Poorly Differentiated Aggressive Sacral Chordoma with Upfront Lung Metastases in a Child - A Case Report

Shubham Dokania[1], Sambit Nanda[1], Shashikant Patne[1], Shabana Azad[1], Rahul Sisodiya[1], and Ashutosh Mukherji[1]

[1]Mahamana Pandit Madan Mohan Malaviya Cancer Centre

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Shubham Dokania, Sambit S Nanda, Shashikant CU Patne, Shabana Azad, Rahul Sisodiya, Ashutosh Mukherji

1. Shubham Dokania, MBBS, Junior Resident, Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Varanasi, India; Email- shubhamdokania3@gmail.com

2. Sambit S Nanda, MD, Associate Professor, Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Varanasi, Homi Bhabha National Institue, India; Email- sambit.sambitswarup@gmail.com

3. Shashikant CU Patne, MD, Professor, Department of Oncopathology, Homi Bhabha Cancer Hospital, Varanasi, Homi Bhabha National Institue, India; Email- scupatne.tmc@gmail.com

4. Shabana Azad, MD, Senior Resident, Department of Oncopathology, Homi Bhabha Cancer Hospital, Varanasi, India; Email- shabazad18@gmail.com

5. Rahul Sisodiya, MD, Senior Resident, Department of Radiation Oncology, Homi Bhabha Cancer Hospital,Varanasi, Homi Bhabha National Institue India; Email- sisodiya.rahul848@gmail.com

6. Ashutosh Mukherji, MD, Professor, Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Varanasi, Homi Bhabha National Institue, India; Email- drashutoshm@gmail.com

Corresponding author- Shubham Dokania, MBBS, Junior Resident, Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Varanasi, Pin-221005, Uttar Pradesh, India, Email- shubhamdokania3@gmail.com

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Key Clinical Message : Sacral chordoma are usually slow-growing. Distant metastases can be seen on prolonged follow-up, but rarely early in the disease course. Lung metastasis at presentation and poorly differentiated tumors have rapid disease progression. Early aggressive treatment including surgery and/or radiotherapy (RT) with exploration of targeted therapy may improve outcome.

1. Introduction

Chordomas are rare tumors of the axial skeleton originating from remnants of primitive notochord and occurring in the midline from clivus to sacrum, anterior to the spinal cord. Historically 50% cases were estimated to originate in the sacrococcygeal region, 35% in skull base, and 15% in mobile spine[1]. Surveillance, Epidemiology, and End Results (SEER) database analysis of 400 patients from 1973-1995 suggested an almost equal distribution in the skull base (32%), mobile spine (32.8%), and sacrum (29.2%). The incidence is 0.08 per 1,00,000, with the prevalence being twice as high in males compared to females. The peak incidence is seen between 40 to 60 years of age, and proportion of cases in first two decades has been reported as low as 2.6%-5% of all[2-3]. No risk factors as such have been identified, however, patients of tuberous sclerosis are at higher risk for the same[4]. These slow-growing malignancies are locally aggressive, but have recurrence rate upto 66% by eight to ten years, depending on the treatment delivered[5]. Distant metastases to lung, bone, soft tissues and liver have been reported in upto 43% patients on prolonged follow-up of 16 years and as low as 5% at presentation or on shorter follow-up duration of five years[6-7]. These figures imply that metastases occur mostly late in the course of disease. Multiple studies have attributed the risk of developing distant metastases to local recurrences, with the risk being much lesser in the absence of local recurrences[8]. We present a rare case of rapidly progressive, both locally and distally, case of poorly differentiated sacral chordoma with histologically proven lung metastases at presentation in a child. Being a case report, this article was not required to be reviewed by the ethics committee. Also, informed consent from the patient's (minor) father has been taken regarding the same.

2. Case history/examination

A seven-year-old child presented in December 2023 with complaint of right sided gluteal swelling for six months. The swelling had a gradual onset following a history of fall and increased progressively in size. It was associated with intermittent febrile episodes. Bowel and bladder habits were normal. The child was alert and playful, however had difficulty in assuming sitting position. The right gluteal swelling was hard and 10x8 cm in size, without any tenderness, skin changes or regional lymphadenopathy.

