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Case Report

Exceptionally giant neglected sacral chordoma in a post-poliotic residual paralysis patient - a rare case scenario

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Abstract: Chordoma is a rare malignant tumour with an incidence of 0.1 case per 1 lakh population per year. The sacrococcygeal region is the most common site to be involved. Herein, we are reporting a case of sacral chordoma, who is a 32-year-old male patient, a known case of post-polio residual paralysis on the left lower limb, who presented with complaint of pain in the lower back and gluteal region for 2 years with swelling in the gluteal region for 1 year, which was gradually increasing in size for 1 year with associated weight loss. MRI revealed an ill-defined lytic expansile altered signal intensity lesion involving S3 to S5 and coccygeal vertebral bodies measuring 13.2 × 16.2 × 14 cm (ap × tr × cc) with adjacent large lobulated heterogeneous soft tissue component and showed multiple coarse calcifications. The lesion anteriorly displaced and abutted the rectum and was deriving its blood supply from branches of bilateral internal iliac arteries. The patient was planned and underwent wide-margin resection (middle sacrectomy with R0 margins with preservation of both S2 and right S3 nerve roots). Histologic Grade was reported to be G2, moderately differentiated, high grade. Pathologic stage classification was reported as pT3a. Postoperatively patient had the same neurological status and was discharged on advice to do full weight bearing walking and self-intermittent catheterisation and laxatives. He was on routine follow up and improved well symptomatically.

Keywords: Sacrum, coccyx, chordoma, management, radiology, histopathology, post-poliotic residual paralysis, en-bloc resection

Introduction

Chordoma is a rare malignant tumour with an incidence of 0.1 case per 1 lakh population per year. It was first described by Virchow in 1857. The sacrococcygeal region is the most common site of sacral chordoma followed by the spheno occipital region and vertebral body. Herein, we are reporting a case of sacral chordoma which is a difficult to treat condition, and is more common among males and the peak age of incidence is around 50 years of age. Chordomas develop from notochordal remnants of the embryo and they are tumours of the axial skeleton [1]. The notochord, which is a central, rod-shaped embryonic structure, expresses important genes that drive skeletal development, such as echidna hedgehog (ehh), sonic hedgehog (shh), collagen II (col2a1), and no tail (ntl) [2, 3]. In humans, the notochord develops during the third week of gestation, stretching from the sacrum to the sella turcica, but it is gradually replaced by fibrocartilage from surrounding tissues during the first 1-3 years of life. However, notochord remnants may persist at the skull base, the odontoid process, intervertebral discs, and the coccyx [4-6]. Rare familial cases have been reported but most of the cases are sporadic.

In normal human development, most of the notochordal remnants disappear by the first year of life and even if they persist, the majority stay harmless. A crucial immunohistochemical indicator in the entire process is brachyury, a T-box transcription factor that governs notochord development and is believed to play important role in pathogenesis [7, 8]. Brachyury is overexpressed in familial chordoma, indicating its significance as a gain-of-function mutation in its origin, although genetic amplification in sporadic cases is more commonly linked to gain

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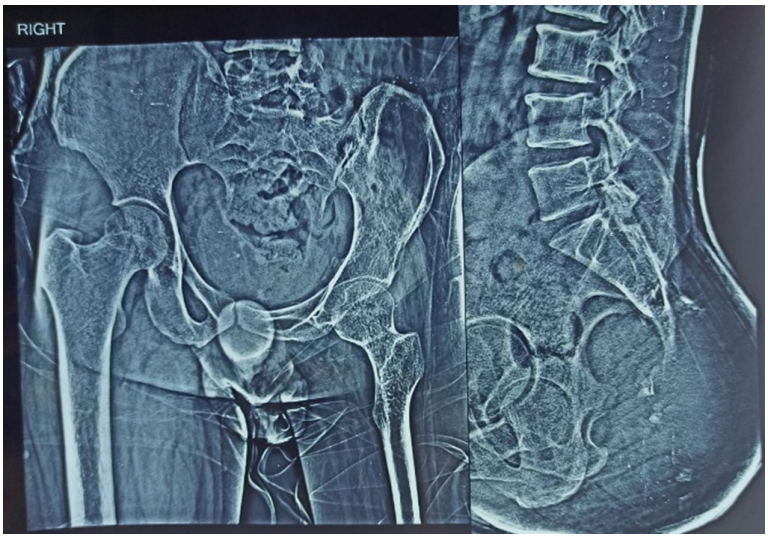

