A 25-year-old Hispanic male was referred to our hospital oral surgery clinic from a local correctional facility for the evaluation of an oral mass. The patient’s chief complaint was a painless, rapidly enlarging swelling of his gingiva of the right anterior maxilla. It was first noticed approximately 8 weeks prior and described by the patient as a small bump between the maxillary right canine and maxillary right lateral incisor teeth. Progressive mobility of his right maxillary anterior teeth and slight drainage were reported. Before referral for lesion evaluation, the patient was treated with oral clindamycin 300 mg, 3 times daily for 10 days by his dentist with no improvement. On presentation to the hospital oral surgery clinic, the patient’s medical and dental histories were obtained and a clinical examination was performed. He denied prior orofacial trauma. The patient’s past medical history was negative for illnesses, hospitalizations, or surgeries. His social history included occasional social alcohol use before his incarceration. He denied tobacco or recreational drug use. On head and neck examination, displacement of the right lip and right naris was evident. No cervical lymphadenopathy was apparent on physical examination. On oral examination, a 5 × 7-cm nodular lesion was visualized involving the right anterior maxillary buccal alveolus with extension to the vestibule (Fig. 1). The lesion extended from the region adjacent to the right central incisor to the first molar. The maxillary lateral incisor, canine, and premolar teeth were displaced distopalatally with clinically detectable mobility. The lesion possessed a nonulcerated surface with mild fissuring and variegated red color with telangiectasia. The texture was soft to rubbery without blanching, pulsation, thrill or bleeding on palpation. Radiographic examination with a panoramic film (not shown) revealed a homogeneous, poorly delineated lucency involving the region associated with the maxillary right central incisor, lateral incisor, and canine.

DIFFERENTIAL DIAGNOSIS

A multitude of benign lesions may appear similar to this patient’s mass lesion, including those of a vascular nature, such as the various types of hemangiomas, arteriovenous malformation, and lymphangioma. On physical examination, this lesion lacked blanching, pulsation, thrill, or bleeding on palpation. Peripheral giant cell proliferations may have a similar clinical appearance, but are most often reactive lesions to underlying inciting factors, such as local irritation or trauma, which were not evident in this case. Aggressive benign tumors may be considered but they generally lack rapid, unchecked proliferation and invasiveness, but rather show more gradual enlargement over months to years. Given the very rapid progression of this patient’s lesion over the course of 8 weeks from what was described by the patient as a small bump to its large size at presentation, malignant neoplasm was given prime consideration in formulation of the differential diagnosis. The rapid proliferation was corroborated by the referring dentist. Cortical bone invasion along with displacement and loosening of the right anterior teeth also suggested rapidity of onset and progression as well as the infiltrative nature of the mass. Rhabdomyosarcoma of the head and neck may arise as a rapidly growing, painless mass. This infiltrative tumor of skeletal muscle origin may originate intraorally or within the maxillary sinus with protrusion into the oral cavity. The most frequent intraoral site is the palate. Embryonal rhabdomyosarcoma occurs most frequently in the first decade. The alveolar variant occurs most frequently between the ages of 10 and 25 years. Lymphoma of the non-Hodgkin type may occur in the jaws in a primary extranodal presentation or in conjunction
with disseminated disease. With the exception of Burkitt lymphomas, which tend to occur in children, the non-Hodgkin variants tend to occur in older populations.3 Presenting features may include nonspecific pain, bony expansion, and eventual perforation and with soft tissue enlargement. Paresthesia may occur with those presenting in the mandible.3 Although this patient’s age is within the first of 2 age-range distributions for Hodgkin lymphoma, this disease most often presents with clinically detectable primary lymph nodal enlargement but without extranodal involvement.

Ewing sarcoma and the primitive neuroectodermal cell tumor both reside within the category of small round cell tumors.4-7 These are rare tumors with the mandible being the most frequent location of these tumors in the head and neck. Loosening of teeth and neurosensory disturbance are frequent presenting signs in Ewing sarcoma. Primitive neuroectodermal tumors (PNET) occur in many locations, primarily in central and peripheral nervous system distribution. They may also appear in a variety of soft tissue locations, including chest wall, trunk, abdominal and pelvic locations.4,5 Rarely do these tumors occur in the head and neck location and when present are referred to as peripheral primitive neuroectodermal tumors (pPNET).4 In the head and neck, they occur primarily in childhood with a peak age of occurrence in adolescence.5 However, several case reports document appearance of these tumors in young adults and elderly individuals.5,7

