Langerhans Cell Histiocytosis of the Maxillary Jaw in an 11-Month-Old Girl

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Abstract
Langerhans cell histiocytosis (LCH), a monoclonal disease of histiocytes, may involve several organ systems but rarely involves the maxillary sinus as a primary site. This report presents an extremely rare case of LCH of the maxillary jaw in an 11-month-old girl. An incisional biopsy for a maxillary lesion was performed, and a histopathological diagnosis of LCH was established. The histopathological examination revealed the proliferation of histiocytes with an infiltration of eosinophils. Histiocytes were positive for S-100 and CD68 (KPI). The patient subsequently underwent chemotherapy with the resolution of LCH in the maxillary jaw, and has continued to show partial response as of 1 year after chemotherapy.

Introduction
Langerhans cell histiocytosis (LCH) is a granulomatous condition derived from a clonal proliferation of histiocytes (1–3). In 1987, the Writing Group of the Histiocytosis Society proposed LCH as the preferred term (3) to replace histiocytosis X, which had been proposed by Lichtenstein in 1953 (4). This disease encompasses three disorders—eosinophilic granuloma (EG), Hand-Schuller-Christian syndrome, and Letterer-Siwe syndrome—according to the clinical and pathological features (4). LCH is a relatively uncommon disease suffered by infants and children. Many factors have been considered as causes for this disease.

LCH is included in the category of histiocytic and dendritic cell neoplasms according to the classifications of the World Health Organization (WHO). LCH can be classified as single-system single-focal type, single-system multifocal type, or multi-system multifocal type. Recently, LCH has been classified by the WHO based on the lineage of the specific histiocytes involved: Langerhans cell; undifferentiated cell; dendrocyte; or macrophage (3, 4).

Case report
An 11-month-old girl was brought in by her parents with painless swelling of the maxillary gingiva that had pushed out a tooth in the past four years. The patient also showed small papules on the skin of the chest, abdomen and back upon the first examination (Fig.1). Upon examination, the lesion was found to be located at the lateral distal cusp region of the first deciduous molar of the right maxilla. Computed tomography (CT) revealed a 30 × 20 mm lesion in the right maxillary sinus (Fig.2A, B). Furthermore, the tumor had destroyed the bone of the eye socket and both
sides of the cranial fossa, and the upper jaw showed destruction of the alveolar bone. Gallium-67 citrate scintigraphy revealed an increased uptake in the right side of the maxillary sinus (Fig. 2C). Blood tests revealed that, the white blood cell count was high (12,700 cells/mm³), but C-reactive protein (CRP) levels in the plasma were normal (0.10 mg/dL). In addition, the proportion of eosinophils was normal (0.7%). No visceral lesions were seen in the systemic survey. An incisional biopsy for the right maxillary lesion was performed (Fig. 3). The histopathological examination revealed the proliferation of histiocytes with an infiltration of eosinophils (Fig. 4A, B). Immunohistochemically, these histiocytes were positive for S-100, CD68 (KPI), and vimentin (Fig. 4C–E). Each of the antibodies of monoclonal anti-S-100 antibodies (Santa Cruz Biotechnology, Santa Cruz, CA), mouse monoclonal anti-CD68 (KPI) antibodies (abcom discover more, Cambridge, MA) and rabbit polyclonal anti-vimentin antibodies (Santa Cruz Biotechnology, Santa Cruz, CA) were used for sections with a VECTASTAIN ABC Standard Kit (VECTOR LABORATORIES, INC, Burlingame, CA). Photomicrographs obtained after staining with antibodies to KPI, a glycoprotein antigen on the cellular surface, showed abundant Langerhans cells. A positive result of staining for S-100 indicates the likelihood that lesional histiocytes are Langerhans cells, indeterminate cells, or interdigitating dendritic cells. The findings indicated a diagnosis of Langerhans cell histiocytosis and therefore, LCH was diagnosed.

