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Case Report

Dedifferentiated chordoma: a case report of a rare subtype of chordoma

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Abstract

Chordoma is a malignant tumour showing notochordal differentiation with three identified subtypes including chordoma not otherwise specified, chondroid chordoma and dedifferentiated chordoma. Dedifferentiated chordoma is rare and carries the worst prognosis of all subtypes due to rapid progression and potential for metastases. It is characterized by a high-grade sarcomatous component juxtaposed to conventional chordoma. We report a case of a dedifferentiated chordoma in a 71 year old woman who presented with pain in the lower back, numbness of feet and loss of weight of recent onset. Per-rectal examination revealed a soft tissue mass in the presacral region while imaging showed a solid and cystic lesion with calcifications in the presacral region. The radiological impression was of a retro rectal cystic hamartoma, an epidermoid cyst, or a chronic abscess. The resected specimen comprised a lobulated mass of soft, gelatinous tissue with haemorrhage and necrosis. Microscopy showed a biphasic tumour composed of conventional chordoma juxtaposed with high-grade sarcomatous component. Morphology and immunohistochemistry were compatible with a chordoma with a focal high-grade spindle cell sarcomatous component in keeping with a dedifferentiated chordoma.

Introduction

Chordoma is a malignant tumour arising from embryonic notochordal remnants but may also arise from a benign notochordal cell tumour [1].

Three histological subtypes of chordoma are identified; chordoma not otherwise specified (NOS), chondroid chordoma and dedifferentiated chordoma (DC). DC is a biphasic tumour with a chordoma NOS component and high grade sarcomatous component. Differentiating between DC and chordoma is important because of the differences in clinical management and prognosis. Conventional chordoma is a slow-growing malignant tumor with a better outcome. In contrast, a DC is characterized by rapid progression, potential for distant metastases and a worse prognosis.

Chordoma accounts for 17.5% of primary axial skeletal tumours with a reported incidence of 0.5 to 0.8 per 1,000,000 population in the United States and typically presents in the sixth to seventh decades of life with a male predominance. The commonest site is the sacrococcygeal region (50%) followed by base of skull (35%) and vertebral column (15%) [2].

The majority of chordomas arise sporadically. Very occasionally it occurs in a familial setting where the inheritance is associated with duplication of the Brachyury gene (T gene). It is rare in children. An association with tuberous sclerosis complex is documented [1].

Survival varies with site and size of the tumour. The overall median survival is about 7 years. The common sites for metastases are lung, bone, lymph nodes and subcutaneous tissue [1].

Clinical presentation of chordomas vary with tumor location, size and behavior. Cranial tumours frequently present with headache, diplopia, cranial nerve palsies, visual loss, seizures, nasal congestion, or dysphagia.

Chordoma of the sacrococcygeal region usually present with chronic low back pain or signs of neural compression, such as coccydynia, bowel or urinary incontinence or sexual dysfunction. A mass can sometimes be palpated during rectal or vaginal examination [3].

Patients usually do not seek medical attention immediately as symptoms are nonspecific making a timely diagnosis difficult despite recognizable features on imaging [2].

Chordomas were first described in 1857, when Virchow identified the characteristic cell and described them as “physaliferous” (Greek for “bubble-bearing”) [1,4]. Chordomas NOS appear as soft, lobulated tumours composed of nests of tumour cells separated by fibrous septae. The cells have round nuclei and abundant, vacuolated, eosinophilic cytoplasm and are embedded in myxoid stroma. Chondroid chordomas display features of chordoma and chondrosarcoma and tend to occur almost exclusively in the skull base.

DC is characterized by a frankly malignant mesenchymal component with a sarcomatoid appearance. The sarcomatous component is a dedifferentiated area which is prognostically significant and commonly represent malignant fibrous histiocytoma, fibrosarcoma, osteosarcoma or rhabdomyosarcoma. DC may involve diverse sites and its etiology is unknown. However, it may arise de novo, following radiotherapy and as recurrences or metastases of chordoma NOS. Metastatic disease occurs in most patients with DC within the first year of diagnosis [2].

It is difficult to distinguish conventional chordoma (chordoma NOS) from dedifferentiated chordoma based on imaging studies.

