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Metastatic Neoplasms to the Oral Cavity

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Introduction

Background

Metastatic tumors to the oral region are uncommon and may occur in the oral soft tissues or jawbones. Because of their rarity, metastatic tumors to the oral region are challenging to diagnose. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to oral region.

The Medscape Head and Neck Cancer Resource Center and the Melanoma Resource Center may be of interest. Additionally, the eMedicine article Metastatic Cancer, Unknown Primary Site might be helpful.

Pathophysiology

The metastatic process is complex and involves sequential steps. Tumor cells must detach from the primary tumor, spread in the tissues, invade blood vessels, and survive their travel in the circulation. Then, the metastatic cells settle in the microvasculature of the target organ, extravasate through the vessel wall, and proliferate within the recipient tissue. Different properties are required for the metastasis of primary tumors to secondary sites than for primary tumorigenicity. The most basic feature is cell movement away from the primary tumor through the extracellular matrix.

Cell motility involves remodeling of the cytoskeleton. During the process of epithelial-mesenchymal transition, cells progressively redistribute their apical and basolateral epithelial-specific tight and adherens junction proteins (including E-cadherin and cytokeratins) and re-express mesenchymal molecules (including vimentin and N-cadherin). These changes lead to the loss of cell-to-cell contacts and the gain of cell motility. Extrinsic factors in the tumor microenvironment can promote the motility of cancer cells; stromal cells have been found to have a role in modulating cancer cell motility by producing growth factors and proteases that support the survival and proliferation of carcinoma cells in a paracrine fashion.

A successful metastatic colony is the result of a complex sequential genetic alteration that enables the tumor cells to reach their final destination. Angiogenesis plays an important role in expanding the tumor mass, and increasing neovascularization is correlated with an increased rate of metastasis.[1] Because small tumors of less than 2 mm in

diameter already receive a vascular blood supply, it is likely that cancer cells have spread throughout the body years before they are first detected. However, only a small proportion of metastatic cancer cells survive in the circulation, probably due to intrinsic inhibition of apoptosis.

Considerable evidence indicates that metastasis of various cancers to distant organs is not a random event, but is a regulated, site-specific process.[2] Gene expression profiling studies indicate that distinct molecular pathways are involved in lymphatic and hematogenous dissemination of several cancers. The oral region is not a preferred site for metastatic colonization; cancers here are usually the result of secondary spread from other metastatic lesions, especially those from the lungs. However, approximately 30% of oral metastases are the first sign of the metastatic disease. In such cases, tumor cells bypass the filtration of the lungs, probably through the valveless vertebral venous plexus. An increase in the intrathoracic pressure directs the blood flow into this system from the caval and azygous venous system and accounts for the increased distribution of axial skeleton and head and neck metastasis.

The pathogenesis of the metastatic process in the jawbones is not clear. In the skeleton, bones with red marrow are the preferred sites for metastatic deposits. Several primary malignancies prefer bone as their metastatic target, especially cancers from the breast, prostate, lungs, and kidneys. Expression of CXC chemokine receptor and its ligand are known to be involved in cancer metastasis.[3]

It has been demonstrated that the ligand is highly expressed in bone marrow. Jawbones have little active marrow, especially in elderly persons; however, remnants of halvato da Windows Internet Explorer 8> Subject: Metastatic Neoplasms to the Oral Cavity: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 01:08:22 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_045C_01CA2CFC.32997920" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_045C_01CA2CFC.32997920 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1079102-print

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A successful metastatic colony is the result of a complex sequential genetic alteration that enables the tumor cells to reach their final destination. Angiogenesis plays an important role in expanding the tumor mass, and increasing neovascularization is correlated with an increased rate of metastasis.[1] Because small tumors of less than 2 mm in diameter already receive a vascular blood supply, it is likely that cancer cells have spread throughout the body years before they are first detected. However, only a small proportion of metastatic cancer cells survive in the circulation, probably due to intrinsic inhibition of apoptosis.

Considerable evidence indicates that metastasis of various cancers to distant organs is not a random event, but is a regulated, site-specific process.[2] Gene expression profiling studies indicate that distinct molecular pathways are involved in lymphatic and hematogenous dissemination of several cancers. The oral region is not a preferred site for metastatic colonization; cancers here are usually the result of secondary spread from other metastatic lesions, especially those from the lungs. However, approximately 30% of oral metastases are the first sign of the metastatic disease. In such cases, tumor cells bypass the filtration of the lungs, probably through the valveless vertebral venous plexus. An increase in the intrathoracic pressure directs the blood flow into this system from the caval and azygous venous system and accounts for the increased distribution of axial skeleton and head and neck metastasis.