3. Methods (differential diagnosis, investigations and treatment)

After a thorough history and physical examination, we had a number of differential diagnoses, namely, hematoma, cyst, chronic abscess and neoplastic growths like rhabdomyosarcoma, soft tissue sarcoma, etc. The T1w Magnetic Resonance Imaging (MRI) of pelvis showed a 6.3x9.5x8 cm sacral mass, with heterogenous post-contrast enhancement, as shown in figure 1. There was diffuse cortical break with associated large extraosseous soft tissue mass, with involvement of spinal canal and exiting sacral nerve roots. Bilateral gluteal muscles were involved, with greater involvement on the right side. The presacral extension displaced the rectum anteriorly without any bowel invasion. Few subcentimetric indeterminate pelvic nodes were noted. The possible differentials now were sacral chordoma and sacral teratoma. Biopsy taken from the lesion revealed a poorly differentiated chordoma with fibrocollagenous tissue infiltrated by tumor arranged in sheets. Individual cells were pleomorphic, round to oval with coarse chromatin, prominent nucleoli and abundant eosinophilic to clear cytoplasm. There were foci of calcification with ˜8/10hpf mitotic figures and no necrosis. On immunohistochemistry (IHC), tumor cells stained positive for AE1/AE3 and brachyury and negative for SOX10, S-100, and desmin. The histological and IHC images have been illustrated in figure 2. 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET) CT was done for metastatic work-up, and showed a 9 mm, FDG avid nodule in upper lobe of left lung, with maximum standardized uptake value (SUVmax) being 4.58.

The patient's sacral lesion was deemed unresectable in view of large size and potential sacral instability as well as loss of bladder and bowel control post resection. CT-guided biopsy from the left upper lobe confirmed

poorly differentiated metastatic chordoma, with lung parenchyma and fibro collagenous tissue infiltrated by tumor cells arranged in sheets and focal cords. Tumor cells exhibited moderate pleomorphism, round to oval hyperchromatic nuclei, inconspicuous nucleoli, eosinophilic to vacuolated cytoplasm. Focal myxoid change and focal areas of necrosis were identified. On IHC, tumor cells stained positive for Brachury (diffuse), AE1/AE3 (diffuse), S-100(focal) and negative for CK7, Napsin A and TTF1. The intent was kept curative as the single metastatic lesion was small and was found amenable for both radiofrequency ablation (RFA) and surgery. He was planned for definitive radiotherapy (RT) to the sacral region. During planning CT scan, the skin overlying the lesion was inflamed and impending ulceration, and the patient was unable to lie flat in supine position for adequate immobilization, so he had to be simulated in prone position using four-clamp abdomino-pelvic thermoplastic cast and five mm bolus on the skin overlying the lesion. The RT planned was for 72 Gray (Gy) in 40 fractions, 1.8 Gy daily fractions, five days a week using volumetric modulated arc therapy (VMAT). However, the lesion had clinically appreciable local progression between the simulation and starting of treatment. The local skin appeared even more inflamed, both in intensity and extent, so the RT plan already made had to be aborted and adaptive replanning was considered, with same setup as before. On account of the rapid progression of the primary lesion, an extended planning CT scan covering whole thoracic region was taken. It showed multiple metastatic nodules in both the lungs, the largest being 1.8x1.7 cm in the left upper lobe. With this, the intent of treatment was changed to palliative and the plan for RFA was deferred. He had already received 22Gy in 11 fractions, out of the planned dose. Further palliative intent RT of 12Gy in 2 fractions, 6Gy weekly fractions, was delivered to the local site for palliation of pain. The child has now been receiving symptomatic palliative treatment under the pain and palliative department of our hospital.

4. Conclusions and Results (outcome and follow-up)

The child on his last follow-up had partial relief from pain. There was mild increase in the size of primary lesion. There was no complaint of any shortness of breath. To conclude, poorly differentiated sacral chordoma, especially in paediatric population tend to have rapid disease progression. Early aggressive multimodal treatment including surgery and/or RT with potential exploration of targeted therapy may improve outcome in such cases. Future such cases should be preferably enrolled in clinical trials to generate meaningful evidences regarding their management.

