Rapidly growing mass of the anterior maxillary gingiva

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CASE REPORT
A 66-year-old man was referred to our department for assessment of a painless swelling of the anterior maxillary gingiva. The patient reported that the swelling had increased rapidly over the course of the 3 preceding weeks. His medical history was unremarkable. There was no history of sinus-related disease or trauma to the maxillofacial complex. The social history of the patient was significant for alcohol and tobacco use.

Clinical examination revealed a 48 × 31 × 25-mm elastic hard gingival mass involving the anterior maxilla and extending from the area of the right canine to the left premolar. An ulcer, measuring 20 mm in greatest dimension, was located in the center of the lesion, exposing the underlying alveolar bone. The patient had a defective fixed partial denture replacing the maxillary incisor teeth (Fig. 1). The patient denied any history of tenderness, paresthesia, or dysesthesia. No regional lymphadenopathy was noted clinically.

Panoramic radiography showed a radiolucent lesion extending bilaterally into the nasal cavity and involving the left maxillary sinus (Fig. 2). Computed tomography (CT) showed a large destructive lesion with irregular margins. Enhanced axial CT scans revealed irregular destruction of the hard palate (Fig. 3, A) and a contrast-enhancing soft tissue mass on the anterior aspect of the nasal cavity. The posterior nasal septum did not appear to be involved (Fig. 3, B).

DIFFERENTIAL DIAGNOSIS
Our differential diagnosis for this rapidly expanding destructive lesion included a locally aggressive infectious process, immune-mediated disease, primary malignant neoplasm, and metastatic disease.

Locally aggressive infectious processes that were considered included the deep fungal infections, such as aspergillosis and zygomycosis, as well as infection with Mycobacterium tuberculosis. Aspergillosis infection can have a variable presentation depending on the strength of the host immune response and the specific Aspergillus species. Fulminant cases of aspergillosis are most commonly seen in immunocompromised patients (e.g., AIDS patients, uncontrolled diabetics, and patients on immunosuppressive therapy following solid organ or bone marrow transplantation). The most common pathogen is Aspergillus fumigatus. These spores typically colonize the upper and lower respiratory tracts, the lung being the most frequent site of primary infection. Only a few cases are related to direct cutaneous inoculation. Aspergillus hyphae tend to invade blood vessel walls, resulting in secondary thrombosis.
and hemorrhage, tissue infarction, and necrosis. Oral aspergillosis is encountered infrequently and may arise either as a primary infection of the gingival tissues or following invasive dental treatment. Direct extension of maxillary sinus disease—typically presenting as painful necrotic ulcerations of the palate, or disseminated disease from the lungs—may also occur.1-3

Similar to aspergillosis, zygomycosis is most commonly seen in the immunocompromised patient. Frequent pathogens, all members of the family Mucoraceae, include Absidia, Rhizopus, Rhizomucor, and Mucor. Zygomycosis of the oral cavity can originate from disseminated infection where the portal of entry is by inhalation or direct wound contamination with subsequent dissemination to other viscera. When originating in the paranasal sinuses, infection may lead to palatal ulceration, necrosis, and exposure of underlying bone.1,3,4 Similar to destructive palatal lesions caused by aspergillosis, necrotic areas typically present as a black eschar.

These destructive deep fungal infections are commonly accompanied by constitutional or systemic symptoms such as fever and malaise. Neutropenia is an important risk factor predisposing these patients to opportunistic infections.1-4 Our patient had no history of immunosuppression; white blood cell, red blood cell, platelet, and neutrophil counts were all within normal limits, and the lesion had attained significant size without systemic symptoms.

Infection with M tuberculosis is usually acquired as a primary pulmonary infection. Extralaryngeal head and neck lesions are relatively uncommon, and in most cases are thought to result from secondary hematogenous spread or direct contact with sputum that harbors live microorganisms. Oral lesions usually present as
persistent, painless, irregular ulcerations involving the tongue or palate, although nodular presentations have been described. Bony involvement, leading to tuberculosis osteomyelitis, may also occur. Coincident pulmonary involvement may be absent, complicating the diagnosis. However, infection with *M. tuberculosis* is usually characterized by slow progression of disease, in contrast to the rapid growth seen in this case.