The pathogenesis of the metastatic process in the jawbones is not clear. In the skeleton, bones with red marrow are the preferred sites for metastatic deposits. Several primary malignancies prefer bone as their metastatic target, especially cancers from the breast, prostate, lungs, and kidneys. Expression of CXC chemokine receptor and its ligand are known to be involved in cancer metastasis.[3]

It has been demonstrated that the ligand is highly expressed in bone marrow. Jawbones have little active marrow, especially in elderly persons; however, remnants of hematopoietic active marrow can be detected in the posterior areas of the mandible, especially in cases of focal osteoporotic bone marrow defects. These hematopoietically active sites may attract metastatic tumor cells.

In the oral soft tissues, the rich capillary network of chronically inflamed gingiva can entrap malignant cells. The proliferating capillaries have a fragmented basement membrane through which tumor cells can more easily penetrate.

Frequency

International

Metastatic tumors to the oral region are uncommon and account for approximately 1% of all malignant oral tumors. However, autopsies of patients with carcinoma reveal a higher frequency of metastatic deposits in the jawbones, which are not manifested clinically. Metastatic tumors to the jawbones are more frequently reported than those in the oral mucosa (by a ratio of 2.5:1). The most common primary sources of metastatic tumors to the oral region are cancers in the breast, lung, kidney, bone, or colorectum. The breast is the most common primary site for tumors that metastasize to the jawbones, whereas the lung is the most common source for cancers that metastasize to the oral soft tissues (see Sex).

Mortality/Morbidity

The prognosis is grave. The time from the appearance of the metastasis to death is several months.

Race

To the authors' knowledge, race has not been studied as a factor in the metastatic process in the oral region; however, changes can occur in different parts of the world, depending on the local prevalence of a particular malignant tumor. For example, in Japanese women, the uterus rather than the breast is reported to be the most common primary sites of cancers that metastasize to the oral cavity.

Sex

The male-to-female ratio is almost equal; however, sites within the oral cavity differ. For the jawbones, the male-to-female ratio is 1:1.1; for the oral mucosa, the ratio is 2:1. The primary site differs between the sexes.

In male patients, the most common primary cancers that metastasize to the oral region are those in the lungs, followed by those in the kidneys, prostate, bone, and skin.

Origin and site of metastatic tumors to the oral region in men are as follows:

- Oral mucosa
    - Lung - 31%
    - Kidney - 14%
    - Skin - 12%
    - Liver - 7.5%
    - Colorectum - 5.2%
    - Bone - 5.2%
    - Testis - 4.5%
    - Esophagus - 4.5%
    - Stomach - 3.7%
    - Rare tumors - 12.4%

Jawbones

- Lung - 25%
- Kidney - 10.8%
- Liver - 8.6%[4]
- Prostate - 7.5%
- Bone - 7.5%
- Adrenal gland (cases of neuroblastoma, including cases from retroperitoneum and mediastinum) - 5.3%
- Colorectum - 4.7%
- Testis - 4.4%
- Esophagus - 3.6%

- Stomach - 2.5%
- Bladder - 2.5%
- Rare tumors - 17.6%

In female patients, the most common primary cancers that metastasize to the oral region are those in the breasts, followed with much lower frequency by those in the female genital organs, colorectum, bone, and kidneys.

Origin and site of metastatic tumors to the oral region in women are as follows:

- Oral mucosa
  - Breast - 24%
  - Genital organs (uterus, ovaries, cervix, fallopian tubes) - 14.8%
  - Kidney - 12%
  - Lung - 9.4%
  - Bone - 9.4%
  - Skin - 6.8%
  - Colo-rectum - 6.8%
  - Rare tumors - 16.8%
- Jawbones
  - Breast - 36.6%
  - Genital organs (uterus, ovaries, cervix, fallopian tubes) 9.5%
  - Kidney - 8.5%
  - Colorectum - 7.1%
  - Bone - 6.7%
  - Adrenal gland (cases of neuroblastoma, including cases from retroperitoneum and mediastinum) - 5.8%
  - Thyroid - 5.4%[5]
  - Rare tumors - 20.4%

Age

Most metastatic tumors to the oral region occur in patients aged 40-70 years.

- On average, patients with metastases to the jawbones are younger (ie, aged 45 y) than those with metastases to the oral soft tissues (ie, aged 54 y).
- The mean ages of these 2 groups differ probably because of cases of metastatic neuroblastoma to the jawbones in children; these cancers have a propensity to metastasize to bones.

