Eye metastasis in breast cancer: case report and review of literature

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Abstract

The paradigm of breast cancer management has been revolutionised, resulting in prolonged survival that echoes an increasing incidence of metastasis in uncommon sites. With orbital metastases – despite being rare – the incidence scales up to 13% of breast cancer cases with no specific management guidelines. We report a case of a 31-year-old luminal B breast cancer patient who initially presented with T2N2M0 disease and received six cycles of adjuvant chemotherapy (5-Fluorouracil (5-FU) 600 mg/m² IV, Doxorubicin 60 mg/m² IV, Cyclophosphamide 600 mg/m² IV), followed by radiotherapy (RTH) and adjuvant Tamoxifen. Two years later, the patient experienced successive bone metastasis, so she received several lines of endocrine therapy as Fulvestrant and aromatase inhibitors in combination with luteinizing hormone-releasing hormone (LHRH) analogues. Later on, she presented with right eye ptosis and magnetic resonance imaging (MRI) showed a soft tissue mass in the superior and lateral rectus muscles. The patient received six cycles of chemotherapy with no improvement. Further disease progression occurred 3 months later, so the patient received palliative RTH resulting in no response. One month later, the patient was deceased, secondary to progressive disease. With the rising incidence of ocular metastasis due to breast cancer, oncologists should be aware of symptoms and use the proper diagnostic modalities. Here we provide a literature review on similar cases and discuss possible treatment modalities for those patients. The main concern is to evaluate the need for chemotherapy in such cases in the presence of highly effective endocrinal treatment.

Keywords: breast cancer, eye metastases, treatment, chemotherapy, radiotherapy

Introduction

Eye metastases are a rare event in cancer patients with breast cancer being the most common primary site (28.5%–58.8%) [1]. The rising incidence of eye metastasis of breast cancer origin can be attributed to the recent advances in the systemic treatment of breast cancer which has resulted in prolonged survival of breast cancer patients in addition to the improvements in diagnostic modalities [2, 3]. In most cases, eye metastasis occurs along with systemic progression of previously diagnosed breast cancer; however, 25% of diagnosed eye metastases are detected in patients with de novo breast cancer as an initial presentation [4].
The aim of this literature review is to demonstrate different treatment modalities in cases described in the literature to help to evaluate best treatment options in addition to explaining our local experience with a case of breast cancer with eye metastasis in terms of the challenges in treatment based on the limited resources available.

**Patient information, clinical finding, diagnostic assessment**

We report a case of a 31-year-old patient who was diagnosed with T2N2M0 Estrogen Receptor(ER)/Progesterone (PgR) positive/HER-2/neu negative, Ki-67 > 30% right breast cancer. She was treated with modified radical mastectomy followed by adjuvant chemotherapy with six cycles of FAC regimen (5-Fluorouracil (5-FU) 600 mg/m² IV, Doxorubicin 60 mg/m² IV, Cyclophosphamide 600 mg/m² IV) every 21 days, radiotherapy (RTH) and adjuvant hormonal treatment with Tamoxifen for 2 years. The patient presented with severe back pain and the bone scan showed multiple bone metastases while multi-slice computed tomography (MSCT) of the chest and pelvis-abdomen were insignificant so she was shifted to luteinizing hormone-releasing hormone (LHRH) analogues in combination with Fulvestrant and palliative RTH. Eleven months later, the patient experienced successive bone progression and thereafter was shifted to aromatase inhibitors. Six months later, on November 2019 (4 years after the initial diagnosis), the patient presented with right eye ptosis, and the magnetic resonance imaging (MRI) of the brain and orbit showed a soft tissue mass in the superior and lateral rectus muscles (Figure 1) with no evidence of visceral metastasis on further metastatic work up except for multiple bone lesions.

**Therapeutic intervention and outcome of treatment**

After a multidisciplinary discussion, she started a combination chemotherapy of cisplatin and gemcitabine with a stationary course followed by Anastrozole. Three months later, the patient experienced further progression of her symptoms, in the form of ulceration, severe pain and pus discharge. The patient received palliative RTH at the dose of 30 Gy in ten fractions with no response (Figures 2 and 3). The patient was deceased 1 month later upon the deterioration of the general condition and further disease progression.

**Discussion**

Metastatic carcinoma of the eye is an uncommon clinical situation, and the most prevalent primary tumour is breast carcinoma which accounts for 28.5%–58.8% of all orbital metastases [3] followed by lung cancer (24%) and skin melanoma (14%) [1]. The increased incidence of eye metastasis of breast cancer follows the advances in diagnostic modalities and the prolonged survival of breast cancer patients. MRI remains the gold standard diagnostic imaging modality [5].