Figure 1. Preoperative radiographs showing pelvis with both hips - anteroposterior view and lumbosacral spine - lateral view.

of whole-chromosome [9, 10]. The fibroblast growth factor regulates expression of brachyury, and its pathway has been implicated in tumorigenesis [11]. Therefore, brachyury is an extremely sensitive and specific histologic indicator of chordoma and is considered to have diagnostic importance [42].

Other important immunohistochemical indicators include epithelial markers (cytokeratin and epithelial membrane antigen - both present in 100% of cases) and S-100 (present in 85.7% of cases) [12]. The Ki-67 is a histopathological measure of mitotic activity, correlated with a worse prognosis when >5% [13]. Chordomas are characterized genetically by the absence of CDKN2A and PTEN expression and significant loss seen in chromosomes 1p, 3, 9, 10, 13, 14, and 18 [14]. The CDKN2A protein p16 is a recognized tumor suppressor that inhibits cyclin complexes responsible for regulating the G1-S phase of the cell cycle, and the loss of its expression is a well-established characteristic in chordoma [15-17]. The loss of 1p36 and 9p has specifically been linked to worse prognosis and decrease survival [13].

Clinical presentation depends on the anatomic location and extent of the chordoma. Headache, neck pain, and cranial nerve palsies are often present in skull-based chordomas, whereas spine and sacral chordoma typically have symptoms of chronic back pain or urinary/bowel dysfunction because of nerve root compression.

Case report

We present the case of a 32-year-old male patient, a known case of post-polio residual paralysis on the left lower limb, who presented to the outpatient department complaining of pain in the lower back and gluteal region for 2 years with swelling for 1 year. Pain was dull aching type and gradually progressive without radiation to lower limbs and was more during the night so the patient had to take painkillers to sleep. The patient noticed swelling in the gluteal region incidentally and it was gradually increasing in size for 1 year with associated weight loss. There was no associated history of fever, night sweats, contact with TB, deterioration of neurology of limbs, bowel bladder complaints and trauma. On examination, we found a firm, non-tender, non-mobile, non-fluctuant swelling over the sacral region without any skin changes without any distal neurovascular deficit.

Plain radiographs of the lumbosacral spine with the coccyx and pelvis with both hips were taken, which showed an ill-defined suspicious lesion in the sacrococcygeal region (**Figure 1**). This was followed by MRI which showed an ill-defined lytic expansile altered signal intensity lesion involving S3 to S5 and coccygeal vertebral bodies with adjacent large lobulated heterogeneous soft tissue component, suggestive of malignancy likely chordoma (**Figure 2**). On CT examination, a large well defined lobulated hypodense mass lesion is seen epicentered in the midline at the caudal end of the spine in the lower back behind the rectum.

The lesion measured 13.2 × 16.2 × 14 cm (ap × tr × cc) and showed multiple coarse calcifications. The lesion was superiorly reaching upto the lower border of the S2 vertebra causing destruction of the sacrococcygeal vertebrae, inferiorly reaching upto the level of anal verge and to the skin, subcutaneous tissue