In the category of immune-mediated disease, Wegener’s granulomatosis was briefly considered in the differential diagnosis. Wegener’s granulomatosis shows clinical and histopathologic features characterized by necrotizing granulomatous inflammation of the respiratory tract, exemplified by widespread multisystem vasculitis and necrotizing glomerulonephritis. Common clinical signs and symptoms include sinusitis, rhinorrhea, nasal stuffiness, and epistaxis. These can be seen with or without fever, arthralgia, and weight loss. With oral involvement, the gingiva will typically appear hyperplastic, with a red to purple cobblestone appearance and characteristic petechiae, termed strawberry gingivitis. Although less common, oral ulceration and necrosis may also be seen in Wegener’s granulomatosis. Destruction of the underlying palatal and alveolar bone with the subsequent development of an oral-antral fistula has been reported. In many cases, this is believed to represent direct extension of nasal or sinus disease. More than 90% of patients with Wegener’s granulomatosis will have pulmonary involvement at some stage in their illness. This is typically characterized by persistent cough, often accompanied by pleurisy, dyspnea, and hemoptysis. Chest radiography may reveal discrete opacities, varying in appearance from nodular masses to diffuse consolidation. Wegener’s granulomatosis was thought to be unlikely in this case because of the extensive destruction, normal chest radiographs, and the absence of respiratory symptoms.

The clinical features and radiographic findings in this case were believed to be most consistent with a malignant neoplasm. Primary squamous cell carcinoma of the gingiva, sinonasal carcinoma, and natural killer/T-cell lymphoma were high on our differential diagnosis. Although less likely, malignant lesions of minor salivary gland origin (e.g., central mucoepidermoid carcinoma) and mesenchymal origin (e.g., chondrosarcoma, fibrosarcoma, and osteosarcoma) were also considered.

Squamous cell carcinoma represents approximately 90% of malignant lesions involving the upper aerodigestive tract. The clinical presentation of a large ulcerated defect with raised margins and exposure of underlying bone, coupled with the patient’s significant history of tobacco and alcohol use, would certainly be compatible with a squamous cell carcinoma of gingival origin.

Sinonasal carcinoma and natural killer/T-cell lymphoma, perforating into the oral cavity, can similarly present with intraoral ulceration. This typically follows destruction of the nasal or sinus floor with subsequent perforation of the alveolar bone or palate. Early symptoms tend to be nonspecific and are often overlooked, leading to a delay in diagnosis. Additional features can include nasal obstruction, local pain, swelling, epistaxis, nasal discharge, epiphora, diplopia, dysesthesia or paresthesia, visual disturbances, and proptosis. Radiographically, the bony destruction in this case was restricted to the inferior aspect of the nasal cavity and appeared to have originated from the anterior maxillary alveolar area as opposed to the midline oronasal region. In addition, the patient had no symptoms of nasal obstruction, epistaxis, or dysosmia.

Metastatic disease to the oral cavity from a malignant lesion at a distant site is uncommon, accounting for approximately 1% of oral malignant lesions. They mainly involve the jawbones, whereas primary metastases to soft tissues are very rare. Although almost all types of malignancy may metastasize to the oral cavity, the most common primary sites are the breast, lung, kidney, other bone, and colon. The primary site differs between the sexes: for women, it is the breast followed by the adrenal, colorectum, female genital organs, and thyroid; for men, it is the lung, followed by the prostate, kidney, other bone and adrenal. The breast is the most common primary site for tumors metastasizing to the jawbones, whereas the lung is the most common site for metastases to the oral soft tissue. Radiographically, the majority of these lesions will present as a destructive, poorly defined radiolucent process, whereas mixed radiolucent-radioopaque presentations are occasionally noted. Although the patient had no history of prior malignancy, in a percentage of cases the discovery of a metastatic lesion to the jaws can be the first presenting symptom of a previously undiagnosed primary malignancy. In addition, chest radiography and systemic scintigraphy showed no evidence of other lesions.

Our final working diagnosis was primary squamous cell carcinoma of the gingiva.

