Oral non-squamous malignant tumors; diagnosis and treatment

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ABSTRACT

Some 90% of oral cancers consist of squamous cell carcinomas that arise from the oral mucosa. The remaining 10% of malignancies consist of malignant melanomas, carcinomas of the intraoral salivary glands, sarcomas of the soft tissues and the bones, malignant odontogenic tumors, non-Hodgkin's lymphomas and metastases from primary tumors located elsewhere in the body. These malignancies will be briefly reviewed and discussed. The emphasis is on diagnosis and management.

Key words: Oral cancer; oral sarcoma, oral malignant melanoma, oral metastases.

INTRODUCTION

Malignancies of the oral cavity largely (90%) consist of primary squamous cell carcinoma arising from the mucosal lining. Tobacco and excessive use of alcohol play an important role in the aetiology of these cancers. The remaining 10% of oral malignancies consist of a heterogeneous group of tumors of unknown aetiology, and comprise malignant melanoma, malignant intraoral salivary gland tumors, sarcomas of the soft tissues and the jaw bones, non-Hodgkin's lymphomas, and the rare oral metastases of primary tumors located elsewhere in the body. These oral non-squamous malignant tumors will be briefly discussed, the emphasis being on diagnosis and management.

ORAL MALIGNANT MELANOMA

Approximately 1% of all malignant melanomas arise in the oral mucosa. There are no known aetiologic factors. Oral pigmented nevi do not seem to be risk markers of future development of an oral malignant melanoma.The patients are usually above the age of 40 years. There is no distinct gender preference. The palate and the upper and lower gingival are the sites of preference (1).

The clinical presentation of a malignant melanoma is usually a brown-black coloured swelling with or without ulceration (Fig. 1). Occasionally, there is no distinct melanin pigmentation, being referred to as an amelanotic melanoma. The diagnosis requires a biopsy. In case of suspicion of a cutaneous melanoma usually an excisional biopsy is recommended, since it has been suggested that an incisional biopsy may enhance the risk of metastatic spread (2). In the oral cavity an excisional biopsy is often not feasible because of the presence of teeth or bones.

The histopathologic features can be misleading, particularly if melanin pigment is not abundant. In such cases tumor markers such as HMB45 may be helpful to identity the nature of the tumor.

There is a clinical staging system for head and neck malignant melanomas, including oral malignant melanomas, that recognizes three stages; furthermore, stage I can be subclassified in three levels (Table 1) (3).

Treatment usually consists of wide surgical excision. The role of postoperative radiotherapy is questionable. Adjuvant chemotherapy does not seem to influence survival (4). Systemic immunotherapy with IL-2 and other cytokines is

Fig. 1. Typical presentation of oral malignant melanoma. Note the surrounding areas of pigmentation.

Table 1. Clinical Staging System for OMM with histopathological microstaging for Stage I (3)

Stage I: Primary tumour present only (T any N0M0)
        level I: Pure in situ melanoma without evidence of
            invasion or in situ melanoma with "microinvasion"
        level II: Invasion up to the lamina propria
        level III: Deep skeletal tissue invasion into skeletal muscle,
            bone or cartilage

Stage II: Tumour metastatic to regional lymph nodes (T any N1M0)

Stage III: Tumour metastatic to distant sites (T any N any M1)

not associated with an improved survival rate either (4). The detection of the so-called cancer testis antigens (CTAs) expression profile in oral malignant melanoma could lead to the development of a new vaccine-based therapy (5). Prognosis is usually poor due to local recurrences and metastatic spread, either through the lymph vessels or the blood stream. Clinical stage at presentation is probably the most important factor in determining outcome (6). In a study on 230 patients surgically treated for roal malignant melanoma, thickness of the tumor, cervical lymph node metastasis, presence or absence of ulceration and the anatomic sites were all independent risk factors (7).

Malignant melanoma is probably often preceded by diffuse areas of seemingly benign melanotic pigmentation, also referred to as melanosis. It is questionable whether treatment of melanosis is effective in preventing the development of a malignant melanoma.

TUMORS OF THE INTRAORAL SALIVARY GLANDS

Tumors of the intraoral salivary glands are relatively rare. The aetiology is unknown. The estimated incidence of benign and malignant intraoral salivary gland tumors together is less than 1 per 100.000 population per year. The patients are usually above the age of 20 years. There is no distinct gender preference.

The posterior part of the palate is the site of predilection, followed by the upper lip. Occurrence of a salivary gland tumor in the floor of the mouth is extremely rare. Interestingly, such salivary gland tumors in this location are nearly almost of a malignant type. Intraoral salivary gland tumors rarely occur in the jaws. If they do, it is usually the mandible.