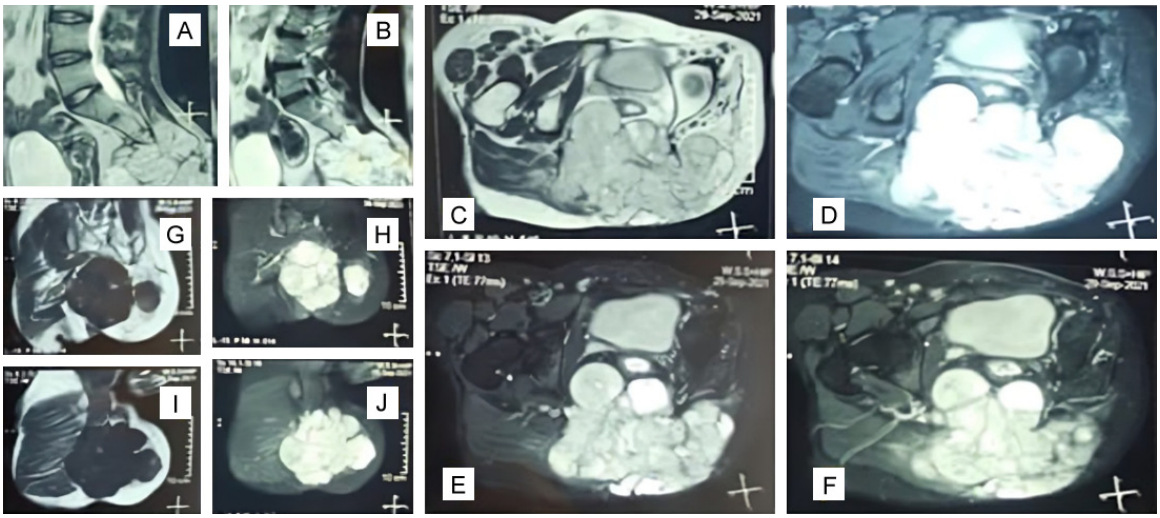

Figure 2. Preoperative MRI of the spine and pelvis showing extension of the mass in the pelvic cavity (A) and (B) T2 weighted image showing saggital cuts, (C-F) T2 weighted TSE SPAIR sequence image showing axial cuts, (G) and (I) T1 weighted TSE SENSE sequence image showing coronal cuts, (H) and (J) T2 weighted TSE SPAIR sequence image showing coronal cuts.

level. The lesion anteriorly displaced and abutted the rectum and showed loss of fat planes with levator ani. The lesion at its right lateral aspect abutted and showed loss of fat planes with the right gluteus maximus and medius. The lesion was deriving its blood supply from branches of bilateral internal iliac arteries. A note was made of a few enlarged enhancing perilesional lymph nodes. On the left, there was significant fatty atrophy of the left iliacus, glutei muscles and thigh muscles.

Contrast enhanced CT scan of the thorax-abdomen-pelvis was done to rule out any other lesions or metastasis and showed multiple enlarged perilesional lymph nodes but no distant metastasis.

A core needle biopsy was done from the lesion and microscopy showed the presence of a tumour arranged in lobules, cords and reticulated pattern separated by fibrous bands. Individual tumour cells exhibit central round to oval nuclei, fine chromatin, inconspicuous nucleoli and moderate bubbly to eosinophilic cytoplasm embedded in an extensively myxoid matrix. Adjacent fibro collagenous tissue shows few congested and dilated blood vessels and occasional foci of necrosis. No significant mitosis was identified in the section examined. These features were suggestive of Chordoma.

The patient was planned and underwent wide-margin resection (middle sacrectomy with R0 margins with preservation of both S2 and right S3 nerve roots) (**Figure 3**). Under GA, the patient positioned prone and a midline vertical incision was done in the lumbosacral region. After midline bilateral dissection of the fascia and the muscles of the lumbosacral region, a large mass was exposed which had invaded the sacrum, coccyx and the gluteal muscles. After determination of S1 and S2 lamina with C-arm (fluoroscopy), Kerrison rongeur used for S2 laminectomy and the thecal sac was ligated above S2 segment. The lesion was exposed superiorly upto the lower border of the S2 vertebra, destruction of the sacrococcygeal vertebrae was observed intraoperatively, inferiorly exposure was done upto the level of anal verge. The lesion anteriorly displaced and abutted the rectum and showed loss of planes with levator ani. The lesion at its right lateral aspect abutted and showed loss of planes with the right gluteus maximus and gluteus medius. Total en bloc resection of the well demarcated huge mass was done by using suction and cautery. The tumor was very hemorrhagic with multiple vascular supplies. As the spine stability was preserved so no devices or implants were needed. Hypotensive anaesthesia and local vasoconstrictors were used to control bleeding intraoperatively and 2 unit of PRBC were trans-