Osteosarcoma, although primarily a disease of long bones, may occur in the head and neck with a mean age of onset of 33 years.8 Clinical presentation may include pain, expansion, and loosening of teeth. Nasal obstruction may result from impingement on the nasal airway with maxillary involvement or paresthesia with mandibular involvement. Radiographic appearance may vary on a spectrum from radiopaque to radiolucent. Widening of the periodontal ligament space is often seen with osteosarcoma of the jaws, which was not evident in this patient.8

Malignant neoplasms of epithelial origin may also be considered in the differential diagnosis of a large nodular mass of the head and neck. Squamous cell carcinoma occurring in an alveolar location with exophytic presentation may occur in the head and neck, most often involving the posterior mandible.9 Risk factors include tobacco use, ethanol consumption, genetic influences and possibly viral influences. These tend to evolve more gradually and manifest a variety of mucosal abnormalities. Surface changes ranging from erythroplakia to leukoplakia tend to precede mass formation. Ulceration is often evident once mass lesions develop. In addition, squamous cell carcinoma mass lesions tend to be very firm with significant bone invasion. Clinically apparent regional adenopathy is often present once the primary lesion has attained a large size.

Angiosarcoma, a rare malignant neoplasm derived from endothelial cells, initially presents as a macular, ecchymotic lesion in cutaneous locations. When presenting in the head and neck, these tend to appear on the face and scalp. These typically occur in elderly patients with male predominance. They may progress to a nodular lesion with induration and surface ulceration. In the rare appearance in the oral cavity, the tongue and mandible are more commonly involved than other oral sites.2

Based on the clinical appearance, biological behavior, and radiologic appearance, malignant neoplasm was highly suspected as the etiology for this lesion, with strong consideration given to sarcoma or lymphoma as the lesion’s identity because of the patient’s age.

**DIAGNOSIS AND MANAGEMENT**

Given the history and clinical and radiologic appearance of the lesion, biopsy was recommended and the patient consented. No other skin or mucosal lesions were apparent on the basis of his physical examination. The lesion was aspirated and, following negative aspiration, a biopsy specimen was obtained and submitted for evaluation by general pathology.

Because of the patient’s refusal to accept intravenous contrast agent, a computed tomography (CT) scan with-
out contrast was obtained. Axial (cross-sectional) and coronal views were examined. The axial views provided the most diagnostic information and are reviewed here. The soft tissue window CT view (Fig. 2, A) shows a soft tissue mass with density equivalent to fat over the mid anterior portion of the right maxilla extending to the anterior nasal floor. The bone window CT view (Fig. 2, B) shows evidence of localized cortical bone invasion. Enlarged regional lymph nodes were also evident in the cervical region, which are suggestive of a malignant origin with regional metastases; however the scan was obtained after biopsy and the nodes may represent reaction to surgical manipulation. Mucosal changes suggestive of chronic sinusitis were also evident on that study (Fig. 3).

Our hospital pathologist, who has both general and oral pathology training, examined the specimen grossly and microscopically. Initial histologic evaluation of the specimen via routine light microscopic examination with hematoxylin and eosin stains, resulted in a preliminary description of a small, round cell malignant tumor. This was followed by immunohistochemistry assays. Pancytokeratin, which is used to identify epithelial neoplasms, was negative. The specimen was also subjected to CD 45, an assay for lymphatic neoplasms, which was also negative. Because of the unavailability of additional immunohistochemical assays, the specimen was submitted to an outside institution for pathology expert consultation. At that institution, further immunohistochemical studies were performed with results that included the following: positive reaction to Melan A and HMB 45, both specific for melanoma-associated antigens, and weakly positive focal reaction to CD 99 and CD 138. Cell markers associated with B-cell lymphoma (thymocytes) and Ewing sarcoma react with CD 99. Plasma cell markers react with CD 138. The neoplastic cells were negative with respect to reactions with lymphoid, hematologic, and sarcoma cell markers. The diagnosis given, based on the panels reviewed by the consulting pathology service, was malignant melanoma. Based on the histologic and immunostaining properties of this lesion, the diagnosis of primary amelanotic melanoma was made.

