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CLINICAL PATHOLOGIC CONFERENCE CASE 4: A 15-YEAR-OLD BOY WITH RADIOGRAPHIC CHANGES IN THE LEFT MANDIBLE

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Clinical Presentation: A 15-year-old boy who experienced pain on chewing was referred regarding mobility of his mandibular left molar teeth. He was otherwise in good health with no relevant medical history. Radiologic examination of the mandible revealed several dental and bony changes: widening of the left ramus of the mandible with a diffuse increase in bone density, the left body of the mandible was vertically enlarged, the third molar crown was deformed and the root was rudimentary or absent, the roots of the mandibular left second molar tooth were shortened, and the second premolar root apex was also slightly foreshortened (Figure 1). A 99mTc MDP (methoxydiphosphonate) bone scan showed extensive uptake in the left mandible (Figure 2). Full blood count was normal.

Differential Diagnosis: Based on the clinical and imaging findings, a variety of differential diagnoses were considered.

Chronic osteomyelitis of the mandible encompasses a spectrum of clinical entities including proliferative periostitis (Garre's osteomyelitis), which is a non-suppurative condition with low-grade diffuse inflammatory reaction, usually associated with a periapical infection, characterized by thickening of the periosteum and subperiosteal deposition of bone, resulting in enlargement of the affected region.

Chronic non-specific sclerosing osteomyelitis/osteitis is currently considered to be an auto-inflammatory disorder that may affect the mandible and is characterized by patchy areas of sclerosis and radiolucency on imaging that may cause mandibular enlargement. The changes represent the manifestation of a chronic inflammatory reaction in both the cortex and medulla, with associated endosteal and periosteal thickening. Subsequent diffuse cortical thickening and narrowing of the medullary canal occurs. The process may occur at any age, although it is most frequent in late childhood and adolescence. There is a slight female predominance and is characterized by relapses and remissions.

Systemic symptoms are rare, along with mild fever and mild elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The process may be unifocal or multifocal and may be recurrent. Non-specific chronic inflammation, which includes plasma cells with reactive sclerosis, is noted histologically. There are no sequestrae, abscess formation is not identified, and culture is negative. Associated pustular skin disorders may occur ('SAPHO' syndrome).[1]

Intraosseous vascular malformations of the maxillofacial region sometimes give rise to dental emergencies because of proximity of the teeth to the intramedullary lesion. Those near the alveolar bone often present with pericoronal bleeding, mobile teeth, and sometimes occlusal anomalies.[2] In contrast to our case, vascular malformations in the mandible and maxilla usually produce a poorly defined, radiolucent lesion with a honeycomb or soap bubble appearance.[2] Root resorption has been observed, creating an appearance of teeth floating in the adjacent alveolar osseous erosion.[3]

Mandibular fractures during childhood may result in altered permanent tooth development and eruption, dependent on the stage of development at the time of fracture. Mandibular growth can be affected in an unpredictable manner and the presence of infection will also have a significant effect. There was no such history in this case.

Based on the presence of a sclerotic lesion, matrix producing tumors including osteoma, osteoid osteoma, osteoblastoma, ossifying fibroma, and fibrous dysplasia were considered. These entities are usually more clearly delineated and well-circumscribed on imaging. Osteosarcoma could be entertained based on the presence of a poorly defined alternating sclerotic and radiolucent lesion, although overt aggressive features are the norm.

In this age group and at this site, chondrosarcoma was considered highly unlikely. Langerhans cell histiocytosis may occur at any age, and the jaw is the second most common site of involvement in the head and neck region. In contrast to our case, these are usually characterized by a radiolucenct appearance, frequently involving one or more areas in one or more quadrants, with loosening of the associated teeth.[4-8] Finally lymphoma may rarely be associated with bone sclerosis.[9]

Diagnosis and Management: A biopsy of the region was performed and the tissues fixed in 10% buffered formalin. The fragments comprised pieces of hard and soft tissue measuring up to 10 mm in size. All were processed in a routine fashion with decalcification of the hard tissue components.

On light microscopy there were multiple fragments of tissue, one of which comprised a portion of dental follicle. Multiple separate fragments of fibrous tissue and bone were present. Within the fibrous tissue, crushed hyperchromatic poorly preserved cells were present. In the bony tissue, better preserved sheets of atypical cells with a high nuclear-to-cytoplasmic ratio

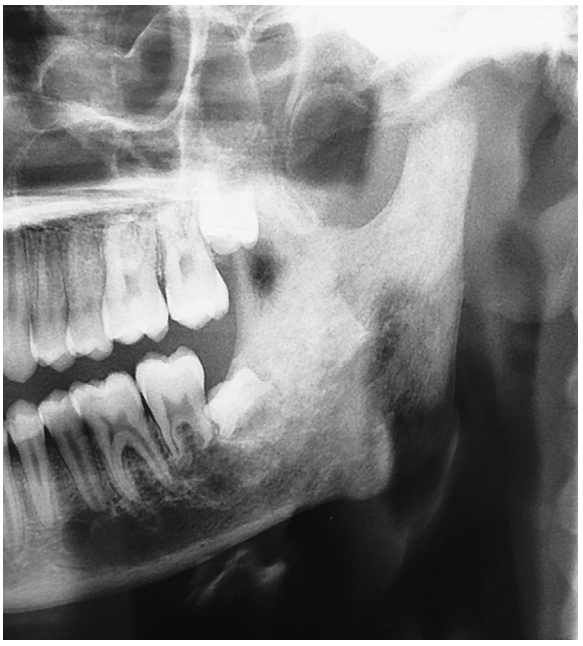

Fig. 1. Radiologic findings. An orthopantomogram revealed widening of the left ramus of the mandible with a diffuse increase in bone density. The left body of the mandible was vertically enlarged. There was relative radiolucency in several regions. The third molar crown was deformed and the root was rudimentary or absent. The roots of the mandibular left second molar tooth were shortened. The second premolar root apex was also slightly foreshortened.

