Ewing's sarcoma of the mandible: a combined approach to treatment

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Ewing's Sarcoma (ES) is a malignant tumor, which arises primarily in children. Most commonly found in the long bones and pelvis, it rarely is found in the bones of the face. This is a report of ES of the mandible in a nine-year-old Caucasian female. Treatment for this malignancy included an incisional biopsy, chemotherapy and radiotherapy protocol to the involved area in accordance with St. Christopher's Hospital and the Children's Hospital of Philadelphia. The patient is currently disease-free and has been for approximately five years.
J Clin Pediatr Dent 26(4): 409-412, 2002

INTRODUCTION

Ewing's sarcoma (ES), a malignant tumor, which arises primarily in children and was first described by James Ewing in 1921.[1] It is a primary malignant neoplasm of bone of unknown origin, but hypothesized to be of neuroectodermal or undifferentiated osseous mesenchymal cells of bone marrow origin.[2-4] It is the second most common malignancy of bone after osteogenic sarcoma.[3] Most commonly it presents in the pelvis and long bones comprising approximately 4-10% of all malignant bone tumors.[4] In the mandible the tumor occurs 4% of the time.[5] Importance is placed on detecting these tumors early, as they are prone to metastasize to bone, lung, or brain.[6] When present in facial bones, the mandible is most commonly affected.[7] Differing data exists as to whether or not a male gender predilection exists.[8] Caucasians are the race primarily affected by ES.[9] although it has been reported in all ages; a majority develops within the first two decades of life. The following is a case report of a nine-year-old female with primary Ewing's sarcoma of the mandible and a discussion of the combined team approach to treatment she received.

CASE REPORT

A nine-year-old Caucasian female had a two-week history of right mandibular swelling and sought treatment by her family physician (Figure 1). The swelling was attributed to an erupting tooth. Her physician prescribed oral Amoxicillin. After one week with continued swelling and a low-grade fever, she was referred to her general dentist, who after completing a clinical examination referred her to an Oral and Maxillofacial Surgeon. A clinical examination revealed significant moderate right facial swelling, which was hard to palpation with expansion of the mandible in a buccal-lingual direction with minimal tenderness. Neither pain nor paresthesia was reported. An extra oral exam revealed non-palpable lymph nodes. She presented in the mixed dentition stage without displacement of teeth. Panoramic radiographic examination revealed a mixed radiolucent/radiopaque lesion of the right mandible (Figure 2).

The patient was admitted to St. Christopher's Hospital for Children in Philadelphia for work-up and treatment. Her past medical history was unremarkable. She was carried to full term and delivered by C-section as were her previous siblings. Her family history was significant for a great aunt with breast cancer and a grandfather with hypertension and status post cerebrovascular accident. She denied the use of medications and had no known drug allergies. The remainder of the physical exam was unremarkable except for the facial and oral findings noted above.

Laboratory data on admission revealed a white blood cell count of 9.9 x 10^3 mm^3 and hemoglobin of 11.5g/dL. She was placed on Penicillin G. The following day she underwent an incisional biopsy of the right

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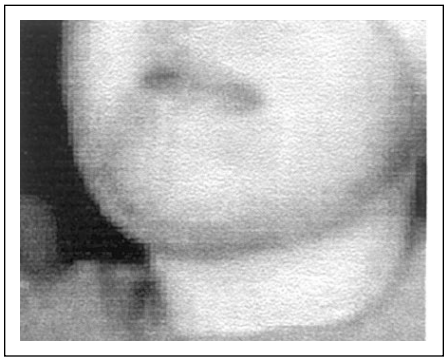

Figure 1. Preoperative photo.

