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Orbital metastases in breast cancer: report of two cases and review of the literature

Received: 28 January 2004 / Accepted: 21 June 2004 / Published online: 7 September 2004
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Abstract Purpose: Intraorbital metastases of solid tumors are a rarely diagnosed clinical condition, even though pathological reports suggest an incidence of up to 30% in cancer patients. We report two cases of intraorbital, extraocular metastases in breast cancer. The first patient was a 45-year-old man who presented with diplopia, upward divergence of the left bulb, and local pain. **Methods:** In the standard cerebral magnetic resonance imaging (MRI) no cerebral or ocular tumor was detectable. A subsequent T1-weighted, contrast-enhanced orbital MRI with fat suppression revealed an infrabulbar mass of 18×13 mm in size. The second patient, a 59-year-old woman, complained of slight diplopia when looking to the left. Cerebral MRI with fat suppression showed a retrobulbar mass with 17×13 mm. In both patients metastatic breast cancer was known for several years, and both had been in a stable disease situation. Both patients were treated with stereotactic radiation, applying a cumulative dose of 35 and 45 Gy, respectively, which resulted in marked improvement of local symptoms. **Summary:** Most eye metastases of breast cancer are located in the choroidea, while an extrabulbar localization within the orbit is rare, with only 3–10% of all ocular metastases. Autopsy reports reveal that an estimated 10–30% of breast cancer patients develop this form of metastasis. This is in strong contrast to rare clinical case reports, suggesting frequently absent to mild clinical signs and difficult diagnosis. **Conclusion:** If breast cancer patients complain of ophthalmological symptoms such as local pain, impaired vision, or diplopia, it is important to consider ocular or orbital metastatic disease.

Keywords Orbital metastases · Ocular metastases · Breast cancer

Introduction

Breast cancer is the most common malignant disease among women in western countries with a lifetime risk of approximately 10%. In contrast, men develop this malignancy seldom, accounting for less than 1% of malignancies in men and approximately 1% of all cases of breast cancer (Giordano et al. 2002). The biological properties and clinical features of breast cancer appear to be similar in both genders. Frequent and well-known locations of metastases are bone, liver, lung, skin and brain, but tumor manifestations have been seen in almost any anatomic site. Herein we present two subsequent cases of intraorbital, extrabulbar metastases of breast cancer in one male and one female patient.

Case reports

Patient 1

The 45-year-old man presented with diplopia and gradually increasing pain in the left eye for approximately 5 days, 2 years after diagnosis of metastatic breast cancer. He had experienced repeated diplopia in the previous weeks, which had resolved spontaneously. Metastatic breast cancer with manifestations in bone, liver, and skin had been known for 2 years. Capecitabine was the current second-line cytostatic therapy, after hormonal therapy had failed. Visceral metastases had been stable for 5 months, as assessed by an ultrasound 8 weeks before onset of the new symptoms. In the clinical examination we found deviation of the left bulb upwards and lateral, suspect for paralysis of the inferior rectus muscle (Fig. 1a). There were no clinical signs of an additional neuromuscular dysfunction of the eye or

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any other neurological disorder. A cerebral MRI showed an osseous metastasis in the clivus area. This could possibly interfere with the right abducens nerve, which was clinically not affected. There was no cerebral metastasis or any tumor within the orbit or in the area of cerebral nerves detectable (Fig. 2a). As the neurological symptoms were accompanied by local pain, an orbital process still seemed probable; therefore, a T1-weighted, contrast-enhanced MRI of the orbit with fat suppression was performed, which revealed an infrabulbar mass, sized 18×13 mm, with infiltration of the left inferior rectus muscle (Fig. 2b). General restaging, which was then performed, showed progression of liver metastases. Therapy included stereotactic radiation of the left orbit with 6-MV photons in fractions of 5 Gy up to a cumulative dose of 35 Gy. Local pain improved after 2 weeks, diplopia after about 4 weeks, and the bulbus deviation gradually decreased after termination of the radiation (Fig. 1b). Figure 2c shows an MRI scan 3 months after diagnosis, with a decrease in tumor size. The cytostatic therapy was changed to docetaxel. Systemic disease was stable for 7 months. Thereafter, liver metastases progressed and routine control MRI revealed intracerebral metastases in the neurologically unaffected patient. Cerebral radiation was performed and CMF therapy was initiated. The patient died 14 months after diagnosis of the intraorbital metastasis due to liver failure. Local symptoms concerning the left eye did not recur.

