IMAGING FEATURES IN THE EVALUATION OF PATIENTS WITH BRAIN AND MANDIBULAR METASTASES IN BREAST CANCER WOMEN FROM THE NORTH-EASTERN REGION OF ROMANIA

Alexandra Vornicu[1], Bogdan Filip[1], Nicolae Ioanid[1], Bogdan Gafton[3], Raluca Pleșca[2], Cristina Terinte[4], Iulian Prutianu[5], Andrei-Ionuț Cucu[6], Cristina-Gena Dascălu[7], Dragos-Viorel Scripcariu[1], Viorel Scripcariu[1], Danisia Haba[6]

1"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Surgical Oncology
2"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Radiology
3"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Oncology
4"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Pathology
5"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Oncology, Neolife Medical Center
6"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Surgery (II)
7"Grigore T. Popa" University of Medicine and Pharmacy Iași, Faculty of Medicine, Department of Medical Informatics and Biostatistics

Corresponding author: andreiucucu@yahoo.com, drfilipbogdan@gmail.com

ABSTRACT

This study aimed to explore the imaging features, immunohistochemical profiles, and molecular characteristics of brain and mandibular metastases stemming from breast cancer (BC). **Introduction:** Brain metastases (BM) represent a common and devastating manifestation of BC. BM are particularly prevalent in BC phenotypes expressing human epidermal growth factor receptor 2 (HER2-positive) marker and triple-negative subtypes and often occur following metastatic spread to various sites. BM represent a major contributor to morbidity and mortality in individuals with metastatic BC. **Material and Methods**: A retrospective analysis was conducted on 47 patients diagnosed with both brain metastases and facial masses as sites of metastases. **The results** predominantly indicated invasive ductal carcinoma, with a slightly higher incidence in cases affecting the right breast. In most cases, the intervention performed was a modified Madden mastectomy. **Discussions:** Our study highlights the greater aggressiveness of BC in younger women and the marked heterogeneity in tumor response to oncological treatment. **Conclusions:** Facial mass involvement resulting from metastases from BC cases is rare, but signifies the increased aggressiveness of these tumors. Further studies on larger patient cohorts are necessary to better understand the etiopathogenic mechanisms underlying the development of this type of metastasis.

Key words: breast cancer, brain metastases, mandibular metastases

INTRODUCTION

Mandibular metastases can occur in advanced stages of BC, typically as a result of hematogenous spread. The mandible often represents a preferred site for such metastases. [1]

Metastases associated with BC are frequently localized to the lungs, liver, skeleton, pleura, brain, and renal structures, while they are less commonly found in the adrenal glands and ovaries. While distant metastases are relatively common, involvement of the head and neck region occurs less frequently. In this area, the most commonly encountered manifestations include supraclavicular lymphadenopathy and bone metastases in the mandible and maxilla, with the mandible being more commonly affected.

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Imaging evaluation of patients suffering from brain and mandibular metastases originating from BC involves the use of advanced imaging techniques to identify, localize, and characterize the metastases, guide treatments, and monitor their response. Both brain and mandibular metastases can have significant clinical implications, making imaging assessment crucial for the proper management of these patients. [2, 3]

Specific regions of the mandible, such as the distal segment, angle, and ramus, are particularly prone to metastases due to factors such as the presence of hematopoietic bone marrow, the anatomical configuration of local vasculature, and slower blood flow. Diagnosing mandibular metastases is often complicated by nonspecific clinical manifestations and prolonged latency, which can significantly delay detection.

The American Association for Dental Research describes temporomandibular disorders (TMD) as a group of conditions affecting the muscles involved in chewing, the temporomandibular joints (TMJ), and surrounding anatomy. These conditions can cause a wide range of symptoms, including headaches, tinnitus, joint noise, difficulty chewing, irregular or limited mandibular function, masticatory muscle pain, and restricted mouth opening. Such definitions provide a valuable direction for diagnosis and integration into specific frameworks for complex oncological treatment approaches, combined with oral rehabilitation.

The approach to treating temporomandibular disorders (TMD) is transitioning from conventional mechanistic dental methods to contemporary biopsychosocial medical models that emphasize multidisciplinary care. Progress in understanding pain mechanisms and addressing chronic pain has resulted in enhanced long-term treatment outcomes. [4]

The clinical manifestations of metastatic tumors in the jawbones include swelling, orofacial pain, neurosensory alterations, soft tissue masses, ulcerations, regional lymphadenopathy, trismus, and, in severe instances, pathological fractures are commonly observed.

