**Case Report:**

Langerhans' Cell Histiocytosis in the Parotid Gland

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Abstract. Langerhans' cell histiocytosis presenting as a parotid gland mass is extremely rare. We report a case of Langerhans' cell histiocytosis in the parotid gland that occurred in a 34-year-old Korean male. The patient underwent parotidectomy followed by adjuvant chemotherapy. There has been no evidence of local recurrence or disease progression during 20 months after the lesion was first diagnosed. Differentiation of Langerhans' cell histiocytosis from Kimura's disease was crucial in this clinical setting. (received 14 December 2001, accepted 22 December 2001)

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Introduction

Langerhans’ cell histiocytosis (LCH) is a proliferation of Langerhans’ cells. LCH encompasses a constellation of syndromes including Hand-Schuller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma. These clinical entities, although of historical importance, have no pathologic basis. LCH can essentially involve any part of the body, but bone is the most frequent site [1,2]. Involvement of parotid gland by LCH is rare and we are unaware of any previously reported case in the English literature. We report a case of LCH presenting as a mass in the parotid gland with involvement of an adjacent lymph node.

Case History

A 34-yr-old Korean man presented complaining of an asymptomatic mass on the left side of his neck.

The patient's family history and past medical history were unremarkable. He had been a heavy smoker and he drank alcohol socially. Physical examination confirmed a mass in the left parotid region.

A computerized tomography (CT) scan of the neck showed an abnormality in the left parotid tail and enlarged level II lymph nodes. These findings were confirmed by magnetic resonance imaging (MRI) of the neck. He underwent a left parotidectomy with level II lymph node dissection. Procedures to evaluate the extent of the disease included chest X-ray, skull X-ray, CT scan of mandible, MRI of brain, pituitary and maxilla, and bone marrow aspiration and biopsy. These examinations failed to show any other site of involvement by LCH. The patient’s pulmonary function tests were normal.

The patient received a six-week course of adjuvant chemotherapy consisting of vinblastine at weekly intervals plus daily prednisone. Subsequently the patient received pulse therapy with vinblastine/prednisone and daily 6-mercaptopurine for a total of six months. The patient is alive and well, with no evidence of residual disease at 20 months after the diagnosis was made.
Materials and Methods

Paraffin-embedded sections of formalin-fixed tissue were studied by routine histology using hematoxylin and eosin (H&E) stain. Immunohistochemical staining was performed with an automated immunostainer (Ventana Corp, Tucson, AZ) using the avidin-biotin complex technique with monoclonal antibodies to CD1a, S-100, CD21, and lysozyme (all from Ventana Corp).

Electron microscopy was performed on glutaraldehyde-fixed tissue by standard methods.

Pathology

The pathology specimen included the left parotid gland and level II lymph nodes. The cut section of the parotid showed an ill-defined nodule that measured 2.5 cm x 1 cm.

Microscopic examination of the parotid parenchyma revealed multiple aggregates of a cellular infiltrate, predominantly composed of large cells with abundant eosinophilic cytoplasm and reniform, irregular, and cleaved nuclei. Nucleoli were generally present, yet inconspicuous. The lesion was diffusely infiltrated by eosinophils and small lymphocytes (Fig. 1A). Foci of necrosis were also present. One of the level II lymph nodes showed a lesion histologically identical to that of the parotid gland, involving the paracortical and subcapsular sinusoids. Light microscopic findings were compatible with LCH.

Immunohistochemical studies of the tumor cells showed positive reactivity for antibodies to CD1a

Fig. 1. Panel A: Langerhans’ cells admixed with eosinophils and lymphocytes invading salivary gland ducts and infiltrating the parotid gland parenchyma (magnification x 200). Panel B: CD1a antibody diffusely staining the Langerhans’ cells (magnification x 400)
(membranous staining), lysozyme, and S-100, but no reactivity for antibodies to CD21 (Fig. 1B). Electron microscopy demonstrated Birbeck granules in the cytoplasm of the tumor cells with folded nuclei (Fig. 2). Based on the light microscopic, immunohistochemical, and electron microscopic findings, the diagnosis of LCH of the parotid gland and an adjacent lymph node was made.

Discussion

In 1868, Paul Langerhans described a dendritic cell in the epidermis, originally thought to be a nerve cell receptor [3]. We now know that the cells described by Langerhans are antigen-presenting cells that are derived from monocyte/macrophage precursors in the bone marrow.