After diagnosis, the patient was referred to the regional cancer center for further workup and definitive treatment. In addition to clinical examination, the patient was evaluated with CT of brain/head, neck, and chest in addition to magnetic resonance angiography (MRA) of the brain and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan. On CT of the head and neck, invasion of the right maxillary alveolus with tumor extension into the right alar cartilage was evident. Several cervical level II lymph nodes were seen, with the largest measuring 1.4 cm. There were no metastatic lesions noted on the brain or chest CT examinations. The MRA was negative for vascular malformations of the head and neck. The 18F-FDG PET/CT revealed the primary lesion and indicated right submandibular lymph node involvement. Panendos-
copy was performed by the treating head and neck oncology surgery service to rule out primary or metastatic tumor involvement of the aerodigestive tract. Before surgery, the patient underwent 3 cycles of neoadjuvant chemotherapy with carboplatin, paclitaxel, and pegfilgrastim, with a significant partial response defined as a significant reduction in tumor size.

Surgical treatment consisted of extraction of maxillary right first and second molars, maxillary left central and lateral incisors, right partial maxillectomy, and right modified radical neck dissection (Levels I-V). A full-thickness skin graft was placed over the defect and immediate obturator placement was performed. Owing to intolerance of severe adverse effects of radiation therapy, the patient completed 50 Gy of his prescribed regimen of 54-Gy external beam radiation to the primary lesion site and lymph nodal basin. He received a single dose of adjuvant chemotherapy consisting of carboplatin and paclitaxel 4 months after surgery, but missed several scheduled follow-up appointments with the medical oncology service. At 5 months postoperatively, the patient presented to the head and neck surgeon and a suspicious, 1.5-cm, brown-pigmented lesion of the posterior aspect of the right inferior turbinate was detected and biopsied. The diagnosis was granulation tissue of respiratory mucosa with acute and chronic inflammation containing focal pigment, consistent with hemosiderin or melanophages. This was read as negative for tumor. At the urgings of his surgeon, the patient eventually presented for follow-up with the medical oncologist, now 7 months postoperatively, suffering from significant weight loss and cachexia. The decision

Fig. 3. A, Photomicrograph showing superficial vascularization of the lamina propria. At deeper levels of the stroma, a dense cellular infiltrate produced dark and clear zones (hematoxylin-eosin stain, ×20). B, Photomicrograph showing the presence of a malignant mononuclear cell infiltrate displaying variation in nuclear chromatism, and what appear to be clear cells owing to retraction artifact of the cytoplasm. A vague nesting of the malignant infiltrate showing lack of cohesion is seen in the upper right field (red arrow) (hematoxylin-eosin stain, ×100). C, Photomicrograph showing lack of cohesion of the malignant mononuclear cells, characterized by the presence of anisonucleosis, scattered mitotic figures, pleomorphism, cells with eosinophilic cytoplasm reminiscent of a “rhabdoid” appearance and nuclear pseudoinclusions. The red arrow identifies a rare melanin-laden malignant cell (hematoxylin-eosin stain, ×400). D, Photomicrograph showing the malignant mononuclear infiltrate expressing MART 1 (Melan A) cytoplasmic signals (MART 1 staining, ×200).
to forgo further adjuvant chemotherapy was made, owing to the significant time-lapse since the completion of surgery and radiation therapy. He was placed on observation, then returned approximately 6 weeks later and was admitted to the hospital with abdominal pain, jaundice, and ascites. Workup revealed multiple metastases to the liver, pancreas, omentum, kidneys, and abdominal wall with diffuse adenopathy. A pericardial effusion was noted, which was suspicious for malignancy. Outpatient salvage chemotherapy was prescribed, which consisted of a 5-day course of intravenous temozolomide, which was to take place every 28 days. The patient tolerated initial doses favorably; however, he returned 4 days after infusion with worsened abdominal pain, intractable ascites, dehydration, and hypotension. The decision to discontinue active treatment was made by the patient and home hospice care was initiated 4 days after acute inpatient admission. The patient died 3 days after entering hospice care, which was approximately 55 weeks after diagnosis.

DISCUSSION

Mucosal melanomas of the head and neck region occur very rarely. In the National Cancer Database report, 84,836 melanoma cases were reviewed over a 10-year interval. Mucosal melanomas comprised 1.3% of the total. Of these, 55.4% were from the head and neck region. Poor survival was associated with head and neck mucosal melanomas with positive cervical lymph nodes.10

With respect to mucosal melanomas, the head and neck is affected more commonly than the anal/rectal mucosa, female genital tract mucosa, or urinary tract mucosa.11 There appears to be a male predilection, with occurrence most frequently in the age range from 20 to 83 years. Oral mucosal melanomas appear to affect those of African, Asian, Native American, and Hispanic descent most frequently.12

Risk factors for the development of oral mucosal melanoma appear to include the presence of oral melanosis and oral melanocytic nevi.13 Authors Hicks and Flaitz11 also suggest that atypical melanocytic hyperplasia may either increase the risk for oral mucosal melanoma development or be an actual precursor of oral mucosal melanoma.