Clinical

History

Symptoms develop in a relatively short period.

- In the oral soft tissues, most patients complain of a lump.
- In the jawbones, swelling, pain, and paresthesia of the affected nerve are the chief complaints.
- Give special attention to patients with numb chin syndrome or mental nerve neuropathy. The numb chin syndrome is the consequence of loss of function of the terminal sensory division of the mandibular branch of the trigeminal nerve. Any pathological process involving the mental nerve, the mandibular nerve, and even the mandibular trunk of the fifth nerve may produce this loss of function. The appearance of a mental nerve neuropathy should always raise the possibility of a metastatic disease in the mandible.[6]

- With the progression of the disease, oral metastatic lesions (especially those in soft tissues) cause progressive discomfort. Pain, bleeding, superinfection, dysphagia, interference with mastication, and disfigurement are some of the main patient complaints.
- In some cases, the metastasis is discovered in a recent extraction site.
    - The main symptom is a soft tissue mass extruding from a recent extraction wound and accompanied by pain.
    - In many of these cases, the metastatic tumor is present in the area before the extraction; it can cause pain, swelling, and loosening of the teeth.
    - These symptoms lead to the extraction of the affected tooth. In some cases, metastasis probably develops after extraction.
    - Tooth extraction can serve as a promoting factor in the metastatic process.

Physical

- The clinical presentation of the metastatic tumors differs among the various oral sites.
    - In the oral soft tissues, the attached gingiva is the most commonly affected site, followed by the tongue and, with much less frequency, the remaining mucosa.
    - The presence of teeth seems to have a crucial effect on the oral site preference of metastases.
        - In the dentulous patient, about 80% have metastasis in the attached gingiva.
        - In the edentulous patient, metastatic lesions are distributed equally between the tongue and alveolar mucosa.
    - In the jawbones, the common location of the metastatic lesion is the mandible; the molar area is the most frequently involved site.
- In its early manifestation, gingival metastasis resembles hyperplastic or reactive lesions (eg, pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis).
- In other oral soft tissue locations, especially in the tongue, the metastatic lesion manifests as a submucosal mass.
- In the jawbones, physical examination reveals a bony swelling with tenderness over the affected area.
- Sometimes, tooth mobility and trismus are present.

Causes

The oral region is an uncommon site for metastatic lesions. However, several factors can enhance metastatic colonization in the oral region.

- In dentulous patients, 80% of the metastatic tumors to the oral soft mucosa are found in the attached gingiva, whereas in edentulous patients, metastatic lesions are equally distributed between the tongue and the alveolar mucosa. The rich capillary network of chronically inflamed gingiva has been suggested as a mechanism that entraps malignant cells.
- The jawbones have little active marrow, which is a preferred site for metastatic deposits in the skeleton. However, in some cases, active marrow can be found in the posterior area of the mandible. In addition, remnants of hematopoietic marrow can be found in an edentulous jaw in cases of focal osteoporotic bone marrow defects. These hematopoietically active sites may attract metastatic tumor cells.

Differential Diagnoses

Malignant Melanoma
Oral Fibromas and Fibromatoses
Oral Malignant Melanoma
Oral Pyogenic Granuloma
Peripheral Giant Cell Granuloma
Pyogenic Granuloma (Lobular Capillary Hemangioma)
Squamous Cell Carcinoma

Other Problems to Be Considered

Oral soft tissues

Pyogenic granuloma

Peripheral giant cell granuloma (only in the gingiva)

Fibrous epulis (only in the gingiva)

Malignant primary tumor (oral cancer, including salivary gland tumor)

Jawbone (differential diagnosis depends on location)

Malignant tumors (eg, primary intraosseous carcinoma, other malignant odontogenic tumors)

Central malignant salivary gland tumors

Sarcoma (eg, malignant fibrous histiocytoma, fibrosarcoma)

Bony lesion can mimic benign lesion (some cases)

Periapical pathology

Infected odontogenic cyst or tumor

Osteomyelitis

Workup

Imaging Studies

- The balance between the activities of osteoblasts and osteoclasts in general determines the phenotype of metastatic bone lesions, either osteolytic or osteoblastic. Metastases from prostate cancer nearly always form osteoblastic lesions in bone[7]; by contrast, bone metastases from kidney, lung, or breast cancers are more often osteolytic.
    - The most common radiographic presentation is that of a lytic lesion with ill-defined margins.
    - Occasional osteoblastic lesions are observed.
    - In approximately 5% of the patients, the radiographs do not reveal any pathologic changes.
- An oral radiography survey may be helpful.
- Periapical and panoramic radiographs, CT scans, and MRIs can be obtained to evaluate the extent of the lesion.
- Lack of radiographic changes does not exclude the possible presence of a small metastatic deposit in the jawbone.

