Treatment of localized langerhans' cell histiocytosis of the mandible with intralesional steroid injection: report of a case

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Localized Langerhans cell histiocytosis (LLCH), formerly known as eosinophilic granuloma, mainly affects the skull, mandible, vertebrae, and ribs in children and the long bones of adults. Symptoms range from none to pain, swelling, and tenderness over the site of the lesion. General malaise and fever occasionally are present. Radiographically, lesions appear as radiolucent areas with well demarcated borders. LLCH may resolve spontaneously after biopsy in a period of months to years. However, if features include continuous pain, decrease of function, pathologic fractures, migration and resorption of teeth, or rapid progression, then active treatment needs to be considered. Treatment approaches include surgery, radiotherapy, chemotherapy, and intralesional injection of corticosteroids. In children with mandibular LLCH, 1 dose of methyprednisolone succinate injection has proven to be adequate. However, injections have not been performed in cases involving pathologic fracture. We report a new case of LLCH of the mandible that caused a pathologic fracture in an adult patient. Repeated intralesional corticosteroid injections resulted in fracture line disappearance within 14 months and lesion healing by the end of the 36-month follow-up. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e53-e58)**

Langerhans cell histiocytosis (LCH), part of a group of clinical syndromes called histiocytosis X, is a rare disease of unknown pathogenesis involving clonal proliferation of Langerhans cells.[1] The disease mainly affects children between 1 and 15 years old, and the occurrence is estimated to be 1 in 2 million.[2] The etiology is unknown, and various theories suggest environmental, infectious, immunologic, and genetic causes. Some even believe that LCH is a neoplastic process.[3]

The term histiocytosis X was introduced by Lichtenstein in 1953 and comprises three disorders: Letterer-Siwe disease, Hand-Schüller-Christian syndrome, and eosinophilic granuloma.[4] Letterer-Siwe disease (acute disseminated form of LCH) is typically characterized by a skin rash, hepatosplenomegaly, anemia, lymphadenopathy, and bone lesions with dissemination, and it runs an acute or subacute course, usually affecting young children. Hand-Schüller-Christian syndrome (chronic disseminated form of the LCH) is classically associated with a triad of punched-out bone lesions, diabetes insipidus, and exophthalmos. This disease normally affects an older age group, often in the second and third decades but sometimes much older.[5]

Localized Langerhans cell histiocytosis (LLCH), formerly known as eosinophilic granuloma, is an intraosseous lesion with an eosinophilic infiltrate localized in the bone without visceral involvement. It accounts for 60%-70% of all cases of LCH and can be seen as solitary or multifocal bone defects. The skull, mandible, and ribs are most frequently affected in children. In adults, however, vertebrae and long bones are most frequently involved. The highest occurrence of the disease is in the first 3 decades of life, with males being affected twice as frequently as females.[6] Symptoms range from none to pain, swelling, and tenderness over the site of the lesion. General malaise and fever occasionally accompany the symptoms. Other clinical symptoms include loose teeth, bleeding, toothaches, headaches, and sensory disturbances.[7] Radiographically, lesions appear as radiolucent areas with well demarcated borders. The overlying cortical bone is often resorbed, and pathologic fracture may occur. If the lesions are located in the jaws, they may resemble periodontal diseases, apical cysts, ameloblastoma, central giant cell granuloma, vascular malformations, and malignancies.[8]

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Table I. Treatment of the mandibular Langerhans cell histiocytosis with intralesional steroid injections in the literature

