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Case report

Previously undiagnosed neuroendocrine tumour mimicking breast cancer metastasis to the orbit

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SUMMARY

Metastatic neuroendocrine neoplasms to the breast are rare and histopathologic overlap with mammary carcinomas has led to misdiagnosis. We present a case of a middle-aged woman with diplopia and a right medial rectus mass. Metastatic breast cancer was initially suspected based on a history of invasive ductal carcinoma. Detailed immunohistochemistry of the orbital biopsy, gallium-68 dotatate positron emission tomography–CT, and reevaluation of her prior breast specimen, demonstrated that her initial breast carcinoma diagnosis was in error and she was ultimately diagnosed with a previously unknown gastrointestinal neuroendocrine tumour metastatic to both the orbit and breast. This case highlights the challenges of differentiating between metastatic neuroendocrine tumours and invasive mammary carcinomas with neuroendocrine differentiation both in the breast and in the orbit. It is important to recognise the overlap so that a primary neuroendocrine neoplasm is not missed, or treatment significantly delayed.

BACKGROUND

Metastatic neuroendocrine neoplasms to the breast are rare and account for 1%–2% of all breast metastases. They show substantial histopathologic overlap with primary in situ and invasive mammary carcinomas with neuroendocrine differentiation and have been reported to be misdiagnosed as an invasive mammary carcinoma. The misdiagnosis often leads to unnecessary surgery and treatment guided by the incorrect mammary carcinoma diagnosis, as well as a failure or delay in identifying the primary neuroendocrine neoplasm.[1 2]

We present a case of a woman with a reported history of primary invasive ductal breast carcinoma presenting with a right medial rectus mass suspicious for metastasis. Histopathologic evaluation of the medial rectus mass was found to be a neuroendocrine metastasis, which ultimately revealed her original invasive ductal breast carcinoma to be a missed metastatic neuroendocrine neoplasm of gastrointestinal origin 7 years after her initial diagnosis. This case highlights the challenges of differentiating metastatic neuroendocrine neoplasm to the breast from invasive mammary carcinoma with neuroendocrine differentiation and how careful histopathologic and immunohistochemical evaluation of an orbital metastasis can reveal a delayed diagnosis of the primary carcinoma.

Although breast carcinomas are recognised as the most frequent metastatic lesions in the orbit care must be taken in distinguishing these tumours from less common metastatic neuroendocrine tumours due to the similar histopathologic characteristics of these two entities.[3–5]

CASE PRESENTATION

A 65-year-old woman with a past medical history of breast cancer presented for management of debilitating binocular diplopia. Outside oncologic records indicated that the patient had been diagnosed 7 years prior to the presentation with stage 1A (T1bN0M0) invasive ductal carcinoma of the left breast; the tumour was oestrogen receptor positive (ER+ 5%), progesterone receptor negative (PR−), human epidermal growth factor receptor 2 negative (HER2−). She was treated with lumpectomy with sentinel lymph node biopsy, radiation therapy and chemotherapy (docetaxel, cyclophosphamide with adjuvant tamoxifen). Sentinel lymph node biopsy of five nodes performed at the time of her lumpectomy was negative.

The patient initially presented to outside providers for binocular diplopia about 10 months prior to seeing our service. MRI of the orbits demonstrated a 2.2×1.4×1.5 cm mass involving the right medial rectus muscle causing both mild proptosis as well as lateral displacement of the optic nerve. Given the patient's history of malignancy, these findings were highly concerning for metastatic breast cancer. She underwent a medial orbitotomy without obtaining tissue from the medial rectus muscle as documented by the outside operative report. Histopathology from the orbitotomy revealed mature fibroadipose tissue and rare lymphoid aggregates; an absence of dysplasia or malignancy was specifically noted with cytokeratin (OSCAR) and beta-catenin immunostaining.

The patient then relocated 4 months later and transitioned care to our service for continued unresolved diplopia. Repeated MRI revealed an essentially unchanged 2.5×1.5×1.6 cm isointense mass of the right medial rectus (figure 1). Ophthalmic examination revealed best-corrected visual acuity of 20/30 right eye (OD) and 20/20 left eye (OS). Pupils were equal and reactive without relative afferent pupillary defect. Intraocular pressures were 11 mm Hg OD and 12 mm Hg OS. Ishihara colour plates were 10/10 in each eye. Hertel's exophthalmometry measured 15 mm OD, 13 mm OS with a base of 95. The anterior segment examination