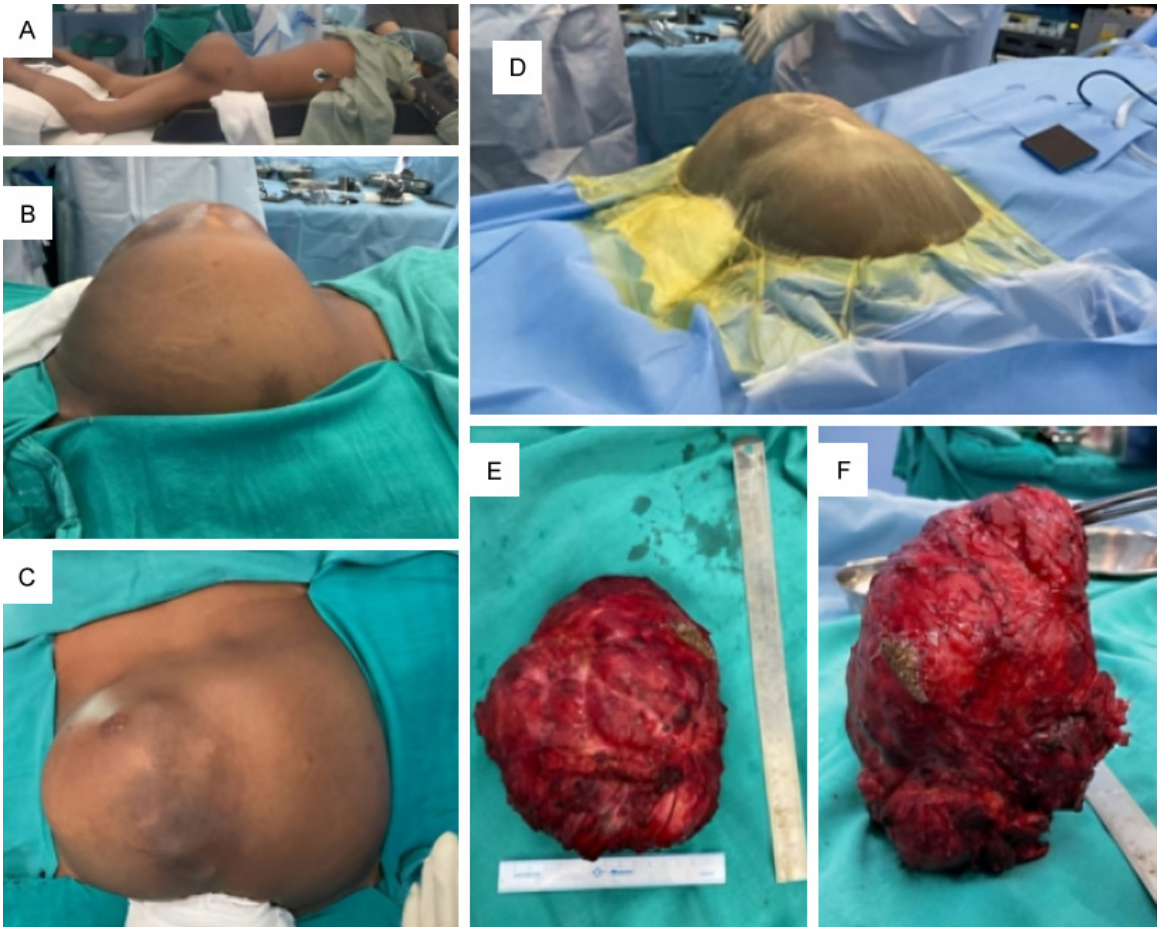

Figure 3. Intraoperative pictures (A) Positioning of the patient, (B) and (C) Clinical picture of the lesion [(B) side view, (C) top view], (D) Draping before commencement of surgery, (E) and (F) Clinical picture of the lesion after excision - capsulated mass measuring 19.2 × 14.8 × 11 cm and weight 1509 gm [(E) top view, (F) front view].

fused. Post-resection, patient tolerated the surgery well without any untoward event.

