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Case Report

Isolated Langerhans cell histiocytosis of the sublingual gland in an adult

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Abstract: Langerhans cell histiocytosis (LCH) is a rare disorder characterized by the proliferation of pathologic Langerhans cells. Its clinical presentation is highly variable, that range from single-system, limited disease to severe, multi-organ disease with high mortality. LCH usually affects children and young adults. The most frequent sites for LCH are the bone, skin, lung, pituitary gland, and lymph nodes. Salivary gland involvement by LCH is extremely rare, and only a few cases of LHC involving the parotid glands have been reported in the English literature. To our knowledge, the involvement of the sublingual gland as a part of single or multisystem LCH has not been previously described. Herein we reported the first case of primary LCH of the sublingual gland. A 40-year-old woman presented with a 2-month history of a painless mass on the right sublingual area. Excision of the lesion including the right sublingual gland was performed. Histopathological diagnosis of LCH was rendered. The patient remains free of symptoms 17 months after surgery.

Keywords: Langerhans cell histiocytosis, salivary gland, sublingual gland

Introduction

Langerhans cell histiocytosis (LCH) is a complex and poorly understood disorder, characterized by the abnormal proliferation of bone marrow-derived Langerhans cells [1, 2]. It is a rare disease with an estimated annual incidence of 4-8 per million children and 1-2 cases per million in adults [1]. The clinical presentation of LCH is highly variable, that range from single-system, limited disease to severe, multi-organ disease with high mortality [1-3]. Historically, LCHs were divided into 3 clinical entities: eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease [1, 2]. Lichtenstein in 1953 recognized these distinct entities as a common nosologic entity of uncertain cause and coined the term histiocytosis X [4]. In 1983, the term LCH was suggested to replace histiocytosis X when the Langerhans cells were shown to be the essential proliferating element in all clinical forms of disease [5]. In 1987, the criteria for diagnosis of LCH were clearly established, requiring the demonstration of the presence of Birbeck granules by electron microscopy or CD1a antigen expression by immunohistochemistry [6]. The prognosis and treatment of LCH depend on the extent and severity of disease [1-3].

LCH can affect any system or organ throughout the body. The most frequent sites for LCH are the bone, skin, lung, pituitary gland, and lymph nodes [1-3]. Salivary gland involvement by LCH is exceedingly rare, and only a few cases of LHC involving the parotid glands have been reported in the English literature [7-11]. To our knowledge, the occurrence of LCH in the sublingual gland, either as a primary isolated manifestation of the disease or as a part of systemic disease, has not been previously described in the literature. Herein, we report a rare case of isolated Langerhans cell histiocytosis involving the sublingual gland in a 40-year-old woman.

Case report

A 40-year-old woman presented with a 2-month history of a painless mass in the right floor of the mouth. Anamnesis revealed that she had