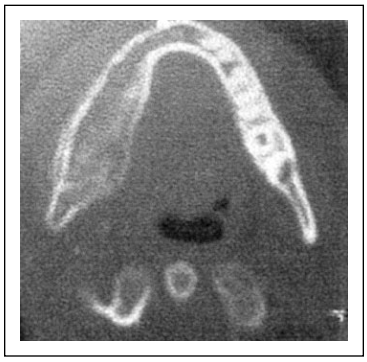

Figure 2. Preoperative CT scan.

mandible and the surgical removal of full bony impacted #32 and malposed teeth T and #31. The biopsy was sent for frozen section, which demonstrated changes consistent with a malignant small cell neoplasm. Pathology findings stated: a tumor consisting of "nests and small sheets of undifferentiated, small round cells, which permeate the marrow spaces and diffusely infiltrate the fibrous soft tissue, the majority of cells have little cytoplasm and the nuclei are round with fairly clumped chromatin and inconspicuous nucleoli, low mitotic activity, no rosette formation, no osteoid." Immunohistochemistry was positive for MIC2 antibody (HBL 71/013, also referred to as Experimental Ewing's Sarcoma Antigen.) LCA, epithelial membrane antigen and desmin were negative. Electron microscopy showed "cells with pools of glycogen and sometimes membrane bound secretory granules. Cell necrosis was evident." Post-operative lab values showed hemoglobin of 8.3g/dL. At this time the diagnosis of Ewing's Sarcoma was firmly established based on the radiographic and histological findings.

Hematology/oncology was consulted. Bronchoscopy and laryngoscopy were completed and potential airway obstruction was ruled out. She also underwent a CT of the head, chest, abdomen, pelvis and a bone scan. All tests were negative for metastasis. She was discharged the following day in stable condition on Amoxicillin 500 mg and iron sulfate.

One week later she returned to St. Christopher's Hospital for placement of a central line for a chemotherapy regimen of Vincristine, Cyclophosphamide with MESNA, and Doxorubicin in accordance with the oncology chemotherapy protocol (Table 1). Throughout the following year, she underwent several admissions secondary to an elevated temperature, elevated white blood cell count, and diarrhea. Cessation of the chemotherapy regimen was required several times for the management of side effects.

After five months of chemotherapy, she underwent extraction of multiple teeth, #1,2,23,24,25,26,27,28,29,30 with alveoloplasty and re-biopsy of the right mandible as a same day admission procedure. The biopsy at this time showed bone without evidence of previous tumor tissue. Nine months after initial diagnosis, she had an episode of bilious emesis. An obstruction series demonstrated dilated bowels and a stool positive for *Clostridium difficile*. She was prescribed a fourteen-day course of Flagyl. A CT of the body and re-biopsy of the initial tumor site was repeated one year after diagnosis without evidence of metastasis or malignancy.

Radiation therapy began 18 months after diagnosis at Temple University Hospital. She received a total dose of 5400 cGy of radiation throughout her treatment. Multiple oral ulcers developed during radiation

Table 1. Chemotherapy regimen.

Vincristine 1.5mg/m2 continuous infusion
Doxorubicin 75mg/m2 IV over 48 hours
Cyclophosphamide 1.2g/m2
Cyclophosphamide 2.1 mg/m2 for 2 days on week 0 and 6 only
Etoposide 100mg/m2/day for five days
Ifosfamide 2.4mg/m2/day for five days
MESNA 360Mg/M2 in D5W 0.45% NS on weeks 0 and 6 with the cyclophosphamide

Table 2. Immunhistochemical results from ES biopsy.

ANTIBODY	*RESULTS*
Leukocyte common antigen	Negative
Cytokeratin	Negative
Epithelial membrane antigen	Negative
Desmin	Negative
Vimentin	Focal positive
Actin (HHF35)	Negative
Smooth muscle actin	Negative
5100 protein	Negative
Neuron specific enolase	Positive
Neurofilament	Equivocally positive
Experimental Ewing's sarcoma antigen (HBA 71)	Positive
B cell (1-26, CD 20)	Negative
T cell (UCHL-1, CD 45 RO)	Negative

