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Oral metastasis of triple negative breast cancer - An overview

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Abstract

Metastasis is a term used to describe the spread of cancer and is reported to be less than 1% in the oral cavity. Metastatic oral malignancies have been reported in the mandible, tongue, and gingiva. Breast cancer oral metastasis usually presents as a benign oral lesion and is less common than metastasis to other sites such as the lung and liver. Triple negative breast cancer (TNBC) is a type of breast cancer which shows Estrogen receptor (ER), Progesterone receptor (PR) and Human Epidermal Growth factor Receptor 2 (HER2) negative. It is common in younger women of less than 40 years of age and tends to be more aggressive with higher chances of metastasis.

Keywords: Metastasis, Oral cavity, Triple negative breast cancer

Introduction

Metastasis in the oral cavity is rare and they involve only the bony structures rather than the soft tissue. In fact, soft tissue involvement of the oral cavity in metastasis occurs in only 0.1% of cases. [1-4] Triple Negative Breast Cancer (TNBC) also metastasize to various parts of the body in which there is increased likelihood to develop central nervous system and visceral metastases.[5]

Metastasis of TNBC to the oral cavity has been reported less, although it is a highly aggressive tumour.

Metastasis

The spread of malignant cells from a primary tumour to distant sites, known as metastasis, is the most difficult problem in cancer treatment and the leading cause of death in cancer patients.[6] The most common form of cancer in women worldwide is breast cancer. The majority of breast cancer-related deaths result from metastasis. The management and prognosis of breast cancer progression depend on the early detection of breast cancer metastasis. In low- and middle-income countries, breast cancer mortality is particularly high due to late presentation and limited access to comprehensive cancer care. [7- 10]

Metastatic breast carcinoma

Breast cancer has the potential to spread to other parts of the body, resulting in metastatic breast cancer (MBC). MBC was diagnosed early in 6–60% of patients with breast cancer.

There are five biological subtypes of breast cancer (Table 1) and the ability of these subtypes to spread to distant organs, specific pathways, and preferred metastatic sites vary. Patients with luminal subtypes of breast cancer, frequently have bone relapses whereas basal subtype breast cancer usually metastasizes to the lungs and brain and less commonly to the liver. HER2 subtype more often shows liver metastasis.[11] It is reported that 3.6% of all breast cancers develop bone metastases to oral cavity.[12]

Triple negative breast cancer

Triple Negative Breast Cancer (TNBC) is defined immunohistochemically as breast cancer that does not overexpress HER2 and is ER, PR negative.[5] It accounts for 10-20% of all cases of breast carcinoma and encompasses a morphologically diverse group of carcinomas, many of which are uncommon. These include invasive ductal carcinomas (IDC) not otherwise specified (NOS), medullary carcinomas, apocrine carcinomas, adenoid cystic carcinomas, and metaplastic carcinomas.[13] They are more common in younger women, particularly those of African American or West African ancestry, and in women with low socioeconomic status when compared to non-TNBCs. Breast carcinomas in African American women are twice as likely to be triple negative as those in white women. TNBCs tend to behave more aggressively than non-TNBCs. Patients with TNBC tend to experience a relapse more quickly and have a higher likelihood of developing central nervous system and visceral metastases.[5]

Triple negative breast cancer metastasis to oral cavity

Metastasis of breast carcinoma to the oral cavity is not uncommon. According to Mur god et al. [14] in a literature review, breast cancer in women is responsible for 25% of all oral metastases. Furthermore, metastasis is more common in the jaw bone than in soft tissue, as shown by Hirshberg et al in 2008, who reviewed 111 cases of breast carcinoma out of 673 oral metastasis cases, in which 91 cases reported jawbone metastasis and 20 cases showed soft tissue metastasis. It usually involves the mandible rather than the maxilla. In the case of soft tissue involvement, the gingiva is the most common site of metastasis.[15]

There are only few cases reported in English literature on triple negative breast cancer in women with metastasis to the oral cavity.

