Case Report
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Chondroblastic Osteosarcoma of the Mandible with Genetic and Environmental Risk Factors: A Case Report

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Abstract

Chondroblastic osteosarcoma is a rare craniofacial malignancy. The purpose of this report is to relate a rare case of chondroblastic osteosarcoma in a 52-year old African American female with genetic and environmental risk factors with an emphasis on clinical, radiographic and histopathologic presentation and management of the tumor. The patient presented with a painful mass in the mandible. Medical history was significant for invasive ductal carcinoma of the breast treated with radiation and lumpectomy and ovarian cancer. Physical exam revealed expansile mass in the left body of the mandible. Imaging study showing radiopaque mass within the left hemimandible with aggressive periosteal reaction, osteoid and chondroid matrix formation. An incisional biopsy was performed, and the histopathologic report was compatible with chondroblastic osteosarcoma. Patient received chemotherapy, segmental mandibulectomy with neck dissection and reconstruction with osteocutaneous fibula free flap. Although osteosarcomas are rare, this well documented case justifies investigation given patient's risk factors.

Introduction

Osteosarcoma is a rare malignant neoplasm with ability to produce immature bone or osteoid; more often encountered in children and young adults [1]. It has been found to primarily affect the metaphysis of long bones of the extremities [2]. Less than 10% of the osteosarcomas has been reported in the head and neck region [3], accounting for less than 1% of all head and neck cancers [4]. There is no sex predilection [5] and 60% occur in the mandible [6]. Genetic profiling has identified several abnormalities, including loss of *IDH1* and alterations in *Rb*, *p53*, *BRCA* genes [7]. The purpose of this report is to relate a rare case of chondroblastic osteosarcoma in a patient with genetic and environmental risk factors with an emphasis on clinical, radiographic and histopathologic presentation and management aspect of the tumor.

Case Description

A 52-year-old female of African American origin, presented to the Oral and Maxillofacial Surgery clinic at the Dental College of Georgia with a growing painful mass in the lower left posterior quadrant of six years duration. Patient stated that she first noticed the mass in 2013, which at the time was a small asymptomatic gingival mass, and it continued to progressively become larger. The patient's medical history was significant for human immunodeficiency virus (HIV), invasive ductal carcinoma of the breast status post chemoradiation and lumpectomy, ovarian cancer status post abdominal hysterectomy, Gastroesophageal Reflux Disease (GERD), and Obstructive Sleep Apnea (OSA).

Extra oral examination was significant for gross facial asymmetry with palpable in duration along left posterior-inferior border of the body of the mandible. No color or texture changes to the overlying skin were appreciated. Mouth opening was found to be unaffected, and there were no signs of trigeminal nerve paresthesia. No palpable lymphadenopathy was noted during the head and neck examination.

Intraoral examination demonstrated expanding irregular mass, approximately 4 cmx4 cm, in the left posterior mandibular quadrant. Overlying gingival tissue was smooth, erythematous and ulcerated (Figure 1). The mass was tender to palpation. The adjacent teeth did not exhibit significant mobility.

A panoramic radiograph (Figure 2) demonstrated widening of periodontal ligament space (Garrington sign), loss of lamina dura and root resorption involving left mandibular first molar. There was a classic sunburst appearance secondary to reactive bone formation surrounding the left

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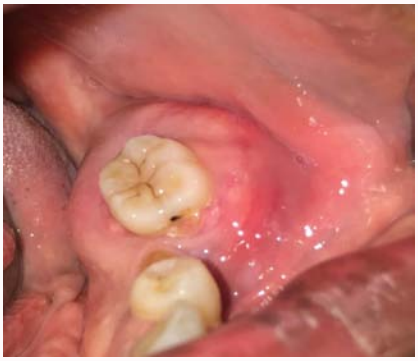

Figure 1: Clinical photograph demonstrating erythematous, nodular, ulcerative growth involving left posterior mandibular body.