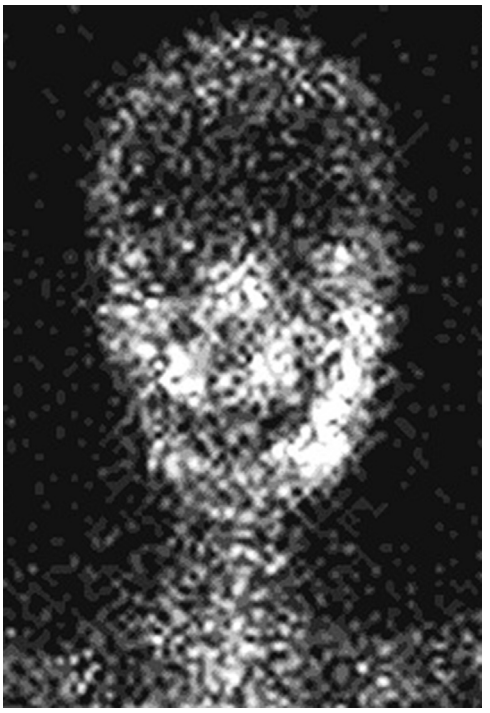

Fig. 2. 99mTc MDP (methoxydiphosphonate) bone scan showed extensive increased uptake in the left mandible.

and mildly variable, enlarged slightly convoluted nuclei were noted. The cytoplasm was inconspicuous. Nucleoli were small and the chromatin evenly distributed and bland. Rare mitoses were noted. The accompanying osseous tissue comprised predominantly woven bone lined by the atypical cells, also noted in osteocyte lacunae. Occasional fragments of immature lace-like/filigree-type osteoid production by tumor cells was seen, focally surrounding and encasing pre-existing mature host lamellar bone characterizing a destructive permeative process (Figure 3).

Histopathologic features were those of a small, round, blue cell tumor with immature tumor osteoid production. Although this prompted consideration of Ewing sarcoma (ES), the presence of atypical/malignant osteoid production in this setting is characteristic of small cell osteosarcoma.

This diagnosis was supported by the presence of distinct sclerosis on imaging.

Immunohistochemical stains showed distinct strong membrane staining for CD99 and FLI1 nuclear positivity was noted (Figure 4). Cytokeratins AE1/AE3 and CAM 5.2, chromogranin, synaptophysin, CD45, CD43, CD3, TdT, CD117, CD1a, and myeloperoxidase were all negative.

Subsequent FISH analysis was performed using LSI EWSR1 (22q12) dual-color break-apart rearrangement probe (Vysis, Abbott Molecular, Des Plaines, IL) which split (rearranged) EWSR1 signals in 94% of cells scored. This is molecular cytogenetic evidence of a translocation involving the EWSR1 gene at 22q12 such as the t(11;22) or t(21;22) (Figure 5).

Although the constellation of histopathology and imaging is in keeping with small-cell osteosarcoma, the positivity for CD99 and FLI-1 raises the possibility of a rarely documented possible variant of Ewing tumor. This was confirmed by FISH testing, in which translocation involving the EWSR1 gene at 22q12 was identified.

The patient was treated with compressed Ewing protocol, which comprised 10 cycles of vincristine, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Resection and reconstruction with a free vascularized graft was successfully performed after 7 cycles of chemotherapy.

A complete response to chemotherapy was achieved on examination of the resection specimen and a further 3 cycles of chemotherapy ensued.

Discussion: Small-cell osteosarcoma (SCO) is a rare variant of high-grade osteosarcoma with clinical features and distribution similar to conventional osteosarcoma but characterized by small, round, blue cells similar to ES, in which at least focal atypical, non-reactive osteoid production is identified. It is usually not associated with the presence of ES translocation and is therefore considered to be a unique entity. SCO can rarely be positive for CD99, but a negative result supports the diagnosis of SCO.[10] Thus far, FLI 1 expression has not been identified in typical forms of SCO.[11]

The ES/primitive neuroectodermal tumor (PNET) family of tumors comprises a group of small round cell tumors genetically defined by a specific reciprocal chromosomal translocation between chromosomes 11 and 22. The t(11;22)(q24;q12) is present in about 85% of cases.[12] The rearrangement results in the translocation of the 3' portion of the friend leukemia virus integration site 1 (*FLI1*) gene from chromosome 11 to the 5' portion of the Ewing sarcoma (*EWS*) gene on chromosome 22.[13] Occasionally, alternative translocations are observed involving chromosomes 22q12 and either 21q22 (10%) or 7p22 and 17q12. Rearrangements of *EWS* with *FLI* or a *FLI*-related gene