Author	*Age, gender*	*Location*	*Symptoms*	*Corticosteroid and dosage*	*Resolution*
Cohen et al. (1980)[11]	5 yrs 9 mos, female	Right side mandible	Swelling, pain, fever	150 mg, 2 injections methylprednisolone	11 mos
Jones et al. (1989)[8]	10 yrs, female	Right side mandible	Pain and swelling	164 mg, 1 dosage methylprednisolone	8 mos
Watzke et al. (2000)[13]	39 yrs, male	Right and left side mandible	Swelling	25 mg, 6 injections triamcinolone	15 mos
Putters et al. (2005)[14]	28 mos, female	Right side body mandible	Pain and swelling	80 mg, 1 dosage methylprednisolone	6 mos
	9 yrs, male	Left side body mandible	Swelling and fracture	40 mg, 1 dosage methylprednisolone	3 mos
	15 yrs, male	Left side body mandible	Pain and swelling	80 mg, 1 dosage methylprednisolone	6 mos
Moralis et al. (2008)[24]	10 yrs, male	Left side angle of mandible	Progressive, pressure-sensitive swelling	200 mg, 1 dosage methylprednisolone	17 mos
Present case	25 yrs, male	Anterior and right side of mandible	Pain and swelling	80 mg, 80 mg, 60 mg, 3 injections methylprednisolone	14 mos

There are many methods used for the treatment of LLCH. These include surgical approaches (resection, curettage), radiotherapy, and chemotherapy, or a combination.[9] Spontaneous healing of the disease has also been described.[9,10] Additionally, there are case reports of treatment of the disease with intralesional injection of corticosteroids, and positive responses were reported in all cases (Table I).[8,11-14] Only 2 previous cases, both in children, involved pathologic fracture of the jaws, and both resolved after a single dose of methylprednisolone injection without repositioning.[8,14] Here we report a new case of mandible LLCH with a pathologic fracture in an adult patient that responded favorably to repeated intralesional corticosteroid injections.

Fig. 1. Panoramic radiograph of the case when first seen. Pathologic fracture was seen on the inferior border of the mandible.

CASE REPORT

A 25-year-old male patient was referred to the maxillofacial surgery clinic in September 2005 with a 1-year history of pain and tenderness in the anterior mandible. He had a recurrence of periodic pain once or twice a month and stated that the pain had a compressive character. He also reported swelling and loose teeth in his anterior mandible. The patient had previously been examined by his dentist, who sent him for evaluation of a radiolucent mandibular lesion seen in the panoramic radiograph.

The patient did not have any systemic diseases, and clinical examination revealed no facial asymmetry in the anterior mandible. The submandibular lymph nodes were palpable, tender, and mobile. Intraoral examination revealed poor oral hygiene. A proliferating mass with buccal expansion extended between the left canine to the right premolar region of the mandible. All anterior teeth and premolars of the right mandible were mobile. On the anterior and right side of the mandible, there was no occlusion between the upper and lower teeth because of the migration of the teeth. A large radiolucent lesion in the anterior and right premolar region of the mandible and pathologic fracture line were seen on a panoramic radiograph (Fig. 1). However, segments of the fracture were not mobile during the clinical examination. An incisional biopsy was performed under local anesthesia. During the biopsy, the mandibular incisors had to be removed owing to extreme mobility.

Histologic examination of the biopsy specimen showed the presence of multinucleated histiocytes, numerous eosinophils, and occasional fibrous tissue (Fig. 2). An S-100 protein antibody labeling procedure showed that these were consistent with Langerhans cells, and the features were diagnosed as LCH (Fig. 3). No additional lesions were found in radiographic examination of the spinal column, the pelvis, and the long bones, and chest radiographs showed no signs of lung involvement.

Intralesional streroid injection was chosen for the treatment. In this case, a 1-stage procedure was performed with injection of corticosteroids into the center of the lesion with an 18-gauge needle. The total volume of injected fluid was dependent on the amount that could be injected with reason-