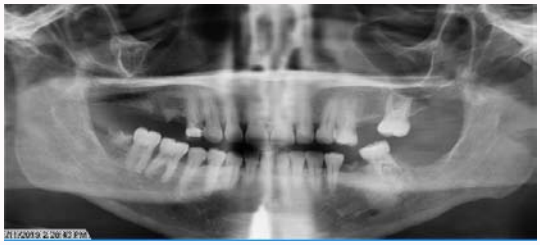

Figure 2: Panoramic radiograph with mass noted on patient's lower left jaw. A widening of periodontal ligament space (Garrington sign), loss of lamina dura and root resorption of the left mandibular first molarcan also be seen.

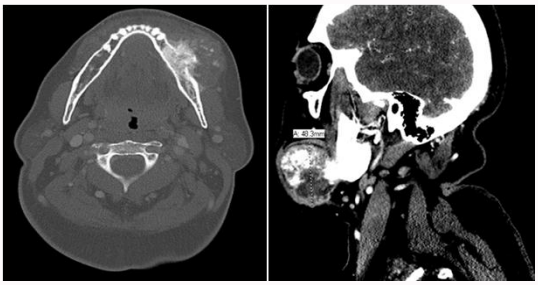

Figure 3: CT demonstrated interval increase of mass (4.4x4.3x4.8 cm) within the left hemimandible with aggressive periosteal reaction and osteoid matrix formation.

mandibular first molar. A Computerized Tomography (CT) scan of Neck/Chest with IV contrast (Figure 3) was obtained after the biopsy, demonstrated interval increase in the size of the mass and a mottled radiopaque mass (4.4x4.3x4.8 cm) within the left hemimandible with aggressive periosteal reaction and osteoid matrix formation. In addition, level 1B lymph node was suspicious for regional metastasis. A Positron Emission Tomography (PET) scan demonstrated soft tissue involvement of left lower anterior neck extending slightly medially into the oral cavity alongside the tongue; however, there was no evidence of distant metastases.

An incisional biopsy of the lesion was performed with a provisional diagnosis of osteosarcoma. The submitted specimen consisted of six tan/brown/black mixed hard and soft tissue fragments and a mandibular molar tooth with a mostly intact crown and extensive, irregular, "spiking" and "melting ice"-like root resorption. The specimen was demineralized. Microscopic examination revealed surfaces of para-keratinized stratified squamous epithelium associated with diffuse and mild infiltrates of acute and chronic

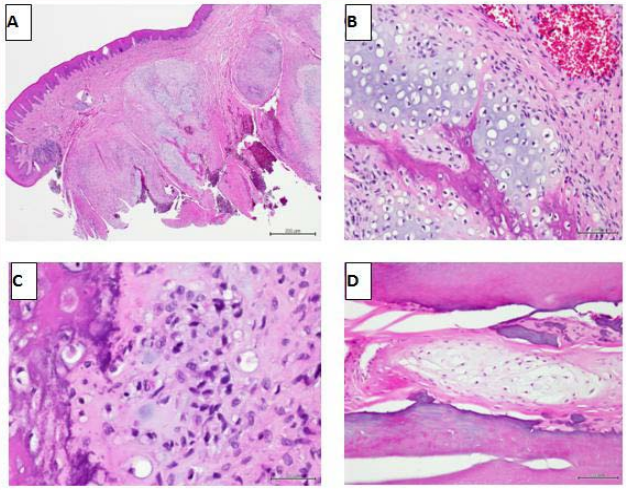

Figure 4: Microscopic Features (50-400X). A) Low power view of one portion of the specimen. Note the multilobular lesion subjacent to the surface epithelium. B) Note the proliferation of spindled cells and deposition pale basophilic chondroid and amphophilic osteoid. C) High-power image of neoplastic cells in direct proximity to the osteoid and chondroid. D) Root canal with neoplastic cells and chondroid.