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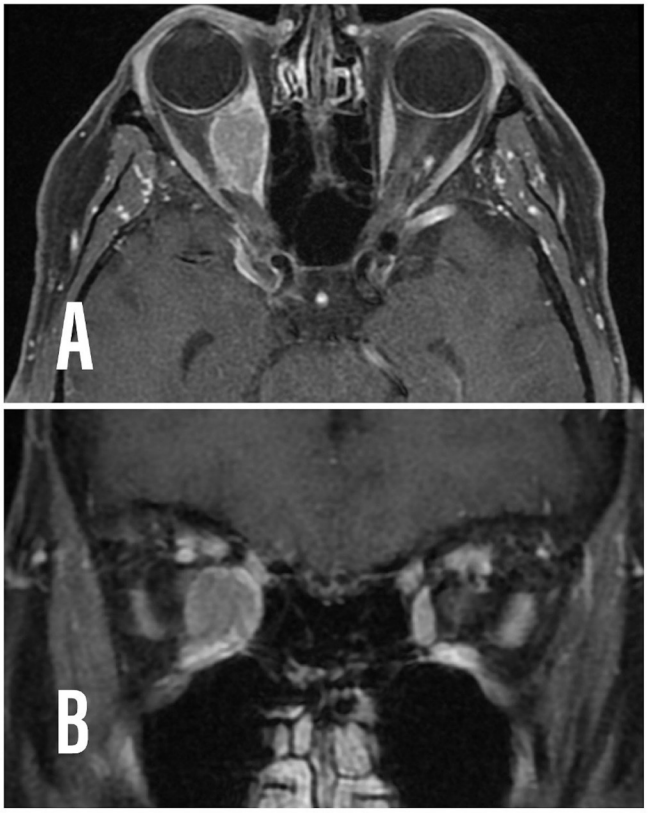

Figure 1 Axial (A) and coronal (B) T1-weighted fat-saturated MRI with gadolinium demonstrating a right isointense medial rectus muscle mass.

was notable for conjunctival injection along the right medial rectus insertion. Posterior segment examination was unremarkable. Motility examination demonstrated a right abduction, adduction and elevation deficit (figure 2). Automated perimetry testing (Humphrey Visual Field (HVF) 24-2 sita-fast) was performed and was full in each eye. As the initial biopsy was non-diagnostic, she underwent repeated orbitotomy with biopsy of the right medial rectus mass. The initial pathology was reported

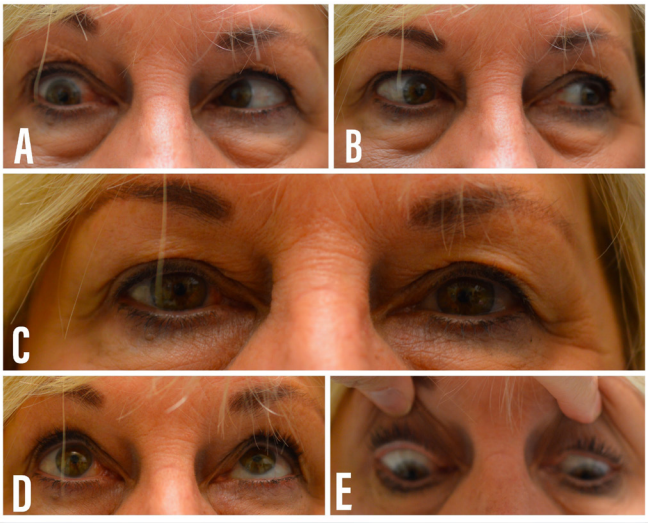

Figure 2 External photograph of patient in (A) right gaze, (B) left gaze, (C) primary, (D) upgaze and (E) downgaze.

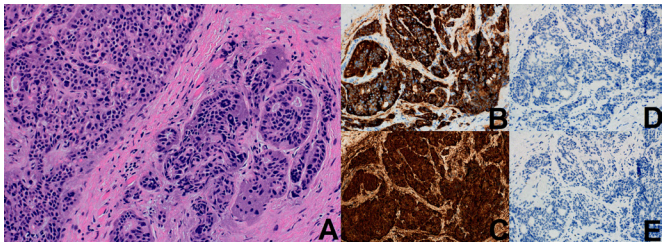

Figure 3 Photomicrograph of a H&E stain at 100× magnification of patient's orbital biopsy (A). Immunohistochemical staining demonstrated strong positivity for synaptophysin (B) and chromogranin (C) but negativity for mammaglobin (D) and GATA3 (E).

as a well-differentiated breast carcinoma metastasis with a low proliferative rate by antigen Ki-67 and ER/PR/HER2 negativity.