Notably, metastases originating from breast carcinoma can occasionally imitate inflammatory or infectious conditions of the jaw and, in certain cases, may present without any symptoms. Radiographically, metastases may range from well-circumscribed radiolucent lesions to poorly defined radiopacities, described as having a "moth-eaten" appearance. Occasionally, these metastases may not be visible on radiographs.

Imaging evaluation of brain and facial metastases in patients with BC is essential for accurate diagnosis and treatment planning. MRI is the reference method for assessing brain metastases, while CT and MRI are useful for evaluating facial metastases. Treatment is multidisciplinary, tailored to the location, size, and number of metastases, including options such as surgery, radiotherapy, and systemic therapy. [5]

HER2-positive BC (HER2+ BC) is a specific subtype characterized by an overexpression of the human epidermal growth factor receptor 2 (HER2) protein. Approximately 8% to 14% of individuals with HER2-positive BC (HER2+ BC) develop brain metastases (BM) [6], with the HER2 protein playing a key role in driving cancer cell proliferation. Approximately one in five BC cases involves cancer cells with additional copies of the HER2-producing gene. Compared to the luminal A subtype, HER2+ BC demonstrates a higher propensity for metastasizing to the central nervous system (CNS), with the CNS being up to three times more likely to serve as the initial site of metastasis in HER2+ BC compared to HER2-negative cases.

On average, CNS metastases develop approximately 12 months after the diagnosis of HER2-positive metastatic BC (mBC). However, this reflects data from before the introduction of HER2-targeted therapies, which have significantly altered the epidemiology of brain metastases in HER2+ BC [7, 8].

MATERIAL AND METHODS

In this retrospective study, information

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was gathered from the electronic medical records of patients diagnosed with brain and facial mass metastases from BC between January 1, 2010, and December 31, 2021, at the Regional Oncology Institute in Iași (IRO). We identified 47 patients with BM, of which 4 had mandibular metastases from a previously diagnosed and treated BC.

The study evaluated various tumor characteristics, including tumor size, histological type and grade, molecular subtype, lymph node involvement, and systemic metastases. Additional factors assessed included patient demographics (including location, cytopathological traits, histopathological subtype [HP], immunohistochemical [IHC] profiles), and the time interval between the initial BC diagnosis and the detection of brain metastases. The study exclusively included women with pathologically confirmed BM originating from BC.

Imaging evaluations were conducted using MRI scans of the patients. Written informed consent for the utilization of clinical and pathological data was obtained from all participants, with approval from the Ethics Committees of the Regional Oncology Institute in Iași and the "Grigore T. Popa" University of Medicine and Pharmacy in Iași, Romania.

RESULTS

The age of the patients in the study ranged from 34 to 85 years, with an average age of 56.98 years. Of the total 47 patients diagnosed with BC, 61.7% (n=29) are from urban areas and 38.3% (n=18) from rural areas. Approximately 2% of patients had bilateral tumors (Fig. 1).

Breast affected		n	%
	bilateral	1	2,1
	right	24	51,1
	left	22	46,8
	Total	47	100,0

Figure 1. Distribution of BC location among the study group

All patients were evaluated using ultrasound, mammography, breast MRI, and thoraco-abdominal CT. In breast ultrasound evaluations, among the 26 patients, 4 presented tumors larger than 5 cm in diameter, 16 had tumors between 2-5 cm in diameter, and 6 had tumors smaller than 2 cm in diameter. Among these, 21 patients had between 1-2 tumors, and 5 patients had more than 3 tumors. Additionally, 16 patients underwent mammography. Breast MRI (3T) was performed in 3 cases, showing multicentric masses, pseudotumoral formations associated with axillary adenopathy, and expansive intraglandular formations.

Four of these patients developed mandibular metastases after a period of 2-4 years from the initial diagnosis and treatment (Fig. 2-4).

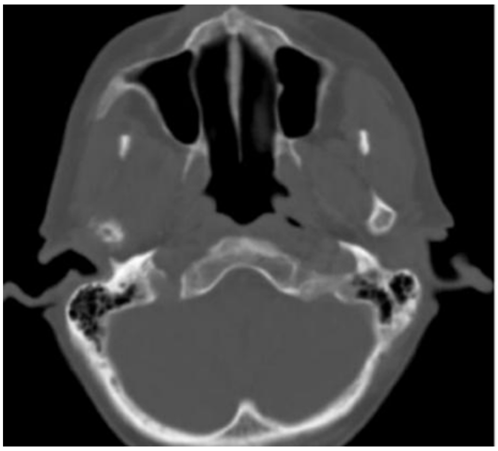

Figure 2. CTNC bone window, BC metastasis in right mandibular condyle; 49 yo woman.

