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Isolated choroidal metastasis as first site of disease progression: a case report

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Summary. *Background:* Choroidal metastasis is rare and ocular examination is not routinely recommended as part of staging work up in breast cancer management. *Clinical picture:* We present a case of choroidal metastasis in female breast cancer. Breast imaging and staging evaluation suggested multicentric breast cancer without lymph node metastasis or systemic metastasis. After total right mastectomy with sentinel lymph node biopsy, the final pathologic stage was pT2N0, ER (+), PR (+), c-erbB2 (2+), and FISH (-). On the third day following surgery, she complained of blurred vision in her left eye. Ophthalmologic evaluation showed choroidal metastasis from breast cancer. The visual acuity in her left eye was 20/50. *Result:* After concomitant delivery of chemoradiation therapy, the choroidal lesions improved dramatically and vision acuity in her left eye recovered to 20/20. *Conclusion:* Clinicians should consider the possibility of choroidal metastasis when breast cancer patients complain of ocular symptoms.

Key words: breast cancer, choroid metastasis, treatment

«Metastasi isolate alla coroide come primo sito di progressione della malattia: caso clinico»
Riassunto. *Background*: le metastasi della coroide sono rare e un esame oculare non è solitamente contemplato nella stadiazione del cancro al seno. *Quadro clinico*: presentiamo il caso di metastasi della coroide in una donna con cancro al seno. Le immagini del seno e la valutazione della stadiazione hanno suggerito un cancro mammario multicentrico senza metastasi ai linfonodi o metastasi sistemiche. Dopo mastectomia totale destra seguita da biopsia del linfonodo sentinella la stadiazione finale della patologia è stata p T2N0, ER (+), PR (+), c-erbB2 (2+), e FISH (-). Il terzo giorno dopo l'intervento chirurgico, la paziente lamentava un offuscamento della vista nel suo occhio sinistro. La valutazione oftalmologica ha mostrato una metastasi della coroide dovuto al cancro mammario. L'acuità visiva nel suo occhio di sinistra era di 20/50. *Risultati:* in seguito a somministrazione concomitante di chemioradioterapia, le lesioni della coroide sono migliorate notevolmente e l'acuità visiva nell'occhio di sinistra ha avuto un recupero pari a 20/20. *Conclusioni:* i clinici dovrebbero prendere in considerazione la possibilità di metastasi della coroide in pazienti con cancro al seno che lamentano sintomi oculari.

Parole chiave: cancro mammario, metastasi della coroide, trattamento

Introduction

Ocular metastasis of breast cancer is considered a rare condition. The incidence of ocular metastasis from breast cancer varies from 9 to 37% according to the literature (1-3). Five percent of 120 screened patients with disseminated breast cancer had an asymptomatic choroidal metastasis (2). Simultaneous involvement of brain metastasis, leptomeningeal seeding and eye metastasis is frequent (4-6). More frequently, ocular

metastases are preceded by metastases to the lungs. Approximately 85% of patients with ocular metastases have evidence of lung metastasis (7).

However, subclinical disease often goes unnoticed in patients with ocular metastases because they usually have metastatic disease to other organs that dominate the clinical picture and routine ocular screening for all breast cancer is not a recommendation. Hence, the true incidence of this condition is difficult to estimate. One is also especially unlikely to suspect choroidal metastasis in a patient presenting clinically with early breast cancer.

However, choroidal metastasis has emerged as an important medical issue, reflecting an increase in incidence and survival of breast cancer. Knowledge of this medical condition may be helpful to surgeons and medical oncologists when managing breast cancer patients.

Here we report a case of isolated choroidal metastasis as a single manifestation of systemic metastasis in female breast cancer presenting as early breast cancer without lymph node metastasis.

Case

The patient was a 45 year-old woman with breast cancer, treated with mastectomy, and subsequently diagnosed with choroidal metastasis in May 2013. Routine mammography, breast ultrasonography, and ultrasound-guided core biopsy suggested multicentric breast cancer. A radionucleotide bone scan, and a computed tomography (CT) scan of the chest, abdomen, and pelvis were negative for signs of metastatic disease.