5. Discussion

Chordomas are low-to-intermediate-grade, midline primary bone tumors, with dual epithelial-mesenchymal differentiation. The origin is attributed to embryonal remnants of notochord, with the strongest evidence being the expression of transcription factor brachyury in undifferentiated notochord as well as in chordomas[9]. Upon reaching 11 mm in embryo development, the notochord undergoes maturation, leading to its obliteration and displacement from the centre towards both cranial and caudal ends. Microscopic foci persist within the vertebral bodies at these locations, which undergo malignant transformation in the third to fourth decade for spheno-occipital lesions and in the fifth to sixth decades for sacrococcygeal lesions. Despite the ectodermal origin, these tumors are usually classified and approached as sarcomas due to being bony tumors. World Health Organization (WHO) classification of tumours of soft tissue and bone 2020 classified chordomas histologically into conventional, dedifferentiated and poorly differentiated, with chondroid chordoma being a subtype of conventional type. Conventional type has characteristic physaliphorous cells, with the matrix appearing like hyaline cartilage in case of chondroid subtype. The latter arise almost always in the base of skull. Dedifferentiated type has a high-grade sarcoma component apart from the conventional chordoma component and are usually diagnosed post RT and in recurrent setting. Role of aberrant p53 inactivation is suggested. Poorly differentiated type is the rarest, with around 60 reported cases, most commonly affecting children and young adults. It usually involves skull base and cervical spine, and rarely the sacrococcygeal region. These tumors usually have loss of INI1 expression, with absence of physaliphorous cells. The prognosis is worse with poorly differentiated and dedifferentiated types[10]. Chordomas are slow-growing tumors and usually clinically silent till late stages, with pain being the most common manifestation, followed by location-specific neurological symptoms like radiculopathy or bowel-bladder dysfunction. There is associated

bony destruction with surrounding soft-tissue mass. Location-wise, sacral chordomas are usually regarded as the commonest ones, with maximum involvement of fourth and fifth sacral vertebrae.

National Comprehensive Cancer Network (NCCN) guidelines 2020 recommend extensive resection of operable chordomas[11]. Positive resection margins and soft tissue mass larger than 7 cm mandate postoperative RT. No response to chemotherapy has been reported[4]. Molecular targeted inhibitors and Brachyury vaccine are upcoming promising options. Complete resection is the cornerstone of treatment, with the extent of resection largely determining the recurrence rate. Poor anatomical accessibility, size of tumor, extent of intraoperative blood loss, and high chances of sphincteric and sexual dysfunction due to sacral nerve roots sacrifice, make wide resection feasible in only small number of patients, culminating in high recurrence risk in sacral chordomas[12]. Among 56 chordomas of sacrum and mobile spine, 33% recurrence rate after extensive resection and 67% after intracapsular or marginal resection have been reported[13]. Similarly, 66% of 48 patients of mobile spine failed locally in an analysis, with those treated with intralesional excision or RT alone having 100% recurrence in a period of 17-20 months, whereas post margin-free en-bloc resection, only 33% recurred at 56-94 months. Even Intralesional extracapsular resection followed by RT had 75% recurrence at 30 months[5].