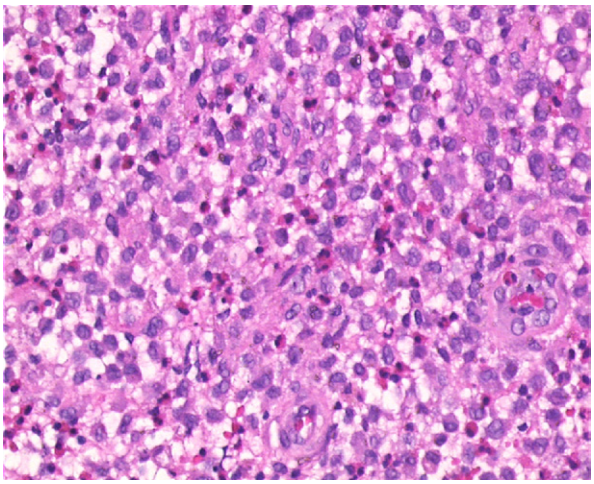

Fig. 2. Histologic details of the lesion, revealing proliferation of eosinophils, lymphocytes, and histiocytes (hematoxylin and eosin, ×100).

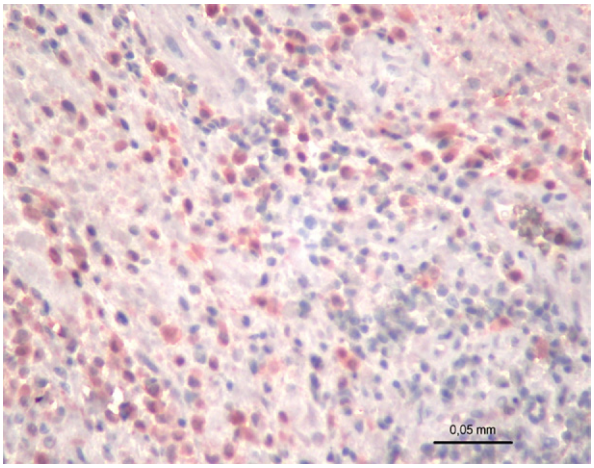

Fig. 3. S-100–positive stained cells were seen on immunohistochemical evaluation.

able resistance. An 80-mg methylprednisolone succinate (2 mL, 40 mg/mL) dose was injected into the center of the lesion under local anesthesia. A few days after the injection, the patient reported complete relief of pain, and all clinical symptoms disappeared within 2 weeks. Secondary complications were not observed after the corticosteroid injection, and the pathologic fracture progressively healed over the next 5 weeks of follow-up (Figs. 4 and 5).

Because an increasing radiolucent lesion was seen surrounding the right first premolar of the mandible, 80 mg methylprednisolone succinate was again injected in the premolar region of the mandible intralesionally in the fourth month (Fig. 6). At the eighth month, an increase in the radiolucent image of the second premolar was detected (Fig. 7). Therefore, 60 mg of methylpredisolone succinate was injected in the same region of the mandible at this appointment. In total, 220 mg methylpredisolone succinate was injected, involving 3 visits during the 8-month period. The patient was observed for clinical and radiologic followup at 1, 2, 4, 8, 14, 24, and 36 months. Near-complete resolution was seen after 14 months (Fig. 8). The pathologic mandible fracture showed no signs of consequent dislocation and exhibited complete reduction after 14 months (Fig. 9). At the time of writing, the patient was clinically well, and nearly complete healing was seen in a radiological image after a follow-up examination at 36 months (Fig. 10).

Fig. 4. A significant improvement was observed on the inferior border of the mandible after 5 weeks.

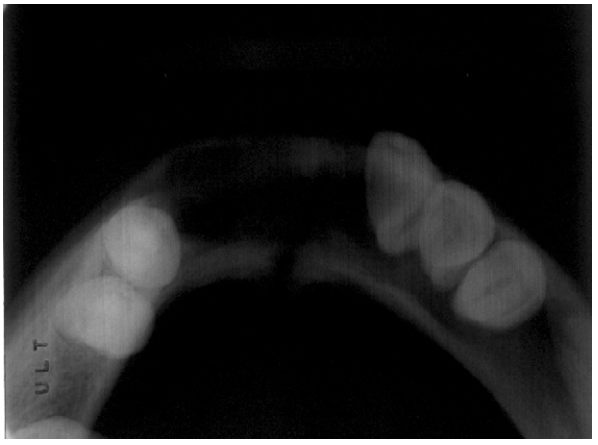

Fig. 5. Pathologic fracture line continued on the lingual aspect of the lesion in occlusal radiography after 5 weeks.