The tumors involved the right breast multicentrically, including the subareolar area and lower outer quadrant, and measuring 2.9 cm × 2.0 cm × 1.5 cm and 1.2 cm × 1.1 cm × 1 cm. Histopathological analysis revealed invasive ductal carcinomas of a micropapillary pattern. The modified Bloom & Richardson`s histologic Grade was III of III, while immunohistochemistry showed the tumor to be ER positive, PR positive, and HER2/neu 2+. Fluorescence *in situ* hybridization (FISH) was negative for HER2/neu gene amplification. Ductal carcinoma *in situ* was present in the background of the tumor, along with lymphatic invasion. Vascular invasion was not identified and lymph node metastasis was not found in the sentinel lymph node. The Ki-67 expression was 60%. E-cadherin expression was preserved subsequently, and a diagnosis of invasive lobular carcinoma was ruled out.

Following complaints of blurred vision in her left eye on the third day after surgery, an ophthalmologic evaluation was performed. Her vision acuity was 20/20 in the right eye and 20/50 in the left eye. Intraocular pressure was normal. Fundoscopy revealed submacular fluid and a choroidal lesion at the superotemporal area of the retina in the left eye, which was suspected of being choroidal metastasis (Figure 1A and 1B). Brain and orbital MRI were negative for signs of metastatic disease. Thus, the choroidal metastasis was considered as a single metastatic focus and the patient was staged as pT2 N0 M1.

Palliative concomitant chemoradiation therapy was administered. Chemotherapy consisted of anthracyclin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by paclitaxel (175 mg/m^2). Palliative radiotherapy with 3500 Gy /14 fr. covering the left eye was administered prior to the second cycle of chemotherapy.

Four weeks after radiotherapy, the submacular fluid collection was almost entirely absorbed and visual acuity in the left eye improved to 20/25. After finishing the last cycle of chemotherapy, her visual acuity recovered to 20/20. She is currently receiving tamoxifen. She has presented no evidence of disease for 18 months after the operation. Choroidal lesions have been clinically stable during the same period. Regular follow-up visits for ophthalmological examinations are scheduled every two months and surveillance for systemic metastasis is planned.

Discussion

Breast cancer is the most common malignancy metastasizing to the uveal tract (8, 9). The uvea is the vascular layer of the eye; it includes the middle choroidal layer of the globe, the cilliary body, and the iris. Most metastases to the eye occur in the uvea, especially the choroid, through hematogenous spread. Shields et al. (8) found that the most common primary tumor

