

CASE REPORT

UDC: 617.711-02::618.19-006-033.2
DOI: DOI: 10.2298/VSP120322040B**Breast cancer metastasis to the conjunctiva****Metastaze karcinoma dojke u konjunktivu****Anica Bobić Radovanović*†, Dejan Rašić*†, Marko Buta‡, Radan Džodić*******Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Clinic of Eye Disease, Clinical Center of Serbia, Belgrade, Serbia; ‡Institute of Oncology and Radiology of Serbia, Belgrade, Serbia****Abstract**

Introduction. Conjunctival metastasis is exceedingly rare, and it is, as a rule, a sign of advanced malignant disease with poor prognosis. We presented a female patient with breast cancer metastasis to the conjunctiva. **Case report.** A 45-year-old premenopausal female patient was presented with a solitary, yellowish, thin, demarcated lesion in the superior nasal quadrant of the bulbar conjunctiva of the left eye noted by chance a week earlier. There was no sign of irritation, and no pain, and no other functional or morphological problem in either eye or orbit. Five years before the appearance of conjunctival metastasis, breast carcinoma was diagnosed and the patient underwent chemotherapy, preoperative radiotherapy and radical mastectomy. Three years later, computed tomography scan showed metastasis in the left hepatic lobe with ascites and the patient underwent chemotherapy again. But, four months prior to the appearance of conjunctival lesion body scintigraphy showed multifocal skeletal lesions and nuclear magnetic resonance revealed diffuse hepatic metastases and bilateral ovarian tumors. Palliative radiotherapy and hormonal therapy (megestrol, 160 mg) were carried out. An excisional biopsy of the observed conjunctival lesion was performed under topical anesthesia and the material was subjected to histopathological (HP) examination. HP and immunohistochemical examinations established the presence of breast infiltrating lobular carcinoma metastatic to the conjunctiva. The patient showed rapid deterioration after intervention, and died after three weeks. **Conclusion.** A survival period less than one month after the appearance of conjunctival metastasis deserves attention because it is unexpected and has never been reported previously. It is not a rule that HP presentation of a metastatic lesion is so characteristic that it is possible to determine a primary tumor.

Key words:**conjunctiva; neoplasm metastasis; diagnosis; histological techniques; breast neoplasms.****Apstrakt**

Uvod. Metastaze u konjunktivu izuzetno su retke i, po pravilu, znak su uznapredovale maligne bolesti sa lošom prognozom. Prikazali smo bolesnicu sa metastazom karcinoma dojke u konjunktivu. **Prikaz bolesnika.** Bolesnica, stara 45 godina, pri dolasku imala je solitarnu, žućkastu, tanku i ograničenu leziju u gornjem nazalnom kvadrantu bulbarne konjunktive levog oka, koja je slučajno zapažena nedelju dana ranije. Nije bilo znakova iritacije niti bola, kao ni drugih funkcionalnih ni morfoloških problema u oku ili orbiti. Pet godina ranije dijagnostikovao je karcinom dojke. Bolesnica je lečena hemioterapijom, preoperativnom radioterapijom i urađena je radikalna mastektomija. Tri godine ranije, kompjuterizovanom tomografijom utvrđene su metastaze u levi hepatski lobus sa ascitesom i bolesnica je ponovo lečena hemioterapijom. Međutim, četiri meseca pre pojave konjunktivalne lezije, scintigrafijom su utvrđene multifokalne lezije u kostima dok su nuklearnom magnetnom rezonancom otkrivene difuzne metastaze u jetru i obostrano ovarijalni tumor. Sprovedena je paliativna radioterapija i hormonska terapija (megestrol, 160 mg). Urađena je ekscizijska biopsija uočene konjunktivalne lezije u lokalnoj anesteziji i materijal poslat na histopatološki pregled. Histopatološkim i imunohistohemijskim ispitivanjem utvrđena je metastaza infiltrišućeg lobularnog karcinoma dojke u konjunktivu. Stanje bolesnice nakon intervencije rapidno se pogoršavalo i umrla je nakon tri nedelje. **Zaključak.** S obzirom na to da je neočekivano i da do sada nije bilo registrovano, preživljavanje kraće od jednog meseca od pojave metastaze u konjunktivu zaslužuje posebnu pažnju. Nije uobičajeno da je histopatološka slika metastatske lezije toliko karakteristična da je na osnovu nje moguće definisati primarni tumor.

Ključne reči:**konjunktiva; neoplazme, metastaze; dijagnoza; histološke tehnike; dojka, neoplazme.**

Introduction

The exact incidence of metastatic tumors to the eye and adnexa is unknown, and the supposed incidence is probably underestimated. A certain number of these metastases are asymptomatic and remain unrecognized. Some of them are not appreciated because of the dominant problems with simultaneous tumor involvement of major organs. The systemic treatment of primary or metastatic disease may also cause regression of ocular metastases as a side effect. On the other hand, the number of tumor patients increases, their survival is prolonged, thus making the possibility of ocular metastases greater.

Among the metastases to the eye and adnexa the most common are intraocular, choroidal metastases, and orbital metastases.