**DIAGNOSIS**

The patient was admitted for additional tests and an incisional biopsy under local anesthesia. At the time of admission, the vital signs of the patient were unremarkable and hematologic parameters were within normal limits. Chest radiography and bone scintigraphy (technetium-99m and gallium-67) showed no evidence of other lesions. An incisional biopsy was obtained from the palatal aspect of the lesion.

Hematoxylin and eosin-stained biopsy specimens demonstrated a malignant tumor with a sarcomatoid
component and a squamous cell carcinoma-like component (Fig. 4, A). The sarcomatoid areas showed a diffuse proliferation of oval to spindle-shaped cells with large, clear nuclei containing distinct nucleoli. Nests of epithelioid tumor cells were also evident intermingled within the sarcomatoid areas. A gradual transition between the 2 components was evident (Fig. 4, B). The nests of epithelioid tumor cells appeared to be continuous with the adjacent gingival mucosa, where dysplastic change was evident in the epithelium. This was most consistent with a lesion of surface epithelial origin.

Both the carcinoma-like and sarcomatoid components were positive for epithelial markers. Only the sarcomatoid element was vimentin-positive (Fig. 5, A, B and Table I). The Ki-67 labeling indices were 12.5% for the spindle cell–like component, and 82.5% for the carcinomatous component. The corresponding p53 labeling indices were 11.5% and 75.5%, respectively.

The final histological diagnosis was spindle cell squamous carcinoma (SCSC). The tumor was staged as T4N0M0.

MANAGEMENT

The patient was treated with TS-1 and cisplatin (CDDP) as neoadjuvant chemotherapy. TS-1 (100 mg/day) was administered orally every day for 21 days, and CDDP (60 mg/m²) was administered as a single course by intravenous infusion on day 8. Two courses of treatment resulted in a marked reduction of the tumor without toxicity. This was followed by surgical treatment, consisting of left subtotal maxillectomy and right partial maxillectomy. Postoperatively, the patient underwent radiotherapy with 60Co to a total dose of 45 Gy. He is alive with no evidence of recurrent or metastatic disease 52 months after the surgical procedure.

DISCUSSION

Spindle cell squamous carcinoma, defined as a carcinoma containing histologic elements resembling
Table 1. Summary of immunohistochemical staining findings

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Type</th>
<th>Source</th>
<th>Spindle cell component</th>
<th>Carcinoma component</th>
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</thead>
<tbody>
<tr>
<td>Keratin</td>
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<td>Polyclonal</td>
<td>Dako</td>
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<td>+</td>
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<td>Cytokeratin</td>
<td>AE1/AE3</td>
<td>Monoclonal</td>
<td>Dako</td>
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<td>Dako</td>
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<td>+</td>
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<tr>
<td>Vimentin</td>
<td>V9</td>
<td>Monoclonal</td>
<td>Dako</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>S-100</td>
<td>S-100</td>
<td>Polyclonal</td>
<td>Dako</td>
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<td>+</td>
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<tr>
<td>Smooth muscle actin</td>
<td>LA4</td>
<td>Monoclonal</td>
<td>Dako</td>
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<td>+</td>
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<tr>
<td>Desmin</td>
<td>D33</td>
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<td>Dako</td>
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<td>±</td>
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<td>Ki-67 labeling index (%)</td>
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<td>Immunotech</td>
<td>12.5</td>
<td>82.5</td>
</tr>
<tr>
<td>p53 labeling index (%)</td>
<td>DO-7</td>
<td>Monoclonal</td>
<td>Dako</td>
<td>11.5</td>
<td>75.5</td>
</tr>
</tbody>
</table>

Immunohistochemical staining (Fig. 5, A, B) was performed on formalin-fixed, paraffin-embedded tissue sections by the Envision method (EnVision +, Dako, Glostrup, Denmark). The labeling indices (LI) for Ki-67 (MIB-1, Immunotech, Marseille, France) and p53 (DO-7, Dako, Glostrup, Denmark) by immunostaining were calculated by counting the positive cells among more than 1000 tumor cells in randomly selected fields.