In the histopathological examination of the lesion - During Gross examination, the external surface was grey-brown, congested with attached fibroadipose tissue and a few skeletal muscle fibres. On serial sectioning, the cut surface was lobulated, firm, grey-white, fleshy, with glistening cartilaginous areas, haemorrhagic and yellowish necrotic areas. Focal myxoid areas are identified. Tumour boundaries are ill-defined, however, the tumour was seen infiltrating into the adjacent fibroadipose tissue.

Histologic Grade was reported to be G2, moderately differentiated, high grade. Multiple sections examined show an invasive tumour arranged in lobules of varying sizes separated by thick fibrous septae. There was extensive chondroid differentiation within the lobules. The tumour was arranged in trabeculae, nests and focally in sheets in the lobules and showed moderate to marked nuclear pleomorphism. These cells had an irregular nuclear membrane, vesicular chromatin and moderate to abundant eosinophilic to clear vacuolated cytoplasm. These vacuolated cells are physaliphorous cells. Few cells show multinucleation and intranuclear inclusions. Large areas of necrosis were noted (40%). The overlying skin is free. Pathologic stage classification (pTNM, AJCC 8th Edition) was reported as pT3a (**Figure 4**).

Postoperatively patient had the same neurological status as in the preoperative period except for weak bowel and bladder control (**Figure 5**). The patient was discharged on advice to do full weight bearing walking and

