Primary Ewing sarcoma of the anterior mandible localized to the midline

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Ewing sarcoma is a malignant, small, round blue-cell tumor of the bone that is usually located in the long bones and the pelvis. Fewer than 3% of all Ewing sarcomas originate in the head and neck region and these are mostly located in the posterior mandible. We report the case of a 17-year-old girl with a primary Ewing sarcoma localized at the midline of the anterior mandible. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e46-e50)

Ewing sarcoma is a malignant, small, round, blue-cell tumor with metastatic potential that usually occurs in older children and young adults. At initial diagnosis, approximately 25% of patients with Ewing sarcoma present with clinically detectable metastases.[1] The most important factor for prognosis is the presence of metastases at diagnosis.[2-7] Although Ewing sarcoma is most common in the long bone and pelvis,[8] there have been reports of Ewing sarcoma in the head and neck area, with a predilection for the posterior mandible.[9,10] Given the rarity of Ewing sarcoma, it is often not considered in a differential diagnosis for radiolucent jaw lesions. This is more so when it occurs in the anterior mandible, crossing the midline. Early diagnosis before metastasis is critical for improved survival in patients with Ewing sarcoma. We report a case of primary Ewing sarcoma of the jaw with unique location at the midline of the anterior mandible.

CASE REPORT

A 17-year-old female was referred by her general dentist for evaluation of a large, lytic lesion in her anterior mandible. She had complained to her dentist that she began to notice numbness and pain when she brushed her lower front teeth. Her dentist detected mobility to her anterior mandibular teeth, which on electric pulp testing were nonvital. There was some swelling and a large radiolucent lesion seen on radiographs, prompting referral for further evaluation.

On presentation, this patient was not in acute distress. She did have noticeable fullness of her anterior mandible and mentum, which deviated to the right. The intraoral examination revealed a bulging lesion extending from premolar to premolar that obliterated the mandibular vestibule. The overlying mucosa was intact but markedly thinned by a bluish-black submucosal lesion. The mandibular teeth from #21 to #28 were not displaced but quite mobile. Panorex and computed tomography (CT) scan revealed a well-delineated multilocular lesion that extended from the mandibular right second premolar to the left second premolar (Figures 1 and 2). There was no resorption of the root of the overlying teeth. In the incisor region, the facial cortex was absent and the lingual cortex was thinned, as was the inferior border. There was some paresthesia to the lower right lip and gingiva, but profound anesthesia was not present. Given the location and the patient's age, the differential diagnosis included central giant cell granuloma, ameloblastoma, and odontogenic myxoma; however, a more ominous lesion could not be ruled out.

An incisional biopsy was performed after aspiration of the lesion was determined to be negative. After carefully elevating a mucosal flap, the lesion could be easily noted. Extreme bone destruction was clearly evident. The lesion consisted of a friable, gelatinous clotlike material. Hemostasis was easily obtained with gelfoam after clorhexidene irrigation and the flap approximated with 4-0 chromic gut suture.

The incisional biopsy specimen consisted of multiple pieces of soft tissue measuring 2.0 × 1.0 × 0.3 cm in aggregate dimension. Histologic examination revealed uniformly bland, small, round tumor cells with well-defined nuclei and ill-defined cell borders. The tumor cells formed variable-sized nests separated by fibrovascular septa in lobular patterns. In other areas, tumor cells formed broad sheets (Figure 3). Few mitotic figures were seen. The cell cytoplasm was positive for periodic acid Schiff stain and diastase labile, which demonstrated glycogen content. The cells were positive for CD99 and Fli-1 (Figures 4 and 5) and were negative

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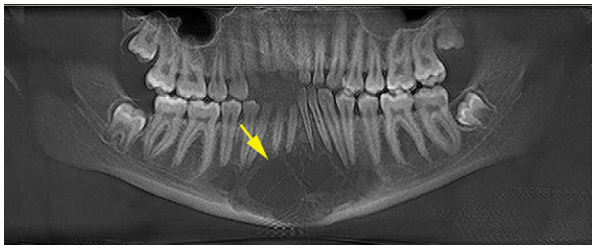

Fig. 1. Panoramic image depicts a large, well-defined, multilocular radiolucent lesion of the anterior mandible with mild displacement of teeth. There is a second more radiolucent area within the lesion indicating perforation (*arrow*). Fine septae within the lesion can be seen.

for CD56, synaptophysin, chromogranin, CD31, CD34, "cytokeratin", desmin, myogenin, and CD45. The histologic diagnosis was most consistent with Ewing sarcoma. Molecular diagnostics confirmed Ewing sarcoma by this fluorescence in-situ hybridization (FISH) analysis using EWSR1 break-apart probe. FISH analysis demonstrated that the cells were positive for rearrangement; a split signal was noted in 87.6% of the cells (Figure 6).

