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Sustained response to imatinib in patient with extraskeletal myxoid chondrosarcoma and novel *KIT* mutation

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SUMMARY

A 55-year-old woman presented with a 3-month history of right groin swelling, discomfort and impaired mobility. On examination, a palpable mass was noted both to the right of midline in the lower abdomen and in the right groin. MRI of the pelvis showed two masses involving the anterior abdominal wall and right groin, as well as lymph node involvement. CT imaging revealed multiple bilateral pulmonary metastases. Pathology demonstrated a myxohayline stroma morphology. Tumour was also notable for *NR4A3* gene region rearrangement and mutation in *KIT* exon 11 at position c.1669 T>G. Based on these findings, she was diagnosed with extraskeletal myxoid chondrosarcoma (EMC). The patient has been on imatinib, a tyrosine kinase inhibitor with activity against KIT, for 3 years with stable disease. Metastatic EMC is generally treated with surgical resection and perioperative radiation therapy with adjuvant chemotherapy and is associated with poor prognosis.

BACKGROUND

Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft-tissue sarcoma (STS) subtype that contains myxoid matrix located in soft tissues, typically occurring near the proximal end of long bones.[1] The cellular lineage of EMC continues to be an issue of debate. Despite its name, the tumour is not considered a subtype of chondrosarcoma, as hyaline cartilaginous neoplastic tissue is not always present.[2] EMC tumours can present variably on imaging, with a majority demonstrating a low-density mass with calcification on CT with mild or no enhancement.[2] These tumours usually present in patients over 40 years of age and are more common in males than females, with one study identifying a distribution of 64% males, and 84% of patients diagnosed after the age of 39.[3] The lower extremity is the most common primary tumour site, with one study identifying 57% of cases with a lower extremity primary.[3] Classically, EMC is characterised by translocations with the *NRA3* gene with *EWSR1* or *TAF15*.[4] Rare cases of *NRA3* translocation with *TCF12* and *TFG*, and RET overexpression have also been reported.[5–7] One rare case reported an in-frame deletion (c.1735_1737del) in exon 11 of *KIT*.[8]

For patients with localised and resectable metastatic STS, the mainstay of treatment remains surgical resection with perioperative radiation therapy in addition to adjuvant chemotherapy.[9 10] EMC is a unique sarcoma with a propensity for local recurrence and metastasis. Localised EMC usually has a relatively indolent course, with a 15-year overall survival of 58%; however, prognosis is much worse in the setting of metastatic EMC, with a reported median survival of <18 months from the onset of metastatic disease. Cytotoxic chemotherapy is relatively ineffective in the metastatic setting, with no significant radiologic or clinical responses noted in a number of trials, with median time to disease progression of 5.2 months.[11] Despite poor responses to cytotoxic chemotherapy, patients have had better response to sunitinib, a vascular endothelial growth factor receptor (VEGF) tyrosine kinase inhibitor.[12]

Here, we report a case of extraskeletal myxoid chondrosarcoma with novel somatic mutation in *KIT* exon 11 at position c.1669 T>G with remarkable and sustained response to imatinib.

CASE PRESENTATION

A 55-year-old woman presented with a 3-month history of right groin swelling, discomfort and impaired mobility. On examination, a palpable mass was noted both to the right of midline in the lower abdomen and in the right groin. Her family history is negative for malignancy of any kind.

INVESTIGATIONS

MRI of the pelvis identified a 6.8×4.3 × 2 cm mass of the midline anterior abdominal wall, a 2.3×2.2 cm mass of the right groin, and two right pelvic lymph nodes. CT imaging revealed multiple bilateral pulmonary metastases.

A partial excisional biopsy of the groin mass was performed, and pathology demonstrated primarily epithelioid cells in nests, cords and sheets in a myxohyaline stroma, as shown in figure 1. An array of immunohistochemical stains was performed on the tumour, including PD-L1, pan-cytokeratin AE1/AE3, OSCAR, CK7, CK20, TTF- 1 and S100 protein, which were negative. In situ hybridisation was notable for *NR4A3* gene region rearrangement. Together, these findings were consistent with high-grade extraskeletal myxoid chondrosarcoma. Interestingly, the cancer mutation analysis was notable for the missense variant c.1669 T>G in *KIT* exon 11, never before seen in EMC. Germline mutation analysis was conducted on a blood sample, and the novel *KIT* mutation was not present, indicating a somatic mutation. One other case reported in the literature demonstrated a deletion in-frame

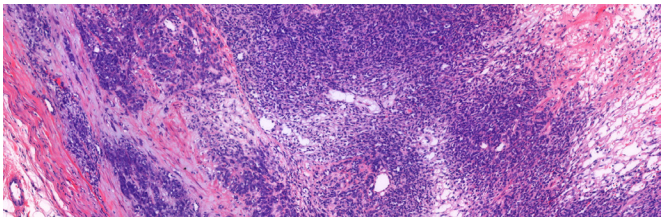

Figure 1 Histopathology of the tumour showing epithelioid cells in nests, cords and sheets in a myxohyaline stroma.

deletion (c.1735_1737del) in *KIT* in exon 11 in a patient with EMC.

TREATMENT

The patient was initially treated with zoledronic acid prior to the results of her mutation analysis. After discovery of the novel *KIT* mutation c.1669 T>G, she was subsequently treated with imatinib, a tyrosine kinase inhibitor with activity against KIT.

OUTCOME AND FOLLOW-UP

Her disease has been stable for 3 years on continued therapy with minimal gastrointestinal side effects.

DISCUSSION

STS account for 1% of newly diagnosed cancers in adults, with EMC being a rare subtype within this group. Doxorubicin with or without ifosfamide has remained the first-line therapy treatment of metastatic STS.[13] Due to the rarity, limited research is available specifically focused on EMC, although previous studies suggest that cytotoxic chemotherapy, including doxorubicin, is ineffective for treatment.[11]

This patient demonstrated the missense mutation in *KIT* exon 11 at position c. 1669 T>G, never before reported in EMC. *KIT*, a proto-oncogene, is known to play an important role in cell proliferation, differentiation, migration and apoptosis. The 1669 T>G mutation is predicted to cause a tryptophan to glycine substitution at the position 557, resulting in a gain-of-function mutationin *KIT*.[14] Gain-of-function mutations in *KIT* are primarily associated with gastrointestinal stromal tumours (GIST) but have also been found in melanoma and acute myelogenous leukaemia.[15–17]

Imatinib is tyrosine kinase competitive inhibitor with activity against KIT, PDGFRA and other tyrosine kinases. Imatinib has shown efficacy in GIST and chronic myeloid leukaemia.[18 19] The patient presented here has been on imatinib for 3 years and continues to have stable disease.

Learning points

- Extraskeletal myxoid chondrosarcomas are extremely rare, with diagnosis relying on pathological, immunohistochemical and molecular evaluation.
- The c.1669 T>G mutation in *KIT* exon 11 has never before reported in extraskeletal myxoid chondrosarcomas.
- Imatinib provided a strong and sustained treatment response, indicating a possible treatment option for any cancers containing a *KIT* mutation regardless of known association.

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