Amelanotic Melanoma of the Oral Cavity: A Case Report and Review of Literature
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Abstract
Oral amelanotic melanoma is a rare neoplasm and represents less than 2% of all melanomas. They have prognosis poorer than the pigmented melanomas because of delay in diagnosis and in the initiation of treatment. Amelanotic melanomas are also thought to be biologically more aggressive than the pigmented melanomas. We present an interesting case of amelanotic melanoma of the mandibular anterior region in a 75 year old woman.

Keyword: Malignant; Amelanotic; Melanoma; Neuroendocrine Tumors; Neural Tissue; Neoplasms; Germ Cell and Embryonal; Oral Cavity.

Case Report
A 75-year-old Indian woman presented to outpatient department with a chief complaint of gradually increasing asymptomatic, exophytic growth (3 × 2 × 2 cm) in the mandibular anterior region of two months duration following extraction of the permanent mandibular anterior teeth. The lesion presented as a soft, exophytic, polypoid, focally ulcerated mass in the mandibular anterior alveolar mucosa (Figure 1a). Head and neck examination revealed firm and palpable right submandibular lymphadenopathy. The patient gave history of tobacco chewing and had a noncontributory family and medical history. Oral hygiene of the patient was poor. An orthopantomogram showed ill-defined radiolucency beneath the mass in the mandibular anterior region (Figure 1b). Based on clinical presentation of a gradually growing exophytic soft tissue mass our differential diagnosis ranged from non-neoplastic to neoplastic lesions. Differential diagnosis included pyogenic granuloma, peripheral giant cell granuloma, primary squamous cell carcinoma, non-Hodgkin’s lymphoma, sarcomas and metastatic tumors.

Pyogenic granuloma (PG) is a common non-neoplastic, tumor-like growth of the oral cavity, usually occurring on the gingiva and presents as an elevated, pedunculated or sessile vascular mass with a smooth, lobulated or even a warty surface with ulceration and shows tendency for hemorrhage. It arises in response to various stimuli such as a chronic low-grade local irritation, trauma, hormonal factors or certain drugs. Its development is typically slow, asymptomatic and painless but may grow rapidly reaching its full extent in week, mimicking some of the clinical features in the present case. PG featured high on our differential diagnosis.

Peripheral giant cell granuloma (PGCG) is a relatively frequent benign reactive lesion of the oral cavity originating from periosteum or periodontal membrane following local irritation or chronic trauma. PGCG manifests as a red-purple nodule located in the region of the gums or edentulous alveolar margins. It is primarily a soft tissue lesion that very rarely affects the underlying bone, though the latter in edentulous areas exhibits superficial erosion with pathognomonic peripheral ‘cuffing’ of the bone. Following pyogenic granuloma PGCG was next favored differential diagnosis.

Oral squamous cell carcinoma (SCC) is the most common malignant tumor of the oral
and maxillofacial region, especially in South-East Asian countries, arising from the epithelium lining the oral cavity; accounts for over 90% of malignant lesions in the mouth and is usually associated with tobacco habit. Lesions on gingiva account for approximately 10% of all intraoral SCC and presents as a slow growing, broad-based and wart-like mass. Majority of gingival SCC occur in relation to mandible and may be insidious in onset and progression, thereby mimicking periodontal disease. Gingival SCC can be particularly deceptive in appearance and may present as an inconspicuous lesion or a localized endoperiodontic lesion, exhibiting exophytic growth following a dental extraction. Though preexisting SCC of gingiva was considered but patient exhibited no growth or lesion prior to extraction. Since patient gave history of tobacco chewing oral SCC was also considered in the differential diagnosis.

Non-Hodgkin’s lymphoma (NHL) accounts for 3.5% of intraoral malignancies, most of these are high grade diffuse large B-cell lymphomas. The incidence of NHL increases throughout life, with a mean age of approximately 59 years. It involves lymph nodes and lymphoid organs as well as extra nodal organs and tissues. The malignancy may develop in oral soft tissues or centrally with in the jaws. Soft tissue lesions appear as nontender, diffuse swelling commonly affect the buccal vestibule, posterior hard palate, or gingiva. NHL involving the jaw more frequently affects the mandible. They usually present with pain, swelling and loosening of the tooth. Radiographs show poorly defined irregular radiolucency, displacement of associated teeth and root resorption. These tumors are found in patients with human immunodeficiency virus (HIV), affecting approximately 3% of all HIV patients. Though NHL was considered in differential diagnosis, NHL of the gingiva is relatively rare compared to the overall prevalence of gingival squamous cell carcinoma.