inflammatory cells. The underlying connective tissue was moderately dense and contained a multilobular cellular mass associated with a large amount of matrix. The neoplastic cells formed sheets and varied from polygonal to ovoid to spindled, with often indistinct cell borders, frequently vesicular nuclei, pale eosinophilic and sometimes vacuolated cytoplasm. Nuclear pleomorphism was mild throughout the mass. In some areas, the cells were smaller, spindled to stellate, with deeply basophilic nuclei, forming clusters and strands separated by abundant eosinophilic matrix that transitioned to mineralizing osteoid or pale-basophilic chondroid. The osteoid often showed a chicken wire-like pattern, and the chondroid also contained areas of mineralization. There was a small amount of residual bone undergoing resorption in association with neoplastic cells. Sections of the molar tooth revealed essentially normal dentinal tubules, and a pulp chamber with viable pulp and vascular congestion. The roots exhibited marked irregular external resorption. The apical portion of one canal contained neoplastic cells along with chondroid and osteoid matrix. A diagnosis of chondroblastic osteosarcoma was rendered.

A multidisciplinary team including Oral and Maxillofacial Surgery, Otolaryngology and Hematology/Oncology was involved in the management. The patient received one cycle of neoadjuvant cisplatin and doxorubicin prior to her surgery; however, it was aborted due to the lack of response. A segmental resection of the left mandibular body with wide surgical margins was performed. In addition, left modified radical neck dissection was carried out and the mandibular defect was reconstructed with vascularized osteocutaneous fibula free flap. Resected tumor exhibited similar histopathological findings and confirmed final diagnosis of Stage IIA pT1N0M0 chondroblastic osteosarcoma. The patient was not given any further adjuvant therapy due to negative margins and the absence of adverse features on the final pathology specimen. The patient was placed on surveillance every 3 months for the first two years and thus far has had no signs of recurrence.

Discussion

Osteosarcomas arise from malignant mesenchymal cells that deposit osteoid and/or chondroid matrixor fibrous tissue [7]. The

incidence is approximately 2 to 3 per 1 million persons per year [4]. Although osteosarcomas are the most common primary malignancy of long bones [8] their occurrence in craniofacial region is rare and accounts for only 6.5-7% of all the osteosarcomas [3]. Osteosarcoma of the jaws is typically seen at a median age between 30 and 40 years [5] with equal prevalence in males and females [6]. Mandible is more commonly affected than the maxilla [6]. Patients with mandibular osteosarcoma were reported to have a 10% better 5-year survival rate than those with maxillary tumors, although the survival differences were not statistically significant [9].

Etiology of osteosarcoma is believed to be multifactorial. Several factors have been implicated such as environmental (ultraviolet and ionizing radiation), genetic (mutations of *Rb* or *p53* gene) and predisposition to diseases involving rapid bone growth (Paget's disease) [10]. Ionizing radiation has been estimated to cause up to 3% of osteosarcoma; some of which can take up to 30 years to appear [11]. Kovac et al., [12] reported that mutations in the *BRCA2* and other genes, such as *p53*, *PTEN*, and *IDH1*, are the main drivers in 87% of the osteosarcoma cases. In addition, mutations described by Kovac et al., [12] are known cancer drivers in other types of cancer. Our patient had multiple risk factors such as ovarian and breast cancer, history of radiation therapy, and immune compromised status secondary to HIV.

Initial clinical presentation of osteosarcomas may be asymptomatic, progressing to pain and swelling. However, pain and swelling are non-specific, as they are also present in a number of other malignancies, infections such as osteomyelitis with proliferative periostitis, and benign neoplastic disease [6]. An important clinical feature is neurosensory change such as paresthesia. Surprisingly, this clinical manifestation was absent in our case. The patient first noticed the lesion in 2013 but did not seek care until 2019 because the lesion was asymptomatic until then. In a case series reported by Padilla et al., [13] the elapsed time between patients being aware of having a lesion and their presentation to an oral health care provider varied between 1 week and 2 years. Other signs and symptoms include displacement and loosening of teeth, and epistaxis with or without nasal obstruction if the lesion involved the nasomaxillary region.