Figure 1. MRI brain at diagnosis: T1 with contrast shows right superior rectal muscle thickening about 14 mm associated with slight proptosis of the right eye.
Figure 2. MRI brain and orbit showed significant increase in the previously described right recti muscles thickness with heterogeneous post-contrast enhancement. There is subsequent proptosis and posterior ocular coat mass lesion just above the optic disc with significant enhancement of all posterior ocular coats. There is extra-orbital spread, and intra-cranial extra-axial leptomeningeal enhancement at the right frontotemporal region.

Figure 3. The presentation of the patient after the end of chemotherapy (a) and on progression after the radiotherapy (b).

A PubMed and Scopus search including English language only was performed using the Med search words 'breast cancer', 'eye metastasis' and/or 'orbital metastasis' until January 2021. The literature search revealed 53 records, of which 13 were included in the review and 40 in the quantitative analysis (Figure 4) with 94 cases collectively which were included in the analysis (Supplementary Table 1).

Eye metastases secondary breast cancer may be presented at any time point of the course of the disease, 38 (40.4%) of cases included in the analysis presented with eye metastases as the initial presentation of breast cancer, while 56 (59.5%) developed eye metastases either as
the only site of metastasis or as a part of the systemic progression of previously diagnosed breast cancer. In those patients, the time interval between the diagnosis of breast cancer and the development of eye metastasis when reported had a wide range from 1 month [6] up to 25 years [7], and 13 cases developed eye metastasis within 5 years of being diagnosed with early breast cancer. In another review, Freedman et al [8] reviewed the charts of 112 patients (141 eyes) and showed that the average time was approximately 4 years (1,266 days) from the breast cancer diagnosis to the occurrence of metastasis to the eye and orbit.

Evaluation of the most common sites of the eye to be affected with metastasis of breast cancer was available for 66 cases as there was an overlap of data presented in one report as shown in Figure 5 [9]. There is controversy about the affinity of the breast cancer cell to specific tissue types within the eye; despite the extra-ocular muscles are rare to be affected [10] – based on the fact that the constant movement of muscles would prevent lodging of neoplastic cells [11] – but they were involved in one-third of the reviewed cases. Orbital involvement with annexes like the lacrimal gland was the second common site followed by the infiltrative mixed lesions that could affect more than one definitive structure. The uveal tract involvement was infrequent when compared with previous reports [12, 13].

Figure 4. PRISMA flow diagram. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/
The infiltrative ductal carcinoma (IDC) represented only half of the cases settling with one-third of patients with infiltrative lobular carcinoma (ILC); that is relatively higher than the prevalence of lobular carcinoma in the general breast cancer population [14]. The infiltrative nature of ILC could explain this discordance; Raap et al [15] reported that orbital metastases were attributed five times to ILC more often than to IDC.

The luminal breast cancer subtype relates to the highest risk of eye metastasis compared with other aggressive subtypes like triple-negative breast cancer [16]. In two cases, the metastatic lesion in the eye turned ER/PR negative in primary hormone-positive breast cancer patients [9, 17] (Table 1). There was a wide range of treatment modalities; mono-therapy or multimodality therapy with variable response outcomes (Table 1). Luminal breast cancer constituted the majority of cases, so we were concerned with treatment options used in hormonal positive breast cancer cases with eye metastasis. The insisting question is whether to consider eye metastasis as a visceral crisis that indicates chemotherapy or tumour progression to shift to other lines of hormonal treatment according to the guidelines [18]. Patients treated 10 years back were shifted from hormonal to chemotherapy when presented with eye metastasis resulting in a modest symptoms improvement with no available survival data [4, 5]. Reports published in the recent 3 years [19–21] showed a clear trend towards CDK4/6 inhibitors instead of chemotherapy. This new era was associated with more local control of the disease with improvement in symptoms and considerable overall survival up to 6 years while kept on under Palbociclib [20]. The results of CDK4/6 inhibitors in the management of eye metastasis confirm the fact that the presence of eye metastasis may not jeopardise survival when treated appropriately.

Recently published cases [20, 22, 23] showed improvement in treatment outcomes secondary to the implementation of CDK4/6 inhibitors in combination with new RTH techniques like Stereotactic Body Radiotherapy (SBRT) [24]. Wiegel et al [26] showed that external beam radiotherapy (EBRTH) leads to stabilised or restored vision in up to 86% of patients; the typical dose varies between 20 and 50 Gy [3, 5, 26, 27].