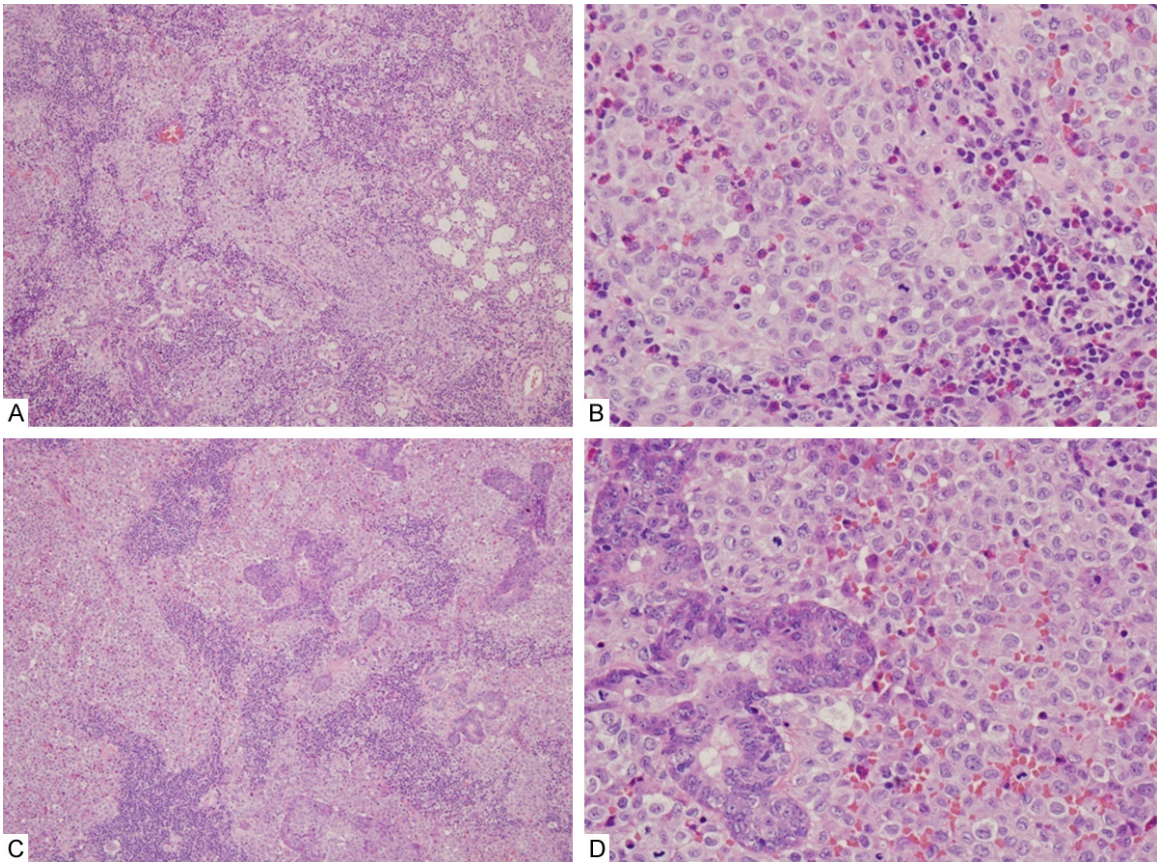

Figure 1. Morphological findings. A. Low power demonstrating accumulating histiocytoid cells admixed with eosinophils and lymphocytes infiltrating the sublingual gland parenchyma (hematoxylin and eosin × 100); B. High power showing histiocytoid cells with abundant cytoplasm and convoluted nuclei, some of which show nuclear grooves (hematoxylin and eosin × 400); C. Histiocytoid cells showing prominent invasion of the ductal epithelium forming an epimyoepithelial island-like structure (hematoxylin and eosin × 100); D. High power showing epimyoepithelial island-like structure. (hematoxylin and eosin × 400).

been receiving perindopril for hypertension for one year and levothyroxine hormone replacement therapy for (antibody negative) hypothyroidism. There was no additional past medical or surgical history. Intraoral examination revealed a 1.5-cm nontender mass on the right sublingual area. Laboratory studies, including urine analysis, a complete blood cells count, erythrocyte sedimentation rate, and serum biochemistry (electrolytes, alkaline phosphatase, and liver function) were within the normal ranges. Chest radiograph was normal. Under the clinical diagnosis as ranula, excision of the lesion including the right sublingual gland was performed under general anesthesia. The specimens were sent for histopathology.

The resected sublingual gland tissue was measured 2.7 × 1.8 × 1.5 cm, with a circumscribed and grey-white nodule measuring 1.5 × 1.5 × 1.3 cm. Microscopically, it was a partially circumscribed mass with an ill-defined border. The tumor was composed of sheets and groups of round to ovoid mononuclear histiocytic cells with infiltrated eosinophils and lymphocytes (**Figure 1A**). The histiocytic cells were characterized by grooved, folded, or lobulated nuclei, fine chromatin, and abundant cytoplasm (**Figure 1B**). Mitoses were occasionally observed and no necrosis was found. The histiocytic cells showed prominent invasion of the ductal epithelium forming epimyoepithelial island-like structures (**Figure 1C** and **1D**). Immunohistochemically, the aggregated histiocytic cells were positive for vimentin, S-100 (**Figure 2A**), and CD1a (**Figure 2B**), but negative for Pan-cytokeratin, CAM5.2, CD20, CD3, CD68, CD30, and CD21. The Ki-67 labeling index was approximately 20%. Pan-cytokeratin highlighted epimyoepithelial island-like struc-

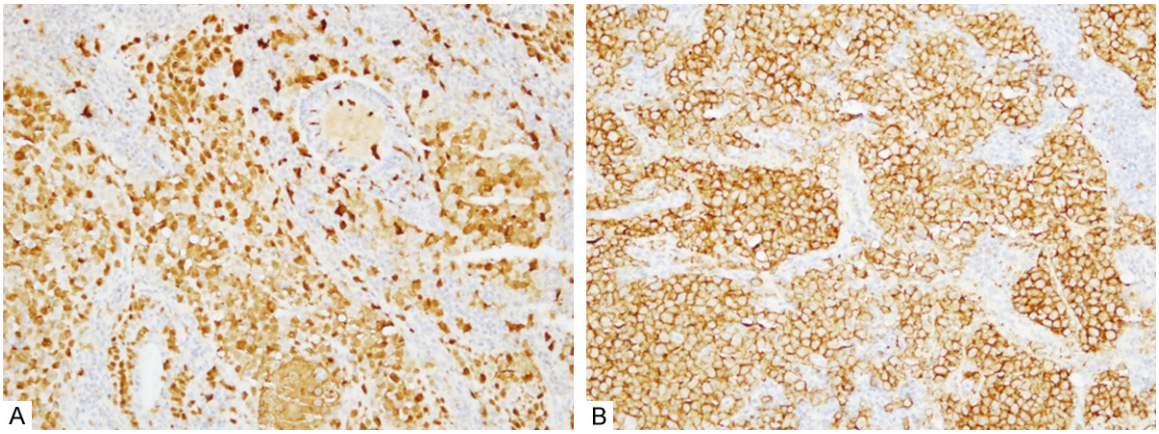

Figure 2. Immunohistochemical findings. (A) Strong immunopositivity of histiocytoid cells for S-100 (A) (× 200); (B) Strong immunopositivity for CD1a (× 200).