Patient 2

A 59-year-old woman complained of discrete diplopia 1 year after diagnosis of metastatic breast cancer. She had experienced this for several weeks but was not seriously affected by the symptom and reported no local pain. There was no obvious bulb deviation and an ophthalmological examination revealed neither a deficiency in vision nor other abnormalities. No neurological deficiencies were found. At the time of onset of diplopia she received paclitaxel as a second-line cytostatic therapy after failure of hormonal therapy. Four-month disease stability had been achieved. Under the

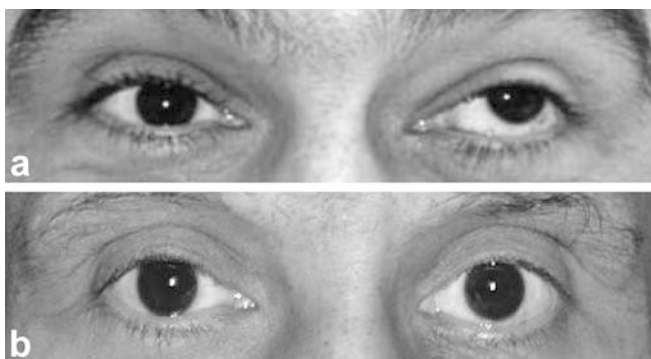


Fig. 1 Patient 1. **a** Deviation of the left eye before radiation therapy. **b** Six months after radiation therapy

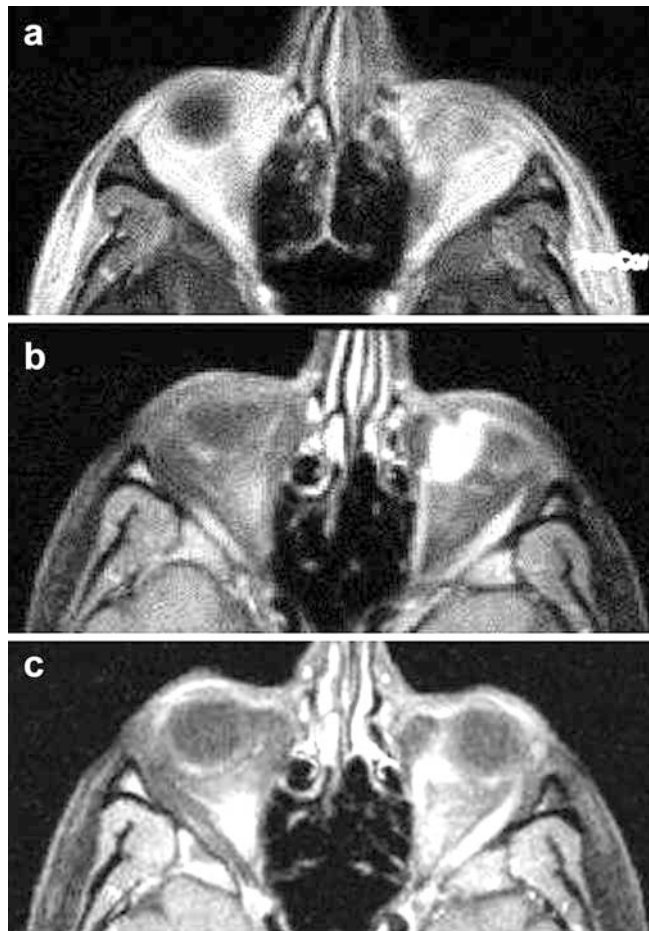


Fig. 2 Patient 1. **a** T1-weighted cranial MRI with bulb asymmetry. **b** T1-weighted, contrast-enhanced MRI with fat suppression: clearly visible tumor inferior of the left bulbus. **c** MRI 3 months after initiation of therapy (T1-weighted, contrast-enhanced MRI with fat suppression)