Radiographically, the lesion can appear radiolucent, radiopaque, or mixed radiolucent-radiopaque. The most common presentation is a mixed radiolucency-radiopaque pattern and poorly defined borders [14]. A sunray/sunburst radiographic pattern, which occurs due to periosteal reaction producing extracortical bone formation, is not a pathognomonic finding as it may be absent or can present in other neoplastic lesions [6]. Other non-specific signs include root resorption and widening of the periodontal ligament space. CT and MRI are essential tools that aid in surgical planning by detecting intramedullary and extramedullary extent of disease, invasion into adjacent tissues and distal metastasis. Distant metastasis was reported in 10-20% of the head and neck osteosarcomas [14], lungs are a common site of distant metastasis [6,8,15]. Although distant metastasis was not found in our case, PET scan revealed invasion into soft tissue of the anterior neck, necessitating neck dissection.

Biopsy of any lesion suggestive of osteosarcoma is warranted as early as possible. A key histopathologic finding is the evidence of direct production of osteoid by malignant mesenchymal cells [7]. Conventional osteosarcomas are classified into histologic subtypes including chondroblastic, osteoblastic, and fibroblastic. The osteoblastic subtype is more prevalent in long bones, whereas the chondroblastic subtype is most prevalent in the craniofacial region [6]. A case series by Mardinger et al., [16] reported following prevalence of subtypes of craniofacial osteosarcomas: chondroblastic (41%), osteoblastic (33%), and fibroblastic (26%). The histopathologic findings in the case described here were classical including indistinct borders, ovoid to spindled cellular features, deeply basophilic nuclei with deposition of eosinophilic matrix that transitioned to areas of mineralized osteoid or pale-basophilic chondroid. However, the presence of predominantly cartilaginous matrix or an inadequate biopsy sample may result in a misdiagnosis of chondrosarcoma, as seen in case report by Akpolat et al., [17]. Immunochemistry can aid to differentiate chondrosarcoma from chondroblastic osteosarcoma. Other histologic variants are also known such as the telangiectatic type consisting of multiple dilated vascular channels and multinucleated giant cells [6]. Previously, the histologic subtype has not been noted to impact patient survival; however, an eleven-year retrospective study by Smith et al., [18] demonstrated lower 5-year survival rate of patients with the osteoblastic type and not otherwise specified subtype when compared to the chondroblastic variant. High-grade osteosarcomas have statistically lower 5 year survival rates compared to low grade osteosarcomas [9].

The 5 year survival rates of patients with craniofacial osteosarcoma range from 35% to 70% [9,18]. The primary treatment modality for craniofacial osteosarcoma is wide surgical excision. Multiple studies reported unclear/positive margin to be a significant prognostic factor affecting the disease outcome [9,18]. A retrospective study involving 137 patients by Chen et al., [9] demonstrated that the 5 year survival of patients who had negative/clear surgical margin was 59.1% while that of patients with positive or near/involved surgical margin was 0.0%. The use of adjuvant chemo- and radiation therapy is controversial. The Canadian Society of Otolaryngology report on a multicenter study of 35 patients with osteosarcoma noted long-term survival was not impacted by adjuvant chemotherapy or radiation therapy [19]. In contrast, Chen et al., [9] reported 5 year survival of 81.8% in the group treated with surgery and adjuvant chemotherapy versus 55.87% in the group treated with surgery alone. DeLaney et al., [20] reported that radiation therapy is beneficial to reduce local recurrence of the disease. In contrast, Chen et al., [9] reported no significant improvement in patient survival when radiotherapy was added to surgery. Therefore, further research is needed to determine the efficacy of adjuvant chemotherapy and radiation. Our patient was treated with 1 cycle of neoadjuvant chemotherapy, but due to the lack of response, it was determined that patient would benefit more from early surgical intervention. No additional post-surgical adjuvant therapy was provided as the excision margins were negative. The patient was placed on three month surveillance for the two years.

In conclusion, osteosarcoma is a rare malignant mesenchymal neoplasm that produces immature bone or osteoid, chondroid and/or fibrous tissue. Considering that certain genetic and environmental factors revealed in the patient's medical history may have predisposed her to developing this malignancy, this case highlights the importance of a thorough medical history taking in addition to clinical, radiographic and histopathologic evaluation. Wide surgical excision is the cornerstone treatment modality, while there is no generalized consensus among the specialties on the utility of adjuvant chemotherapy and radiotherapy.

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