Less than 20% of total body sarcomas occur in the head and neck region. The most common being rhabdomyosarcoma (RMS) followed by malignant fibrous histiocytoma, fibrosarcoma and neurofibrosarcoma. Oral RMS primarily occurs in the first decade of life, is rare in people older than age 45 and approximately 60% of all cases occur in males. Most oral soft tissue sarcomas are often a painless, infiltrating mass that may grow rapidly. Though sarcomas are rare in oral cavity, gingival origin is still rarer. Finally metastatic tumors were also considered. The oral region is an uncommon site for metastatic tumor cell colonization and is usually evidence of a wide spread disease. The jaw bones, particularly the mandible, are more frequently affected than the oral soft tissues. In the oral soft tissues gingiva was most commonly affected site (54%). The breast and the lung are the most common primary tumor sites for women and men respectively. A total body CT scan helps to identify presence of any unknown primary tumor or other metastatic lesions.

The clinical findings of a gradually growing, ulcerated, exophytic, soft tissue mass with evidence of bone involvement following dental extraction and history of tobacco chewing, the final working diagnosis of oral squamous cell carcinoma was made.

The routine hematological examination was within normal range. Patient was found to be HIV seronegative. Fine needle aspiration cytology was performed on right submandibular lymph node and found to be reactive in nature. An incisional biopsy of the mass was carried out under local anesthesia. Microscopic examination of hematoxylin and eosin (H and E) stained tissue section revealed oval to epithelioid cells with monomorphic and hyperchromatic nuclei and scanty cytoplasm in subepithelial areas (Figure 1c). The surface epithelium was ulcerated at places. Under light microscopy the diagnosis of blue round cell neoplasm was made (Figure 1d), which included poorly differentiated squamous cell carcinoma, poorly differentiated neuroendocrine carcinoma, lymphoma, plasmacytoma, melanoma and sarcomas. Subsequently the tissue was subjected to a series of immunohistochemical markers. Tumor cells were immunonegative for cytokeratin, vimentin, desmin, smooth muscle actin and HMB 45 and showed strong immunoreactivity for Melano-A (Figure 1e) and S-100 (Figure 1f).

After correlating the clinical presentation, histopathological features and immunohistochemical findings of the lesion, a final diagnosis of primary oral amelanotic melanoma was established. Patient was referred to oncology centre for further treatment; however patient denied any active treatment and hence home hospice
care was advised. The patient died three months after the diagnosis.

Figure 1: The intraoral photograph showing exophytic, polypoid, focally ulcerated mass in the mandibular anterior region (a) with orthopantomogram showing ill-defined radiolucency beneath the mass (b). The photomicrograph showing diffuse cellular infiltrate within the lamina propria (c) (H & E 10x) with the presence of oval to epitheloid cells demonstrating hyperchromatic nuclei with scanty cytoplasm (d), and lack of cohesion of the malignant mononuclear cells along with variation in nuclear chromatism (inset). The immunohistochemical staining of neoplastic cells expressing Melano-A cytoplasmic signals (e) and S-100 positivity (f).

Discussion
Primary malignant mucosal melanoma of the head and neck is a rare entity. Weber, in Germany in 1856, was the first person to describe mucosal melanomas. Over 90% of melanomas occur on the skin with slightly over 1% of melanomas arising from mucosal surfaces. Poor survival and positive cervical nodes are associated with head and neck mucosal melanomas. Higher percentages of OMMs are reported in Japanese, Uganda Africans, or other non-white races. Age
ranges from 35-80 years with a male preponderance. The lesion is much more common on the upper jaw than the lower jaw, making palate the most common location followed by maxillary gingiva. Other sites include the buccal mucosa, mandibular gingiva, lip, tongue and floor of mouth.

No risk factors for development of OMMs have been clearly identified to date. It has been suggested that presence of oral melanosis, oral melanocytic nevi and atypical melanocytic hyperplasia may either increase the risk for oral mucosal melanoma development or be an actual precursor of oral mucosal melanoma. One-third of the patients are asymptomatic at the time of diagnosis. Bony erosion, swelling, bleeding, pain or loosening of teeth may develop eventually. Ulceration is a sign of deep invasion and advanced disease. Melanotic pigmentation prior to diagnosis of melanoma is found in one-third of the patients.

Clark and his coworkers (1975) documented two phases in the growth of primary melanoma: a radial growth phase, where the neoplastic process is confined to epithelium, and a vertical growth phase, in which the neoplastic cells populate the underlying dermis. Metastasis is possible once the melanoma enters the vertical growth phase. Clinically OMMs are classified into five types: 1) pigmented nodular; 2) non-pigmented nodular; 3) pigmented macular; 4) pigmented mixed; 5) non-pigmented mixed type 1, 2.