A case reported by Dobromir a Niko love et al in 2021 in which the patient with metastatic breast carcinoma (triple negative) to maxillary mucosa, passed away 5 months after the maxillofacial procedure. The cause of

death was deemed to be the widespread metastatic triple negative disease.[16]

Wuraola et al. in 2021[9] reported a case of infiltrating ductal carcinoma NOS (triple negative) showing metastasis to maxilla and palate presenting as a diffuse mid-facial swelling with a Bucco-palatal fungating mass and the overlying mucosa was hyperaemic with areas of ulceration and necrotic sloughs.

Sunny Jain et al. in 2013,[17] reported a case of infiltrating ductal carcinoma (triple negative) with metastasis to buccal mucosa that occurred one year later and presented as a hard, painful swelling in the right cheek, which was progressively increasing in size. She did not had consent for surgery and was taken up for palliative treatment with docetaxel and cisplatin-based chemotherapy regimen.

Among these cases, the sites of metastasis were involving soft tissue covering the maxilla and one involving the maxillary bone and soft tissue involving palatal mucosa. (Table 2) All these cases showed ulcer proliferative growth clinically. [9,16,17]

Possible mechanism of metastasis to gingiva

Gingiva is the frequently affected site of metastasis in the oral soft tissues.

This is probably due to the circulating tumour cells that may become entrapped in the rich capillary network of chronically inflamed attached gingiva and the new proliferating capillaries have a fragmented basement membrane and are leaky, making them more permeable to tumour cells than mature vessels[16,18,19] and further the periodontal inflammation promotes metastasis of breast cancer by recruiting myeloid- derived suppressor cells by pyro ptosis- induced IL-1β generation and downstream CCL2, CCL5, CXCL5 signalling.[20] (Fig 1)

Diagnostic approach

A panel of diagnostic markers used to determine the origin of metastatic carcinoma in female patients includes ER, pan cytokeratin, TRPS1, and GATA3. ER can be used as both a diagnostic marker and a treatment target, in contrast to HER2, which is typically only used as a therapeutic target. Breast and gynaecological carcinomas are the two distinct female tumours for which ER is a specific marker, and luminal invasive breast carcinomas (IBCs) are highly sensitive to ER. TRPS1 and GATA3 are used in conjunction because they can support one another. GATA3 can detect IBC with apocrine features, a unique type of TNBC that is negative for TRPS1, while TRPS1 detects almost all GATA3 negative and triple-negative IBC-NSTs (IDC). [21,22] Even though they are characterized immuno histochemical Ly, histologic features also suggest a triple-negative immuno phenotype. TNBCs are distinguished by a high histologic grade, central necrotic zones, and pushing borders. Triple-negative tumours frequently exhibit cellular fibrous proliferation, whereas non-TNBCs have fibrosis with a higher degree of hyalinization. TNBCs frequently have variable-sized blood vessels, including thick-walled vessels.[5]

Prognosis

Patients with TNBC have a relatively poor outcome and cannot be treated with endocrine therapy or therapies targeted to HER2. Consequently, this type of metastatic breast cancer requires special treatment approaches.[11] Patients with triple-negative breast cancer have an increased likelihood of distant recurrence and death compared with women with other types of cancer. These triple negative breast cancers experienced high rates of recurrence only in the period from 1 - 4 years after diagnosis. The risk declined rapidly thereafter and no recurrences occurred after 8 years of follow-up. Despite

having a high risk of early recurrence, it seems that women with triple-negative breast cancer who are disease-free for eight years are unlikely to die of breast cancer.[23] The majority of breast cancer-related deaths in women occur as a result of the disease's metastatic spread rather than the development of the primary tumour. As a result, prognostic factors can be used to successfully identify patients who are at a high risk of developing metastatic breast cancer and to individually choose the most effective treatment for each cancer patient.

Conclusion

Triple negative breast cancer rarely metastasizes to the oral cavity, especially the gingiva and may present as a reactive lesion. A biopsy is necessary in these situations, especially in patients who have a history of malignant disease, in order to determine the exact histopathological correlation because the clinical presentation and radio graphic findings of a metastatic lesion can be misleading and result in the misdiagnosis of a benign process. In order to make the diagnosis, a comprehensive medical history and a panel of immuno histochemical stains may be beneficial. The follow up PET CT is mandatory which shows distant metastasis to various organs. Sometimes oral lesions may be the first to manifest clinically and may play a vital role in diagnosing the primary tumours. TNBCs often indicate a poor prognosis, yet in certain cases, early identification may render the possibility of improved outcomes.