Subsequently, the patient was referred to a pediatric hematology/oncology center for further evaluation and treatment. Magnetic resonance imaging (MRI) was performed for primary tumor assessment, and confirmed the presence of a 3.4 × 2.8 × 4.8-cm enhancing lesion arising from the mentum of the mandible (Figure 7). A positron emission tomography/CT scan revealed increased fluorodeoxyglucose uptake at the site of the primary mandibular lesion, but no evidence of lung or other metastases. Bilateral bone marrow biopsies revealed no evidence of bone marrow metastases. The patient was started on a chemotherapeutic regimen of vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide/etoposide (following a recent Children's Oncology Group protocol for localized Ewing sarcoma, AEWS0031). She has had 3 cycles of chemotherapy thus far, and her lesion appears smaller. Radiation therapy and possible surgery are planned.

DISCUSSION

In 1921, James Ewing described material curetted from bone tumors of unknown origin and nature as a diffuse endothelioma of bone. He described the material as having broad sheets of small cells with hyperchromatic nuclei.[11] Three years earlier, Arthur Purdy Stout described what may have been the first reported case of primitive neuroectodermal tumor, calling it *peripheral neuroepithelioma*.[12,13] More recently, Askin et al.[14] found a small, round-cell lesion localized to the chest wall. Subsequent cytogenetic studies have shown that Ewing sarcoma, primitive neuroectodermal tumors, and Askin tumor share the same genetic translocation, t(11; 22), which led to the proposal to call these malignancies (which have similar sites of origin, patterns of metastases, and clinical behaviors) the Ewing family of tumors.[15-17]

Ewing sarcomas are malignant small, round, blue-cell tumors that primarily arise in bone and soft tissue with limited neuroepithelial differentiation.[5,15] Although the exact histogenesis is unknown, they are thought to represent primitive mesenchymal cells with limited neural differentiation potential.[5,18] However, neural, endothelial, and epithelial origins have all been hypothesized as the original cell lineage.[19] Ewing sarcoma is considered to be the second most common primary malignancy of bone in children. Ewing sarcoma primarily affects older children and adolescents and is rare before the age of 5 and after 30 years of age. It has a predilection for white individuals and is uncommon in African Americans and is seen more frequently in males. The most common location for Ewing sarcoma is in the long bones and pelvis.[6,8,13] When Ewing sarcomas metastasize, the most common locations are to lungs and to bone.[20] Ewing sarcoma rarely spreads to lymph nodes.[6]

Ewing sarcoma is rare in the head and neck region, affecting the bones of the skull or face in about 1% to 4% of the cases.[9] Of the gnathic bones, the mandible is more commonly affected than the maxilla, with an incidence from 1% to 10%.[9,10] In addition to our case, we know of only one other primary Ewing sarcoma that involved the anterior mandible.[10] Given the rarity of Ewing sarcoma in the mandible, data on clinical outcomes are lacking for patients with jaw lesions compared with other sites. In larger studies, mandibular primaries are often merged into the broader category of "head and neck." In 1987, The InterGroup Ewing Sarcoma Study reported 6 cases of primary Ewing sarcoma from the mandible of 29 primary cases from the head and neck. The authors concluded that primary Ewing sarcoma of the head and neck had a better survival rate than primaries from other sites.[9] In a 10-year retrospective review of Ewing sarcoma, 5 of 70 cases were located in the head and neck region, and only 3 of the 5 cases were located in the mandible.[21]

Clinically, the most common presenting symptom is a slow-growing, firm, enlarging mass with or without pain or tenderness. Some cases also present with systemic symptoms, such as fever.[6,13,21] In the oral cavity, swelling of the affected area is seen along with pain, loosening of teeth, and paresthesia.[10,22] Radiographically, Ewing sarcoma presents with poorly defined osteolytic lesions, cortical erosion, sun-ray spicules of periosteal bone, and displacement of teeth. There is often a soft tissue mass adjacent to the destructive site.[22]

Histologically, small, round, blue cells in the pediatric population have a wide differential that includes Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, and lymphoma. Although not specific, most Ewing