In 1893, Alfred Hand reported a case of a 3-year-old child presenting with thirst, polyuria, and exophthalmos, which he initially attributed to tuberculosis [4]. Arthur Schuller in 1915 and Henry Christian in 1920 described similar cases, which prompted Hand to reconsider tuberculosis as the etiology of his case [5,6]. The classic triad of calvarial defects, diabetes insipidus, and exophthalmos was then named Hand-Schuller-Christian (HSC) disease after the physicians who first described it.

Letterer in 1924 and Siwe in 1933 reported 2 infants with fever, generalized lymphadenopathy, hepatosplenomegaly, and rash [7,8]. Abt and Deneholz in 1936 first adopted the term Letterer-Siwe (LS) disease to describe a case similar to the original 2 cases [9]. In addition to bone lesions, all of these cases shared a rapidly fatal course. Farber and Green in 1942 reported bone lesions composed of aggregates of phagocytic cells admixed with eosinophils; hence eosinophilic granuloma [10].

In 1953, in an attempt to unify HSC disease, LS disease, and eosinophilic granuloma, Lichtenstein [11] coined the term Histiocytosis X, pointing to the histiocytic origin of this constellation of disorders. In 1973, Nezelof proposed that Histiocytosis X is caused by proliferation of Langerhans'-like cells [12]. Thereafter, the term Langerhans’ cell histiocytosis was suggested. Lieberman et al [1] adopted the term Langerhans’ cell granulomatosis to avoid confusion with Histiocytosis X. However, Langerhans’ cell histiocytosis is more uniformly accepted and is currently the preferred terminology.

Langerhans’ cell histiocytosis may present either unifocally or multifocally. Lieberman et al [1] reported 238 patients with LCH, of whom 153 (64%) had unifocal disease. By far, bone was the most common site of solitary lesions. Only 9% of the unifocal lesions involved organs and soft tissues other than bone including lung, lymph nodes, submaxillary gland, and skin [1]. Favara and Steele [13] reported isolated lymph node involvement revealed at the time of biopsy in only 11 of 37 cases. LCH remained confined to a single lymph node in only one adult and one child (5% of cases) after a 31-month follow-up. Broadbent et al [2] reported 90 children with median age of 2.4 yr of whom 33 (37%) had multisystem disease and 57 had single-system involvement. A solitary osteolytic lesion in a flat or long bone is the most common presentation of unifocal LCH [2].

Parotid gland involvement by LCH has been rarely cited in the English literature. Lieberman et al [1] reported involvement of parotid gland by LCH occurring along with involvement of parotid-
associated lymphoid tissue. Weinmann et al [14] studied 13 patients using somatostatin receptor nuclear imaging as a diagnostic tool for LCH. Their results showed increased uptake in the salivary glands of two patients with multisystem disease without further elucidating the precise location of salivary gland involvement.

We document a case of a 34-yr-old Korean male with LCH involving the parotid gland and an adjacent lymph node. An extensive investigation failed to show any other lesion in the body. Parotid gland involvement in our case may be explained by a primary LCH of the gland or by a secondary spread from the contiguous lymph node. The presence of a parotid mass determined the operative approach. Pathologic examination confirmed parotid gland involvement by LCH.

Langerhans’ cell histiocytosis is a proliferation of Langerhans’ cells of unknown etiology. The clonality of Langerhans’ cells in LCH has been shown in several studies [15-17]. Willman et al [15] demonstrated monoclonality in CD1a-positive cells in 9 of 10 patients with various forms of LCH using X-linked polymorphic DNA probes. These authors concluded that LCH is a monoclonal disease with the reservation that clonality alone will not predict biologic behavior and clinical course [15]. In fact, some clonal lesions notoriously follow a benign clinical course, eg lymphomatoid papulosis and transient abnormal myelopoiesis in neonates with Down’s syndrome [18,19]. In a study of pulmonary LCH, Yousem et al [20] showed clonality in only 7 (29%) of 24 nodules examined. They concluded that pulmonary LCH is distinct from systemic LCH because the former is non-clonal, smoking-related, and frequently regresses [20].

Lieberman et al [1] believe that LCH is a reactive process more akin to sarcoidosis. The reactive nature of LCH is supported by the work of Yousem et al [20] who proposed that the polyclonal proliferation of Langerhans’ cells in the lung may be triggered by smoking. They also concluded that the reactive nature of LCH readily explains the benign clinical course in these patients.