A second interpretation of her orbital biopsy by a breast pathologist was requested. This interpretation of the orbital biopsy specimen was significant for a well-differentiated neuroendocrine tumour on the basis of the cribriform morphology with poorly formed tubules comprised of cells with neuroendocrine chromatin and subnuclear granules. This impression was supported by the positive staining for synaptophysin and cytokeratin and negativity for mammaglobin and GATA3. Positive staining for CDX2 suggested a possible gastrointestinal origin (figure 3).

Her systemic workup demonstrated that serum levels of chromogranin A were significantly elevated at 165 ng/mL (normal 0–95). She was also evaluated for systemic disease with positron emission tomography (PET)–CT . The PET (with fludeoxyglucose F18) demonstrated a hypermetabolic lesion in the right orbit as well as lymphadenopathy in the chest and abdomen concerning for metastasis. A gallium-68 (Ga-68) dotatate PET-CT was obtained to evaluate for the suspected neuroendocrine tumour and confirmed metastatic activity in the previously reported sites. This study also identified a site in the terminal ileum/cecum suspicious for a primary tumour that corresponded to a 10 mm nodule biopsied during colonoscopy. This biopsy revealed a grade 1 neuroendocrine tumour with positive staining for synaptophysin (figure 4).

These findings prompted the review of her original breast biopsy specimen by our institution. Interestingly, these samples were also consistent with metastatic neuroendocrine adenocarcinoma of enteric origin (CDX2, villin, synaptophysin, chromogranin positive; mammaglobin and GATA3 negative (figure 5)). The reviewing pathologist commented that the patient's original breast biopsy was only weakly ER positive and appeared nearly identical to the tissue recovered from her cecum. These results refute the patient's original diagnosis of invasive ductal breast cancer and argue that the patient's orbital and breast

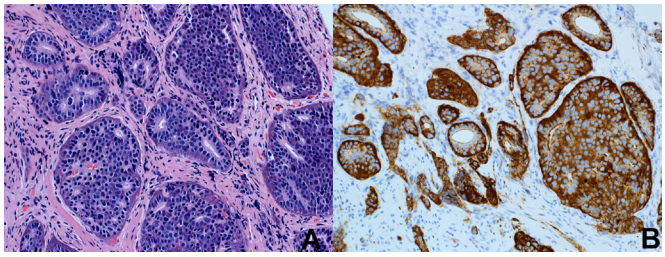

Figure 4 Photomicrograph of H&E stain at 100 × magnification of the patient's ileal nodule consistent with a grade 1 neuroendocrine tumour (A) demonstrating positivity for synaptophysin (B).

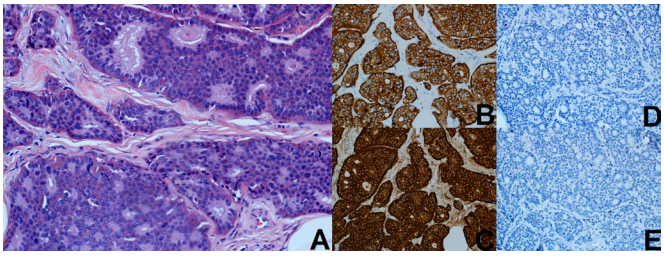

Figure 5 Photomicrograph of H&E stain at 100 × magnification of the patient's initial breast biopsy (A). The tumour is again positive for synaptophysin (B) and chromogranin (C) but negative for mammaglobin (D) and GATA3 (E).

lesions were most likely metastases from the same gastrointestinal neuroendocrine tumour. All the histopathology slides of the original breast lesion, orbital lesion and cecum were reviewed by an additional outside academic centre which concurred with the diagnosis of neuroendocrine adenocarcinoma with metastases to the breast and orbit.

OUTCOME AND FOLLOW-UP

The patient has gone on to receive treatment with orbital radiotherapy and systemic therapy with octreotide. Her diplopia is being managed with prism correction. Her imaging shows stable disease in both the orbit and affected lymph nodes at over 1-year follow-up. The patient provided her consent for the publication of this report.