The main challenges were the unavailability of CDK4/6 inhibitors or SBRT and the exhaustion of available hormonal treatment on managing rapidly progressive hormonal resistant metastatic breast cancer. That situation left chemotherapy the only reserve when presenting with eye metastasis with no response. Conformal RTH applied afterward to the persistent huge eye lesion – that was resistant to previous treatment – resulted in disease progression and symptoms worsening.
Table 1. Summary of cases reported on the literature on eye metastasis of breast cancer origin.

| Number of cases | 94 (100%) |
|-----------------|-----------|
| **Age**         |           |
| - Median        | 56        |
| - Range         | (33–76)   |
| **Histopathology** |       |
| - IDC\(^{a}\)   | 51 (54.3%)|
| - ILC\(^{b}\)   | 28 (29.8%)|
| - Rare histology | 11 (11.7%)|
| - Unknown       | 4 (4.2%)  |
| **Immunohistochemical subtype** |   |
| - Hormonal receptors positive | 75 (80%) |
| - HER2 neu enriched | 9 (1%)   |
| - Triple negative | 19 (2%)  |
| - Not identified | 16 (17%) |
| **Treatment modality** |       |
| - Mono-therapy treatment: |   |
| Surgery alone   | 23 (24.4%)|
| EBRTH alone\(^{c}\) | 13 (13.8%)|
| Hormonal alone  | 3 (3.2%)  |
| Chemotherapy alone |      |
| - Multimodality treatment: |   |
| Chemotherapy + anti-HER2 neu | 2 (2.1%) |
| Hormonal + RT   | 4 (4.2%)  |
| Chemotherapy + RT |      |
| Surgery + chemotherapy + RTH + hormonal | 1 (1.06%) |
| Surgery + chemotherapy + RTH | 1 (1.06%) |
| Surgery + RT    | 2 (2.1%)  |
| RTH + chemotherapy + hormonal | 38 (40.4%) |
| Not identified or overlap of data |      |
| **Primary response** |   |
| Partial/complete response | 14 (14.8%) |
| Stable disease   | 2 (2.1%)  |
| Progression      | 4 (4.2%)  |
| Not reported     | 73 (77.6%)|

\(^a\)Infiltrating ductal carcinoma  
\(^b\)Infiltrating lobular carcinoma  
\(^c\)External beam radiotherapy

**Conclusion**

With the rising incidence of ocular metastasis due to breast cancer, oncologists should be aware of symptoms and the proper diagnostic modalities. Follow-up on the outcome of treatment is extremely crucial in the absence of guidelines that could help clinical decision. Implementation of CDK4/6 inhibitors and new techniques in RTH in the treatment of breast cancer with eye metastasis opens up new horizons for improving outcomes. We believe that reporting and sharing experiences with these cases is paramount given the relative scarcity of data in this domain.
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Conflicts of interest

The authors have no conflicts of interest to declare.

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Supplementary Table 1. Summary of cases reported on the literature on eye metastasis of breast cancer origin.

| Case num | Year of publication | Age | Symptom | Histopathology | Molecular subtype | Course of disease | Site of metastasis | Intervention | Outcome | Ref |
|----------|---------------------|-----|---------|----------------|-------------------|-------------------|-------------------|-------------|---------|-----|
| 1        | 2021                | 50  | Foreign body sensation and exophthalmos in her right eye | IDC with neuroendocrine differentiation | ER+ PR+ Her2 - | Initial presentation and only site of metastasis | Extraocular muscles and bone destruction | 3 cycles nab-paclitaxel followed by Abemaciclib plus Letrazole | Marked reduction of size of mass with improvement in visual acuity | [1] |
| 2        | 2021                | 74  | Left eye enophthalmos and ptosis. | IDC | ER+ PR+ Her2 - | Initial presentation and only site of metastasis | Optic nerve | Letrozole for one year then addition of Palbociclib on bone progression | Control for one year on Letrozole then kept on follow-up for 6 years on Palbociclib with preserved visual acuity | [2] |
| 3        | 2021                | 76  | Enophthalmos and ptosis. | IDC | ER+ PR+ Her2 - | Initial presentation and only site of metastasis | Extraocular muscles, lacrimal gland and the optic nerve | Letrozole and Palbociclib then SBRT on progression | Progression on hormonal treatment after few months with OS of three years. | [2] |
| 4        | 2021                | 33  | Blurring vision | N/A | ER+ PR+ | Previously diagnosed with EBC one month | Medial rectus muscle and the optic nerve | Treated as an EBC case with surgery followed by adjuvant chemoradiotherapy and hormonal treatment | Stable disease at three month follow up | [3] |
| 5        | 2020                | 54  | Blurring vision | IDC | ER- PR- Her2 - | Previously diagnosed with EBC 4 years followed by metastasis to bone and lung | Choroid | Cyberknife 18 GY in single fraction | Total blindness with partial response of the choroid mass | [4] |
### Supplementary Table 1. Summary of cases reported on the literature on eye metastasis of breast cancer origin. (Continued)