+, positive; ±, focally positive; −, negative.

both a squamous cell carcinoma and a spindle cell neoplasm,12 is a relatively rare malignant neoplasm that can arise in a variety of sites, including the upper respiratory tract,13 esophagus,14 lung,15 and oral cavity.16-19 This neoplasm has been described using various terms, including spindle cell carcinoma, sarcomatoid squamous cell carcinoma,20 carcinomasarcoma,21 pseudosarcoma,22 and pleomorphic carcinoma,23 reflecting the varied interpretations of the spindle cell component as reactive, neoplastic, mesenchymal, or epithelial origin. Recent studies suggest that the spindle cell component of SCSC represents metaplastic alteration of the carcinoma component.24-25 This interpretation appears to be supported by histologic, electron microscopic, and immunohistochemical findings.24-27 Histologically, a transition from squamous cells to spindle cells has been documented.17,28 Electron microscopy has also demonstrated a transition from cells with epithelial features to cells with increasingly more mesenchymal characteristics.24,26,27 Although ultrastructural examination was not performed in our case, a gradual transition between the carcinomatous component and the spindle cell component was seen microscopically. Nappi et al.28 reported that the carcinomatous component is immunoreactive for keratin but nonreactive for vimentin, whereas the spindle cell component is positive for vimentin and negative for keratin. Our results were similar, with the exception that the spindle cell component exhibited focal positivity for keratin and EMA. These tumors should be considered aggressive in their biologic behavior, with a reported incidence of metastasis of 36% and a 2-year survival rate of 55% for tumors involving the oral cavity.29

Ki-67 antigen, expressed in the G1, S, G2, and M phases of cycling cells, but not in resting cells (G0 phase), can be employed as a marker to evaluate cellular proliferating activity.30 Although Ki-67 activity of SCSC has been examined by a number of authors,14,31-32 few studies have investigated the proliferative activity of oral SCSC.19 Lauwers et al.14 reported that the proliferative activity of the spindle cell component was higher than that of the carcinomatous component in esophageal tumors, suggesting that the spindle cell component had a significant "growth advantage" over the carcinomatous element. It has been suggested that this could potentially contribute to the higher metastatic potential of SCSC compared with conventional squamous cell carcinoma. However, these findings are in contrast to those reported by Hansen et al.31 and Lewis et al.32 with respect to SCSC of the oropharynx. Based on a comparison of Ki-67 labeling indices in conventional oral squamous cell carcinomas (ranging from 15%-50%),33-35 it has been suggested that the proliferative activity of the carcinomatous component in SCSC is higher than that in conventional squamous cell carcinoma.

The Ki-67 labeling index of the carcinomatous component was higher than that of the spindle cell component in the tumor of our patient, although the overall Ki-67 labeling index of the spindle cell component (12.5%) was lower than previously reported (20%-69%).14,19,32 Mutations in the p53 gene have been extensively documented in oral squamous cell carcinoma.36,37 p53 protein overexpression, due to p53 gene mutation, has been correlated with carcinogenesis and cellular proliferation,33,36,37 and can be detected by immunohistochemistry. Previously, we reported that p53 expression was associated with Ki-67 expression.35 In this patient, p53 and Ki-67 labeling indices were similar, with p53 nuclear staining more abundant in the carcinomatous than the spindle cell component. Immunohistochemical features suggest that SCSC...
exhibit aggressive behavior due to the cellular-biologic characteristics of the carcinomatous component.

Surgery appears to be the most effective treatment modality for SCSC. Colozza et al. reported beneficial results using neoadjuvant or adjuvant chemotherapy with CDDP and 5-fluorouracil. Our patient was administered neoadjuvant therapy using a combination of CDDP and TS-1, a novel oral fluoropyrimidine anticancer drug composed of tegafur, gimestat, and ostastat potassium, prior to undergoing radical surgical resection.

Although radiation as a single treatment regimen appears to be ineffective, postoperative radiotherapy may improve local and regional control. Long-term follow-up is important because of the potentially aggressive nature of SCSC.

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review of 26 cases including DNA content and immunohistochemistry. Human Pathol 1997;28:664-73.

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