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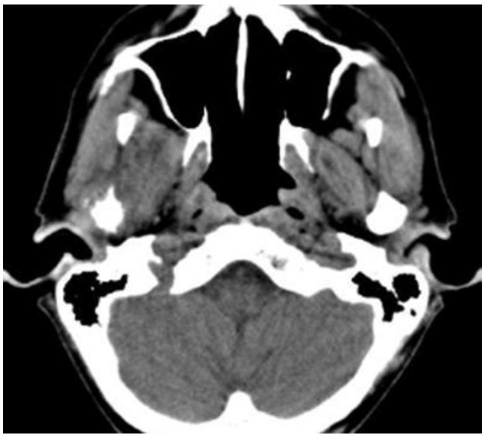

Figure 3. CTNE soft window, BC metastasis in right mandibular condyle with irregular aspects; 65 yo woman.

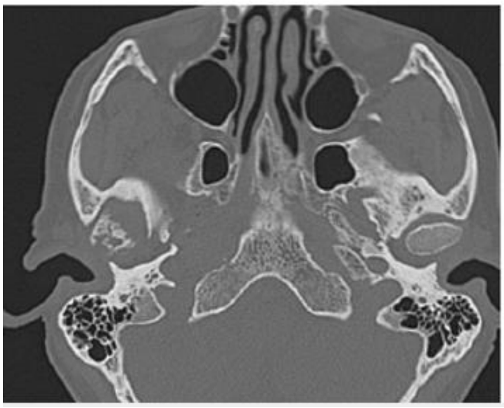

Figure 4. CTNE bone window**,** BC metastasis in right condyle and right sphenoidal bone; 57 yo woman.

Axillary lymph node metastases were classified as follows: 1-3 nodes = 2, 4-9 nodes = 2, > 10 nodes = 7, and subclavicular nodes: 1-3 nodes = 2 and > 10 nodes = 3. Multiple metastases were detected in various locations, including pleuropulmonary (n=6) and bone metastases (n=4).

Of the 47 patients, one had bilateral BC and a family history of cancer, while 45 underwent a modified Madden mastectomy (a technique that includes the entire breast, the areola-nipple complex, and axillary lymph nodes from stations I and II). In contrast, conservative surgery with axillary lymphadenectomy was performed in 2 cases.

Among the 47 cases, 32 patients received neoadjuvant chemotherapy, 1 patient received neoadjuvant chemotherapy combined with hormonal therapy, and 4 received targeted biological therapy. Only 2 patients underwent sector resection, while the others underwent mastectomy followed by chemotherapy (CHT) and radiotherapy (RT) (Fig. 5).

Neoadjuvant treatment	n	%
absent	14	29,8
CHT	32	68,1
CHT + RT	1	2,1
Total	47	100,0

Figure 5. Distribution of CHT and RT treatment options within the study group.

Following the TNM staging, the lymph nodes were classified as Nx (n=2), N0 (n=10), N1a (n=12), N2a (n=14), and N3a (n=9). The stage of metastases was determined as follows: M1 (n=8), M0 (n=35), and Mx (n=4).

Subsequently, 33 patients received adjuvant radiotherapy (RT), 16 received adjuvant hormone therapy (HT), 24 received adjuvant chemotherapy (CHT), and 14 received biological therapy. The histological types of these BCs were: in situ (n=1), invasive ductal carcinoma NOS (n=40), mixed (n=2), and lobular (n=4) [Fig. 6-8].

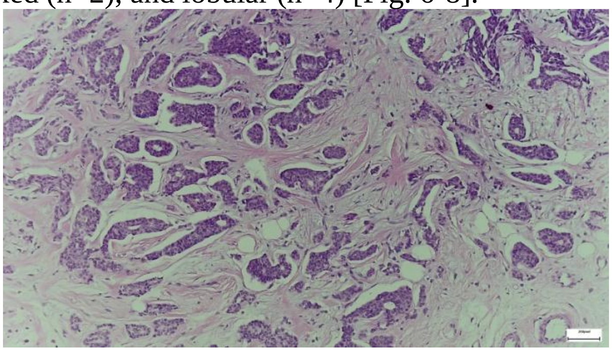

Figure 6. Invasive cribriform carcinoma with an extensive in situ component; 56 yo woman; (HE stainig, x100). HE: Hematoxylin–Eosin;