| Case ID | Year | Age | Symptoms | Type | ER | PR | HER2 | Presentation | Diagnosis | Initial Treatment | OS |
|---------|------|-----|----------|------|----|----|------|--------------|-----------|------------------|-----|
| 6       | 2020 | 55  | N/A      | N/A  | 14 | 9  | 3    | Initial      | 14        | Letrozole         | 82.1|
| 7       | 2020 | 46  | Left eye swelling and exophthalmos | IDC | ER+ | PR+ | HER2- | Initial presentation | Lateral rectus muscle and optic nerve | N/A | N/A |
| 8       | 2020 | 50.8| 18 decreased visual acuity, 16 pain | IDC | ER+ | PR+ | HER2+ | Initial presentation | Lateral rectus muscle and optic nerve | N/A | N/A |
| 9       | 2020 | 65  | Blurring vision | IDC | ER+ | PR+ | HER2- | Previously diagnosed with EBC 4 years ago | Optic disc and optic nerve | SBRT | Partial response improvement of visual acuity |
| 10      | 2019 | 60  | Blurring vision, proptosis | IDC | ER+ | PR+ | HER2- | Previously diagnosed with EBC 3 years ago | Inferior rectus muscle | Fulvestrant and Palbociclib, followed by radiation therapy | Follow up for 6 months, she was free clinically and radiologically |
| 11      | 2019 | 63  | Diplopia | IDC | Primary ER/PR+ HER2- Metastasis Triple negative | Previously diagnosed one year before with MBC ** | Right medial rectus muscle | Diagnostic biopsy followed by palliative radiotherapy and chemotherapy | Partial improvement |
| 12      | 2019 | 61  | orbital fullness with worsening vision and eye pain | NA | ER+ | | Initial presentation | large ill-defined orbital mass encasing the globe | Evisceration | recovered |
### Supplementary Table 1. Summary of cases reported on the literature on eye metastasis of breast cancer origin. (Continued)

| Case No. | Year | Age | Symptom | Initial Diagnosis | Tumor Characteristics | Treatment | Outcome |
|----------|------|-----|---------|-------------------|-----------------------|-----------|---------|
| 13       | 2019 | 39  | Decrease visual acuity | IDC | ER + | Previously diagnosed 6 years ago for EBC | Mass in the right optic disc with infiltrative optic neuropathy | NA | NA | [12] |
| 14       | 2018 | 58  | Orbital mass | Infiltrating carcinoma | ER + PR+ HER2 - | Initial presentation | Superior orbital rim | Indoximod plus Docetaxel | NA | [13] |
| 15       | 2018 | 46  | Diplopia | NA | NA | Previously diagnosed as MBC | Upper left oblique muscle | Liposomal Doxorubicin as well as local stereotactic radiotherapy. | Showed a gradual improvement of the local symptoms and signs | [14] |
| 16       | 2017 | 46  | left eye pain | NA | NA | Previously diagnosed 2 years as locally advanced breast cancer | Subretinal mass | NA | NA | [15] |
| 17       | 2017 | 56  | Diplopia, decreased visual acuity and limited eye movement | IDC | ER + | Initial presentation | Intracanal compartment of the left orbit and invading the adjacent muscles | Excisional biopsy | NA | [16] |
| 18       | 2015 | 77  | Proptosis | IDC | ER + PR - HER2 - | Previously diagnosed 11 years with EBC | Lateral and superior rectus muscle, and eroded the lateral orbital wall and roof | Palliative radiotherapy | Died 9 months later | [17] |
| 19       | 2015 | 69  | Proptosis | IDC | ER + PR - HER2 - | Previously diagnosed one year for EBC | Lacrimal gland | Palliative radiotherapy and one cycle chemotherapy | Died 3 month later | [17] |
| 20       | 2019 | 56  | Decreased visual acuity | IDC | NA | Initial presentation | Choroidal | NA | NA | [18] |
| 21       | 2014 | 84  | Diplopia | NA | NA | Previously diagnosed 14 years EBC | Orbit | NA | NA | [19] |
| Case | Year | Age | Symptoms | Tumor Type | Hormone Status | Primary Treatment | Metastatic Treatment | Outcome |
|------|------|-----|----------|------------|----------------|-------------------|---------------------|---------|
| 22   | 2012 | 48  | Blurring vision | IDC | NA | Previously diagnosed 13 years ago as EBC | Choroidal mass | Surgical enucleation | NA [20] |
| 23   | 2012 | 53  | Proptosis and diplopia | NA | NA | Initial presentation | Right orbit and skull base | Surgery and palliative radiotherapy | NA [21] |
| 24   | 2011 | 73  | Exophthalmus | IDC | ER+PR+HER2+ | Previously diagnosed 3 years before as EBC | Suprabulbar tumor mass, with osseous infiltration of the orbital roof | Palliative chemotherapy plus bisphosphonates | Improvement in symptoms and continue chemo then hormonal treatment [22] |
| 25   | 2011 | 38  | Visual discomfort | NA | NA | Previously diagnosed 3 years with MBC | Bilateral orbital involvement | SPRT | Corrected visual acuity but died 19 month later [23] |
| 26   | 2010 | 66  | Swelling and visual disorders | ILC | ER+PR+HER2- | Initial presentation | Right peri-orbital soft tissues | Surgery for primary and metastasis then FEC and palliative radiotherapy followed by hormonal treatment | Total resolution [24] |
| 27   | 2009 | 46  | Diplopia, proptosis | IDC | ER+PR+HER2- | Previously diagnosed 4 years ago as MBC | Intra-orbital extra-bulbar mass | Chemotherapy plus Cyberknife | Gradual improvement in symptoms Free of ocular for 18 months [25] |
| 28   | 2009 | 70  | Dimension of vision | NA | NA | Previously diagnosed 9 years early EBC | Choroid | NA | NA [26] |
| 29   | 2008 | 73  | Ptosis and diplopia | ILC | ER+PR+ | Previously diagnosed 25 years ago for EBC | Extrinsic muscles and the surrounding tissues | NA | NA [27] |
| 30   | 2008 | 50  | Diplopia | ILC | ER+PR+ | Previously diagnosed 5 years for stage III | Bilateral extra-ocular muscles | High dose radiotherapy, hormonal and chemotherapy | NA [28] |
Supplementary Table 1. Summary of cases reported on the literature on eye metastasis of breast cancer origin. *(Continued)*