Since the patient had the multi-system multifocal type, she was treated with chemotherapy without curettage of the
Cytarabine (100 mg/m² per day) and vincristine (0.05 mg/kg per day) were used in accordance with the protocol of the Japan LCH Study Group (JLSG), for a month. At the follow-up, she continued to show partial response, and magnetic resonance imaging (MRI) showed a decreased lesion size in the right maxillary sinus (Fig. 5A, B). The small papules on the chest, abdomen and back skin disappeared. Gallium-67 citrate scintigraphy did not show any uptake (Fig. 5C). Next, she was treated using cytarabine (150 mg/m²/day) and vincristine (0.05 mg/kg/day) or methotrexate (1 mg/kg/day, intravenously) each week from September to October. Afterwards, vinblastine (6 mg/m², intravenously) was given to her once every 2 weeks, and 6-mercaptopurine (1.5 mg/kg/day, orally) was administered every day for ten months. An MRI showed a decrease-of-signal change in the right maxillary sinus lesion (Fig. 6A), and gallium-67 citrate scintigraphy showed uptake to the right thymus two years later after start of therapy (Fig. 6B).
Discussion

LCH is a rare disease involving antigen-presenting cells derived from marrow, and is characterized by permeation or increased numbers of the Langerhans cell. LCH represents an abnormal proliferation of tissue macrophages called Langerhans cells in one or more organs, including the spleen and bone marrow. In our case’s immunohistochemically, the tumor cells were positive for KPI, S-100 protein and vimentin. In addition, the proliferation of histiocytes had

Fig. 5. After treatment with cytarabine and vincristine. T1-weighted coronal (A) and axial (B) magnetic resonance imaging (MRI) reveals a hyperintense lesion to the right of the maxillary sinus (arrows). Gallium-67 citrate scintigraphy did not show a hot lesion (C).

Fig. 6. After chemotherapy, T1-weighted coronal MRI (A) shows a decrease in lesion size at the right side of the maxillary sinus (arrows). Gallium-67 (B) citrate scintigraphy shows a hot lesion to the right of the thymus (arrows).
appeared. Therefore, she was diagnosed with LCH. However, it was impossible to establish a diagnosis of EG, Hand-Schuller-Christian syndrome, and Letterer-Siwe syndrome according to the clinical and histopathological findings. Patient age ranges from 5 to 15 years in about 90% of cases, with a slight predominance among boys. LCH represents less than 1% of tumor-like lesions involving bone, and the majority of cases show solitary lesions (79%).

The most frequent site is the skull, followed in decreasing order of frequency by the femur, jaw, pelvis, ribs, spine, scapula, humerus, clavicle, and mandible. Hartman reported that 53% of LCH cases in the oral cavity were generated in a mandible. In addition, the predominant site of the posterior jaw region in the mandible was involved in 73 percent of the cases. Furthermore, the mandible is the most affected bone in cases of LCH. Dagenais et al. in a review of 29 cases of LCH found the majority of bone lesions presented in the posterior section of the mandible (distal and canine region) and in the ramus of mandible. When osteolysis is found in the anterior area of the mandible it is as an extension of the posterior. The present case represents an extremely rare case of LCH appearing in the right maxillary sinus. In addition, many bone lesions are seen in single-system LCH, while multi-system LCH is developed in the skin, liver, spleen, bone marrow, lymph nodes, lungs and central nervous system. Dagenais et al. in a review of 29 cases of LCH found the majority of bone lesions presented in the posterior section of the mandible (distal and canine region) and in the ramus of mandible. When osteolysis is found in the anterior area of the mandible it is as an extension of the posterior. The present case represents an extremely rare case of LCH appearing in the right maxillary sinus. In addition, many bone lesions are seen in single-system LCH, while multi-system LCH is developed in the skin, liver, spleen, bone marrow, lymph nodes, lungs and central nervous system.

As for the treatment of LCH, there are surgical treatment of extraction or curettage, chemotherapy using steroidal hormones and/or anticancer agents, or radiotherapy. Surgical treatment is chosen in most cases of LCH involving bone in the oral and maxillofacial domain. However, a lesion involving multiple internal organs or LCH of infants are recommended for chemotherapy using anticancer agents or subsequent bone marrow transplantation. The tumor in this case was reduced in the right maxillary sinus, and no tumor presence was evident in the oral cavity after chemotherapy. Yet, a new hot lesion in the thymus appeared on Gallium-67 citrate scintigraphy. Chemotherapy was performed for 1 year, and chemotherapy using cytarabine, vincristine, methotrexate, and 6-mercaptopurine seems to have been effective. However, a new thymic tumor was identified immediately after chemotherapy, thus, chemotherapy seems to have been ineffective against the new tumor. The thymic tumor suggested that the existing tumor in the right maxillary sinus represented a different type. The purine nucleoside analogue 2-chlorodeoxyadenosine (2-CDA) has been reported as being effective for infants with recurrent LCH. As this chemotherapy was not applied, the effectiveness of 2-CDA in the present case is unknown.

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**Consent**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

**References**