Conjunctival metastases of distant solid tumors are extremely rare. In an experiment on rabbits, only one case of conjunctival metastasis was identified among 67 ocular metastases after injection of Brown-Pearce tumor cells into the left ventricle¹. A clinical survey of 1,643 patients treated for conjunctival tumors over a 28-year-period revealed only 13 cases of metastatic tumor, less than 1%².

Breast carcinoma, being the most frequent malignancy in female population, is also the most frequent site of primary tumor to give ophthalmic metastases in females^{3,4}.

Autopsy studies have found the presence of ocular metastases in 8.3%⁵, 36%⁶ and even 41%⁷ of patients who died of breast carcinoma. In a clinical series the incidence of ocular metastases in patients with breast carcinoma is between 8% and 10%^{8,9}. However, screening for ophthalmic involvement in 68 visually asymptomatic patients with locally advanced or metastatic breast carcinoma after a median period of 5 years from the diagnosis of cancer, has shown only one case of orbital metastasis, a deposit in the lateral rectus muscle, three cases of ophthalmic manifestations of neurological problems, and two cases of ocular complications of treatment. The conclusion of the study was that there was, therefore, no need for routine screening¹⁰.

Breast carcinoma is the most common malignancy to metastasize to the conjunctiva. Shields et al.² found that breast cancer is a primary tumor site for 39% of conjunctival metastases.

In Serbia there is only one Laboratory for Ophthalmopathology, and despite its 60-year history this was the first diagnosed conjunctival metastasis of breast carcinoma.

Case report

A 45-year-old premenopausal female patient was presented with solitary, yellowish, thin, demarcated lesion in the superior nasal quadrant of the bulbar conjunctiva of the left eye. There was no sign of irritation, and no pain. The lesion had been noted by chance a week earlier. An ophthalmologic examination showed no other functional or morphological problems in either eye or orbit.

Five years before the patient had presented with 30 mm lump in the left breast, passive infiltration of the overlying

skin and left axillary lymphadenopathy. Tumor biopsy showed lobular infiltrative breast carcinoma with estrogen receptor (ER) and progesterone receptor (PGR) positive and human epidermal growth factor receptor (HER) 2+ negative receptors. Patient underwent IV cycles of FAC chemotherapy, preoperative radiotherapy of the left breast and radio-castration, followed by left modified radical mastectomy (Madden). Sixteen of the 17 removed axillary lymph nodes were positive. The patient received V more cycles of FAC chemotherapy to the cumulative dose and 20 mg tamoxifen daily was introduced. Three years later computed tomography (CT) scan showed metastasis in the left hepatic lobe, 20 mm in diameter with ascites. The patient underwent VIII cycles of taxol CBDCA chemotherapy followed by anastrozole 1 mg daily. Four months prior to conjunctival lesion body scintigraphy showed multifocal skeletal lesions, and nuclear magnetic resonance (NMR) revealed diffuse hepatic metastases and bilateral ovarian tumors. Palliative radiotherapy and megestrol 160 mg were carried out.

An excisional biopsy of the conjunctival lesion was performed under topical anesthesia and a material was subjected to histopathological examination.

Within conjunctival connective tissue stroma histopathology revealed the presence of small, round and ovoid tumor cells with little cytoplasm and with visible intracytoplasmic lumina. The nuclei of those tumor cells were more or less eccentrically placed with little pleomorphism. Mitoses were infrequent. Tumor cells exhibited a diffuse infiltrative pattern with a single file of "targetoid" infiltration. Conjunctival epithelium was unremarkable (Figure 1).

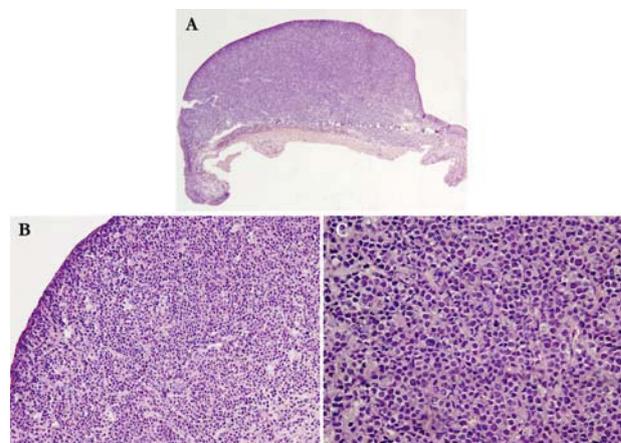


Fig. 1 – A) A conjunctival subepithelial tumor nodule. Intact overlying epithelium exhibits no pathology, entire conjunctival substantia propria is diffusely involved by tumor cells, resection lines are free [Haematoxylin and Eosin (H&E), original magnification $\times 40$]; B) Small, round and ovoid tumor cells with little cytoplasm and with visible intracytoplasmic lumina, arranged in single files and/or cords, exhibit infiltrative pattern. A marked vascularisation of tumor nodule is also evident (H&E, original magnification $\times 200$); C) Nuclei of the tumor cells more or less eccentrically placed with little pleomorphism are well preserved, some of them with a vesicular appearance and also with prominent nucleoli. Mitoses are infrequent. Also, there is a single file of "targetoid" pattern/infiltration (H&E, original magnification $\times 400$)

