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# ORBITAL TUMOUR AS A PRESENTING SYMPTOM OF BREAST CARCINOMA: VALUE OF DETECTING HORMONE RECEPTORS

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## SUMMARY

**A 54-year-old woman was referred for evaluation of an orbital tumour after 5 months of non-specific ophthalmic symptoms. Tissue obtained by an open orbital biopsy was highly suspicious for asymptomatic metastatic breast carcinoma, which was discovered a few weeks later. Unlike the primary tumour, which was an invasive lobular breast carcinoma, the metastatic tissue was repeatedly negative for oestrogen and progesterone receptor markers. A possible reason is a change in cellular cytoplasmic and nuclear protein composition during the metastatic process. Since the primary tumour was positive for the hormone receptors, the patient was treated by chemotherapy and tamoxifen. The follow-up supports a favourable effect of adjuvant endocrinological therapy even in cases with receptor-negative metastatic tissue. This report is in partial contradiction to some previously published cases and emphasises the role of receptor status in the primary tumour.**

Breast carcinoma is one of the most common malignant diseases in women. The common sites of remote metastases are bone, lung and liver.<sup>1</sup> Metastases to the eye (choroid) and the ocular adnexa account for 2–4% of all metastatic sites,<sup>1</sup> but have also been reported to have a prevalence of 27% when undiagnosed cases are included.<sup>2</sup> However, from an ophthalmologist's point of view, breast cancer metastasis to the eye is a common entity responsible for the majority of ocular metastases.<sup>3,4</sup> Although orbital metastases are less common than intraocular metastases, breast carcinoma still has the highest prevalence among other primary sites: in an evaluation of studies performed over the past 30 years Goldberg *et al.*<sup>5</sup> estimated a prevalence of 42% for breast metastases. It is not surprising that among

women this figure is as high as 62%.<sup>6</sup> Orbital metastases from breast cancer have an average delay of some 3–5 years after detection of a primary tumour.<sup>3,7–9</sup> Therefore, there are only sporadic reports in the literature where the diagnosis of metastatic mammary carcinoma ('occult primary') was made on orbital tissue.<sup>3,7,8,10,11</sup> In view of the increasingly sophisticated methods available for the detection of the primary cancer one would expect a decrease in the number of such reports.

Within the last decade, the development of techniques for the detection of oestrogen receptors (ER) and progesterone receptors (PR) in tumorous tissue suggests that testing orbital biopsy tissue for the presence of these receptors is of value.<sup>11</sup> In the following case of an occult breast carcinoma we report our experience in hormone receptor testing on metastatic tissue. We also discuss its value and possible pitfalls.

## CASE REPORT

A 54-year-old white woman was referred to our department with a 3-week history of a painless firm mass in the inner part of the left upper lid. She reported recurrent 'conjunctival and corneal inflammations' for the preceding 5 months. The referring ophthalmologist obtained a CT scan that showed a 'parabulbar tumour'; no further details were given. The patient's medical and ocular history was negative except for mild hyperopia, presbyopia and an appendectomy.

On examination, the corrected visual acuity was 20/20 (1,0) in the right eye and 20/25 (0,9) in the left eye. There was a moderate left upper lid ptosis. A firm mass 1.5 × 0.7 mm was palpable at the medial aspect of the upper lid and appeared to adhere to the upper orbital margin. There was no proptosis, but left elevation and abduction were partially impaired. Slit lamp and fundus examination as well