Fig. 6. Radiolucent image was detected on the first premolar after 4 months.

Fig. 7. Enlargement of radiolucent image of the lesion continued on the left premolar area in the eighth month.

Fig. 8. Nearly complete resolution was seen after 14 months.

Fig. 9. Occlusal radiography of the lesion 14 months after treatment.

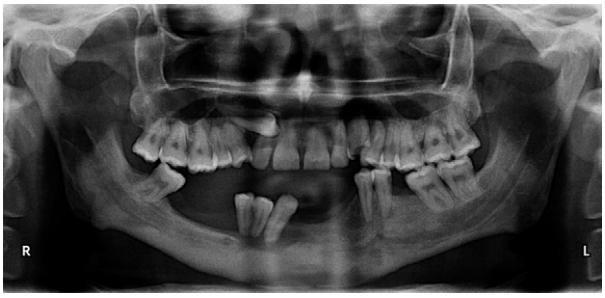

Fig. 10. State of healing 36 months after treatment.

DISCUSSION

Conventional treatment modalities of LLCH involve surgical interventions (i.e., curettage or resection) and radiotherapy and chemotherapy used either alone or in a combined fashion.[8] Although some lesions tend to heal spontaneously,[6,10,15] certain circumstances (such as persistent pain, mandibular dysfunction, pathologic fracture, migration or resorption of teeth, and rapid progression of the lesion) require active treatment.[8,14] Resections require demanding reconstructive procedures along with possible undesirable outcomes, such as paresthesia, abscess formation, and excessive bone loss after the reconstruction.[12] Although vigorous surgical curettage is known to yield successful outcomes, a number of recurrences have been reported with this technique. Damage to the teeth and their tooth buds, alveolar bone loss, and mobility of bony fragments, along with pathologic fracture,[14] are other possible complications. The efficiency of radiotherapy in LLCH of the jaws is controversial; although several observational studies have suggested that radiotherapy might produce local control of bone lesions in LCH,[7,16,17] Watzke et al.[13] have recorded completely unsuccessful results. An immediate intervention with relatively low doses is recommended for symptomatic lesions with significant risk of fracture, functional abnormality, or cosmetic disruption.[18-20] Radiotherapy for LCH is usually reserved for patients with inaccessible lesions in weight-bearing bones, and systemic therapy is usually reserved for the other forms of LCH.[25,26]

An alternative treatment approach for LLCH is intralesional steroid injection. This approach was first used involving a bone cyst by Scagletti et al.[21] A 2-year experience with 72 cases followed for more than 18 months revealed that 69 (96%) showed clearly positive results after the injection. Since then, others have obtained similar healing responses in bone cysts treated with one or more injections of methylprednisolone.[22,23]

In the present patient, we diagnosed a pathologic fracture before treatment. This fracture healed entirely at the end of the fourteenth month after treatment with intralesional corticosteroids without the need of repositioning or fixation. Concomitantly, the patient's complaints resolved within 1 week after the injection. In the literature, there are a few studies of intralesional steroid injection in treatment of LCH of the mandible (Table I). As far as we know, the method was first performed in eosinophilic granulomas of the bones by Cohen et al. in 1980.[11] Those authors injected a single dose of methylprednisolone directly into solitary eosinophilic granulomas of bones in various parts of the body. They