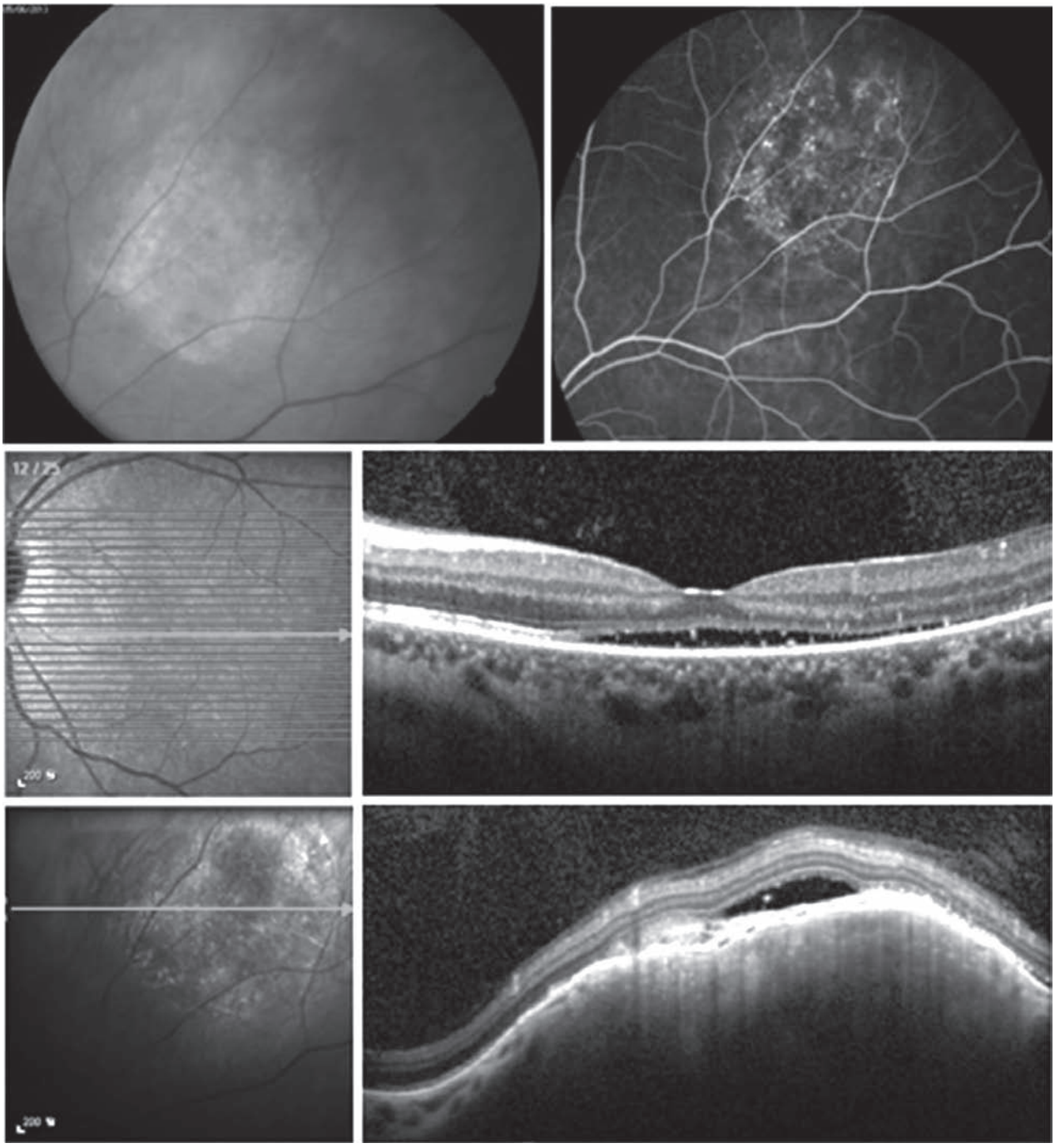

Figure 1A. Response of choroidal metastasis during chemoradiation therapy. (A) Initial presentation of a patient: fundus photograph (upper left column), fluorescein angiography (FA) (upper right column), macular optical coherence tomography (OCT) (middle), and regional OCT (lower). Fundus photograph showed elevated subretinal lesion with alterations in the retinal pigment epithelium (RPE) in the superotemporal area. FA shows typical pinpoint hyperfluorescence with leakage of dye at the central mass lesion. OCT reveals submacular fluid collection (middle) and a peripheral choroidal mass with exudation (lower).