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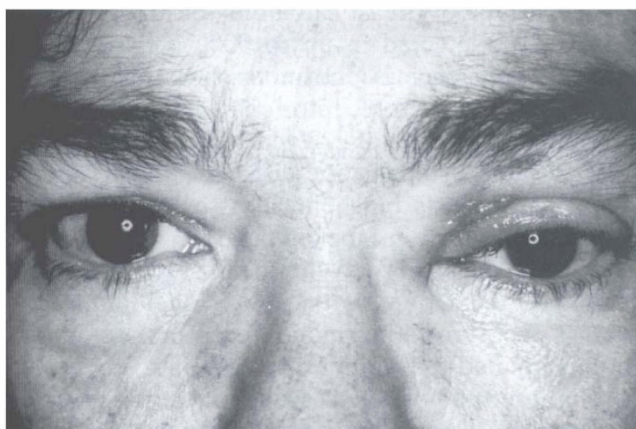
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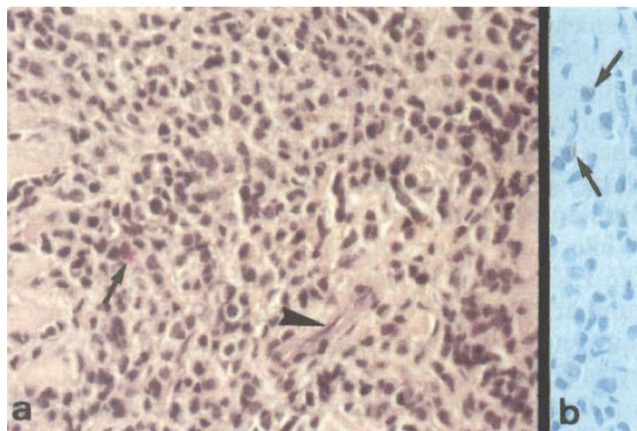
**Fig. 1.** On contrast-enhanced CT scan a large radiopaque mass infiltrating the retrobulbar fat partially obscures the medial rectus muscle. Some tissue swelling is seen in the medial and lateral canthal region.

as computer visual fields did not show any significant abnormalities.

A- and B-scan ultrasonography demonstrated a supero-medial and partially retrobulbar lesion with a low internal reflectivity and a probable erosion of the orbital roof. A contrast-enhanced CT scan in our hospital revealed diffuse infiltration of the orbital fat posteriorly with involvement of the medial rectus muscle and some soft tissue changes in the medial and lateral canthal regions (Fig. 1). The list of differential diagnoses included lymphoma, optic nerve sheath meningioma, glioma and chronic inflammatory pseudotumour. The findings of a general physical examination, liver ultrasound and chest radiograph in the Department of Oncology



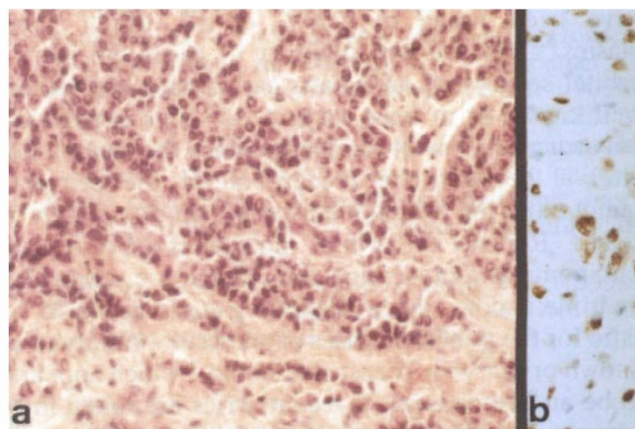
**Fig. 2.** Clinical photograph after the incisional biopsy. A considerable mass is seen at the medial aspect of the upper lid associated with moderate ptosis and swelling of the lid margin. A small wound underneath the eyebrow corresponds with the biopsy site.



**Fig. 3.** (a) Histology of the incisional biopsy specimen. Striated muscle fibres (arrowhead) and orbital connective tissue are diffusely infiltrated by bundles of atypical cells with a large and irregular nucleus. Occasional cells contain PAS-positive cytoplasm (arrow). PAS, original magnification  $\times 400$ . (b) Positive intracytoplasmic staining for pancytokeratin (arrows) on conventional immunohistochemistry. Original magnification  $\times 640$ .

were reported as negative. Thus, a decision was made to proceed with an orbital incisional biopsy through a transpalpebral approach. At surgery the lesion infiltrated the orbicularis muscle and was partially adherent to the dermis. The clinical appearance immediately after biopsy is shown in Fig. 2.

