A Complete Response of Orbital Metastases in Breast Cancer Patient Treated with Oral Chemotherapy: Case Report and Literature Review

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Abstract
Discrete extraocular muscles (EOMs) metastases are extremely rare events. Here is a case of isolated orbital metastases involving EOMs in a female patient who was previously diagnosed with triple-negative breast cancer. She received chemotherapy followed by radiotherapy. Years later, the patient complained of gradually progressive ptosis of the right eye that was associated with mild restriction of ocular movements. Magnetic resonance imaging showed a suspected metastatic lesion. An open biopsy was performed for pathological evaluation. Metastases from breast cancer were confirmed. Immunohistochemistry showed discordance of the estrogen and progesterone receptors. She received oral capecitabine (Xeloda®) and vinorelbine (NVB) followed by hormone therapy. At the time of reporting, our patient remained in remission for 28 months as from her initial diagnosis of orbital metastases.

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Introduction

The orbit is uncommon site for metastases; only 2–3% of all cancer patients will develop orbital metastases [1]. Metastases can be localized within any part of the orbit including bone, fat, or even extraocular muscles (EOMs). Involvement of EOMs separately is an extremely rare event [2]. The most common primary tumor metastasizing to EOMs is breast cancer (BC) [3]. Although invasive ductal carcinoma (IDC) is the most common type of invasive BC, the majority of orbital breast metastases are from invasive lobular carcinoma [4]; it is probably due to the expression of E-cadherin in IDC which limits cell dispersion and makes it rarely to spread to the orbit [5]. The clinical picture is usually nonspecific, including diplopia, motility disturbances, proptosis, ptosis, and palpable mass [6]. A final diagnosis is made by biopsy and treatment is usually palliative to preserve vision. We reported a case in which metastases from IDC were found in EOMs isolatedly and a complete response to oral chemotherapy has been achieved.

Case Report/Case Presentation

A 46-year-old female was presented with a lump in the left breast. The lump has gradually increased in size in the last 2 months without nipple discharge. There was unknown family history of cancer. Clinical examination of the breast and regional lymph node revealed a hard, nonmobile palpable mass in the upper outer quadrant of the left breast, adherent to the skin, and in the underlying tissue also axillary lymphadenopathy has been noticed. An excisional biopsy was performed and showed a poorly differentiated IDC (Grade III). Immunohistochemistry discovered the negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2/neu). Modified mastectomy and axillary lymph node dissection were performed and then sent to the pathology lab. Report from pathologist showed 23 of 24 axillary lymph nodes had metastatic deposits. The computed tomography (CT) scan did not find any signs of metastases. The patient staged as T2pN3M0 (Stage IIIC) according to American Joint Committee on Cancer Staging Manual 7th Edition (2010). The patient was put on chemotherapy regimen comprising 4 cycles of AC (doxorubicin and cyclophosphamide) followed by 4 cycles of docetaxel. Then she received external beam radiation therapy. A close follow-up was done, including regular medical visits and physical examination every 3 months and a mammography study for the other breast every year.

Four years after the diagnosis of BC, she complained of slowly progressive drooping of upper eyelid of the right eye. She was menopausal at this time. Ophthalmological examination showed ptosis and slight proptosis of the right eye. Also, local eye redness in the superior aspect has been noticed. Ocular movements’ examination revealed a limitation of elevation and abduction of the right eye with mild pain at movement. The two pupils were symmetrical and reactive to light. Best-corrected visual acuity was (6/6) within both eyes. Slit-lamp examination was normal. Magnetic resonance imaging without contrast of the brain and orbit revealed no brain abnormalities, but there was a marked enlargement of the superior rectus and levator palpebrae superioris muscle complex; also lateral rectus muscle was affected with mild proptosis (Fig. 1). For diagnostic confirmation, an open biopsy from superior rectus muscle was taken and showed invasion of striated muscle fibers by neoplastic cells (Fig. 2). Immunohistochemistry study showed positive results for cytokeratin AE1/AE3 and GATA3, supporting the diagnosis of metastatic breast carcinoma. ER and PR were positive, but human epidermal growth factor receptor-2 (HER-2/neu) was negative (Fig. 2). A CT with contrast to chest, abdomen, and pelvis failed to detect any evidence of metastases. She started with oral capecitabine (Xeloda®) 500 mg/m² twice daily from day 1 to day 14 plus oral vinorelbine
(NVB) on day 1, 8, with both medicines repeated every 3 weeks for 4 cycles. Clinical improvement of affected eye was noticed. She received additional 4 cycles of oral capecitabine and vinorelbine; then she put on letrozole 2.5 mg once daily. Follow-up was done over a period of 28 months, from the initial diagnosis of metastases to the time of this report, and found out that ptosis has partially disappeared and elevation of the right eye has totally recovered (Fig. 3). She is still receiving hormone therapy and checkup.
Discussion/Conclusion

Metastasis from breast carcinoma can be developed in approximately 40% of all patients during their lifetime [7]. Site distribution of metastatic lesions can be varied and regulated by multiple factors such as subtypes of cancer, molecular features of cancer cells, and host immune microenvironment [8]. IDC – which is the most common subtype of BC – is found to metastasize at higher frequency in bone (76%), lung (37%), liver (30%), and brain (8%) [9]. It is not commonly spread to the orbit [4, 6]

