cells punctuated by tingible body macrophages and apoptotic bodies (Fig. 1E). Eosinophils are however absent or scarce. The hint is nuclear grooving in the histiocytes. Even though the presence of eosinophils in the background of atypical histiocytes is a hint, in some cases the eosinophils dominate and mask the histiocytes or form massive sheets without histiocytes (Figs. 1F, 3A, B). Intraepithelial and subepithelial eosinophils when accompanied by edema and cleft like-pattern may mimic oral dermatoses, drug and parasitic reactions (Fig. 1F). Numerous eosinophils forming allergic mucin-like materials with crystals and fungal-like bodies (Fig. 3A, B), could be confused with fungal sinusitis or allergic lesions. Some cases may be complicated by a sinus formation with superimposed Actinomyces infection (Fig. 3C). Because ulceration is a common presentation, submitted materials may show granulation tissue and pyogenic granuloma-like inflammatory nodules (Fig. 3D–F). The hint is to scrutinize all of the submitted pieces including small pieces, crushed areas and particularly areas adjacent to the granulation tissue to look for atypical histiocytes with nuclear grooves and folds highlighted by proper immunomarkers (Fig. 3). LCH may induce stomatitis and leukoplakia-like reaction of the mucosa and cyst formation without direct involvement of LCs (Fig. 2). The lesion may lie deep in the tissue and sometimes may be crushed warranting IHC to uncover the diagnostic cells (Fig. 2). Metastasis to gingiva, for example from lung, renal cell carcinoma, breast, melanoma and mesothelioma can occur with lymphovascular tumor emboli. LCs may permeate lymphatic channels simulating carcinoma or melanoma tumor emboli (Fig. 4A). In