An immunologic aberration has also been suggested as an etiologic mechanism for LCH. In this theory an inciting agent, such as a virus, is thought to trigger the activation and modification of the lesional histiocytes [21].

Langerhans’ cells are derived from monocyte/macrophage progenitor cells in the bone marrow. Langerhans’ cells are 15-20 µm in size with abundant cytoplasm. Their nuclei are vesicular and characteristically exhibit a long central longitudinal groove. Ultrastructurally, Langerhans’ cells contain Birbeck granules. These tubular granules show a pentalaminar configuration with a zipper-like central core. Occasionally, the granules are expanded at one end imparting a tennis-racket shape. Birbeck granules probably originate as invaginations of the cell membrane [1]. According to Favara [21], Birbeck granules are identified in 2 to 79% of histiocytes in LCH. There is no significant difference in size or shape of the granules between normal Langerhans’ cells and CD1-positive cells in LCH.

Langerhans’ cells normally reside in the skin, but they are also recognized in vaginal and buccal mucosa, lower respiratory tract, thymus, blood vessels, and lymph nodes [21]. Langerhans’ cells are a subset of histiocytic cells, which Foucar and Foucar [22] classify under the mnemonic M-PIRE (mononuclear phagocyte and immunoregulatory effector). M-PIRE comprises bone marrow-derived histio-cytes, which share functional and phenotypical characteristics. These antigen-presenting/immuno-regulatory cells consistently express HLA-DR, lysozyme, and leukocyte common antigen (CD45). Expression of S-100, CD4, CD15, and CD1 is more variable. The constituents of M-PIRE system include tissue histiocytes, dendritic reticulum cells, interdigitating reticulum cells, and Langerhans’ cells. Despite general phenotypical similarities, there are distinct differences among these cells. For instance, Langerhans’ cells consistently express CD1, which is only variably expressed in other histiocytic cells. Also Langerhans’ cells are unique in showing Birbeck granules, which are lacking in other histiocytes. Langerhans’ cells in LCH share most of the attributes of normal Langerhans’ cell with slight differences. These lesional histiocytes express CD11, CD14, and placental alkaline phosphatase, which are not expressed in normal Langerhans’ cells [23,24]. The histiocytic cells in our case showed CD1a, lysozyme,
and S-100 positivity. These immunohistochemical results and the presence of Birbeck granules confirmed that these histiocytic cells are Langerhans' cells. Staining for CD21, which is more consistently expressed in dendritic reticulum cells, was non-reactive in our case.

The prognosis of LCH rests on several factors including age, number of organs involved, and organ dysfunction [24,25]. Younger infants with organ dysfunction tend to follow a more aggressive course. Lieberman et al [1] reported 8 deaths in 153 patients with unifocal disease (mean follow-up, 14.3 yr); none of the deaths was attributable to LCH. The remainder of the patients with unifocal LCH were free of disease at last follow-up [1].

Treatment of unifocal disease consists of bone curettage, surgical excision, and/or radiotherapy. Radiotherapy is especially reserved for the treatment of lesions in weight-bearing bones or when organ function is threatened [25]. Chemotherapy is recommended in the management of LCH, particularly when the disease is multifocal. The currently recommended regimen includes vinblastine, corticosteroids, and 6-mercaptopurine, with or without etoposide [25]. Etoposide was withheld in our patient because of its potential toxicities and the long-term risk of secondary leukemia. Interestingly, pulmonary LCHs frequently undergo spontaneous regression or simply respond to smoking cessation [20].

Clinically, the differential diagnosis in our case included all the benign and malignant lesions known to occur in the parotid. It was important to consider the possibility of Kimura's disease. Oriental ethnicity, involvement of parotid gland, and the prominent eosinophilic component of the lesion validated inclusion of Kimura's disease in the differential diagnosis of our case.

Kimura's disease is a distinctive inflammatory lesion occurring primarily in the head and neck region in people from the Far East. Histologically, Kimura's disease is characterized by lymphoid follicles, eosinophilic infiltration, vascular proliferation, and fibrosis. Parotid gland involvement has been frequently reported [26,27]. However, the presence of characteristic Langerhans' cells with CD1a expression and the presence of Birbeck granules confirmed the diagnosis of LCH in our case.

In summary, we report a rare case of LCH in the parotid gland. The patient was treated with parotidectomy and adjuvant chemotherapy. There has been no evidence of recurrent disease after 20 mo of follow-up.

References

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