Metastatic Breast Cancer Presenting as a Primary Hindgut Neuroendocrine Tumour

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Abstract. The examination of limited, potentially non-representative fragments of tumour tissue from a core biopsy can be misleading and misdirect subsequent treatment, especially in cases where a primary tumour has not been identified. This case report is of a 65-year-old woman presenting with a destructive sacral mass, diagnosed on radiological imaging and core biopsy as a hindgut neuroendocrine tumour, which on histopathological review of the subsequently resected tumour was found instead to represent a metastasis from an occult hormone-positive breast cancer with neuroendocrine features.

Case Presentation

A 65-year-old Caucasian woman presented with a six-month history of severe refractory left buttock pain radiating to the S1 dermatome. The patient’s past medical history included hypothyroidism, for which she was on long-term thyroxine replacement and a previous total abdominal hysterectomy and bilateral oophorectomy for uterine fibroids, following which she received no hormone replacement therapy. Family history included bowel and breast cancer in three separate first-degree relatives, all diagnosed after the age of 60.

The patient underwent magnetic resonance imaging (MRI) of the dorsal spine which demonstrated a 3.5x5 cm mass arising from the left side of the sacrum, causing expansion of the sacrum and thinning and destruction of the overlying cortex. The left S1 nerve root was displaced and compressed by the mass, which had a central cystic, necrotic area. Figure 1a is an axial T1-weighted MR image showing intermediate signal intensity tumour infiltrating the left side of the sacrum (white arrow). It encases the left S1 nerve root and displaces it posteriorly (arrow head). The right S1 nerve root (black arrow) is normal. Figure 1b is a sagittal T1-weighted MRI scan showing intermediate signal intensity tumour (arrow) destroying the upper sacrum.

Histopathological examination of fragments of tissue obtained by a computed tomography (CT)-guided biopsy of the sacral mass revealed islands of monotonous epithelial cells with granular eosinophilic cytoplasm. There was low mitotic activity, and minimal pleomorphism. Immunocytochemistry showed expression of cytokeratin (AE1/AE3) CD56, synaptophysin and chromogranin. Proliferation assessed by staining for MiB1 (Ki-67) was low (1-2%). The appearances were considered to be consistent with a well-differentiated neuroendocrine tumour (NET).

A staging CT scan of the thorax, abdomen and pelvis demonstrated the known destructive sacral mass, four peripheral parenchymal lung metastases, bilateral hilar and mediastinal lymphadenopathy and a bony metastasis involving the posterior right eighth rib.

Serum fasting gut hormones including gastrin, pancreatic polypeptide, glucagons, vasoactive intestinal peptide, somatostatin and chromogranin A and B and 24 hour urine collection for 5HIAA were within normal limits. Octreotide radiolabelled with 111indium (111IN) and 123iodine (123I) meta-iodo-benzylguanidine (MIBG) scans were negative for uptake in the bony, lung and nodal disease.

Due to refractory pain, the patient was treated with palliative radiotherapy (25 Gray in 5 fractions, CT-planned) for a presumed diagnosis of metastatic hindgut NET with an initial symptomatic response. However, due to an escalation of pain 2 weeks post treatment which was poorly controlled by increased opiate analgesia, palliative chemotherapy was instigated. The patient completed 2 cycles of streptozocin 1000 mg/m² day 1 and capecitabine 1250 mg/m² days 1-21 every 21 days with no symptomatic response and was therefore referred for consideration of palliative surgical intervention. The patient subsequently underwent a joint neurosurgical and orthopaedic excision of the left sacral mass.
with complete decompression of the sacral nerve and resolution of pain. Histopathological examination of the resected mass demonstrated widespread infiltration of fibrous tissue and bone by a tumour with similar features to those seen in the core biopsy. Immunohistochemistry performed on the resected specimen demonstrated positive staining for CD56 and neuron-specific enolase (NSE) and focal weak staining for chromogranin with strong expression of the oestrogen receptor (ER). No evidence of a tailgut cyst was seen.

The differential diagnosis was a tailgut NET with ER positivity, or a ductal breast cancer with neuroendocrine differentiation. While breast examination was normal, the mammogram revealed a central, ovoid left breast density and ultrasound-guided core biopsy confirmed a grade 2 ductal carcinoma with neuroendocrine differentiation which was strongly ER positive (8/8), weakly positive for progesterone receptor (PR) (2/8) and human epidermal growth factor receptor-2 (HER-2) negative. The tumour marker cancer antigen 15-3 (CA15-3) was elevated, consistent with a primary breast cancer. Treatment was commenced with letrozole 2.5 mg daily and monthly zoledronic acid, with subsequent normalisation of CA15-3. Figure 2a, b and c show H&E stains for the CT-guided biopsy, surgically excised sacral mass and the breast biopsy respectively. Figure 3 demonstrates important diagnostic immunohistochemical stains: a: sacral biopsy chromogranin expression; b: sacral excision CD56 expression; and c: sacral excision ER expression.