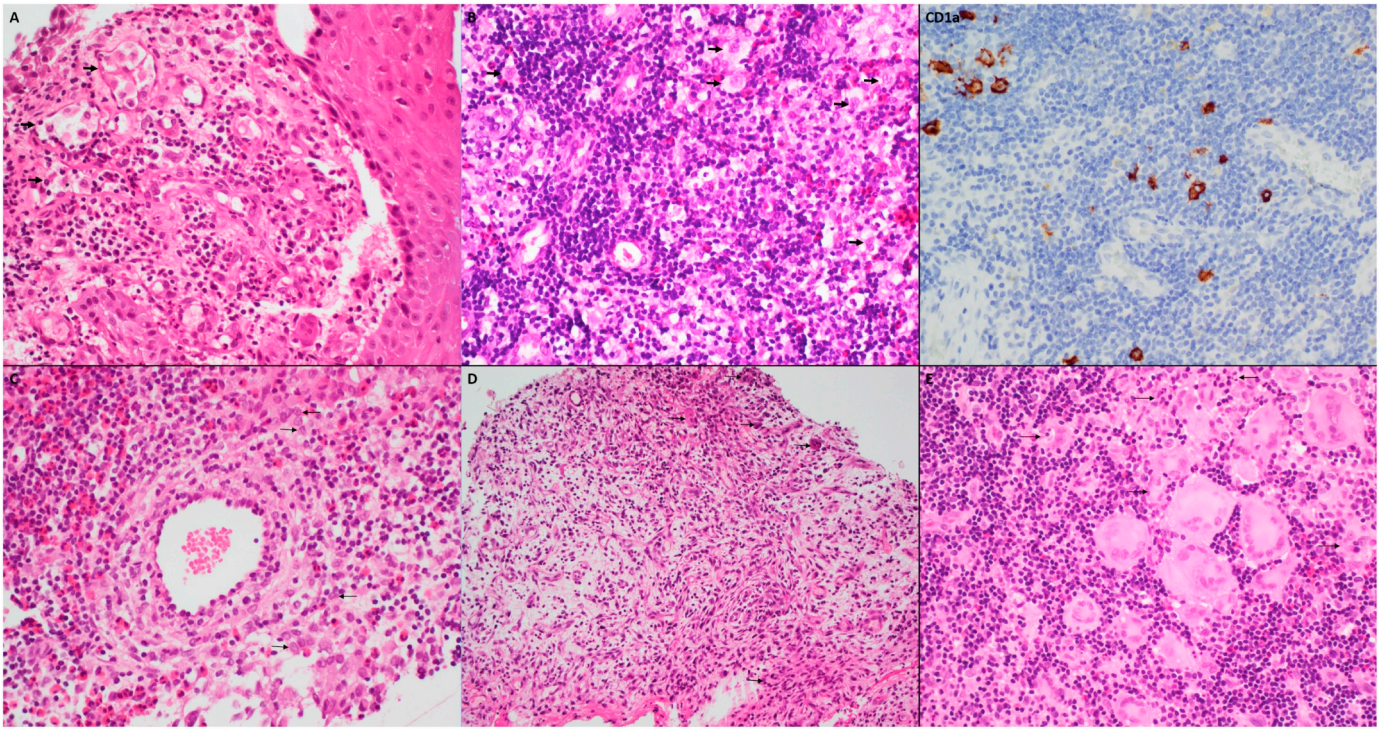

Fig. 4. A) A focus of subepithelial tissue shows dilated lymphatics (arrows) lined by endothelial cells and filled with tumor emboli of large atypical eosinophilic cells, mimicking carcinoma or melanoma cells. Similar single individual cells are scattered within the inflamed subepithelial edematous granulation tissue. Contrast the thin slender endothelial cells of the lymphatic channels with the large plump endothelial cells of capillaries and venules of the granulation tissue with empty lumina (H&E ×400). B) An area with a dense lymphocytic infiltrate composed of small lymphocytes admixed with scattered histiocytes and granulocytes punctuated by large atypical Hodgkin-like cells (arrows); a picture mimicking mixed cellularity Hodgkin lymphoma (H&E ×200). CD1a highlights the scattered Langerhans cells embedded within the dense lymphocytic background. They were CD30 and CD15 negative excluding Hodgkin cells (Dako CD1a ×400). C) A focus shows an arteriole wall infiltrated and expanded by a lymphohistiocytic infiltrate mimicking angioinvasive T-cell lymphoma cells or vasculitis. The background shows a mixed inflammatory background with prominent eosinophils. Foci of large atypical histiocytes few with nuclear grooves and folds (arrows) are present (H&E ×400). D) A piece of a polypoid nodule of granulation tissue with eroded surface and scattered multinucleated giant cells (arrows) with fibrinous exudate material; features mimicking peripheral reparative giant cell granuloma (H&E ×200). E) A collection of multinucleated foreign body-type and Langhans horseshoe-type multinucleated giant cells surrounded by a dense lymphocytic infiltrate with few scattered eosinophils. Few of the giant cells (arrows) engulf neutrophils, lymphocytes and plasma cells. A careful look at some of the nuclei of the giant cells shows few with nuclear grooving (H&E ×400).

some areas, LCH induces a dense lymphocytic infiltrate with scattered large atypical LCs cells that might mimic Hodgkin cells (Fig. 4B). In these cases, IHC helps distinguish LCs from look-a-like cells (Fig. 4C). Another feature is when LCs accompanied by reactive lymphocytes infiltrate the walls of blood vessels simulating angioinvasive lymphoma or vasculitis (Fig. 4D). Eosinophils in this situation are not helpful because they are usually present in these lesions. A careful look for nuclear grooves should raise suspicion of LCH. Giant cells can occur in LCH. However, LCH may induce peripheral giant cell granuloma-like granulation tissue with non-Langerhans multinucleated giant cells (Fig. 4E). On the other hand, Langerhans cells may form prominent collections of closely packed confluent multinucleated giant cells of various types, some with phagocytosis and vacuolated lipidized cytoplasm, within a lymphoplasmacytic background without eosinophils (Fig. 4F). They may mimic the giant cells of Rosai Dorfman disease, juvenile xanthogranuloma, xanthoma, foreign body giant cell reaction and other granulomatous diseases, for example sarcoidosis. The hint is the nuclei of giant cells may still show nuclear grooves (Fig. 4F). Even though the giant cells in Rosai Dorfman disease and other lesions may be positive for S-100 and CD68, they are negative for CD1a and langerin.