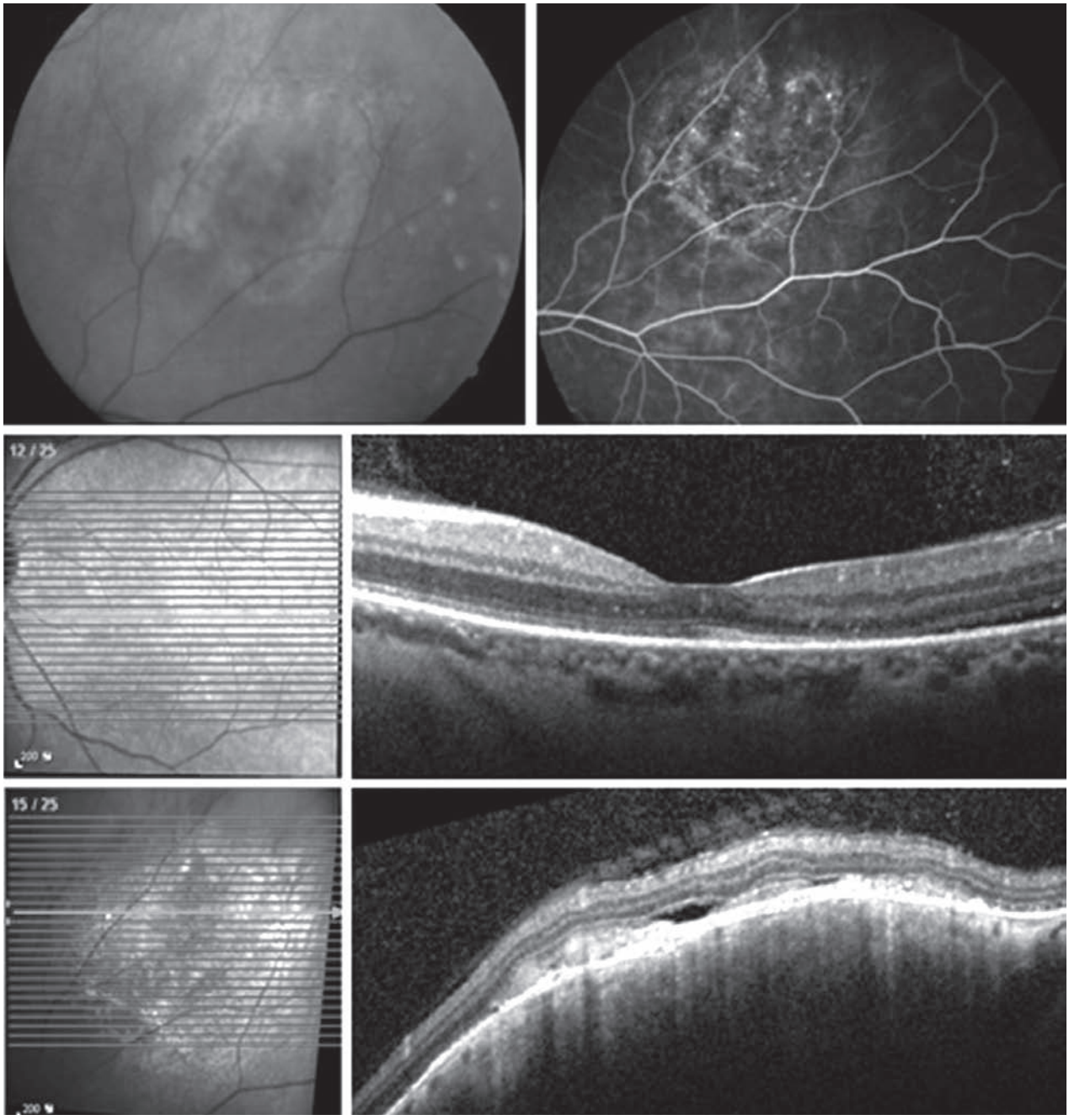

Figure 1B. Response of choroidal metastasis during chemoradiation therapy. (B) Ophthalmologic presentation at the last follow-up. The fundus photograph shows retinal pigment clumping at the center of the lesion and choroidal atrophic change. In the FA, the initial multiple pinpoint hyperfluorescence remains; however, central leaking of fluorescent dye has decreased remarkably. The OCT finding reveals disappearance of submacular fluid as well as reduced choroidal mass and serous detachment.

site was the breast (47%), followed by the lung (21%), and gastrointestinal tract (4%).

Commonly, the choroid is diffusely filled with many metastatic deposits. Simultaneous involvement of brain metastasis, leptomeningeal seeding and eye metastasis is frequent (4). Ten out of 32 patients with eye metastases also had brain or meningeal metastases (5). Demirci *et al.* (6) found 6% of ocular metastases cases associated with brain metastases prior to ocular diagnosis, and 28% of brain metastasis post ocular diagnosis. More frequently, ocular metastases are preceded by metastases to the lungs. Approximately 85% of patients with ocular metastases have evidence of lung metastasis (7). Other parts of the eye and orbit, including the optic disc, conjunctiva, lacrimal gland, periorbital fat, muscle, bone, optic nerve, and eye lid might be involved; however, the incidence is very low (10-12). Involvement of the optic nerve is related to central nervous system involvement with cells that may migrate through the cerebral spinal fluid around the optic nerve (12).

In our case, choroidal metastases had developed as the first site in early breast cancer without any regional lymph-nodes metastasis. Correlation of choroidal metastasis and any specific subtype of breast cancer is not evident in the literature. Lobular carcinoma subtypes are known as having a greater propensity to metastasize to rare sites of metastatic location such as the leptomeninges, peritoneal surface, gastrointestinal tract (13) or soft tissue of the orbit (14). These characteristics have been explained by loss of expression of the adhesion molecule E-cadherin which makes tumor cells loosely cohesive (13). In our case, E-cadherin expression was preserved, so a diagnosis of lobular subtype was excluded. Our patient likewise presented favorable factors such as T2N0, ER positivity, though the possibility of aggressive tumor properties was supported by several pathologic findings. The tumor had micropapillary components, as in one of the aggressive subtypes of breast carcinoma. The histologic grade was 3/3, lymphatic invasions were frequent, and Ki-67 was highly expressed. The presence of these factors might be the explanation for the solitary choroidal metastasis in this patient.