Chordoma are seen as osteolytic lesions of the bone with a sclerotic bone reaction on X-Ray. Computed tomography (CT) scan or Magnetic Resonance Image (MRI) studies evaluate the extent of the tumor with CT scan showing an expanding, destructive, osteolytic lesion with a soft tissue mass while MRI gives better resolution of the soft tissue component [5,6].

Most chordomas, exhibit near diploid or moderately hypodiploid karyotypes, with several numerical and structural rearrangements. The most common cytogenetic abnormalities are monosomy of chromosome 1 and gain of chromosome 7. Copy number gain of the brachyury 7q33 locus, and the EGFR 7p12 locus are also common [1].

The uniquely high levels of expression of the Brachyury protein in chordomas allow differentiation from other tumors of the neuroaxis, such as chondrosarcomas, with relatively high sensitivity and specificity. The degree of Brachyury expression however, has not shown a prognostic indication in chordomas. Interestingly, silencing of the Brachyury gene in chordoma cells invitro leads to complete growth arrest and senescence [3].

Recent molecular analyses have revealed additional genetic abnormalities involved in the pathogenesis of chordomas. Evidence of activation of the PI3K/AKT/TSC1/TSC2/mTOR signaling pathway was detected in chordoma cells. Furthermore, the activation of the IGF1R and loss of MTAP, an essential enzyme in the purine salvage pathway were also detected. The analysis of existing chordoma cell lines has revealed additional genetic aberrations, including loss of p16, PTEN, CDKN2a/CDKN2b, and PDCD437[3]**.**

Case Report

A previously well 71-year-old woman presented to National Hospital Kandy with pain in the lower back, numbness of feet and loss of weight for 2 weeks. She did not have altered bowel habits or urinary symptoms. She was on treatment for bronchial asthma but gave no other significant past medical or surgical history. She was pale and emaciated on examination with no significant cardiovascular or respiratory abnormality. There were no palpable lymph nodes. Abdominal examination was unremarkable. Per-rectal examination revealed a soft mass in the presacral region. There were no rectal masses found. Examination of the nervous system did not reveal any abnormality.

Haematological and biochemical investigations were unremarkable except for a mild anaemia. CT scan of abdomen showed a well-defined heterogeneously enhancing cystic and solid mass lesion with coarse calcifications (Figure 1) in the presacral area measuring 6.7(AP) x 6.4(TRV) x 6.9(CC) cm. The sacrum and neural foramina were uninvolved. Except for compression of the adjacent rectum, the large bowel appeared normal. There was no regional para-aortic or mesenteric lymphadenopathy. Rest of the abdomen and lung bases were unremarkable. There was no ascites or evidence of bone lesions to suggest metastases. The radiological impression was of a retrorectal cystic hamartoma, an epidermoid cyst, or a chronic abscess. The lesion was excised. The specimen received was a mass of soft tissue measuring 70 x 80 x 50mm (Figure 2) Cut sections were gelatinous and lobulated.

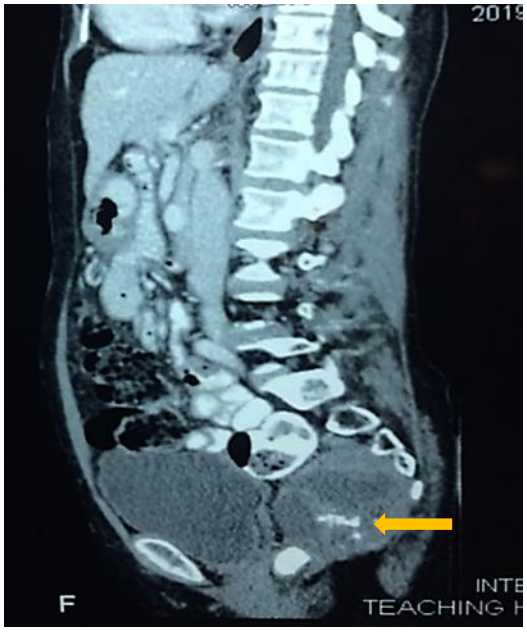

Figure 1*: CT scan image of the tumour shows a solid and cystic lesion in the presacral region with calcifications (arrow).*

Microscopy of the mass revealed an infiltrating tumour with lobulated architecture and fibrous bands separating lobules of tumour cells (Figure 3A). Cells were epithelioid having abundant clear cytoplasm with a bubbly appearance resembling Physaliferous cells (Figure 3B) The stroma showed abundant myxoid material (Figure 3A &B). In some areas the tumour cells were spindly, arranged in diffuse sheets (Figure 3C) showing markedly pleomorphic nuclei with high mitotic activity (Figure 3D) Foci of necrosis were also seen. These high-grade areas juxtaposed with low-grade areas of chordoma NOS.