suspicion of cerebral or ocular alterations, a cerebral MRI with additional T1-weighted contrast-enhanced sequence with fat suppression was performed and revealed a 17×13-mm tumor in the right orbit, posterior and medial to the bulb. Stereotactic radiation with single doses of 2.5 Gy up to a cumulative dose of 45 Gy was performed as local therapy. Systemic cytostatic therapy was changed to vinorelbine. Under this chemotherapy and radiation the systemic disease was stable and the diplopia improved. Ten months later she complained again of diplopia and the MRI showed a contralateral retrobulbar tumor, which is currently under radiation therapy.

Discussion

We describe two patients with orbital metastases of breast cancer. Both patients have had metastatic disease for several years, and both suffered from hormone-receptor-positive tumors. Ocular metastases in male breast cancer patients have been reported in four cases

(Garcia et al. 1998; Schlaen and Naves 1986; Silvestris et al. 2003; Stuntz et al. 2000), while there is a series of reports in female breast cancer patients (Amichetti et al. 2000; Bullock and Yanes 1980; Burmeister et al. 1990; Ferry and Font 1974; Font and Ferry 1976; Glazer et al. 1991; Jacobs and Bengler 1989; Ratanatharathorn et al. 1991; Reeves et al. 2002; Saitoh et al. 1997; Shields et al. 2001; Stefanyszyn et al. 1987; Toller et al. 1998; van der Heijden et al. 1991; Wolstencroft et al. 1999). Ocular metastases are predominantly localized in the highly vascular choroids, followed by the anterior segment, other orbital structures, and the optic nerve (Ferry and Font 1974; Merrill et al. 1991). Bilateral disease is frequent, occurring in 20–40% of the patients (Merrill et al. 1991).

Metastases of the eye have been described for various solid tumors, but breast cancer accounts for the majority of ocular and orbital metastases (Albert et al. 1967; Amemiya et al. 2002; Demirci et al. 2003; Fahmy et al. 2003; Ferry and Font 1974; Freedman and Folk 1987; Shields et al. 2001). Although this mainly reflects the high incidence of this tumor entity, there also might be an affinity of breast cancer for metastasizing to the eye. It is, however, unclear which factors might determine this preference.

In daily clinical practice, ocular or orbital metastases in breast cancer seem to be a rare problem; however, pathological reports suggest that 10–37% of patients with breast cancer have detectable ocular or orbital metastases (Albert et al. 1967; Ferry and Font 1974; Guethert et al. 1965; Merrill et al. 1991). At our center, approximately 300 patients with metastatic breast cancer are treated each year. In the past 5 years only the reported two cases with intraorbital metastases were diagnosed. Considering the above-cited data, orbital or eye metastases often remain subclinical, mostly due to late onset in the course of the disease and other predominant problems. By ophthalmological screening of asymptomatic patients with advanced breast cancer, Wiegel et al. found 5% (6 of 120) patients with choroidal metastases. Risk factors were dissemination of disease in more than one organ and the presence of lung and brain metastases (Wiegel et al. 1998). Fenton and coworkers screened for any ophthalmic involvement in asymptomatic breast cancer patients and found 5.8% positive, but no choroidal metastases (Fenton et al. 2004). It is not clear, however, whether diagnosis and treatment in patients without ophthalmological symptoms is beneficial; thus, routine ophthalmic assessment is currently not recommended in asymptomatic patients with advanced breast cancer.

