

BMJ Case Reports

TITLE OF CASE

Metastatic Chordoma with Pancreatic Disease and Response to Imatinib

SUMMARY

A 45-year-old lady presented with a left sided neck swelling following treatment a year prior for cervical spine chordoma. She had initially been managed surgically with a cervical vertebrectomy and a course of proton beam therapy. Although there had been a degree of residual tissue, her disease remained stable radiologically and clinically. Repeat MRI demonstrated an increasing left paravertebral mass and a head of pancreas metastasis, which shared pathological characteristics with chordoma. Given the advanced metastatic nature of her disease, imatinib was offered with a palliative intent. Whilst waiting for treatment she developed a spinal cord compression, managed with radiotherapy. She commenced imatinib and her disease remained stable for 9 months before progressing clinically and radiologically. This case demonstrates an unusual pattern of metastatic chordoma and provides further rationale for imatinib in such patients.

BACKGROUND

Chordomas are rare tumours arising from embryological remnants of the notochord and totalling 1-4% of skeletal malignancies. They are most commonly found in the sacrum, skull base and vertebrae and predominantly affect males. Chordomas are rarely identified in those below the age of 40, with a peak incidence between 50-60 years old. Median survival is 6 years. Although low grade, chordomas are locally invasive and have an insidious course. Therefore patients often have a delayed presentation with 5% having metastatic disease.[1] Common sites for metastases include skin, bone, lungs and brain.[2] Clinical features of chordoma vary widely depending on site affected and can be non-specific, ranging from cranial nerve palsies, radiculopathies and bone pain to loss of bladder and bowel function.

Histologically, chordomas can be classified as classical, chondroid or dedifferentiated, with the former being associated with an improved prognosis. They are classically described as having a characteristic physaliferous appearance with immunopositivity for epithelial markers, such as keratin, and S-100.[3] Chondroid appearance has been associated with improved outcomes in contrast to dedifferentiated chordomas, which have a clinically more aggressive nature.[4]

Their clinically indolent presentation, in addition to anatomical location and need to preserve healthy neurological tissue, can present challenges to surgical resection. Proton-beam therapy is often used in

conjunction with surgical excision. However, chordomas are relatively chemo- and radioresistant, meaning treatment options are limited in patients presenting with recurrence (>20%).

There are few current treatment protocols for recurrence. However, imatinib mesylate, a tyrosine kinase inhibitor (TKI), has been demonstrated to have some efficacy as a targeted therapy, with research demonstrating a period of disease stabilisation.[5][6]

This case demonstrates an extremely rare pattern of metastases in a patient with recurrent chordoma and disease stabilisation with imatinib.

CASE PRESENTATION

A 45-year-old female initially presented with severe neck pain (December 2015) and a left sided neck lump (March 2016) in Cyprus, where she held dual residence. She had a background of mild asthma and anaphylaxis to penicillin and took no regular medication. She was a non-smoker and drank alcohol within limits. Her father died of liver cancer and mother died in February 2019 (we are not clear on cause of death). She had 2 healthy brothers.

Following further imaging and multi-disciplinary team (MDT) discussion, and appearances were in keeping with chordoma. She underwent a C3-5 vertebrectomy, tumour debulking and insertion of iliac bone graft in July 2016. Pathology was consistent with chordoma, with expression of CAM 5.2, MNF and S100 demonstrated. Samples were also positive for brachyury. Post-operative MRI imaging demonstrated significant tumour bulk with residual left paraspinal soft tissue. She completed a course of proton beam therapy in Florida, USA and repeat imaging between December 2016 and June 2017 showed reduction in the size of the tumour.

In June 2018, she noted a small swelling above the wound site and later attended for review with her Neurosurgical team. No neurological deficit was noted, and a local recurrence was diagnosed.

INVESTIGATIONS

Initial CT and MRI imaging at presentation demonstrated a heterogeneously enhancing 62 x 39mm mass in the prevertebral region of the lower neck, invading posteriorly into the C3-C5 vertebral bodies (figure 1).

Following her representation in November 2018, MRI demonstrated a significant increase in the size of the left paravertebral soft tissue mass with components identified from C3 to T1 (figure 2). There was associated deviation of surrounding structures with deposits adjacent to the left sternocleidomastoid. She underwent excision of deposits adjacent to the previous incision and the larger deposit in the lower neck. Pathology confirmed deposits of chordoma in the former (positivity for cytokeratin AE1/3 and brachyury, patchy positivity S100, CK7 negative) but not the latter. No EGFR

mutation was detected; PDGFR was not analysed. A CT chest, abdomen and pelvis revealed bone involvement in the anterior left iliac crest and a 22 x 20mm pancreatic neck lesion (figure 3); following discussion at both National Sarcoma and pancreatic MDTs, a biopsy was attempted to help guide management. Due to difficult pharyngeal anatomy, multiple endoscopic ultrasound attempts were unsuccessful. A CT-guided biopsy of the head of pancreas mass revealed metastatic chordoma (positive for AE1/3, MJF, S100 negative). All serum tumour markers to date have been negative.