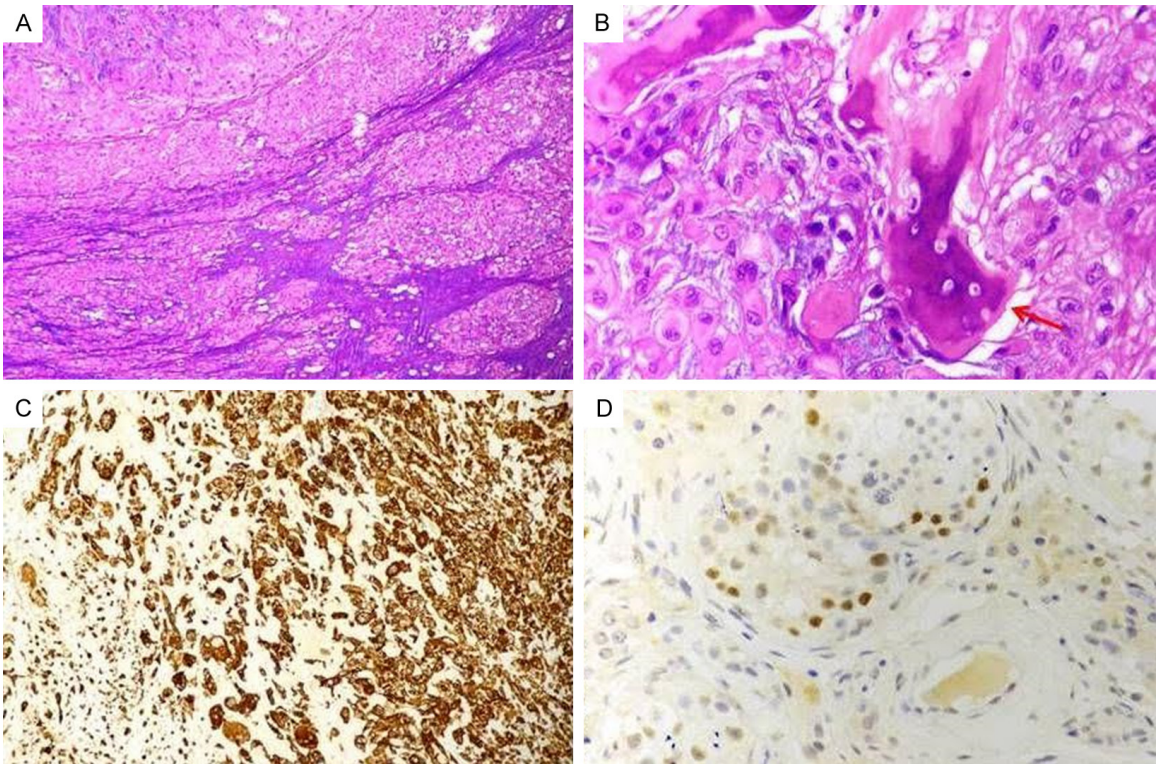

Figure 4. Histopathological study. A. Low-power view shows a tumour composed of lobules of large epithelioid cells interspersed with hyaline cartilaginuous matrix (H&E × 100×); B. High power view shows entrapped cartilage (red arrow) surrounded by physaliphorous cells (bubbly cytoplasm) and a myxoid matrix (H&E × 400×); C. The tumour cells are immunopositive for panCK (IHC × 100×); D. Brachyury (IHC × 400×). H&E: Hematoxylin and Eosin; panCK: pancytokeratin; IHC: Immunohistochemistry.

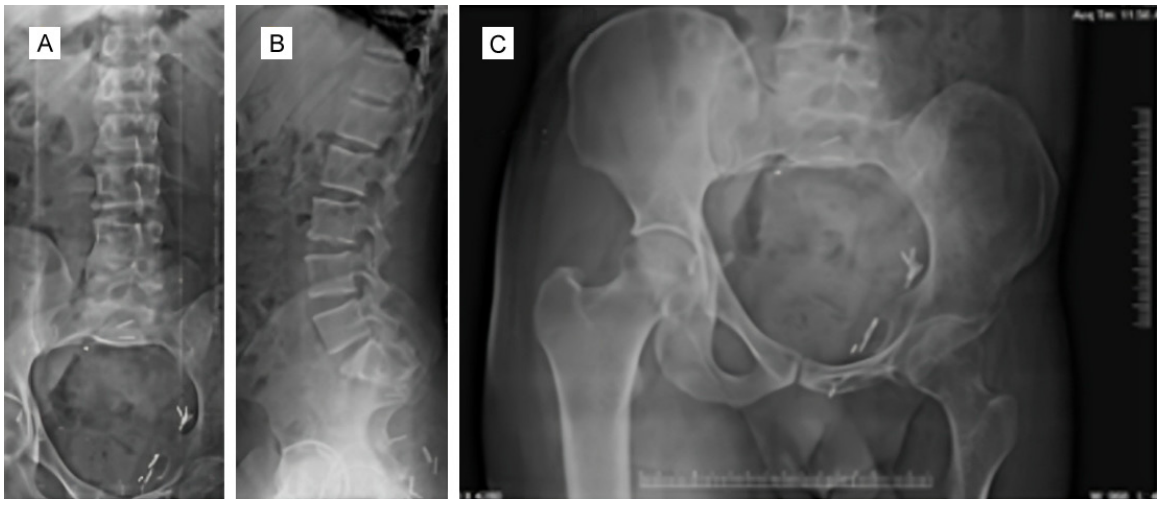

Figure 5. Postoperative radiographs showing lumbosacral spine - (A) Anteroposterior view and (B) lateral view, (C) postoperative radiographs showing pelvis with both hips - anteroposterior view.

self-intermittent catheterisation and laxatives. He was on routine follow up and improved well symptomatically and bowel bladder control also improved.

Discussion

According to Jianhua MD et al., younger age, and differentiated tissue on Histopathology

examination are predictors of good prognosis and old age, dedifferentiated tumour, bowel bladder involvement at presentation, recurrence and metastases are the predictors of poor outcome [42]. Clinical presentation depends on the anatomic location and extent of the chordoma. Headache, neck pain, and cranial nerve palsies are often present in skull-based chordomas, whereas spine and sacral chordoma typically have symptoms of chronic back pain or urinary/bowel dysfunction because of nerve root compression.