In 12–31% of the affected patients (Ferry and Font 1974; Glazer et al. 1991; Reeves et al. 2002; Stuntz et al. 2000) eye metastases are the first sign of malignant disease or metastatic spread.

Presenting symptoms vary due to the affected site in the ocular region. When the tumor infiltrates the choroids, blurred vision is the predominant affection, whereas glaucoma might occur in cases with manifestations in the anterior eye. When orbital metastases are

present, diplopia can be the first symptom and can be minimal, as reported in case two. Exophthalmus and bulb divergence occur when large tumors are present. Enophthalmus was reported in a woman with a metastasis from scirrhous breast cancer (Ferry and Font 1974). Local pain has been described in patients with metastases in all orbital and ocular regions (Ferry and Font 1974; Garcia et al. 1998; Merrill et al. 1991; Toller et al. 1998; van der Heijden et al. 1991).

If patients present the mentioned symptoms, ophthalmological examination, including assessment of vision and ultrasound, is recommended. If there is predominantly diplopia, bulb deviation and limitation of ocular movements, tomographic imaging techniques, such as computed tomography (CT) or MRI, should be applied (Merrill et al. 1991). While CT is generally considered equal to MRI in orbital diagnostic (Belden and Zinreich 1997; Char et al. 1997), special techniques, such as fat and water suppression or high-resolution MRI, proved superior in difficult diagnostic situations (Jackson et al. 1999; McCaffery et al. 2002). If the origin of the tumor is uncertain, a biopsy or fine-needle aspiration is recommended, especially when a therapeutic enucleation for suspected choroidal melanoma is considered (Ferry and Font 1974).

The therapy of eye metastases is mainly local. In most patients, radiation therapy appears to be safe and effective with objective response rates (CR and PR) up to 79% (Ratanatharathorn et al. 1991). The most common modality is external beam radiation. There are wide variations in utilized techniques; stereotactic radiation is preferred where possible. If the lacrimal apparatus and the anterior eye are not involved, these structures should be spared. Energy beams include Co^{60} , 4 or 6-MV X-rays. Total doses range from 32 to 50 Gy, depending on the tumor location relative to the anterior eye, delivered with conventional fractionation (Ratanatharathorn et al. 1991; Wiegel et al. 2002). Vision can be preserved or improved in >90% of the patients (Amichetti et al. 2000; Ratanatharathorn et al. 1991). As in the presented cases, most patients with ocular metastases due to breast cancer suffer from metastases at other locations as well; therefore, a systemic treatment is indicated for most of the patients. Recently, one case of dramatic local response of a unilateral choroidal metastasis in Her2/neu-positive breast cancer to systemic therapy with trastuzumab and vinorelbine was reported (Wong et al. 2004). If patients receive systemic treatment and there is no rapid progress concerning the ocular metastases, it might thus be possible to await a local effect. Radiotherapy could subsequently be applied if the ocular symptoms do not improve. Enucleation offers no advantage concerning disease progression or survival and should be preserved for (very rare) cases where intractable pain is present (Ferry and Font 1974).

Prognosis concerning local symptoms and vision is generally good with clinical improvement in 60–80% of the patients (Merrill et al. 1991; Ratanatharathorn et al.

1991). The prognosis *quoad vitam* is generally not determined by the ocular metastases. As these mainly occur in patients with advanced disease, the survival time is limited by organ dysfunction due to other metastases. The median survival time for patients with ocular metastases due to breast cancer ranges from 5 to 17 months (Amichetti et al. 2000; Merrill et al. 1991; Ratanatharathorn et al. 1991).

Conclusion

In conclusion, breast cancer patients can develop metastases in the orbital and ocular region. Due to mild symptoms, other predominant clinical problems, and diagnostic difficulties, these might be recognized late; therefore, clinicians should consider this metastatic location in patients with breast cancer in the presence of ocular disturbances.

Acknowledgement We thank B. Sander, Berlin, for providing the MRI images.

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