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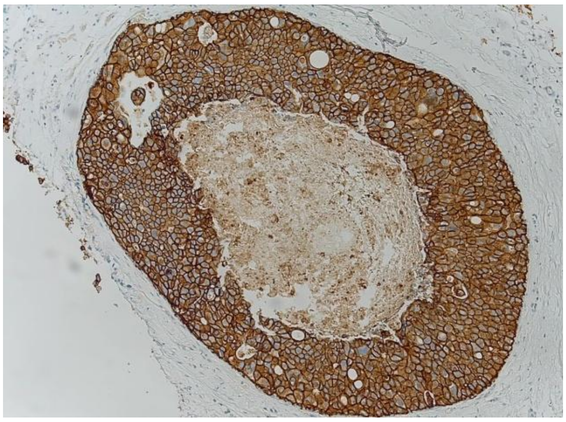

Figure 7. Microinvasive ducal carcinoma; 65 yo woman; HER2x10

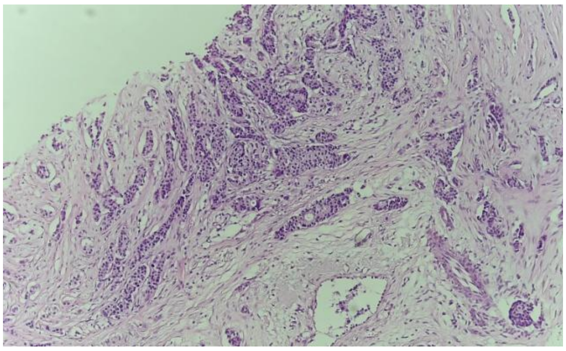

Figure 8. Invasive ductal carcinoma NOS of the breast - G2 (Nottingham score 6); 68 yo woman, (HE stainig, x100). HE: Hematoxylin–Eosin; NOS: Not otherwise specified.

Tumor differentiation, based on the Nottingham grading scale, was categorized as G1 (n=1), G2 (n=6), G3 (n=5), Gx (n=24, unspecified grade), and unspecified (n=10), with one case of G2 in both breasts (n=1). Each of the 47 cases was classified into four phenotypes: ER+/PR+ (n=22), ER-/PR+ (n=0), ER+/PR- (n=7), and ER-/PR- (n=18). The most common immunophenotype was ER+/PR+, with both receptors positive. The Ki67 proliferation index was significantly high in 38 cases. The HER2 status was fully evaluated and revealed 10 HER2 3+, 9 HER2 2+, 4 HER2 1+, and 16 HER2 0. The molecular subtypes identified were Luminal A (n=9), Luminal B (n=15), HER2-(n=10), and triple-negative (n=0).

Of the 47 patients, 11 had tumor recurrence at the postoperative scar, and tumor excision was performed. In the two cases where sector resections were performed initially, total mastectomy was later performed. After tumor recurrence, 6 patients underwent adjuvant chemotherapy (CHT) and 3 adjuvant radiotherapy (RT). Ten patients with brain and facial mass metastases, either single or multiple, from BC underwent craniotomy, and one patient underwent L3 corpectomy via a left anterolateral retroperitoneal approach, with reconstruction using an expandable cage and fixation with screws and rods from L2 to L4. Two months later, posterior fixation was performed from L2 to L4 on the right side and from L1 to L4 on the left side.

All patients were aware of their BC diagnosis at the time of their brain metastases (BM) diagnosis. Patients over 60 received a diagnosis of BM more than 20 months after their BC diagnosis, while those under 60 were diagnosed within 20 months. Upon presentation to the Neurosurgery Clinic, 16 patients had multiple BM (>2), and 5 had a single BM.

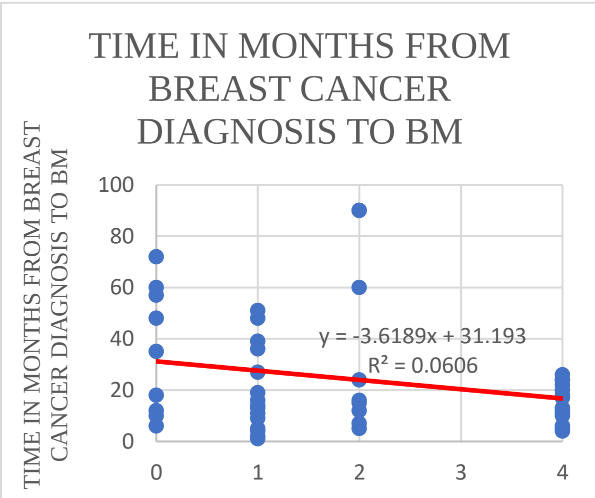

Figure 9. The time elapsed from the diagnosis of BC to the appearance of brain and mandibular metastases.