AMs are extremely rare variant of mucosal melanomas that lack pigmentation both clinically and histopathologically. Less than 2\% of all melanomas lack pigmentation. In the oral mucosa, however, up to two-thirds of cases are amelanotic. The specific cause for the lack of melanotic pigmentation in these lesions is unclear. Speece et al., proposed that there is a deficiency in tyrosine and an enzyme required for melanin production. As cited in Fitzpatrick, Comstock et al., postulated that this enzyme system is intact and can produce melanin, but the quantity is insufficient to be seen with histological methods. 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.

Histopathologically, OMMs seem to be undifferentiated and have high cellular activity. They demonstrate a myriad of cell morphologically ranging from epitheloid, spindle, or mixed (epitheloid and spindle) to undifferentiated cells. On pathologic grounds, an amelanotic lesion should be distinguished from poorly differentiated carcinoma, small cell carcinoma, lymphoma, sarcomas, and metastasis from a primary skin melanoma. Therefore, immunostaining for S-100 protein, HMB-45 and Mart-1 should be used to establish correct diagnosis.

The important prognostic factors in cutaneous melanomas are the depth and the level of invasion. However, the assessment of the level of invasion is much more difficult to judge in OMMs because of the presence of muscle bundles and the lack of a true dermis. Also it is not known whether it has the same prognostic significance. Oral submucosal connective tissues are more varied and less layered than the cutaneous stromal tissues, so the more recent Breslow classification appears more appropriate for evaluation of oral lesions. The Breslow system is based on the actual measurement of the distance from the top of the granular cell layer to the deepest identifiable point of tumor invasion. As much of the oral mucosa lacks an identifiable granular cell layer, the surface keratin layer is alternatively used for oral melanoma. Based on local or regional involvement a clinical staging system was proposed by some authors for mucosal melanomas, defined as localized tumors (Stage I; TanyN0M0), tumors metastatic to regional lymph nodes (Stage II; TanyN1M0), and tumors metastatic to distant sites (Stage III; TanyNanyM1), appears to be the most significant prognostic factor for mucosal melanomas.

Prasad et al., proposed a prognostically significant three-level, microstaging system to assess the depth of invasion in OMMs for stage I into 3 categories representing different microanatomic compartments separated by tissue barriers: level I: in situ mucosal melanoma without invasion or with micro invasion; level II: invasion up to the lamina propria; and level III: deep invasion into bone, cartilage, or skeletal muscle. The presence of vascular invasion, necrosis, and polymorphous tumor cell morphology also provide significant predictive value and imply a less favorable outcome.
The 5 year survival for patients with OMM is only 5%.[3] However Nandapalan et al., reviewed 257 mucosal melanomas of the head and neck region and reported that amelanotic melanomas had a 20% survival at three years, whereas pigmented melanoma had a 58% survival at three years, with a significant difference. These results indicate that among mucosal melanomas, AMs have a particularly disastrous prognosis.[2] The poor survival after AM may be attributed to delay in diagnosis, due to lack of pigmentation, biologic aggressiveness, rapid growth, a high incidence of local recurrence, high vascularization of maxillofacial region, the age of the patient, and lastly by lack of defined treatment guidelines.[12,13,21] Anatomic consideration makes radical surgery difficult in the mouth, and many lesions are not detected until they are large.[14] It is suggested that invasion of greater than 0.5 mm correlated with a poor prognosis.[24]

The recommended treatment for OMM is surgery in combination with chemotherapy and to a lesser extent immunotherapy or irradiation therapy. OMMs are traditionally considered to be radiation-resistant tumors, although irradiation therapy as a primary modality is occasionally used for the elderly and medically compromised and is also used after surgery when adequate margins cannot be achieved. Preoperative chemotherapy is occasionally used to reduce the size of the melanoma and impose surgical management. Radical bone resection may be indicated if there is difficulty obtaining tumor-free margins.[12,13] Decision regarding radical surgical approach need to be critically tempered in view of the rate of local failure and functional outcome.

Melanomas that exceed a thickness of 3 mm, lymph node dissection should be performed even with clinically negative nodes except if extra nodal metastatic disease is present.[25] It is still not clear to what extent lymph node involvement may influence the prognosis but an apparent correlation between the degree of invasion and incidence of lymph node metastasis has been established.[12] Once metastases develop amelanotic melanomas rapidly prone to be fatal and that the median survival time in patients who died of amelanotic melanomas was only 22 months. The most common sites of metastasis are lymph nodes, liver and lung, with widespread involvement occurring in advanced tissue.[26] Our patient died within three months after the diagnosis.

In summary, AM should be included in the differential diagnosis of any rapid, non-pigmented gingival enlargement. The current case posed difficulty in diagnosis of the lesion based on the uncharacteristic clinical appearance and atypical histologic features. Early diagnoses by histological examination together with immunohistochemistry are the keys to improving the survival for patients with oral amelanotic melanoma.

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