Pathologists should be aware that eosinophils have two faces of the coin. LCH may be confused with other eosinophilic rich lesions, for example Hodgkin lymphoma, anaplastic large cell lymphoma, mastocytosis, Kimura disease, autoimmune connective tissue diseases, allergic, drugs and parasites-related reactions (Table 1) [10]. The hints are the morphology of the histiocytic nuclei. In doubtful cases, IHC should resolve the confusion. Some areas show numerous eosinophils without LCs, while other areas show LCs without eosinophils. Even though eosinophils could be a clue, they are not reliable. A careful scrutiny of the entire submitted pieces supplemented with deeper levels looking for diagnostic LCs is warranted. Pathologists should be familiar with the different histomorphologic features and various tissue reaction patterns of oral LCH, especially in clinically unsuspected patients. They should always include CD1a and langerin in their differential IHC panel. Even though some of these unusual histomorphologic appearances, for example necrosis, granulomas and granulation tissue can be seen in LCH involving other nonoral tissues, other patterns are peculiar to oral lesions due to the nature of oral cavity and different reaction patterns of intraoral tissues. Pathologists should also be able to differentiate LCH from other histiocytic tumors (Table 2) [11-13]. Because LCH may show various patterns of tumor necrosis accompanied by variable cytologic atypia and mitosis, it should not be mistaken for Langerhans cell sarcomas (LCS). LCS is a rare malignant histiocytosis characterized by highly pleomorphic LCs with large hyperchromatic or vesicular nuclei, prominent nucleoli, conspicuous mitoses including abnormal mitotic figures, increased apoptotic bodies and coagulative necrosis. LCH and LCS share similar immunophenotypic, ultrastructural and genotypic features (Table 2). It arises de novo, but some cases of transformation from LCH and transformation into leukemia have been reported [11-13]. It must be also differentiated from undifferentiated carcinoma, melanoma, pleomorphic sarcomas and anaplastic lymphomas by an appropriate panel of IHC (Table 2).

Treatment options for LCH are dependent on site, extent of disease

Table 1
Granulomas and eosinophilic rich lesions of the head and neck region.

Granulomatous lesions	
Autoimmune	Granulomatosis with polyangiitis (Wegner granulomatosis) Churg-Strauss syndrome Crohn's disease Rheumatoid arthritis Relapsing polychondritis
Infectious	Mycobacterial infection (e.g. Tuberculosis, nontuberculous, Leprosy) Spirochetes (e.g. Syphilis) Fungal infection (e.g. Histoplasmosis, Blastomycosis) Bacterial infection (e.g. Actinomycosis, Rhinoscleroma, Cat-Scratch disease)
Idiopathic	Sarcoidosis
Hereditary	Chronic granulomatous disease Melkersson-Rosenthal syndrome
Others	Foreign body giant cell reaction (e.g. iatrogenic, myospherulosis, vegetable, cholesterol, cocaine, talc, beryllium)

Eosinophilic rich lesions
Kimura disease
Angiolymphoid hyperplasia with eosinophilia
Allergic (fungal) mucin/chronic sinusitis
Parasitic infestations
Tongue ulceration with eosinophilia
Sinonasal eosinophilic angiocentric fibrosis
Inflammatory (allergic) polyps
Mucocutaneous dermatologic lesions (e.g drug reaction, bullous disorders, insect bite)
Autoimmune inflammatory connective tissue disease (e.g. Churg-Strauss syndrome)
Hematologic disorders (e.g Hodgkin lymphoma, anaplastic large cell lymphoma, granulocytic sarcoma, mastocytosis)
Tumor-associated tissue eosinophilia (e.g. squamous cell carcinoma)

and risk organs stratification [1,2,5]. Several multimodality treatment approaches include systemic chemotherapy, steroids, purine analogue antimetabolites, targeted therapy, radiotherapy and surgery [1,2,5]. Lung lesions benefit from smoking cessation. Cases of LCH have been found to harbor mutations in BRAF V600E oncogenes and diverse MAPK/ERK (Ras-Raf-MEK-ERK)-kinase signalling pathway mutations [1,11-13]. In addition, a link to Merkel cell polyomavirus has been reported [14]. Apart from their diagnostic utility and pathogenetic significance of categorization of LCH as a virus-linked neoplasm, they carry prognostic and therapeutic implications for patients. BRAF and MEK inhibitors are successfully being used in the treatment of multi-systemic LCH [1].