The patient presented in this report was a young adult and was moderately differentiated on histopathological examination. The tumour resolved after surgery and no recurrence was reported in 2 years follow up.

Sacral chordoma is a primary bone tumour that primarily affects men and affects people between the ages of 30 and 60 with a high mortality rate. It makes up less than 5% of all bone tumours [39]. A sacral lesion with heterogeneously high signal intensity and criss-crossing septa on long-repetition-time imaging, well-encapsulated pseudopodia-like or lobulated appearance, and gluteal muscle infiltration were among the characteristic findings recorded by Sung et al. in their study based on 30 MRIs of patients with sacral chordoma. This observation was supported by MRI, which showed some degree of gluteal muscle infiltration in the patient.

Sacral chordomas are difficult to manage tumours because of their location close to vital structures and are usually diagnosed at late stages. Surgery is the main mode of treatment, and research is ongoing on the efficacy of radiotherapy. Chordoma, metastasis, myeloma, osteoblastoma, giant cell tumour, neurofibroma, teratoma, aneurysmal bone cyst (ABC), lipoma, osteosarcoma and chondrosarcoma, anal fistulas, sacral dermatoid, and postpartum lesions are few common differentials for the pathologies found in the sacrococcygeal region [40, 43, 44].

The extensive myxoid matrix with various lobules, solid nests, cords and strands of physaliferous cells, along with their enlarged, atypical nuclei and eosinophilic cytoplasm with variable-sized vacuoles, are seen in the histopathology. It is conceivable for high-grade sarcoma regions to grow and dedifferentiate.

In their investigation, Xu et al. found that the gigantic chordoma specimens tested positive for vimentin, cytokeratin, Ki-67, S100, and epithelial membrane antigen [1]. Familial chordomas have been linked to the brachyury gene [9]. Due to unusual signs and symptoms, the histological examination of the condition is frequently delayed.

Our patient was having slow progression over 2 years and the patient was having vague symptoms that were gradually progressive hence patient ignored for 1 year and the diagnosis was delayed because of that. Studies have shown that there is a male predominance in chordoma. Skull base chordomas are usually diagnosed in earlier age groups compared to vertebral and sacrococcygeal chordoma. Sacral chordomas often grow very large even before causing symptoms so the prognosis is poor compared to other chordomas [50].

A combination of surgical excision and adjuvant radiotherapy has been shown to have better outcomes compared to surgery alone [50]. Adjuvant radiotherapy plays a role in the prevention of local recurrence. The rate of local recurrence is high in sacral chordoma. Our patient was managed by wide resection with preservation of both S2 and right S3 nerve roots. The patient had partial urinary incontinence and required bowel medications after surgery for constipation.

The exact benefits of radiation therapy although aren't completely established, evidence indicates that it can enhance outcomes, especially in cases of partial tumor removal and when dealing with recurring tumors in the sacrum and spine [21-27]. Despite the belief that chordoma is typically resistant to radiation, research suggests that high-dose photon and proton radiotherapy could enhance local control for tumors that can't be removed [25, 28]. In a retrospective study involving 15 patients with sacral chordoma, it was found that the average time before recurrence was 2 years even after the entire tumor was removed, but there was a tendency towards better survival when immediate postoperative radiotherapy was given, indicating that additional therapy could be advantageous [29]. In a retrospective study of patients with spinal and sacral chordoma, it was indicated that neoadjuvant radiation appeared to enhance local control, and they recommend-

ed to consider neoadjuvant high-dose radiotherapy due to the risk of tumor seeding during intra-lesional resection [30]. Overall, neoadjuvant radiation therapy showed a tendency towards improved local tumor control [22, 42].