Given the lack of a clinical staging system specific for mucosal melanomas, there is inherent difficulty in determining prognosis based on clinical features of the primary lesion. Clark’s level histologic staging system is not applicable to mucosal melanomas, as mucosa lacks the important histologic landmark, dermis. Breslow’s depth histologic classification is perhaps better suited for use in assessing levels of invasion of mucosal melanomas because of its use of lesion thickness rather than histologic levels.11,13 Although not formally recognized, multiple authors have advocated the use of a 3-tiered system for mucosal melanoma staging, based on the nature of local or regional involvement. The system is the following: stage I, tumors with localized disease only; stage II, tumors with lymph node involvement; stage III, tumors with distant metastases.14-16

Prasad et al.17 proposed a microstaging system for stage I tumors with survival inversely related to depth of histologic invasion. Three levels were described, including level I as melanoma in situ; level II as invasion into lamina propria only; and level III as deep tissue invasion into skeletal muscle, bone, or cartilage. Use of this microstaging system is advocated owing to the reproducibility of features that are easily identified with light microscopy.17

Amelanotic melanomas are extremely rare, accounting for approximately 2% of all melanomas.14,15 The most common oral mucosal sites of occurrence of malignant melanoma appear to be the palate and maxillary gingiva.13,16,18 In one of the largest case series, Ariel15 reports male preponderance with an average age of 44 years. Of these 77 patients, 10 had unknown primary sites. The overall 10-year survival rate was 30% with 10-year survival rates of 55% for stage I disease and 17% for stage II disease.15 Our patient was 25 years old at the time of his presentation with the sizable, nonpigmented lesion located in his anterior maxilla. This patient’s disease was classified as stage II, given regional lymph node involvement with no distant metastases at the time of initial presentation.

Several theories exist as to why these mucosal melanomas appear to lack pigment. Deficiency of the enzyme tyrosinase, required for melanin production, was proposed by Speece et al.19 on the basis of their microspectrophotometric autoradiographic study. Comstock et al.20 postulated that melanin was indeed produced by amelanotic melanoma cells, but at concentrations that were nondetectable by routine light microscopic examination. More recently, electron microscopic identification of premelanosomes has led several authors to favor the low melanin concentration theory for the clinical and light microscopic appearance of amelanotic melanoma.18,21 Amelanotic melanomas exhibit biologically aggressive behavior with undifferentiated, anaplastic histologic characteristics. This may lead to impairment of the functional differentiation required for pigment production.

The mainstay of treatment for amelanotic melanoma is surgery, including wide excision of the tumor with neck dissection of node-positive necks. Although cutaneous and mucosal melanomas are relatively radioreistant, irradiation of the regional lymph nodes and...
metastatic foci is advocated as adjuvant therapy. Chemotherapy with or without immunotherapy is used in an adjuvant or neoadjuvant role, based empirically on regimens used in cutaneous melanoma treatment. Our patient received presurgical neoadjuvant chemotherapy with good response. After surgery, he received regimens of adjuvant radiation and chemotherapy, only partially administered because of poor tolerance. A brief attempt at salvage chemotherapy was also poorly tolerated.

In their study of treatment outcomes, Patel et al. found that amelanotic melanomas had more significant distant failure rates than pigmented mucosal melanomas. Stage at presentation, lesions thicker than 5 mm, vascular invasion, and distant failure were independent predictors of outcome.22

Amelanotic mucosal melanoma may represent a less differentiated form of mucosal melanoma, accounting for the aggressive nature and poor response to surgical and medical therapies. A high index of suspicion for malignancy should be adopted when patients present with rapidly enlarging lesions of the oral cavity. This patient’s lesion had clinical characteristics that resembled many other lesions. The current case illustrates the inherent difficulty in diagnosis based on the lesion’s uncharacteristic clinical appearance and atypical histologic features. Routine histologic staining must often be supplemented with immunohistochemical analyses to arrive at the precise tissue diagnosis to facilitate prompt medical and surgical therapy. Despite exhaustive diagnostic workup and multimodality therapy, this aggressive disease carries a poor prognosis for 5- or 10-year survival.

REFERENCES