Immunohistochemical phenotype was: ER + ; HER-2/neu (c-erbB/2) - ; E-cadherin - ; CK17 - ; BRCA1 + ; EMA + (Figure 2).

conjunctival metastasis. Two out of 4 patients with conjunctival metastasis of breast carcinoma had a concurrent choroidal metastasis. Benzimra et al.¹³ reported a case of metastatic

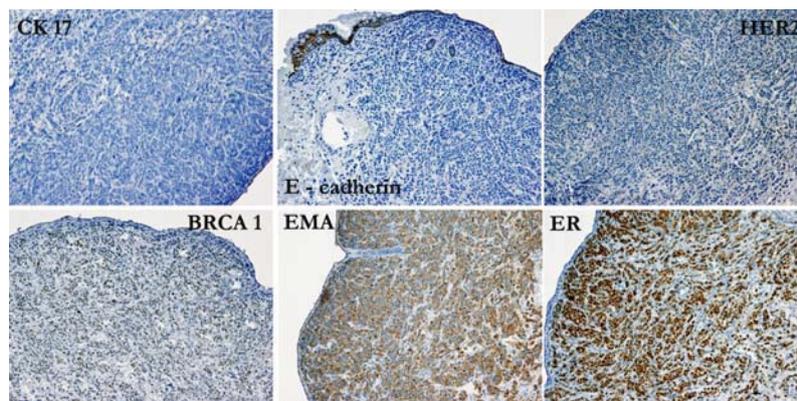


Fig. 2 – Immunohistochemical staining of tumor cells suggesting an infiltrative lobular breast carcinoma metastasized to the conjunctiva (× 100)

Histopathological and immunohistochemical examination established the presence of breast infiltrating lobular carcinoma metastatic to the conjunctiva.

The presented patient showed rapid deterioration after the intervention, and died three weeks later.

Discussion

Conjunctival metastases are most commonly localized on the bulbar conjunctiva. All 13 conjunctival metastatic tumors reported by Shields et al.² had bulbar localization. Three out of four metastases of breast carcinoma were on the bulbar conjunctiva¹¹. Clinical presentation of conjunctival metastasis is not characteristic. It usually presents a solitary, yellowish, painless lesion not adherent to the underlying sclera with a variable amount of conjunctival irritation. The presented patient referred with an unremarkable lesion of the bulbar conjunctiva, which is typical for conjunctival metastasis.

There is currently no consensus on the treatment of conjunctival metastasis and the therapeutic modality must be individualized. Treatment modalities are excision, local radiotherapy and systemic chemotherapy. In the presented case an excisional biopsy was both a diagnostic and therapeutic procedure.

Conjunctival metastasis of breast carcinoma usually occurs after a relatively long period of time, a few years after diagnosis of the primary tumor. The interval between diagnosis of primary and secondary tumor was more than 5 years in Kiratli et al. study¹¹, but Skalicky et al.¹² reported a case of conjunctival metastasis after only 9 months. In the presented patient conjunctival metastasis was recognized 5 years after the diagnosis of breast tumor.

As a rule, conjunctival metastases are a part of an advanced malignant disease, with other organs or ocular structures already involved. In the study of Kiratli et al.¹¹ only 2 out of 10 patients with conjunctival metastasis, and only 1 of 4 patients with conjunctival metastasis of breast carcinoma were free of nonocular metastases at the appearance of con-

breast carcinoma to the anterior chambre angle and conjunctiva. The presented patient experienced no other ocular metastases, but multiple bone and liver metastases were present.

The prognosis of patients with conjunctival metastases is mainly poor. The main survival time reported for patients with conjunctival metastasis is 9 months, but for patients with conjunctival metastasis of breast carcinoma it is a little bit longer, 14 months¹¹. Our patient died only three weeks after the diagnosis of conjunctival metastasis. Such a short survival period is very unusual and totally unexpected. This could reflect more aggressive tumor biology in stage IV breast cancer patient.

A histopathological picture of a metastatic tumor may recapitulate the appearance of the primary lesion, or it may appear less differentiated. It is not always possible to differentiate a primary tumor on the basis of metastasis. In the presented case the histopathologic appearance of conjunctival metastasis was typical enough to make the right diagnosis.

Conclusion

We reported exceedingly rare conjunctival metastasis of breast carcinoma. The interval between diagnosis of the primary tumor and conjunctival metastasis, the presence of synchronous or metachronous metastases, the location and clinical presentation of conjunctival lesion and local treatment methods have been discussed. Histopathologic presentation of a metastatic lesion is not by the rule so characteristic to make it possible to determine the primary tumor. A survival period less than one month after the appearance of conjunctival metastasis was unexpected and had never been reported previously.

Conjunctival metastases of breast carcinoma, although uncommon, have clinical importance as the signs of the advanced stage of a systemic malignant disease with poor prognosis. The clinical presentation of metastasis is unremarkable, nevertheless it certainly should attract full attention of an ophthalmologist, and deserves appropriate treatment.

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