DISCUSSION

Among all patients with breast cancer metastasis to the orbit is uncommon (<1%).[3] However, when examining cohorts with orbital tumours, over 50% of metastatic orbital tumours originate from a breast primary. Metastasis specifically to the extraocular muscle is rare and ductal tumours (as in this patient) are less likely than lobular tumours to spread to this location.[4 5] Primary neuroendocrine tumours of the orbit are limited to isolated case reports in the literature.[6–8] Metastatic tumours are more common and have been previously reported as metastatic to the recti muscles.[9 10] A pooled analysis of case reports involving metastasis to the extraocular muscles identified melanoma (22%), breast carcinoma (15%) and neuroendocrine tumours (14%) as the most likely to metastasise in this fashion.[11] In these rare cases of extraocular muscle metastasis, differentiating between these most common etiologies is necessary to determine prognosis and appropriate treatment.

Distinguishing between breast carcinoma and neuroendocrine tumours histologically is challenging as the two tumours may exhibit similar morphologies. Specifically, both entities may share a nested and trabecular architecture, minimal tubular differentiation and a 'salt and pepper'-like nuclear chromatin.[1] Case series in the literature have reported an initial misdiagnosis rate of neuroendocrine tumours as invasive breast carcinoma on the order of 14%–44% due to these morphologic similarities.[1 12] The rare incidence of metastatic neuroendocrine tumours to the breast also contributes to its misdiagnosis.[1] Immunohistochemistry may help differentiate between breast carcinoma and neuroendocrine tumours as neuroendocrine tumours typically demonstrate positivity for synaptophysin and chromogranin; unfortunately, subtypes of breast carcinoma with neuroendocrine differentiation also express these markers. Quantification of hormone receptor positivity by immunohistochemistry is not infallible and as many as 56% of patients with a 'low-positive' ER status of 1%–10% (as in our patient) were actually negative by more accurate PCR-based techniques.[13] Non-breast neuroendocrine tumours may exhibit ER positivity with 2 of 16 (13%) lesions in a recent review showing some degrees of positivity.[1] Additional markers have been proposed to aid in distinguishing these entities and include CDX2 (small bowel neuroendocrine tumours), mammaglobin and GATA3 (breast carcinoma).[12 14]

Advanced imaging modalities may also aid clinicians and PET is particularly promising. PET using radiolabelled 18-fluorodeoxyglucose highlights areas of increased metabolic activity non-specifically and does not have much value in differentiating between malignant processes. In recent years, the specificity of PET has been improved by using radiolabelled peptides to detect cells expressing relevant surface receptors. For neuroendocrine tumours, in particular, this has been done using radiolabelled octreotide. However, more recently, Ga-68 dotatate (a somatostatin analogue that is bound by cell surface somatostatin receptors) has been employed to preferentially highlight neuroendocrine tumours in vivo.[15] The Ga-68 dotatate PET-CT is now the Society of Nuclear Medicine and Molecular Imaging's preferred modality for the initial diagnosis of neuroendocrine tumours as well as for selection of patients appropriate for peptide receptor radionuclide therapy.[16]

Utilisation of these advanced histologic and radiologic techniques to distinguish between these tumours is crucial as treatment options may differ radically and inaccurate diagnosis results in unnecessary exposure to toxic chemotherapeutics as well as reduced treatment response. The treatment of metastatic breast cancer is highly dependent on tumour specifics and typically includes cytotoxic agents and oestrogen targeted therapies.[17] On the other hand, treatment for neuroendocrine tumours often involves octreotide or, more recently, everolimus both of which are fairly well tolerated.[18–20] In our case, the patient was treated with both cytotoxic agents and endocrine-driven therapy targeting invasive ductal carcinoma; these do not appear to have been effective against her neuroendocrine primary neoplasm, as she went on to develop additional orbital metastasis that has caused unnecessary morbidity.

This case highlights the challenging complexity of differentiating between metastatic neuroendocrine tumours to the breast and invasive mammary carcinomas with neuroendocrine differentiation. They share morphologic similarities on histopathology and immunohistochemical positivity and both have been shown to metastasise to extraocular muscles in the orbit. It is critical to understand the overlap between the two diagnoses and recognise

Patient's perspective

It has been quite a journey with more than a couple of twists and turns, but thanks to the diligence of UCD (University of California Davis) teams I am on a good course and plan to manage my neuroendocrine tumours. I do hope that my case will be helpful for the medical professionals to assist others who might have a case similar to mine.

Learning points

- Maintain a high index of suspicion for metastasis in any patient with a prior history of carcinoma.
- Do not dismiss non-diagnostic specimens as 'benign'.
- Challenge prior diagnoses and obtain additional opinions with complex cases.

the possibility of a metastatic neuroendocrine neoplasm to the orbit, even in a patient with a previous diagnosis of breast carcinoma, so that a search for the primary neuroendocrine neoplasm is not missed or significantly delayed.

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