| No | Year | Age | Symptom | Pathology | ER, PR, HER2 | Diagnosis | Treatment | Response |
|----|------|-----|---------|-----------|-------------|-----------|-----------|----------|
| 31 | 2008 | 66  | Unilateral eyelid edema | NA | ER + PR+ HER2 + | Previously diagnosed with stage III | Soft tissue mass in orbit | Trastuzumab, Docetaxel, Tegafur and Cyclophosphamide | Complete response [29] |
| 32 | 2008 | 60  | Diminution of vision | IDC | ER + PR+ | Previously diagnosed 3 ys for EBC | Uveal tract of the right globe and optic disc | Radiotherapy 44 GY | Complete response [30] |
| 33 | 2006 | 53  | Orbital pain and ptosis | ICL | NA | Initial presentation | The medial wall of the left orbit, orbital connective tissue, muscles, and lacrimal gland | NA | NA [31] |
| 34 | 2006 | 58  | Swelling in lower eye lid | ILC | ER + PR + | EBC 24 month before | Mass in lower eye lid | NA | NA [32] |
| 35 | 2005 | 75  | Binocular diplopia | NA | NA | Previously diagnosed 2 months EBC | Extraocular muscles bilaterally | NA | NA [33] |
| 36 | 2005 | 52  | Progressive visual loss and ptosis | IDC | NA | Previously diagnosed as MBC | Bilateral thickening of all extraocular muscle | NA | NA [34] |
| 37 | 2004 | 35  | Diplopia and blurred vision | ILC | NA | Previously diagnosed 3 years ago for EBC | Right lateral rectus muscle | Palliative chemotherapy | Died after 10 days [35] |
| 38 | 2004 | 57  | Decrease in visual acuity | IDC | Primary ER/PR+ Metastasis HER2 +, ER/PR - | Previously diagnosed 13 ys with EBC | Unilateral choroidal metastasis | Trastuzumab plus Vinolerabin | Complete response [36] |
| 39 | 2002 | 61  | Red eye and ptosis | IDC | ER + | Initial presentation | Mass filling the left orbit posteriorly and extending forward in the eyelids | Surgery and local radiotherapy 3000 cGy | NA [37] |
| 40 | 2001 | 40  | Loss of vision | NA | NA | Previously diagnosed EBC | Isolated choroid metastasis | Radiotherapy palliative, chemotherapy plus acetazolamide | Clinical and radiological remission [38] |
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