Procedures

- The following steps constitute the diagnostic algorithm for evaluation of oral metastases:
    - Review the clinical history.
    - Review the available radiographic findings.
    - If a history of a previous tumor exists, obtain the slides and reports for review.
    - Perform a biopsy of the lesion.
    - Evaluate the light microscopic features of the neoplasm. On the basis of the histologic features, determine the need for special studies (eg, histochemical staining, immunohistochemical tests, electron microscopy).
    - In cases in which the primary tumor is not found (unknown primary), look for signs and symptoms in an attempt to identify the potential primary. This can be accomplished with a complete history and physical examination, with special attention to the breast, rectal, and pelvic examination findings.
        - The standard battery of laboratory tests includes a complete blood cell count, liver function tests, calcium level, urinalysis, and serum creatinine value. A chest radiograph is also always indicated. Chest radiographs and chest CT scans have proven to be useful in the detection of primary lung tumors.
        - Sex-specific tests include serum prostate-specific antigen assay and transrectal ultrasound for male patients and mammography and cervical Papanicolaou test (Pap smear) for female patients.
        - Additionally, a CT scan of the abdomen and pelvis has been used in some series; it has been shown to identify the primary tumor in 10-35% of patients. A CT scan can identify primary tumors in the pancreas, liver, adrenals, kidney, gallbladder, ovaries, and stomach.
        - Positron electron transmission scanning with fluorodeoxyglucose is rapidly gaining favor in the evaluation of unknown primary cancers, particularly in instances in which other image modalities have failed to identify a source

- Plan the treatment protocol based on the clinical, pathological, and radiographic information.

Histologic Findings

The diagnosis is always based on histologic findings in the biopsy specimen. The clue to the diagnosis is the resemblance of the metastasis to the primary tumor. If a history of a previous tumor exists, compare the current histologic findings with those of the preexisting primary malignant tumor. In some cases, histochemical staining, immunohistochemical tests, and electron microscopy should be performed to identify the primary source of the metastatic tumor.

Attend to the differentiation of the primary intraoral malignancies from metastatic tumors. Several primary intraoral malignancies (especially those originating from salivary glands) have histologic features similar to those of tumors in distant organs: for example, primary ductal carcinoma of a salivary gland origin versus metastatic breast carcinoma, primary intraoral clear cell carcinoma versus metastatic renal cell carcinoma, primary intraoral squamous cell carcinoma versus metastatic squamous cell carcinoma from the lung, or primary intraoral malignant melanoma versus metastatic malignant melanoma. Malignant soft tissue tumors may originate intraorally, but, because of their rarity, one should always consider a metastatic origin.

Treatment

Medical Care

Oral metastases usually indicate widespread disease. Treatment modalities are limited to palliation. In some cases, surgical treatment, sometimes combined with radiation therapy and/or chemotherapy, can improve the patient's quality of life.

Surgical Care

Adequate surgical treatment can improve the prognosis in some cases in which the oral region is the single metastatic site.