Intracytoplasmic glycogen was demonstrated with Periodic Acid Schiff (PAS) stain with the glycogen in cells staining a strong magenta colour (Figure 4).

Figure 2: *The gross appearance of the resected tumour. Cut surface was gelatinous and lobulated.*

Tumour cells in chordoma NOS were strongly and diffusely positive for pancytokeratin (PCK) AE1/AE3, S100 and EMA (Figure 5 A, B, C) while the tumour cells in DC areas showed weak and focal positivity for these markers. Tumour cells in both chordoma NOS and DC were negative for CK 7, CK 20, GFAP and CDX2. Ki67 index was around 5% in chordoma NOS low grade areas and was around 40 % (Figure 5D) in DC areas. Accordingly, the tumour was diagnosed as a chordoma with focal high-grade spindle cell sarcoma or DC.

Discussion

Symptoms of chordoma largely depend on location and the size of the tumour and are mostly neurological. In this patient the tumour was located in the presacral region. Accordingly, she presented with lower back pain and numbness of feet with worsening of symptoms within 2 weeks indicating recent rapid enlargement of the tumour.

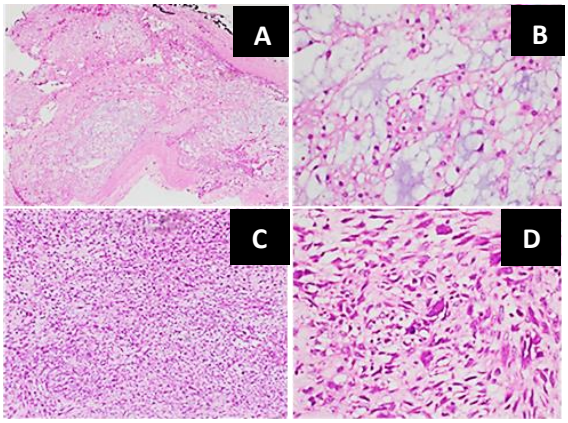

***Figure 3: A**- Chordoma NOS with lobular arrangement of tumour cells in a myxoid stroma (H &E x 40). **B** - Chordoma NOS physaliferous cells (H & E x400). **C** - DC with spindle tumour cells arranged in diffuse sheets. (H & E x100). **D** - DC showing markedly pleomorphic nuclei with high mitotic activity. (H & E x400).*