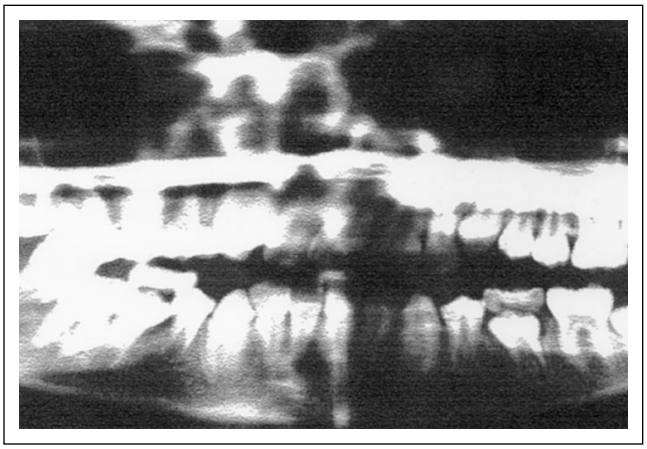

Figure 3. Preoperative panoramic radiograph.

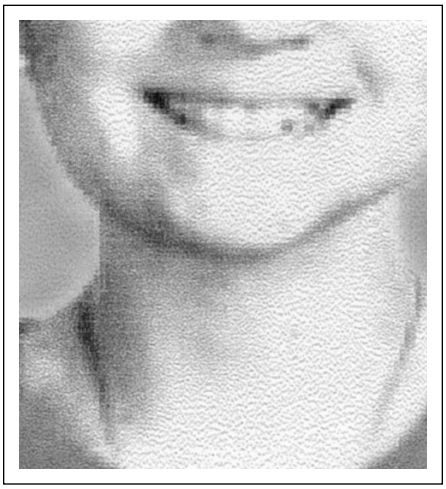

Figure 5. Post operative photo.

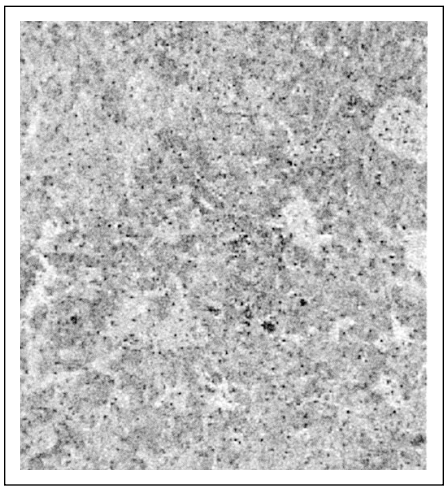

Figure 4. Histology staining from biopsy.

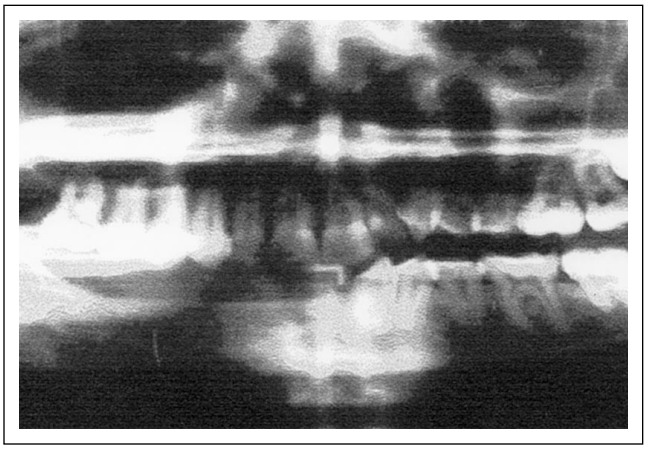

Figure 6. Postoperative panoramic radiograph.

and were treated palliatively with a combination of viscous lidocaine, benadryl, and Maalox, also known as "Magic Mouthwash."

The patient has been disease-free now for approximately five years. Anticipated future treatment includes hyperbaric oxygen treatment preceded by implant placement to restore function to the right mandible. Figures 4 and 5 show the two-year postoperative picture and panoramic radiograph.

DISCUSSION

Ewing's Sarcoma is a rare occurrence in the mandible and especially as the primary source being in the mandible. There is no national database on the occurrence, but a literature review for facial ES revealed approximately 100 reported cases in the mandible and maxilla. Although the origin of the tumor is still the subject of debate, immunohistochemical studies strongly support origin of ES being an uncommitted, primitive, mesenchymal cell.[9] The defect responsible for ES is thought to occur on chromosome 22. However, one report encountered questions if the disease does not have a viral association like Epstein Barr virus and a form of Burkett's lymphoma. Currently, a positive diagnosis is made with the use of electron microscopy and immunohistochemistry studies.