Although conventional chemotherapies failed to prove success in the management of chordoma [31-33], Irinotecan is the only drug tested in a phase 2 of clinical trial, with a response in just 1 patient of the total 15 patients evaluated in the study [34]. Due to recent advancements in understanding of pathogenesis of chordoma, more targeted therapies are in its early stages. Trials of Tyrosine-kinase inhibitors such as sunitinib and imatinib have been done with limited success [35-37]. An mTOR inhibitor drug, Sirolimus, was found to have a synergistic effect when combined with imatinib in advanced chordoma resistant to imatinib [36]. Trials of erlotinib and lapatinib, EGFR inhibitors, done with moderate success in advanced chordoma [37, 38]. EGFR antagonist, such as Cetuximab, and checkpoint inhibitors, such as nivolumab and ipilimumab, monoclonal antibodies are currently undergoing early-phase trials for treatment of chordoma as both a monotherapy and combination therapy [38, 42].

Cheong et al., reported that preservation of bilateral S3 nerve roots are essential for complete preservation of bowel bladder function and if one S3 nerve root was sacrificed, one out of 3 patients developed partial urinary incontinence and 2 out of 3 patients required bowel medications. Those in which bilateral S3 resected, all of them had to do intermittent self-catheterisation and bladder medications. In those bilateral S2 roots resected, they observed complete urinary and bowel incontinence [19].

Because of the slow biological growth rate and low incidence of metastatic dissemination, surgery is the only treatment for this uncommon bone tumour [18-20, 45]. An important prognostic indicator that is connected with both overall survival and the frequency of local relapses is the extension of margins. There is strong evidence linking local recurrence to a higher risk of metastasis and problems connected to the tumour [18-20, 46, 50]. However, since in the anatomical areas of the Sacrococcygeal chordoma, there is involvement of complex tissues, such as bones, nerves, mesentery, etc., this potentially curative margin-free "en bloc" excision is frequently very difficult to obtain.

Although not seen in this case, Sacral chordomas frequently have large cavities and soft-tissue abnormalities; they can lead to problems such as sacrococcygeal skin necrosis, infection, and delayed or non-healing wounds [41, 47]. According to Pillai and Govinder's analysis, the most prevalent clinical manifestation is low back pain that worsens when sitting and is not relieved by non-steroidal anti-inflammatory medicines [44]. Up to one-third of patients also have urinary problems. While radiography might guide the treatment of individuals presenting with similar clinical problems, histopathology is still the gold standard for diagnosing chordoma and distinguishing it from other illnesses that may require alternative courses of treatment [48].

The most commonly recommended treatment plan for tumour progression-free survival of more than 60 months is surgical resection with extensive excision, either with or without radiotherapy, as highlighted by Ahmed et al. in their comprehensive analysis [39]. This is consistent with observations made by Barber et al. and Walcott et al. [43, 48]. In light of the aforementioned circumstances and the body of literature, it is determined that prompt diagnosis, precise preoperative staging, a decisive and sufficient surgical resection with established tumour-free cut margins, and vigilant observation and follow-up are necessary for the effective therapy of coccygeal chordoma [41, 47]. Conservative treatments, such as radiotherapy with thorough monitoring, can be taken into consideration for patients who are refusing surgery.

Although the advancement of recent surgical techniques and some favourable results with the use of targeted therapy, there is still decreased control of the disease and poor prognosis in long-term follow up [49, 50]. Nevertheless, patients' quality of life and, outcomes improve if managed by a multidisciplinary team (surgeons, medical oncologists, pathologists, radiologists, and radiotherapists).

Conclusion

Sacral chordoma is a rare malignant tumour of the axial skeleton developing from notochordal

remnants of the embryo. Brachyury gene is important immunohistochemical indicator in its pathogenesis. Symptoms of chronic back pain or urinary/bowel dysfunction because of nerve root compression are common in patients with sacral chordoma. X rays, CT scan and MRI are investigations crucial to delineate the size and extent of the lesion and en bloc resection is commonly done in such patients. Post operatively, Histopathology report confirms the diagnosis. Although not completely established, high-dose photon and proton radiotherapy could enhance local control for tumors that can't be removed. Irinotecan, sunitinib, Sirolimus, erlotinib, lapatinib are some of the drugs currently undergoing trials in the management of this condition.

Disclosure of conflict of interest

None.

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