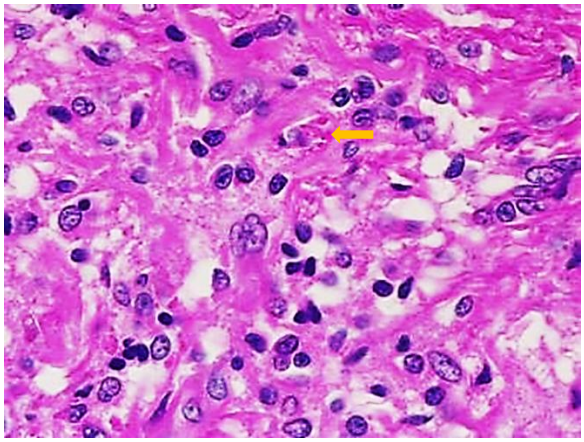

***Figure 4:** PAS stain highlights intracytoplasmic glycogen in tumour cells in magenta colour (arrow) (x400).*

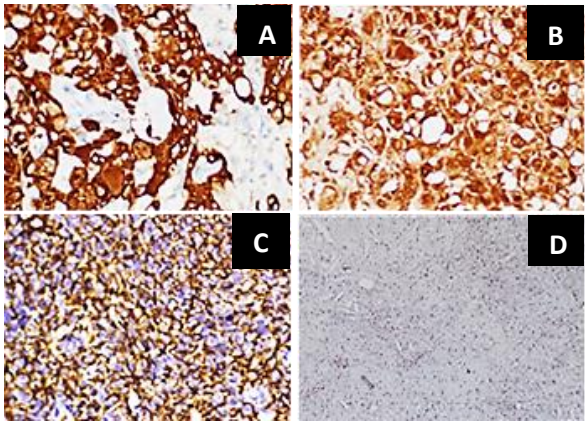

***Figure 4: A** - Pancytokeratin shows strong cytoplasmic positivity in tumour cells of chordoma NOS (x400). **B** - S100 shows strong cytoplasmic and nuclear positivity in tumour cells of chordoma of NOS (x400). **C** - EMA shows strong membrane positivity in chordoma NOS (x100). **D** - Ki 67 index is around 40% in DC (x100)*

Chordoma NOS cannot be differentiated from DC with imaging unless distant metastases are present. Radiological impression of this tumour was that of a solid and cystic lesion with the possibilities including a retrorectal cystic hamartoma, an epidermoid cyst, or a chronic abscess. The diagnosis of a chordoma with a dedifferentiated component was made based on histomorphology and immunohistochemical stains. However, CT scan or MRI studies are helpful in evaluating the extent of the tumor infiltration to the surrounding tissue.

The chordoma component in DC may mimic a chordoid meningioma, myxopapillary ependymoma, chondrosarcoma or metastatic carcinoma especially from mucinous adenocarcinoma with or without signet ring cells or clear cell renal cell carcinoma.

Chordoid meningioma is characterized by cords and trabeculae of epithelioid cells that may be eosinophilic or clear, resembling physaliferous cells within a mucin rich or myxoid stroma. Tumour cells are positive for EMA and S100 variably and negative for PCK.

A Myxopapillary ependymoma is characterized by well differentiated cuboidal to elongated tumour cells, radially oriented around vascularized myxoid cores with a myxopapillary appearance and positivity for GFAP. S100 positivity is seen in 50% of tumours with PCK negativity.

Chondrosarcoma are hypercellular tumours with sheets of chondrocytes showing a lobular growth pattern, arranged in clusters with variable atypia. Tumour cells are positive for S100 and negative for EMA and CK.

Metastatic deposits from mucinous adenocarcinoma are characterized by atypical glands lined by pleomorphic cells with expression for epithelial markers. They are typically negative for S100.

This patient presented with a tumour in presacral region. Histological assessment showed a biphasic tumour with an area resembling chordoma NOS comprising large physaliphorous cells showing immunoreactivity for PCK, S100 and EMA.

These cells did not express CK 7, CK 20, GFAP or CDX2. A separate high grade spindle cell component was also present representing a sarcomatous component juxtaposed to conventional chordoma. Thus, the diagnosis of a chordoma with focal high grade spindle cell sarcoma or DC was justified.

Brachyury is a transcription factor of the T-box family typically expressed in a chordoma. It is the best marker with 98% sensitivity and 100% specificity for the identification of chordoma. This marker is expressed in dedifferentiated components as well [7]. Unavailability of brachyury and facilities for cytogenetic studies is a limitation in our setting.

Dedifferentiation within a chordoma has a dismal prognosis with an aggressive clinical course and rapid metastasis. The metastatic foci commonly show the dedifferentiated sarcomatous component [7]. Several studies have indicated that the proportion of the dedifferentiated component has significant impact on survival.

Our patient developed symptoms in a short period of time. There was no past history of chordoma or radiotherapy to sacrum. Therefore, this tumour is likely to be a DC, denovo from notochordal remnants. Clinically and radiologically, there was no evidence of metastases at the time of presentation. However, the presence of a sarcomatous component predicts a poor outcome for the patient. Currently the patient is on treatment with regular follow up at the oncology clinic.

Conclusion

Precise diagnosis of DC is of paramount importance for prognostic and treatment implications, as patients with DC exhibit significantly higher rates of metastases, as well as shorter overall survival rates, compared to conventional chordoma. As there is difficulty in distinguishing conventional chordoma NOS from DC based on imaging studies, with the diagnosis solely based on histomorphology, extensive sampling of the specimen for histological assessment is crucial for the diagnosis DC.

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