performed a second injection in the case of the mandible. Jones et al.[8] reported that a single intralesional dose of 165 mg methylprednisolone was administered to a 10-year-old girl who had LCH. They indicated that complete resolution of the lytic lesion of the mandible was observed after the eighth month. Watzke et al.[13] reported a patient with multifocal LCH of the mandible who failed to respond to radiation therapy and systemic therapy with etoposide and prednisone. Subsequently, the authors injected 2 mL 25 mg/mL triamcinolone into the lesion 6 times on a weekly basis. By the fifteenth month, complete remission was achieved. Putters et al.[14] added 3 new cases to the literature. Three patients (28 months, 9 years, and 15 years) with LLCH of the mandible were treated in a 1-stage procedure with intralesional injection of 80, 40, and 80 mg of methylprednisolone succinate, respectively. They reported that the lesions showed clinically and radiologically complete remission approximately 6 months after treatment. Moralis et al.[24] applied a single dose of 200 mg intralesional methylprednisolone into the lesion of the mandible. They reported that complete resolution of the lesion was observed after 17 months.

In the present case, we administered a second and third injection during the fourth and eighth months, respectively, because radiographically expansion of the lesion border along the left premolar area of the mandible was observed. We believe that the methylprednisolone did not initially diffuse into the whole lesion, such that a 1-stage procedure with intralesional injection was not sufficient in this adult. Regarding this point, Scaglietti et al.[21] reported that if the cavity persisted or there was only scanty osteogenic repair, local injection was repeated up to a maximum of 6 times at the same frequency. Moreover, they also reported that no abnormal biochemical findings due to excessive doses of corticosteroids were noted. In our opinion, local injection of the corticosteroids can be repeated if the lesion does not respond radiographically. At this point, the most important factor is adequate time between injections, because of the increased risk of adrenal suppression and other adverse effects. Based on the current literature, the adequate time between injections is estimated to be a minimum of 4-6 weeks.[27]

Long-term use of corticosteroids can cause various adverse effects, such as peptic ulcer, iatrogenic Cushing syndrome, delayed wound healing, and a tendency for infections and weakness. When corticosteroids are used over the physiologic dosage, occurrence of these adverse effects is likely to increase.[28] As far as we know, there are no adverse effects reported in treatment of LLCH with the technique of intralesional injection. As with the therapeutic injection procedure, there are some contraindications, including history of allergy or anaphylaxis to injectable pharmaceutics, peptic ulcer, Cushing syndrome, renal failure, uncontrolled diabetes mellitus, anticoagulation therapy, varicella zoster infection, and fungal diseases.[27]

Many questions and mechanisms still remain to be elucidated to understand the treatment pathway of corticosteroids in LCH. It is unknown whether steroids suppress the Langerhans cells, T lymphocytes, or eosinophils or, in contrast, stimulate osteogenesis.[14,29] Scaglietti et al.[21] suggest that microcrystals of the corticosteroid cause destruction of the connective tissue coating of the cyctic wall, thus allowing secondary osteogenic repair. In general, this hypothesis explains the injection of corticosteroids only in bone cysts and does not apply to LLCH, because no membrane covers the lesion. Another suggestion is that the biopsy reverses bone destruction. Therefore, it is generally accepted that LLCH heals spontaneously. In the present case, there was no spontaneous healing; the lesion expanded to the premolar area in the fourth month.

Intralesional injection of corticosteroids in the case of LLCH of the mandible is not difficult to perform. However, several precautions should be taken when using steroid injections. For instance, the injection should always be performed using sterile procedure to prevent secondary infection. Moreover, knowledge of the anatomy of the area is important. The injection should not be performed into the adjacent nerves of the target area. Furthermore, intravenous injection should be avoided because of systemic adverse effects such as adrenal suppression.[27]

In conclusion, the accumulating evidence suggests that intralesional corticosteroid injection is well tolerated by patients, the probability of postoperative complications is less than those of other methods, healing and the reduction are achieved without the need for surgical reconstruction of the pathologic fracture, and patient complaints and pain diminish rapidly (within the first week). This method is also minimally invasive and relatively inexpensive, although some adverse effects are possible. Further studies are required to evaluate the safety and efficacy of this treatment.

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