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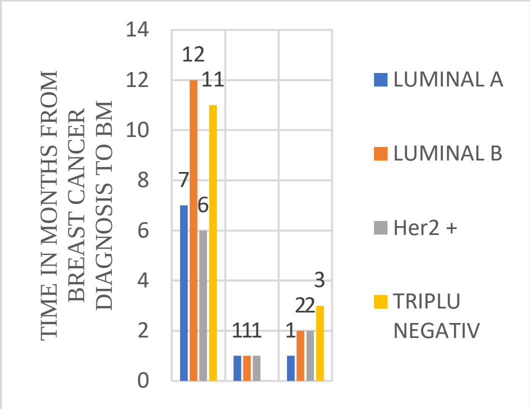

Figure 10. The first two columns on the left represent living patients, with MB (first column) and without MB (second column); the third column represents deceased patients, with or without MB.

In all four cases diagnosed with mandibular metastases, these were found to be synchronous with cerebral metastases. There were no cases of mandibular metastases occurring independently of secondary lesions in the central nervous system. The locations of brain metastases diagnosed included the cerebral hemispheres (16 cases), cerebellum (13 cases), fourth ventricle, lateral ventricle, and paraventricular region (3 cases), left hippocampus (2 cases), transverse sinus (1 case), temporomandibular joint (3 cases), and multiple metastatic locations (9 cases).

DISCUSSIONS

Our results showed that BC metastasized to the mandible and even to the temporomandibular joint (TMJ) in 8.1% of cases. The predominant histological type of mandibular metastases identified was invasive ductal carcinoma not otherwise specified (NOS), with other subtypes, such as tubular carcinoma and lobular carcinoma, also observed. Immunostaining patterns revealed three distinct profiles: (i) CK5/6+/-, mammaglobin+, ER+, PR-, typical of NOS BC; (ii) CK5/6-, mammaglobin+, ER-, PR-, associated with tubular BC; and (iii) CK5/6+/-, mammaglobin-, ER-, PR-, characteristic of lobular BC.

Although the jaws and oral cavity are rare locations for metastatic lesions, accounting for only 1% of oral cancers, actual incidences may be underestimated. Studies indicate micrometastatic deposits in 16% of autopsied carcinoma cases, even when radiological findings are negative [9]. Mandibular metastases from extraoral malignancies represent a particularly rare phenomenon, constituting just 1% of oral malignancies. In men, lung, kidney, liver, and prostate cancers are common primary sources, while in women, breast, genital, renal, and colorectal cancers are more frequently implicated.

The probability of mandibular metastasis is influenced by several factors, including the primary tumor's type and stage, involvement of lymphatic and vascular structures, regional lymph node status, tumor dimensions, and histological traits, immune status, genetic factors, and the tumor microenvironment at both the primary and metastatic sites. The mandible's rich vascular network increases its susceptibility to metastatic deposits. Delayed detection and treatment of primary tumors further elevate the risk of metastatic spread [10, 11].

Numb chin syndrome (NCS) is an uncommon but clinically significant condition, presenting as unilateral anesthesia or paresthesia of the chin. It typically arises spontaneously, without any preceding trauma, infection, or identifiable odontogenic cause. This syndrome is a critical diagnostic clue, as it may indicate underlying systemic malignancy or serve as an initial manifestation of multiple sclerosis (MS). It is also observed in cases of mandibular metastases from BC**.** The differential diagnosis of the primary tumor is made by correlating the patient's history, imaging detection of the metastasis, and biopsy findings**.** [12-15]

The prognosis for patients with mandibular metastasis from BC generally reflects the overall stage of the disease. Mandibular metastasis typically develops in the later stages of BC and is frequently linked to a poor overall prognosis. However, with appropriate

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management, patients can experience symptom relief and improved quality of life. [16, 17]

Our study revealed that brain metastases originating from BC exhibit heterogeneity, though not as much morphological diversity. In this study, the risk of developing brain metastases was observed to be higher in patients over 50 years old, with metastases often exhibiting negative PR and ER status. These insights may aid oncologists in devising more targeted preventive and therapeutic strategies.

CONCLUSIONS

Mandibular metastasis in BC remains a rare but clinically important manifestation, often associated with advanced-stage disease. Early recognition and a comprehensive treatment strategy involving imaging, biopsy, and multidisciplinary care are crucial for improving outcomes and the quality of life for affected patients. Understanding the clinical and radiological features of mandibular metastasis can aid in the timely diagnosis and management of this condition.

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