Follow-up

Prognosis

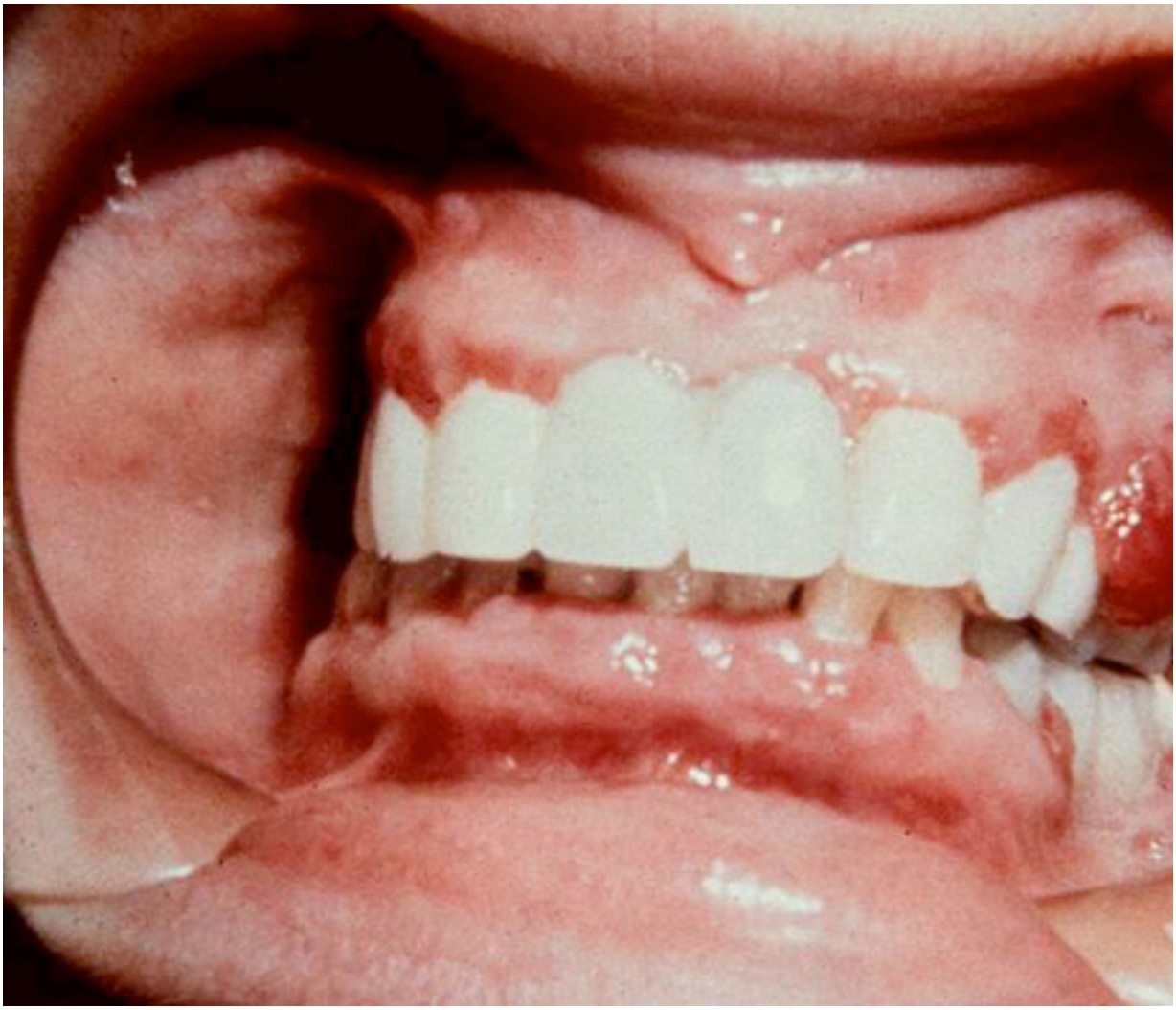
- Oral metastases usually are evidence of a widespread disease and indicate a grave prognosis.
- The time from the appearance of the metastasis to death is several months.

Miscellaneous

Medicolegal Pitfalls

- Misdiagnosis of a metastatic lesion as a benign reactive lesion may delay diagnosis and treatment.
- Metastatic tumors should always be considered in the differential diagnosis of benign-looking lesions in the oral cavity, especially in patients with a previous history of a malignant disease.
- Biopsy is mandatory to establish an accurate diagnosis.

Multimedia



Media file 1: A large pedunculated mass on the gingiva resembles a pyogenic granuloma and peripheral giant cell granuloma in a 44-year-old woman with metastatic breast carcinoma.

Media file 2: A large soft-tissue mass on the gingiva resembles pyogenic granuloma and peripheral giant cell granuloma in a 51-year-old man with metastatic renal cell carcinoma.

References

1. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med*. Jan 1995;1(1):27-31. [Medline].
2. Dai CY, Haqq CM, Puzas JE. Molecular correlates of site-specific metastasis. *Semin Radiat Oncol*. Apr 2006;16(2):102-10. [Medline].
3. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer*. Jul 2004;4(7):540-50. [Medline].
4. Pires FR, Sagarra R, Corrêa ME, Pereira CM, Vargas PA, Lopes MA. Oral metastasis of a hepatocellular carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. Mar 2004;97(3):359-68. [Medline].
5. Whitaker B, Robinson K, Hewan-Lowe K, Budnick S. Thyroid metastasis to the oral soft tissues: case report of a diagnostic dilemma. *J Oral Maxillofac Surg*. May 1993;51(5):588-93. [Medline].
6. Laurencet FM, Anchisi S, Tullen E, Dietrich PY. Mental neuropathy: report of five cases and review of the literature. *Crit Rev Oncol Hematol*. Apr 2000;34(1)