Clinical–Pathological Conference: Case 6

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Clinical Presentation

A 47-year-old male presented with a 5 cm, firm, painful swelling over the left mandibular ramus that had progressively enlarged and was associated with limitation of mandibular opening and trismus. He related that he first noted symptoms from the area shortly after dental treatment involving a tooth in his left lower jaw 2 months previously. He indicated a 72 pack-year history of cigarette smoking and currently smoked two packs of cigarettes per day. He reported minimal alcohol consumption.

Since the swelling was initially believed to represent a lesion of the soft tissues, a fine needle aspiration biopsy was performed. When this did not yield diagnostic information, a computed tomographic (CT) scan was obtained. At the time of the scan, paresthesia of the left lower lip was observed.

The CT scan revealed an expansile, aggressive-appearing process with a sunburst-type periosteal reaction surrounding the angle and ramus of the left mandible with extension into the infratemporal fossa just below the

mandibular condyle (Figs. 1, 2) and overlying soft tissue involvement. Neoplastic growth was highly suspect.

Differential Diagnosis

Based on the clinical history, particularly the presence of pain, swelling and paresthesia, along with available imaging, the differential diagnosis is heavily swayed towards a malignancy capable of inducing calcified matrix production. The most likely considerations include osteosarcoma, chondrosarcoma, and metastatic disease.

Osteosarcoma of the jaws typically presents in the 4th decade as a bony swelling that may also elicit pain and occasionally causes a neurologic deficit [1, 2]. Mandibular lesions most often affect the posterior body and ramus and often show extension into soft tissues [2]. Radiographically, lytic lesions are most often observed [1] followed by a sclerotic or mixed appearance. The classic “sunburst” pattern noted in lesions of the long bones is uncommon in the jaws [1]. While this patient is a little older than the typical average age at presentation, the signs, symptoms, location and radiographic features all support a clinical diagnosis of osteosarcoma.

Chondrosarcoma of the jaw is a rare tumor which most often affects the maxilla and is most often reported in the 5th decade with a wide age range [3]. Clinically, the tumor is characterized by swelling; pain is an unusual complaint [3]. Radiographs often show an ill-defined radiolucent mass exhibiting bone destruction, with variable calcification and soft tissue extension [3]. The age of the patient and location in this case could be consistent with a diagnosis of chondrosarcoma but the presence of pain and particularly paresthesia would generally be less likely for this tumor.

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Fig. 1 Coronal CT image (soft tissue window) exhibiting a lobular, sunburst-type periosteal reaction consisting of calcified spicules extending from the medial and lateral cortices of the left mandibular ramus into the surrounding soft tissues

Fig. 2 Axial CT images (bone windows) exhibiting minimal bony expansion with destruction of the medial cortex and a sunburst radiographic pattern of calcified material extending into the medial and lateral soft tissue surrounding the left mandibular ramus

Metastasis to the jawbone typically presents in the 5th–7th decades of life [4], and most commonly affects the mandibular molar region followed by the mandibular ramus [5]. The presence of swelling, pain and paresthesia (e.g. “numb chin” syndrome) is typical [4], with one series reporting that all patients who reported paresthesia had metastases to the mandibular ramus [5]. Tumor spread to the jaws is most often a carcinoma originating from a long list of potential primary sites with breast, lung, kidney and adrenal comprising the top contributors [4]. When only males are considered, metastasis from lung and prostate are the two most common primary locations [4, 6]. Radiographically, most cases show an ill-defined, lytic lesion; pure osteoblastic or mixed areas of radioopacity can be

seen in up to 17% of cases [4]. Tumors from the prostate or breast are commonly reported as having the capacity to induce bone formation [7], imparting a mixed radiographic appearance. In the present case, the clinical history is compatible with metastatic disease, particularly given that the lesion is epicentered on the mandibular ramus. While a purely osteoblastic radiographic appearance without significant lytic destruction of the cortex is unusual for metastasis to the jaw, such features have been reported [8].

Diagnosis and Discussion

Clinical information was withheld from the discussant in order to facilitate the academic exercise of formulating a differential diagnosis for this clinical pathologic conference. The most significant finding withheld was the existence of an adenocarcinoma involving the lower third of the esophagus.

The patient reported that his jaw symptoms arose synchronously with the onset of dysphagia and odynophagia. Esophagogastroduodenoscopic examination revealed an ulcerated mass above the gastro-esophageal junction that occupied over one-third of the esophageal lumen, extending through the gastroesophageal junction to involve the proximal stomach. Computed tomographic examination of the thorax exhibited a 4 cm mass of the gastroesophageal junction.