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Tables

Table 1: Molecular subtypes of breast cancer[4]

Molecular subtypes of breast cancer4
Human epithelial growth receptor type 2 (HER-2) positive
Luminal A- ER positive, HER2 negative, Ki 67 low, PR high
Luminal B- ER positive, HER2 negative, either Ki 67high or PR low
Claudin-low- Low expression claudins 3, 4 and 7, occluding and E-cadherin
Basal-like- Robust cluster of genes expressed by epithelial cells in the basal or outer layer of the adult mammary gland

Table 2: Clinical presentation of reported cases of triple negative breast carcinoma with oral metastasis[3, 8, 9]

Age(years)/ Gender	Type of breast carcinoma	Site of metastasis	Involvement of bone/ soft tissue	Survival
44/ F	Triple-negative carcinoma	Maxillary mucosa	Mucobuccal, mucolabial fold and palate (Soft tissue)	< 3 years

42/F	Infiltrating ductal carcinoma Not Otherwise Specified(Triple negative)	Maxilla and palate	Right maxillary central incisor region to the right maxillary tuberosity (Bone and soft tissue)	< 1 year
30/F	Infiltrating ductal carcinoma (triple negative)	Buccal mucosa	Soft tissue	Not mentioned

Figure

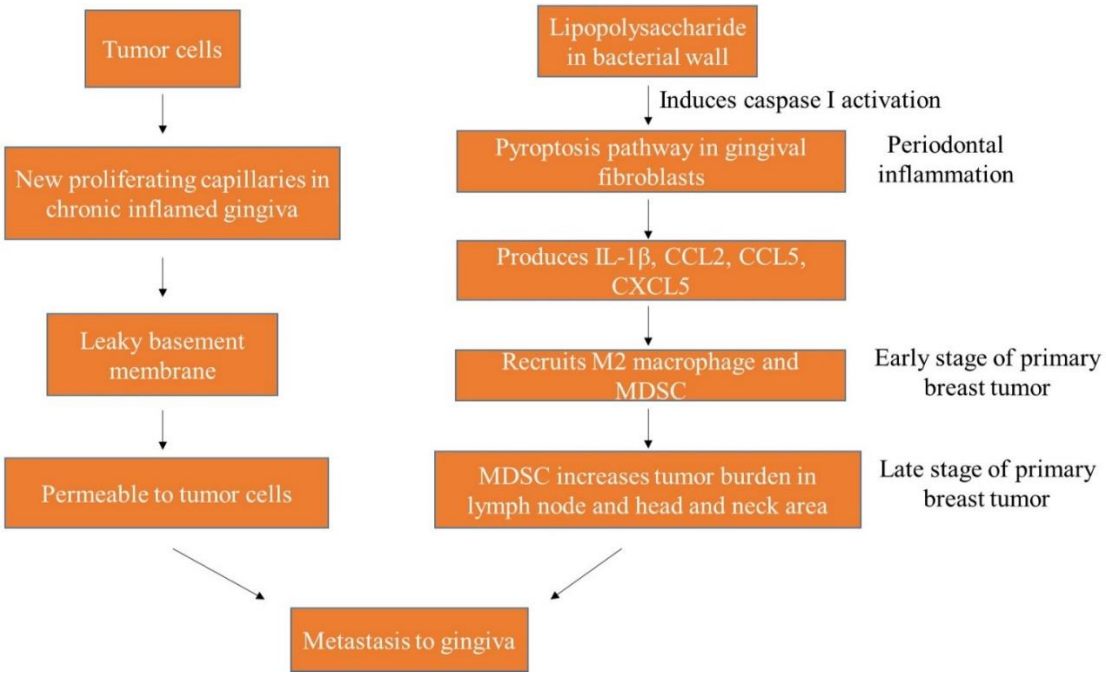

Fig 1: Possible underlying mechanism of gingival metastasis