NETs of the breast are uncommon, comprising fewer than 5% of all primary breast cancers (1, 2). Using the 2003 World Health Organisation Classification, breast neuroendocrine carcinomas (NECs) are sub-divided into solid NETs, atypical carcinoid, small cell/oat cell carcinomas and large cell neuroendocrine carcinomas (3). Prior to the publication of this classification, NECs were considered to represent one end of the spectrum of breast cancer with neuroendocrine differentiation, rather than a distinct histological sub-type. Some degree of neuroendocrine differentiation has been described in 8-50% of breast cancers (4, 5).

Immunohistochemical markers of NECs include NSE, synaptophysin, chromogranin A and CD56 (2). The expression of a neuroendocrine marker in >50% of cells of typical neuroendocrine morphology is diagnostic of a breast NEC (3). Neuroendocrine differentiation has been described in both in situ and invasive ductal carcinomas (6) and appears to be more frequent in elderly patients (2). Association with oestrogen and progesterone receptor expression has been described (2), but the presence of neuroendocrine differentiation and HER-2 expression appear to be mutually exclusive (2, 7) which is consistent with the case described. While used as a diagnostic cut-off, the significance of >50% neuroendocrine differentiation is unclear in the prognosis of breast carcinomas and focal neuroendocrine differentiation is of no prognostic or clinical significance (8). Histological sub-type in this group has an uncertain effect, except in the case of small cell carcinoma, which is associated with a poor prognosis (5, 9).

Somatostatin receptors are expressed in 70-90% of carcinoid tumours and somatostatin receptor scintigraphy has a reported sensitivity of 80-100% for the detection of carcinoid tumours.

Figure 1. Axial (a) and sagittal (b) T1-weighted images of the sacral tumour.
and MIBG scintigraphy has a sensitivity of 50% for detecting carcinoid tumours (10). The combined negative results from the MIBG and somatostatin scans in this patient did not exclude the diagnosis of a carcinoid tumour as this has been previously described in 7/46 patients (15%) in one case series of neuroendocrine tumour (11). Normal serum fasting gut hormones can also be expected in hindgut carcinoids, which are usually non-functioning (10) and therefore rely heavily on anatomical location and histology for diagnosis. Primary NETs of the sacrum are rare, with only a single case of primary intraosseous carcinoid tumours reported in the literature (12). However, tailgut NETs arising in the pre-sacral space are more common, with 21 cases reported (12).

While tailgut NETs can be associated with a tailgut cyst, this is an uncommon finding and therefore the absence of a cyst in the resection specimen did not further delineate the diagnosis. Only seven cases of carcinoid tumours arising in tailgut cysts have been described (13-18). Similarly, ER and PR immunoreactivity have been previously described in a tailgut carcinoid tumour (13).

With the exception of small cell tumours, the management of breast NECs aligns with that of other breast carcinomas and can include hormonal treatment, targeted anti-HER-2 therapy and a multitude of chemotherapeutic options. Management decisions are influenced by the stage, grade and receptor status of the breast cancer, rather than the presence or absence of neuroendocrine differentiation. Treatment therefore differs considerably from that recommended for primary NETs of the gut, which are viewed as a separate histological entity from other gut malignancies. Management of these may comprise long acting somatostatin analogues, surgical debulking or combination chemotherapy with streptozosin, cisplatin and a fluoropyrimidine for symptomatic patients or progressive disease. However this tumour is frequently chemorefractory. Radiolabelled somatostatin or MIBG may be indicated in patients demonstrating radionuclide uptake.

This case study reports a rare case of breast cancer with neuroendocrine features presenting as a sacral mass, mimicking a tailgut NET. This case illustrates the importance
of accurate pathological diagnosis due to the diversity in management based on histology and the difficulty in identifying a primary source for any malignancy with neuroendocrine features. The examination of limited, potentially non-representative fragments of tissue can be misleading and misdirect subsequent treatment, especially in cases where a primary tumour has not been identified. While core biopsies are increasingly relied upon due to the improvement in imaging-guided techniques, in this case, the correct diagnosis of a primary breast neuroendocrine carcinoma was established only on a larger surgically-resected specimen, demonstrating the difficulty an anatomical pathologist faces with limited tissue. As the gastrointestinal tract is the most common source of NETs and given the anatomical location of the tumour in this case despite negative octreotide and MIBG scans, it was reasonable to treat as a hind gut primary carcinoid. However, this case highlights the need for early reassessment of the management plan and diagnosis when unusual tumour behaviour arises and that the benefit of a surgically-obtained biopsy can outweigh the risk in the palliative setting.

References


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