In conclusion, because intraoral LCH is relatively uncommon and has a wide clinical spectrum, pathologists have an important role to guide clinicians to the correct diagnosis and patients' management. Diagnostic cells may be missed or misinterpreted because of different tissue reaction patterns that vary in the multiple fragmented pieces of oral specimens. Pathologists should be familiar with the different histomorphologic manifestations of LCH in intraoral specimens to avoid pitfalls. A careful examination of all the pieces looking for diagnostic Langerhans cells supplemented with the correct panel of IHC should confirm the diagnosis.

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None to be declared.

Declaration of competing interest

No conflict of interests or financial disclosure to be declared by the authors.

Table 2
Histiocytic neoplasms (histiocytoses).

Histiocytic neoplasm	Salient diagnostic features	Ancillary workup	Molecular genetics
Langerhans cell histiocytosis	Intermediate to large cells with abundant pale eosinophilic cytoplasm, irregular elongated nuclei, nuclear grooves and folds, fine chromatin, indistinct nucleoli. ± multinucleated giant cells, inflammatory eosinophil-rich background infiltrate, necrosis, granuloma, fibrosis	S-100 protein, CD1a, langerin +ve CD4, CD45, BRAFVE1 +ve, CD68 ± CD21, CD30, CD35, B-cell/T-cell markers −ve Ultrastructure: cytoplasmic Birbeck granules	BRAF V600E mutation (50–60%) RAS/MAPK mutations (35%) MAP2K1 (80%), ARAF Pathogenetic link to Merkel cell polyomavirus (MCPyV)
Langerhans cell sarcoma	Highly pleomorphic Langerhans cells with large hyperchromatic or vesicular nuclei, prominent nucleoli and conspicuous mitosis ± epithelioid cells, chronic inflammatory infiltrate with eosinophils, apoptotic bodies, coagulative necrosis	S-100, CD1a and langerin +ve CD4, CD163 +ve, CD68 ± B-cell/T-cell markers, melanoma markers, cytokeratin, MPO, ALK and CD30 –ve Ultrastructure: cytoplasmic Birbeck granules	± BRAF V600E mutation Possible link to MCPyV
Erdheim-Chester disease	Infiltration by large foamy xanthomatous mononuclear histiocytes with prominent fibrosis ± Touton giant cells, lymphoid aggregates, lymphoplasmacytic infiltrate, neutrophils, emperipolesis	CD68, CD163, CD14, FXIIIa +ve BRAFVE1 ± , S-100 ± CD1a, langerin −ve Ultrastructure: no Birbeck granules	MAPK pathway mutations (70%) BRAF V600E (50–60%) ± MAP2K1, MAP2K2, ARAF KRAS, NRAS, PIK3CA PI3K-AKT mutation (70%)
Juvenile xanthogranuloma	Uniform foamy histiocytes with ample eosinophilic vacuolated cytoplasm, round-oval nuclei, small nucleoli ± xanthomatous lipidized foamy cells, spindle cells, multinucleated Touton and foreign boy giant cells, fibrosis, neutrophils, eosinophils, lymphocytes, plasma cells	CD68, CD163, FXIIIa, CD4, CD45 +ve S-100 ± CD1a, langerin −ve Ultrastructure: no Birbeck granules	No BRAF mutation ± MAPK mutations reported
Rosai-Dorfman disease	Large histiocytes with vacuolated lipidized cytoplasm, large round vesicular nuclei, small to prominent nucleoli, emperipolesis, plasma cells, lymphocytes, fibrosis ± multinucleated giant cells, spindle cells, neutrophils, eosinophils	S-100, CD68, CD14, CD4, CD163 +ve CD1a, langerin −ve ± IgG4 plasma cells Ultrastructure: no Birbeck granules	No BRAF mutation ± MAPK mutations (KRAS, SMAD4, MAP2K1) reported in extranodal cases
Histiocytic sarcoma	Large cells with variable pleomorphism, abundant eosinophilic vacuolated cytoplasm, irregular nuclei, prominent nucleoli, conspicuous mitosis ± giant cells, erythrophagocytosis, lymphophagocytosis, necrosis, mixed inflammatory and fibrotic background	CD68, CD163, CD4, CD14, CD45 +ve, B-cell/T-cell markers, CD1a, langerin, CD21, CD35, CD33, MPO, ALK, CD30, cytokeratin, melanoma markers −ve, S-100 ± Ultrastructure: no Birbeck granules	BRAF mutation (60%) ± Ras/Raf/MEK/ERK

+ve: positive, −ve: negative, ± : variably present or expressed,

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