The pathological specimen measured  $6 \times 5 \times 5$  mm, was firm and of a reddish colour. Microscopy disclosed multiple striated muscle fibres and connective tissue with some orbital fat. The entire structure was diffusely infiltrated by bundles of atypical middle-sized cells with partially irregular nuclei (Fig. 3a). Some of the cells contained cytoplasmic vacuoles that were positive on periodic-acid-Schiff (PAS) stain (Fig. 3a). Because of a high



**Fig. 4.** Microphotograph of the primary infiltrating lobular breast carcinoma. The tumour consists of mid-size to large polyhedral cells. H&E, original magnification  $\times 300$ . (b) A strong immunoreactivity for nuclear oestrogen receptors on conventional immunohistochemistry. Original magnification  $\times 640$ .

suspicion of metastatic breast carcinoma, immunohistochemistry was carried out using a cytokeratin marker (clone MNF 116, code no. M0821, DAKO, Denmark), as well as monoclonal antibodies against nuclear oestrogen (DAKO-ER, 1D5, DAKO, Denmark) and progesterone receptors (DAKO Anti-Human PR, code no. A 0098, DAKO, Denmark). While there was positivity for cytokeratin (Fig. 3b) the ER and PR reaction was *negative*. As expected tumour cells did not react with vimentin, leucocyte antigen (LCA), B-lymphocytes (L26) or T-lymphocytes (UCHL-1, CD 20-RO).

When the patient was informed, she said she had a small 'superficial ulcer close to the right nipple' of a few days' duration. She was referred to the Department of Gynaecology and Obstetrics and a bilateral breast carcinoma with lymph node involvement was discovered. A bilateral mastectomy with dissection of the axillary lymph nodes was performed 6 months after the onset of ocular symptoms and 9 weeks after the initial presentation to an ophthalmologist.

On histological examination the breast tumour was diagnosed as an invasive lobular carcinoma. The cytology of the cells (Fig. 4a) was very similar to that seen in the orbit. Surprisingly, the primary tumour was highly positive for ER (Remmele score = 12) (Fig. 4b) and positive for PR (score = 4). The final TNM staging was pT4 Nbiii G1. Since the mastectomy the patient has received six chemotherapy cycles (VNC = Vindesine, Novantrone, Cyclophosphamide) and is on tamoxifen 30 mg/day. The swelling of the left upper lid disappeared and the motility disturbances resolved. Over 2 years after the first presentation the patient is well with no other metastases detected.

### COMMENT

Orbital metastases as a cause of an orbital tumour have been found in 6-10% of all orbital neoplasms.<sup>5,10</sup> In the vast majority of cases the extra-orbital sources of metastatic carcinomas are either well known or at least suspected.<sup>10</sup> This is particularly true for a breast carcinoma, since the mean time interval between the recognition of the primary tumour and the orbital metastasis is approximately 5 years.<sup>8</sup> Reports on orbital metastases of a breast carcinoma as a presenting clinical sign are scarce. In their meticulous review, Goldberg *et al.*<sup>5</sup> give a 25% ratio for the published cases of an occult primary to a known primary for breast carcinoma – which appears to be an overestimate if recent series are taken into account. Indeed, in the series of Bullock and Yanes<sup>8</sup> only in 1 of 30 cases was orbital involvement a presenting sign. Henderson<sup>10</sup> reported an 8% incidence (3/34 patients), while Font and Ferry<sup>3</sup> found only 1 case in a total of 8 mammary cancers. In Goldberg and Rootman's own recent series<sup>12</sup> none of

the 13 metastatic breast carcinomas presented first as an orbital metastasis. Similar to the present case, publications dealing with 'occult primaries' of breast carcinoma are mainly individual case reports,<sup>7,11,13</sup> whereas metastases from a known source are under-represented in the literature since they are relatively common. Because of the progress in clinical diagnosis and widespread screening programmes a further reduction in undetected mammary carcinomas should be expected. For that reason cases of pure negligence (see Bedford and Daniel<sup>14</sup>) should be 'remembrances of things past'.