The most common presentation of the patient is a complaint of increased temperature and increased swelling generally mimicking an infection.[8-12] Other presenting signs include pain, paresthesia to the chin, albuminuria, loose teeth, elevated eosinophil sedimentation rate, and anemia.[13-15] Dehner states that a decrease in the hemoglobin level is indicative of a systemic nature of the disease.

Radiographic presentation has been traditionally described as being "onion skin" or "sun ray" in appearance. The onion skin appearance is thought to be a result of the periosteal reaction to elevation and invasion. However, a critical review of radiological features shows that onion skin and sun ray appearances are exceptions rather than the norm.[9] The most common radiological finding is that of an osteolytic poorly defined image.[18]

There is debate as to whether the onion skin appearance occurs or if it is obscured due to the complex facial

architecture upon radiograph. Other radiographic features, which have been described, are astrolytic lesions and destruction of the tooth follicles.[18] Hematogenous metastatic spread may occur to long bones and bone marrow.[15] Lymph nodes are rarely invaded due to sarcomas tendency to metastasize through blood.[17,16]

One should consider a differential diagnosis of: osteomyelitis (especially if febrile), eosinophilic granuloma, giant cell tumor, osteosarcoma, primary lymphoma of bone, spindle cell sarcoma of bone, Histiocytosis X, metastatic carcinoma, neuroblastoma, and rhabdomyosarcoma when presented with similar clinical and radiographic findings.[18] Evaluation of the lesion should identify the full extent with the use of plain films, CT's, MRI's, bone scans and biopsy. Goldstein *et al*. found 11% of patients diagnosed with ES had multiple lesions.

Macroscopically, Ewing's Sarcoma will often present as a whitish friable or gelatinous material with necrotic areas. Microscopically it is described as a small, round, blue cell tumor with a monotonous population of small round cells with hyperchromatic nuclei, nonconspicuous nucleoli, and scant cytoplasm. Focally, the neoplastic cells show considerable pleomorphism.[2] Histologically one would see a monomorphic proliferation of small round cells with clear cytoplasm arranged in sheets. The glycogen containing cells would stain PAS positive. Figure 3 shows the immunohistochemistry results obtained in an ES positive biopsy.

ES has been treated with chemotherapy and radiotherapy since the late 1960's. Since then, the addition of chemotherapy for ES treatment has raised the 5 year survival rate from 16% to 74%.[18] Ewing's of the head and neck area are generally more amenable to surgical resection, unlike the tumors of the long bones, where surgical resection is often more complicated and chemotherapy and radiation therapy are the preferred treatment methods of choice. Even with an isolated area of ES, the risk of metastasis is so great as to warrant chemotherapy as the mainstay for treatment.

CONCLUSION

In general, Ewing's Sarcoma is a rare malignancy, which may present in the facial bones. It should remain as a differential diagnosis of radiolucent or mixed radiolucent/radiopaque lesions of the facial bones when placed in the proper clinical setting. Methods of treatment of Ewing's Sarcoma are still debated. However, review of the literature supports the use of chemotherapy and radiation treatment in conjunction with surgery to provide the best prognosis. Patients should receive radiation therapy to the site of the primary lesion unless a complete resection of the primary lesion has been completed with an adequate margin of one-centimeter bony lesions with preferably 2-5 cm of normal marrow. The treatment for this patient consisted of an incisional biopsy for diagnosis, chemotherapy, multiple tooth extractions, and radiation therapy. She is presently status post 5 years without recurrence of disease.

The pediatric dentist plays an important role in disease detection and maintenance therapy during disease treatment. A panoramic radiograph should be considered in a situation such as this to rule out bony changes not detected on periapical films. Patients should receive care by their dentist during treatment, as chemotherapy can lead to oral infection, which should be detected and treated early.

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