DIFFERENTIAL DIAGNOSIS

It was crucial to obtain a biopsy from the pancreatic mass to characterise the nature of it. Metastatic chordoma with pancreatic metastasis is extremely rare and a secondary synchronous pancreatic tumour had to be excluded.

TREATMENT

Given the metastatic nature of the patient's chordoma, further surgery or radiotherapy were felt to be inappropriate. Funding for imatinib was sought and granted, with palliative intent to limit tumour growth, as guided by the local oncology team.

Prior to starting imatinib, the patient had an emergency admission to her local District General Hospital with a collapse. She was found to have impending malignant spinal cord compression, with increase in size of both the primary chordoma and the pancreatic metastasis. She was transferred to the regional Oncology centre where she completed palliative radiotherapy (30 Gy in 10 Fractions over 2 weeks) and started imatinib in May 2019.

OUTCOME AND FOLLOW-UP

Imatinib therapy was tolerated well with little toxicity for the duration of treatment. In August 2019, CT imaging demonstrated response of both the cervical and pancreatic lesion. However, further radiological investigation in February and May 2020 demonstrated increasingly rapid progression of both the left paratracheal and pancreatic lesions. Imatinib was discontinued in August 2020 to allow the patient to explore experimental therapies given the given the speed and degree of growth. Unfortunately her disease continued to progress and she died 9 months later.

DISCUSSION

Metastases in chordoma affect 40% of patients, most commonly in the skin, bone and lungs.[4] The identification of a pancreatic metastasis in our patient is extremely rare, with few cases reported in the

literature.[7] It is not uncommon for patients with chordoma to have symptoms of spinal cord involvement, given the primary tumour site and predilection for local invasion.[8] However, the combination of cord compression and pancreatic disease demonstrates an extremely unusual pattern of recurrent metastatic chordoma.

Imatinib is a TKI which is already licensed in several malignancies, including gastro-intestinal stromal tumours and chronic myeloid leukaemia. It inhibits multiple receptors including platelet-derived growth factor receptor- β (PDGFRB) and KIT, both implicated in oncogenesis.[9][10] A number of small scale studies have demonstrated efficacy in advanced chordoma.[5][11] In a Phase II trial by Stacchiotti et al 64% of a cohort with advanced PDGFRB positive chordoma had a clinical benefit (RECIST complete response + partial response + stable disease \geq 6 months).[6] Our case report correlates with the clinical response demonstrated in this paper and provides rationale for further, larger scale research into the efficacy of imatinib in this orphan malignancy. Other compounds have demonstrated promising results, including erlotinib and multikinase inhibitors such as sorafenib, with the latter having progression-free rates of 57.4% at 9 months, compared to 41% for imatinib.[12] However, cohort sizes remain small and there have not yet been randomised trials to demonstrate best standard of care in chordoma.

In our patient, imatinib was well tolerated, with minimal toxicity. While adverse events have been reported in chordoma patients managed with imatinib, such as oedema and fatigue, these are generally in line with those reported in other setting where imatinib is commonly used, such as GIST, and managed with dose reduction.[6][13] In comparison, a cohort of patients on sorafenib experienced grade 3 and grade 4 toxicity in 77.8% and 14.8% of patients respectively.[12] Given the lack of systemic therapy available for chordoma and the relatively minimal toxicities of imatinib, these should not present a barrier to further investigation of this compound in advanced chordoma.

There is no current UK or international guideline for clinical management of recurrent metastatic chordoma, and no suitable clinical trials for such patients.[14] Given the clinical benefit of imatinib to our patient and minimal toxicities experienced, there is reasonable rationale for further investigation into the utility of imatinib in this cohort, and compassionate use in the intervening period.

LEARNING POINTS/TAKE HOME MESSAGES

- This is evidence of unusual pattern of disease with pancreatic involvement; consider unusual sites of metastases in patients with advanced chordoma
- Imatinib should be considered as a systemic immunotherapy in advanced metastatic chordoma, particularly where local therapy is not an option given its potential efficacy and minimal toxicity
- There are many promising targeted compounds in addition to imatinib, such as sorafenib; further randomised trials are needed into precision therapy for chordoma to establish best standard of care.

REFERENCES

TIP: Include only relevant references, including guidelines, in [\(14\)](#).

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FIGURE/VIDEO CAPTIONS

TIP: We do not have a limit on illustrations, but choose only what illustrates your case most effectively and ensure that the patient cannot not be recognised by cropping the image as close as possible.

We encourage colour images and videos.

Figure 1 – Sagittal view of T2 weighted MRI demonstrating initial cervical lesion.

Figure 2-Sagittal view of T2 weighted MRI neck demonstrating recurrence of cervical disease

Figure 3 – Axial view of CT abdomen demonstrating pancreatic head lesion

PATIENT'S PERSPECTIVE

TIP: This is an important section and gives the patient/next of kin the opportunity to comment on their experience. This enhances the case report and is strongly encouraged.

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