Our patient is in many respects interesting for review purposes. At the time of initial presentation she was 54 years old – the mean age given by Bullock and Yanes<sup>8</sup> in their series of 30 patients. Similarly, typical findings in breast metastasis are ptosis, a palpable mass and ocular motility restriction<sup>7,9,13,15</sup> – the last sign noted by Horner as early as 1864.<sup>7</sup> Enophthalmos or proptosis may also be seen depending on the metastatic growth pattern (infiltration versus mass)<sup>12</sup> and histological type.<sup>10</sup> The involvement of the superior orbit is very common,<sup>5</sup> explaining the observed ptosis.

The most striking finding in our case was the discrepancy in the hormonal receptor status between the orbital open biopsy tissue and the primary tumour. While the metastatic tissue was repeatedly negative for both oestrogen and progesterone receptors, the scores for the main tumour were 12 (maximum) and 4, respectively. We are aware of four cases in the literature where the metastatic tissue was submitted for receptor analysis: Bullock and Yanes<sup>8</sup> reported two of three positive, and Reifler and Davison<sup>11</sup> one positive. The last case is almost identical to our patient for two reasons: (1) receptors were tested on both metastatic and primary tumour specimens and (2) histologically, the primary tumour was an infiltrating lobular carcinoma. In that particular type of breast carcinoma oestrogen receptors can be detected in up to 90% of cases.<sup>1</sup> The clinical significance is enormous, because with the use of the oestrogen receptor competitor tamoxifen, an average remission of 2–3 years can be achieved in the treatment of metastatic disease.<sup>15</sup> In the above-mentioned reports biochemical assay<sup>8</sup> and a histochemical fluorescein-labelled assay<sup>11</sup> were used.<sup>17</sup> Meanwhile, a further development of immunohistochemistry techniques with monoclonal antibodies against the steroid hormone receptors, as in our case, simplified the routine testing.

What are the possible reasons for the discrepancy in receptor testing between the primary and the metastatic tumour tissue?

1. To exclude technical reasons we repeated immunoperoxidase immunohistochemistry using new monoclonal antibodies on a second block of the

orbital biopsy tissue at the time of preparation of this manuscript. Again the results were negative.

2. The orbital tissue was fixed in Karnovsky's fixative (4% paraformaldehyde, 2.5% glutaraldehyde buffered in 0.1 M Na<sub>2</sub>HPO<sub>4</sub> and 0.1 M KH<sub>2</sub>PO<sub>4</sub>). The breast tissue was fixed in formaldehyde. Although formalin is considered to be superior to glutaraldehyde for immunohistochemistry, in our experience immunoperoxidase technique on glutaraldehyde-fixed tissue is as useful. Even in the present case our unequivocal results using the pancytokeratin marker support this statement.
3. Oestrogen receptors (ER) and progesterone receptors (PR) are proteins, which could have undergone either degradation or a change in surface properties during metastatic spread. Similar change from positive (primary tumour) to negative (distant metastasis) receptor status and vice versa can occur in some 20% of all cases of mammary cancer.<sup>18</sup> In a recent study by Nedergaard *et al.*<sup>19</sup> the ER status in primary breast carcinomas and their axillary lymph node metastases was discordant in 21%. A change in the ER status over time in the primary tumour also has been reported.<sup>20</sup>

Our patient has been receiving tamoxifen from the beginning of the chemotherapy. Although the follow-up period is 2 years only, the patient is in remission with resolution of ophthalmic symptoms. Whether this beneficial effect is to be ascribed to chemotherapy alone or its combination with tamoxifen is a matter of conjecture. Since a highly positive ER assay on the primary tumour was clearly shown to predict the response to the subsequent therapy for metastatic disease,<sup>20</sup> adjuvant hormone therapy should be recommended even in patients negative for hormone receptors on metastatic tissue.

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Key words: Occult breast carcinoma, Oestrogen and progesterone receptors, Immunohistochemistry, Metastatic carcinoma, Orbital metastasis.

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