These tumors are resistant to conventional radiation doses less than 60 Gy[14]. Dose escalation upto 78Gy attempted with image-guided intensity modulated radiation therapy (IG-IMRT) was shown to decrease five-year local failure rates to 48%, compared to 83% in patients with surgery alone or low-dose RT[15]. Various studies have highlighted the role of higher doses in skull-base chordomas, especially with particle radiation (alone or in combination with photons), though the dose-response relationship is not consistent across all series[14]. Following resection of spinal chordoma, adjuvant RT with proton therapy was shown to have 40% recurrence risk, compared to 88% with photons, though the ratio of patients in both arms was skewed[16]. Five-year local-progression-free survival rate 53%-85% has been reported with proton RT even in sacral and mobile spine chordomas[17]. The median survival as per the analysis of400 patients, published in 2001, is 6.29 years with 5-year, 10-year and 20-year survival rates decreasing significantly to 67.6%, 39.9%, and 13.1%, respectively, irrespective of race and sex[2]. Another review of 682 patients, published in 2017 showed the median survival as 9.5 years, with 5-year and 10-year rates as 76% and 47% respectively, likely indicative of the improvement in survival due to advances in treatment modalities. Their multivariate analyses showed that age less than 18 years increased the likelihood of recurrence as well as death, sacral origin was negative predictor of progression-free survival (PFS) and the overall survival (OS) was decreased with recurrence and metastases[3]. Local recurrence has been regarded as the most significant determinant of mortality, other important factor being distant metastases. A review of 53 cases of poorly differentiated chordomas revealed the mean age of presentation as 9.7 years, the range being 3 months to 42 years old. 100% of the patients' specimen stained positive for brachyury and panCK, and 96% had INI1 loss. Around 96% had origin in clivus, skull base or cervical spine, and only 3 cases (6%) were reported in sacral region. Out of the 41 patients whose follow-up data was available, only 7 patients (17%) were alive and free of disease. The median survival was reported as 46 months, much lower than that by other studies[18].

Due to the usually late diagnosis of chordomas, distant metastases are likely, but less than 5% are detected at presentation, with most being detected way further in the disease course[7]. Metastases to lung, bone, soft tissues and liver have been reported in upto 43% patients on prolonged follow-up of 16 years[6]. As per an analysis of 219 patients of chordoma by Young et al, the median time from initial diagnosis to metastasis was 4.8 years, with the median survival after the detection of metastases being 1.7 years, varying with the location of the primary and the metastases[8]. Others have reported the mean interval from surgery to metastases as six years, with a mean survival of 0.2 years post detection of metastases[19]. Young et al also showed that 17.8% patients developed metastases, out of which 53.8% did to the lungs. However, 11.8% metastases occurred in the setting of local recurrence and only 5.9% occurred with locally controlled disease, showing statistically significant correlation between local recurrence and metastasis[8]. Yang et al corroborated the significant difference in the rate of metastases with (33.7%) and without (6.7%) local recurrence[20].

The mainstay of treatment of such metastatic as well as advanced or relapsed patients are molecular tar-

geted inhibitors, selected based on gene mutation screening and IHC[21]. Tyrosine kinase inhibitors (TKI) monotherapy can be used as first-line therapy with Imatinib being the most widely used one[22]. In case of drug-resistant chordoma, two TKIs or TKI plus mammalian target of rapamycin (mTOR) inhibitor is preferred[23]. Brachyury vaccine (recombinant Saccharomyces cerevisiae encoding brachyury) followed by RT could not show any difference in overall response, compared to placebo arm, yet remains a good target for developmental therapeutics in chordoma[24]. Role of Immune checkpoint inhibitors looks promising as per few case series, and multiple trials are ongoing regarding the same[25]. Enrolment of such patients in clinical trials will pave the way for generation of evidences regarding these newer modalities. Unfortunately, our patient could not be given any systemic therapy due to financial constraints.

In our patient, the rapid growth of local and distant disease can hence be attributed to paediatric age group, sacral origin and the poorly differentiated histology. The peculiar characteristics of our case include poorly differentiated histology in sacral disease, presence of lung metastases upfront, diagnosis of chordoma in paediatric age group and a chordoma progressing rapidly. Ours is probably the only case reported till date with these unique features. The diagnosis at an early age is justified by the poorly differentiated histology, which also justifies rapid local progression and development of early lung metastasis. However, association of this histology with sacral chordoma is very rare. The review of literature shows that paediatric chordomas with poor differentiation have really bad prognosis, hence such cases should be started on definitive treatment without any undue delay. The quest for an effective targeted therapy for INI1 deficient tumors has remained elusive.

Author Contributions-

Writing - original draft preparation: Shubham Dokania, Sambit S Nanda

Writing - review and editing: Ashutosh Mukherji, Sambit S Nanda, Rahul Sisodiya

Resources- Shashikant CU Patne, Shabana Azad

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