Overall, primary neoplasms of the orbit are more common than metastasis [10]. Orbital metastasis has been estimated to be only 1–13% of all orbital tumors [1]. Metastatic tumor emboli reach the orbit via the blood stream and are located in fat, bone, or muscles or can involve the orbit diffusely. Discrete EOMs metastases are extremely rare [2]; it is only accounting for 9% of all metastases to the orbit [11]. Although it is not well understood why metastatic cancers are rarely seen in these voluntary muscles, previous studies suggested that the constant movement of muscles may prevent the neoplastic cell deposit or produce an unsuitable chemical environment for continued neoplastic growth [12]. In addition to that, adhesion molecules that are site specific for EOMs may be expressed by only a few numbers of tumor cells [13]. Other causes that have been mentioned in the literature explaining the low incidence of metastases to the voluntary muscles are the activation of lymphocytes and natural killer cells in skeletal muscle and the muscle’s ability to remove tumor-produced lactic acid associated with angiogenesis [14, 15]

Breast carcinoma and melanoma are the most common primary tumors that are metastasizing to EOMs [2, 3, 16, 17]. In particular, metastases from breast carcinoma are found to be unilateral [18] and have a tendency to lodge in EOMs and the surrounding fat [11]. Right and left orbit can be affected by metastatic lesions. However, the association between metastases and orbital side has not been established [19–21]. On the other hand, metastases to EOMs have been noticed to involve the horizontal rectus muscles more commonly than the vertical rectus or oblique muscles [3, 22, 23]. In our case, metastatic lesions were found in the superior rectus and the lateral rectus muscles of the right orbit

There is no specific sign or symptom for metastatic involvement of the EOMs. Clinical manifestations are diplopia, motility disturbances, palpable mass, ptosis, and proptosis [3, 6, 17].
Eade et al. [17] found that all patients with a metastasis from a breast carcinoma have a light degree of proptosis between 1 and 3 mm. However, pain is a less observed symptom [11, 17]. Some studies showed that the absence of pain was often used as a marker of malignancy [2, 24]. In two series, the mean age of ophthalmic complain was 58.6 and 60 years, respectively [3, 6], whereas the mean span between detection of primary breast carcinoma and orbital metastasis was 5.9 years [25]. Our patient was 50 years old when she was presented with ptosis to clinic and she was diagnosed with breast carcinoma before 4 years.

Differential diagnosis was proposed. However, almost of patients (90%) with orbital metastases of BC had a diagnosis of BC before presentation to ophthalmic complain [25] so that patient with past medical history of BC presented with diplopia and motility disturbance should initially exclude the suspicion of tumor involvement of EOMs [26]. Imaging with CT or magnetic resonance imaging is indicated to evaluate the suspected lesion. Imaging characteristics of metastasis are not diagnostic unless there is a clear active metastatic disease with multi-organ involvement [22].

The definitive diagnosis requires biopsy of affected tissue. Biopsy is indicated in our patient to confirm diagnosis and evaluate ERs, which makes hormonal therapy an appropriate treatment [26]. Open biopsy is preferred in those patients rather than fine needle aspiration biopsy; this is because of reported dissemination of tumor cells with the fine needle aspiration biopsy [27].

Immunohistochemical staining plays an important role in identification of different types of cells. GATA binding protein 3 (GATA3) is a very specific marker for BC [28]. GATA3 and ER positive with clinical oncological history provides final diagnosis of metastatic carcinoma from primary BC.

In breast carcinoma, discordance of ER, PR, and HER2/neu status between the primary tumor and subsequent metastases is well recognized [29]. The discordance rates have been reported up to 40% [30]. Loss of receptor expression was more incidental than gain [31]. Chemotherapy, especially anthracycline-based chemotherapy, was associated with switch in ER status [32], as our patient was previously treated. The primary tumor in our patient was triple negative. However, metastatic lesion in the superior rectus muscle demonstrated ER positive, PR positive but HER2/neu still negative, indicating discordance with the primary tumor [23].

Treatment is usually palliative and the cornerstone is a patient’s comfort and preservation of vision. Also, improvement in survival rate should be considered. The options of treatment are various, including radiotherapy (RT), chemotherapy, hormone therapy, surgery, and immunotherapy. The optimal choice depends on the histological study and anatomical extent of the metastases. RT has been reported to provide relief of symptoms and improvement of ocular function with rapid rate [1, 33]. On the other hand, chemotherapy is associated with providing prolonged remission and prolonged survival rate but with slower response rate [23, 33]. RT is not an available option in our case due to the remote residence of the patient. There are no specific chemotherapies that are designed for treatment of orbital breast metastases. Oral capecitabine/vinorelbine have been considered the agents of choice in relapsed BC after both previous anthracyclines and taxanes [34]. This combination is effective and well tolerated [35] with an improvement in the overall survival [36]. ER-positive BCs carry substantial risk of late recurrence [37] and adjuvant therapy with aromatase inhibitors such as letrozole has led to a reduction in new or recurrent BCs and improved rates of disease-free survival [38].

In conclusion, any patient with past medical history of BC developing ocular symptoms should be evaluated for orbital metastases. Once diagnosis is confirmed, treatment is a real challenge. We report a case of IDC involving EOMs with complete clinical response to oral chemotherapy in the absence of short-term side effects. Long-term follow-up will be required to show the effectiveness of remission and any long-term side effects.
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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Majd Sharaf: writing article and final manuscript approval. Yousef Al-Oudat: writing article. Maher Saifo: diagnosis and treatment of the patient and final manuscript approval.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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