tures invaded by the histiocytic cells. Because these aggregated histiocytic cells shared morphologic and immunohistochemical features with Langerhans cells, the diagnosis of LCH was established. The patient was investigated further to rule out multisystem involvement. A whole-body bone scan, abdominal ultrasonography, and thoracic computed tomography (CT) scan were done, all of which revealed no evidence of multifocal disease. The patient remains free of symptoms 17 months after surgery.

Discussion

LCH is a rare disorder characterized by the proliferation of pathologic Langerhans cells. The etiology is unknown and is still debated. The morphology of its proliferating cells and its characteristic inflammatory infiltrates suggested that LCH may be an inflammatory disorder. Nonetheless, recent observation that LCH is a clonal process with activating BRAF mutations suggests that LCH is a neoplastic condition [1-3]. It usually affects children and young adults. The average age of onset is 1 to 3 years, and the disease occurs more commonly in males [1-3]. The current clinical classification of LCH describes a broad spectrum ranging from localized single-system involvement to disseminated multisystem disease. In unifocal disease, bone involvement is present in more than 90% of cases. Extra-skeletal involvement may involve a variety of organs, including the skin, lymph nodes, lung, liver, spleen, bone marrow or central nervous system, leading to a variety of possible presentations [1-3]. Salivary gland involvement by LCH is exceedingly rare, and there have been several case reports of LCH with parotid glands involvement. Darvishian et al. reported one case in a 34-year-old male with LCH involving the parotid gland and an adjacent lymph node [7]. Iqbal et al. reported a case of multisystem LCH involving bilaterally the parotid gland in an 18-month-old boy [8]. Kojima et al. described a case of Langerhans cell histiocytosis involving bilaterally the parotid gland in an 81-year-old woman [9]. Takahama et al. reported a case of LCH involving all the left parotid gland in a 3-year-old boy, with a recurrence in the temporal bone extending to the orbit three months after surgery [10]. Babacan et al. reported an isolated case of Langerhans cell histiocytosis of left parotid gland in a 46-year-old male [11]. To our knowledge the involvement of the sublingual gland as a part of single or multisystem LCH has not been previously described.

LCH lacks pathognomonic clinical or radiographic characteristics. A definitive diagnosis should be based on the histological and immunohistochemical study of lesional biopsy specimens [12]. Histologically, LCHs were characterized by a proliferation of large cells with elongated, grooved and folded nuclei, fine chromatin with delicate nuclear membrane, inconspicuous nucleoli, and moderate amounts of cytoplasm. The tumor cells were accompanied by mixed and variable inflammatory cells including eosinophils, neutrophils, lymphocytes, and conventional histiocytes. Eosinophils can be quite prominent, and are a good clue to the diagnosis. However, their presence is not man-

dated to achieve the diagnosis. Mitotic figures and necrosis are features that can be seen in LCH. Histological diagnosis of LCH can be confirmed by using dendritic cell markers such as CD1a and langerin (CD207), which is specific to Langerhans cells with or without S100. Moreover, Birbeck granule is definitive ultrastructural finding for diagnosis [1-3, 12]. The association of S-100 and CD1a in this case confirmed the histopathological diagnosis.

The treatment for LCH is variable, depending on age, extent of disease and risk factors [1-3]. Therapeutic modalities include surgical excision, radiation therapy, topical therapy or systemic chemotherapy. The clinical course of LCH varies from lesions that spontaneously resolve, to a chronic disease, or can be disseminated and life-threatening. Age at presentation, multisystem involvement, and vital organ dysfunction are the most relevant prognostic factors [1-3]. Generally, prognosis of single system disease is good, with 99% or greater 5-year survival rates reported [13]. The treatment of salivary gland LCH is not well defined, because there have been only few case reports. As the lesion in this case was restricted to one site in the right sublingual gland, and there was no systemic involvement, surgical resection was performed. The patient remains free of symptoms 17 months after surgery. Long-term follow-up to exclude progression of the disease and systemic involvement is necessary [12].

In conclusion, isolated LCH of the sublingual gland is quite rare and should be considered in the differential diagnosis. Its diagnosis can be challenging for a clinician. A definitive diagnosis of LCH is made upon biopsy, yielding cells that are morphologically and immunohistochemically compatible with Langerhans cells. Owing to its rarity and varied presentation, management of LCH is multidisciplinary. Local excision is the treatment of choice for isolated LCH, and long-term follow up is necessary.

Disclosure of conflict of interest

None.

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