Symptoms of ocular metastasis depend on the site of the carcinoma. In cases of choroidal metastasis, patients might be asymptomatic or they might complain of blurred vision, metamorphopsia, pain, and rarely diplopia (4). Ocular examination may show the signature signs of choroidal metastasis. Choroidal metastases are rarely pigmented, in contrast to ocular melanoma. Fundus photography shows yellow placoid lesions, usually in the superior and temporal areas, with serous retinal detachment, alteration of retinal pigment epithelium, choroidal detachment, and glaucoma. Mottling of the retinal pigment epithelium, called peau d`orange, is characteristic and diagnostic (4).

Ultrasound helps in the treatment response evaluation but it is not diagnostic. Because ocular metastatic lesions are less than a few millimeters long, CT scans, ocular magnetic resonance imaging, and positron emission tomography (PET) scans may miss lesions. To rule out other metastatic organ involvement, brain MRI for central nervous system metastasis and pulmonary CT are necessary. Fluorescein angiography is useful in clarifying metastatic sites, but is rarely diagnostic.

External beam radiation is the primary treatment tool. In the Demirci *et al.* series, 59% of all patients underwent radiotherapy (6). Sixty-four percent of the patients' eyes showed regression after radiation and an additional 18% showed stable disease. In the Kanthan *et al.* (15) review, visual acuity stabilized or improved in 57-100% of all cases treated. Techniques available for more focused local control include stereotactic radiotherapy, proton beam therapy, and episcleral brachytherapy (16-18). Cases selected for stereotactic radiotherapy should be well demarcated and solitary. Treatment responses are similar to the responses to external beam radiation therapy (17). Sometimes surgical localization is required when using focused radiotherapy, so that conventional methods are more appropriate, particularly in patients with short expected survival periods. Side effects occur in a small number of patients and include transient keratoconjuctivitis, subconjunctival hemorrhage, radiation retinopathy, optic neuropathy, exposure keratopathy, neovascularization of the iris, cataracts, and glaucoma (4).

The mainstay of treatment for ocular metastases has been a course of external beam radiotherapy. However, case reports are increasingly presenting treatment response in the eye from hormonal, chemotherapeutic,

and target agents. Most reports of systemic therapy for ocular metastases are case reports. Manquez *et al.* (19) reported the effect of aromatase inhibitors in 17 women, with a response in 10 women. They described the ocular response as concordant with the systemic response in most of the responders. Of interest is a report of intravitreal infusion of bevacizumab in a case of solitary choroidal metastasis. Dramatic reduction of the lesion and improved visual acuity was reported in that case (20).

Survival data after treatment of ocular metastasis is disappointing. The average survival has been estimated to be 6 to 17 months (3, 9, 21). Wills eye data from 264 women demonstrated overall survival of this medical condition. Overall survival after diagnosis of uveal metastases was 65% after 1 year, 46% after 2 years, 34% after 3 year, and 24% after 5 years (6).

In our case, concomitant chemoradiotherapy was safely delivered, and the patient complained of moderately dry eye because of keratoconjunctivitis. Other significant complications associated with chemoradiotherapy were absent. Choroidal metastasis is the systemic dissemination of breast cancer and concomitant delivery of chemoradiotherapy might be useful, provided it does not delay the application of local or systemic control of the disease.

Conclusion

Choroidal metastasis is a rare condition. Here, we report one such case in female breast cancer. Usually choroidal metastasis appears with disseminated disease of other organs, though in this patient choroidal metastasis was the only isolated focus of clinically apparent distant metastasis in breast cancer. Ocular examination is not a routine recommendation as part of the work up in breast cancer treatment. However, due to recent advances in breast cancer treatment, patients are living longer and preserving vision will be an important quality-of-life issue for these patients. Treatment providers should consider the possibility of choroidal metastasis when breast cancer patients complain of ocular symptoms.

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