Endoscopic biopsy of the primary esophageal lesion revealed a poorly-differentiated adenocarcinoma with signet ring cell features. Histochemical stains for mucin were positive for both intracellular and extracellular mucin (Fig. 3). The biopsy of the mandibular lesion revealed a

Fig. 3 Endoscopic biopsy of the ulcerated mass of the lower third of the esophagus, exhibiting a poorly-differentiated adenocarcinoma infiltrating beneath the stratified squamous epithelium of the lower esophagus. There are numerous cells with signet ring features and abundant stromal mucin. Histochemical stains were positive for intracellular and extracellular mucin. (Hematoxylin and eosin stain, original magnification $\times 40$)

Fig. 4 Biopsy of lesion of left mandibular ramus exhibiting trabeculae of woven bone intimately associated with sheets of epithelioid cells that exhibited immunoreactivity for cytokeratin (AE1/3 immunostain, inset), confirming their epithelial nature. (Hematoxylin and eosin stain, original magnification $\times 10$)

Fig. 5 Biopsy of left mandibular lesion exhibiting sheets of variably-sized epithelial cells with a moderate amount of eosinophilic cytoplasm and hyperchromatic, pleomorphic nuclei. Histochemical stains for mucin exhibited occasional intracytoplasmic positivity. There were focal, vague, acinus-like structures (not shown in this field). (Hematoxylin and eosin stain, original magnification $\times 20$)

poorly-differentiated metastatic carcinoma extending between woven bone trabeculae (Figs. 4, 5). The tumor cells were of variable size with a moderate amount of eosinophilic cytoplasm and moderately pleomorphic, hyperchromatic nuclei. Focally, there was a suggestion of acinus formation. Histochemical stains for mucin demonstrated occasional intracytoplasmic mucin positivity.

Comparison of the metastatic jaw tumor with the original primary tumor (Fig. 6) revealed that they were morphologically similar. The primary lesion exhibited

Fig. 6 Comparison of the histomorphologic features of the metastatic mandibular lesion and the esophageal primary tumor (*inset*). The metastatic lesion exhibited neither the signet ring morphology nor the copious extracellular mucin of the primary tumor (Hematoxylin and eosin stain, original magnification $\times 40$)

prominent signet ring cell formation with abundant stromal mucin positivity. The metastatic lesion, however, lacked signet ring cell morphology and stromal mucin. Both were positive for carcinoembryonic antigen (CEA) and cytokeratin-7 (CK-7), although the jaw tumor showed a lesser degree of positive staining than the original esophageal adenocarcinoma. Both the esophageal tumor and the jaw tumor were negative for thyroid transcription factor 1 (TTF-1). While the original tumor showed positivity for CK-20, the jaw tumor was negative. While not entirely identical, the histomorphology and the histochemical and immunohistochemical staining of the jaw lesion were consistent with metastatic adenocarcinoma arising from the distal esophageal region.

Additional skeletal metastases were identified in the calvarium, pelvis and sacrum as well as in the lung parenchyma and in multiple lymph node chains. The patient's skeletal disease was treated with bisphosphonates. In view of the incurable nature of his condition, which included an unresectable primary tumor and widespread metastases, the patient received palliative chemotherapy. Additionally, palliative radiation therapy to the left mandible was effective in reducing the size of the metastatic mandibular mass and achieving complete resolution of his tumor-related jaw pain. He was able to tolerate limited oral intake of a soft diet. His only primary tumor-related complaint was that of an extremely unpleasant taste and smell after eructation.

His clinical course was complicated by deep venous thromboses involving both the upper and lower extremities, pulmonary embolism and gastrointestinal hemorrhage. Throughout his treatment he continued his tobacco habit.

His family history was non-contributory for his current malignancy, but interestingly and enigmatically, his wife also suffered from esophageal carcinoma of similar histology and advanced disease concurrently with her husband.

Metastasis to the gnathic bones is an unusual event. The mechanism by which a metastatic lesion from an esophageal primary tumor might present in the mandible was elucidated by Batson [9], who observed that the characteristic spread of prostatic carcinoma to the pelvic bones and vertebrae did not correspond to the lymphatic drainage of the area. He demonstrated a valveless, vertebral plexus (Batson's plexus) that is likely responsible for this paradoxical distribution of metastasis that does not primarily involve the lungs [9].

The majority of metastatic carcinomas to the gnathic bones induce bone resorption and exhibit a lytic radiographic appearance. Bone resorption is mediated by parathyroid hormone-related peptide (PTHrP) production by tumor cells. PTHrP stimulates production of a cytokine, the receptor activator of nuclear factor kappa beta (NF- κ B) ligand (RANKL) by osteoblasts and stromal cells. RANKL then binds to and activates its receptor, RANK, which is expressed by osteoclasts, leading to osteolysis [10]. The blastic radiographic appearance associated with certain metastatic carcinomas, notably those of prostate and breast, is mediated by production of growth factors, including endothelin-1, transforming growth factor beta (TGF- β), insulin-like growth factor 1 (IGF1) and fibroblast growth factors, that directly stimulate osteoblastic bone production [10].

The “seed and soil” metaphor provides a useful concept in describing the propensity of certain tumors to involve particular metastatic sites. In osteolytic bone metastases, there is a reciprocal interaction between the tumor cells (the “seed”) and the metastatic microenvironment (the “soil”). As the bone matrix is resorbed by osteoclasts,

growth factors, including TGF- β and IGF1, are released from the matrix. These growth factors, in turn, stimulate additional tumor cell proliferation and further production of PTHrP leading to enhanced osteoclast activation. This leads to a “viscous cycle” between the tumor cells and bone, promoting increased osteolysis. Bisphosphonate drugs are effective in interrupting the “viscous cycle” by inhibiting osteoclasts and significantly reducing the incidence of skeletal complications related to metastatic bone lesions [10].

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