The clinical presentation of both a benign and a malignant intraoral salivary gland tumors is often a slow growing, otherwise asymptomatic swelling with no characteristic features (Fig. 2). In other words, the nature of a salivary gland tumor, being benign or malignant, can not reliably be predicted on the clinical presentation alone. Usually preference is given to an incisional biopsy above fine needle aspiration cytology to arrive at a proper preoperative diagnosis. Only in well-circumscribed nodules in the lips or the cheek mucosa an excisional biopsy may be considered. Approximately 50% of all intraoral salivary gland tumors are malignant. One of the common malignant intraoral salivary gland tumors is the adenoid cystic carcinoma.

Fig. 2. Slowly growing, otherwise asymptomatic salivary gland tumor of the palate. The biopsy showed the presence of a pleomorphic adenoma.

In 2005 the World Health Organisation has issued a revised histopathological classification (8). Histopathologic typing can at times be difficult, even more so in tumors of the minor salivary glands than in tumors of the major glands. There are several histopathological pitfalls, such as necrotising sialometaplasia and metastatic tumors that may mimic salivary gland tumors. Tumor markers are in general of limited help in the histopathologic classification of salivary gland tumors. Grading of such tumors is of limited value with the possible exception of mucoepidermoid carcinomas.

Treatment consists of surgical removal and, on indication, of postoperative radiotherapy. Prognosis mainly depends on stage and histological type.

SARCOMAS OF THE ORAL SOFT TISSUES (EXCLUDING KAPOSI'S SARCOMA)

The estimated annual incidence of sarcomas of the oral soft tissue is approximately one per million population. They constitute less than one per cent of all oral malignancies. There are no known aetiologic factors. Soft tissue sarcomas may occur at all ages. There is no gender preference.

The clinical presentation is not characteristic and usually consists of a firm elastic swelling (Fig. 3). There is a wide variety of histological types, such as fibrosarcoma, liposarcoma, rhabdomyosarcoma. In 2002 a revised clas-

sification of soft tissue tumors has been published by the WHO (9). Numerous types and subtypes have been identified in that classification. Many of these are difficult to classify histopathologically with certainty in spite of the use of tumor markers. Furthermore, some of these tumors are classified as intermediate tumors, between the category of benign and malignant ones, since metastases may occasionally occur in such tumors, e.g. in solitary fibrous tumor and hemangiopericytoma. Histopathological grading, taking into account tumor differentiation, mitotic counts and tumor necrosis, evaluates the degree of malignancy and the probability of distant metastases (9). In general, three groups are recognised, high, intermediate, and low grade malignancy. Staging, based on both clinical and histopathological parameters, provides information on the extent of tumor.

Fig. 3. Fibrosarcoma of the gingiva and alveolar mucosa of 11 and 12. No bone involvement.

Treatment usually consists of wide surgical excision with or without (neo)adjuvant chemotherapy. In deeply located soft tissue sarcomas or in case of irradical removal of a soft tissue sarcoma, postoperative radiotherapy is often used, although no evidence-based data about the efficacy of such treatment is available. Prognosis mainly depends on stage and histological type (10, 11).

OSTEOSARCOMAS OF THE JAWS
Approximately 5% of all osteosarcomas that may occur in the skeleton arise in the jaws. Chondrosarcomas rarely affect the jaw bones. Osteosarcomas may affect children and young adults (12). There is no distinct gender preference. There are no known aetiologic factors other than the rare event of previous irradiation (13).
Clinical signs and symptoms may be inconspicuous, consisting of a low growing bony hard swelling of the jaw bone. Mobility of teeth only occurs in a late stage. In case of mandibular involvement the first sign of malignany may be paraesthesia or anaesthesia of the ipsilateral site of the lower lip. The radiographic appearance may vary from diffuse radiolucent to densely opaque. Radiographic features suggestive of osteosarcoma are irregular widening of the periodontal ligament and loss of decortication of the follicular crypts of embedded teeth (Fig. 4).

Fig. 4. Irregular widening of the periodontal ligament of 11, suggestive of osteosaroma.

Histopathologically, osteosarcoma may present in a wide range of morphologic variations and may mimic, amongst others, fibro-osseous lesions, giant cell granuloma, cementoblastoma, and osteoblastoma. Conventional osteosarcoma is divided in three subtypes: 1) osteoblastic, 2) chondroblastic, and 3) fibroblastic type (9).
Treatment consists of (neo)adjuvant chemotherapy and surgery (14). There is hardly a role for postoperative radiotherapy. If radically excised, the prognosis of osteosarcoma of the jaws is rather favourable. If metastases occur, the lungs are the most commonly affected organs.

NON-HODGKIN'S LYMPHOMA
The oral cavity may be the primary site of non-Hodgkin's lymphoma. The estimated annual incidence is 1:1.000.000 population. There is no gender preference. Non-Hodgkin's lymphoma usually affects patients above their sixth decade.
There are no known aetiologic factors for non-Hodgkin's lymphoma, except the rare event of an underlying human immunodeficiency virus infection. All sites of the oral cavity may be affected, but the palate seems to be a site of preference. The clinical presentation may vary considerably with involvement of either the soft tissues or the bone. Non-Hodgkin's lymphomas are occasionally very fast growing tumors but they also may present in a rather indolent way (15). Ulceration of the overlying epithelium may or may not be present (Fig. 5).

Fig. 5. Non-Hodgkin's lymphoma of the palate presenting as a slowly growing mucosal swelling. No bone involvement.

Table 2.   WHO REAL classification of non-Hodgkin lymphomas according to clinical aggressiveness (16).

Indolent lymphomas
    B-cell neoplasms
        Small lymphocytic lymphoma/B-cell chronic lymphocytic leukaemia
        Lymphoplasmocytic lymphoma (± Waldenström's macroglobulinaemia)
        Plasma cell myeloma/plasmacytoma
        Hairy cell leukaemia
        Follicular lymphoma (grades I and II)
        Marginal zone B-cell lymphoma
        Mantle cell lymphoma

    T-cell neoplasms
        T-cell large granular lymphocytic leukaemia
        Mycosis fungoides
        T-cell prolymphocytic leukaemia

    Natural killer cell neoplasms
        Natural killer cell large granular lymphocytic leukaemia

    Aggressive lymphomas
        Follicular lymphoma (grade III)
        Diffuse large B-cell lymphoma
        Peripheral T-cell lymphoma
        Anaplastic large cell lymphoma, T-null cell

    Highly aggressive lymphomas
        Burkitt lymphoma
        Precursor B lymphoblastic leukaemia/lymphoma
        Adult T-cell lymphoma/leukaemia
        Precursor T lymphoblastic leukaemia/lymphoma

    Special group of localized indolent lymphomas
        Extranodal marginal zone B-cell lymphoma of MALT type*
        Primary cutaneous anaplastic large cell lymphoma

   * MALT = mucosa-associated lymphoid tissue

Table 3. Ann Arbor staging system (17).

Stage	Defining status
Stage I*	Restricted to single lymph node region (I) or a single extranodal site (I-E)
Stage II*	Two or more areas of nodal involvement on same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E)
Stage III*	Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen* (III-S), or both (III-SE)
Stage IV	Liver, marrow, or other extensive extranodal disease
Substage	
Substage E	Localised, extranodal disease
Substage A	Absence of systemic signs
Substage B	Presence of unexplained weight loss (≥ 10% in 6 months), and/or unexplained fever, and/or night sweats

  * The spleen is considered nodal

Table 4. International Prognostic Index (18).

Parameters
- Age ≥ 60 years
- Advanced stage (III of IV)
- Extranodal involvement of > 1 site
- Performance status ≥ 2
- Serum lactate dehydrogenase level raised

Risk group stratification

0 – 1	Low-risk
2	Low intermediate risk
3	High intermediate risk
4 - 5	High risk

A biopsy is required to arrive at a proper diagnosis. Lymphoid tissue should be handled with care, since mechanic forces easily damage the cellular morphology, making the assessment of a reliable histopathological diagnosis difficult if not impossible. Most of the oral non-Hodgkin's lymphomas are of the B-cell type (Table 2) (16). Before treatment is instituted patients will be staged according to the Ann-Arbor-system (Table 3) (17). In a group of 40 patients with an oral non-Hodgkin's lymphoma, in whom the oral lesion was the presenting manifestation, 24 were staged as stage I, 12 as stage IV and 1 and 2 as stage II and III, respectively (15). Treatment consists usually of chemotherapy. The prognostic parameters are listed in table 4 (18).

ORAL METASTASES
Approximately 1% of all oral cancers consist of metastases derived from tumors located elsewhere in the body. In one-third of the patients the oral lesion is diagnosed before the primary (19).
The primary is located in the common tumor sites, such as lung, breast, prostate and kidney. Oral metastases may either occur in the soft tissues or in the bone. In soft tissue involvement ulceration may or may not be present (Fig. 6)

Fig. 6. Palatal metastasis of a breast carcinoma three years after treatment of the primary.

Tumor markers may be of help in identifying the primary site. A well-known example is the use of prostate specific antigen in case of a metastasis of a prostate cancer.
In general, treatment possibilities of oral metastases are limited because of the often presence of multiple metastases.

CONCLUSIONS
The oral non-squamous malignant tumors form a heterogeneous group of tumors of unknown aetiology. In contrast to oral squamous cell carcinoma these non-squamous cell oral cancers are not preventable.
Probably due to their rare occurrence the signs and symptoms are often not recognized at an early stage. The histopathologic diagnosis may at times be difficult to establish with certainty. For the majority of these malignancies, non-Hodgkin's lymphomas and oral metastases excepted, surgery is the treatment of choice, whereas the value of postoperative irradiation is questionable. Prognosis mainly depends on clinical stage and histopathologic type.

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