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Review Paper

A review study on pathogenesis, symptoms, diagnosis, and treatment options of chordoma

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ABSTRACT:
Cancers result from uncontrolled division of cells that disrupt the normal activity of organs. Cancer is classified according to the origin organ. Chordoma (notochordal sarcoma) is a slowly progressing tumor of the spine. These tumors may develop in any part of the spinal cord but mostly develop near the tail bone also called sacral tumors. The most common types of chordoma are cranial chordoma, sacral chordoma, and spinal chordoma. The common sites for this cancer are the sacrum, skull base, and spine. These are diagnosed in about 1 individual in 1 million people every year. These tumors develop in late age and demonstrate poor prognosis. Additionally, these tumors also create many challenges to treat. The most common ways to diagnose chordoma are biopsy, magnetic resonance imaging, and computed tomography imaging. In this review article, we have briefly discussed chordoma's pathophysiology, diagnosis, and treatment options.

Keywords: Cancer; Chordoma; Chordoma Diagnosis; Chordoma Risk Factors; Chordoma Treatment

INTRODUCTION:

Cancer is a well-defined disease developed due to the uncontrolled growth of cells and these cells spread into nearby tissues or other parts of the body. These cells form tissue which are further termed as tumors. These tumors may be noncancerous (benign) or cancerous (malignant tumors). Cancer can develop in any part of the body, and it spreads to other parts of the body by metastasis. These are solid tumors and blood cancers like leukemias. There are more than 100 types of cancers and these are generally termed based on the origin organ like lung cancer, breast cancer, and blood cancer, etc. Some other categories are also made to classify cancer such as carcinoma (cancer of epithelial cells like adenocarcinoma, basal cell carcinoma, Squamous cell carcinoma, Transitional cell carcinoma), sarcoma (developed in soft tissues, bones like osteosarcoma), leukemia (cancer in blood forming tissue), lymphoma (cancer developing in lymphocytes; Hodgkin lymphoma, Non-Hodgkin lymphoma), multiple myeloma (cancer developing in plasma cells), and melanoma (cancer developing in melanocytes) (Fig. 1). Other types of tumors are germ cell tumors, neuroendocrine tumors, and Carcinoid tumors (NIH: What is cancer, 2021). Though, benign tumors do not invade nearby tissues, but these cancers can be life-threatening; for example, the cancers of the benign tumors of the brain. These cells are found to have many mutations due to which cancers are also termed as genetic diseases. These mutations in cancerous cells may be developed during cell division, or by other factors such as ultraviolet radiation. The main types of genes associated with cancer are tumor suppressor genes, proto-oncogenes, and DNA repair genes.

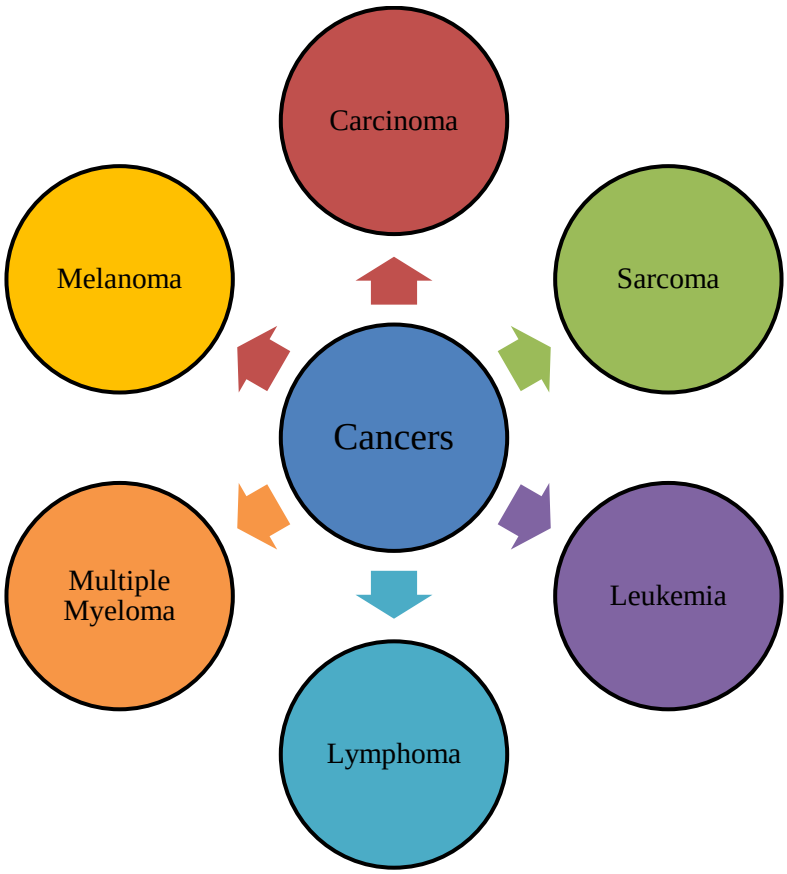

Fig. 1: Different categories of cancers

Chordoma which is also known as notochordal sarcoma is a type of slow-growing cancer of tissue (NIH: Chordoma, 2019). It is a low-grade, but locally invasive and aggressive type of sarcoma with poor prognosis (Walcott et al., 2012). These are developed by remaining of the notochord and developed along the midline spinal axis situated between the clivus and the sacrum (Tenny and Varacallo, 2023). It is most often found near the tailbone which is known as a sacral tumor or at the base of the skull which is known as clival tumor (NIH: Chordoma, 2019).

GENERAL DESCRIPTION OF CHORDOMA:

World Health Organization (WHO) recognized chordoma of three types such as; classic/conventional chordoma, dedifferentiated chordoma, and poorly differentiated chordoma (Cleveland Clinic: Chordoma, 2022; Fletcher et al., 2020). Out of these, conventional chordoma is the common type, while poorly differentiated chordoma is a rare type of chordoma and is characterized by deletion of *SMARCB1*, or *INI1* (Cleveland Clinic: Chordoma, 2022). Conventional chordomas are also suggested to have the characteristic feature of the absence of cartilaginous or additional mesenchymal structures. Moreover, both chordomatous and chondromatous properties are observed in chondroid chordomas (Chugh et al., 2007). Although skull base chordoma and chondrosarcoma have similarities in clinical presentation, anatomic site, and radiologic outcome, but based on origin and histology, the chordoma and chondrosarcoma are different (Almefty et al., 2007).

Chordomas grow very slowly, and most people are diagnosed with chordoma in their 50s and 60s. It is also found that sacral chordomas are about 50%, skull base chordomas are about 35%, and 15% are found in the vertebral bodies of the mobile spine (Fig. 2; Tenny and Varacallo, 2023). However, the detailed mechanism of development of chordoma is not well-understood, but scientific studies have demonstrated several chromosomal and cell cycle aberrations that are considered associated with chordomagenesis. The overexpression of both CDK4 and p53 has been observed in some chordomas and it is correlated with reduced overall survival (Yakkioui et al., 2014). Some

other genes also have been found associated with chordoma such as brachyury, PTEN, and CDKN2A, etc. (Gulluoglu et al., 2016; Yang et al., 2020), but no definitive marker has been identified. Chordomas are developed from notochord remnants (Williams et al., 2013). Molecular signaling pathways include platelet-derived growth factor (PDGF), receptor tyrosine kinase (RTK) pathway mediated by PI3K/Akt and mTORC1 (Tamborini et al., 2006).

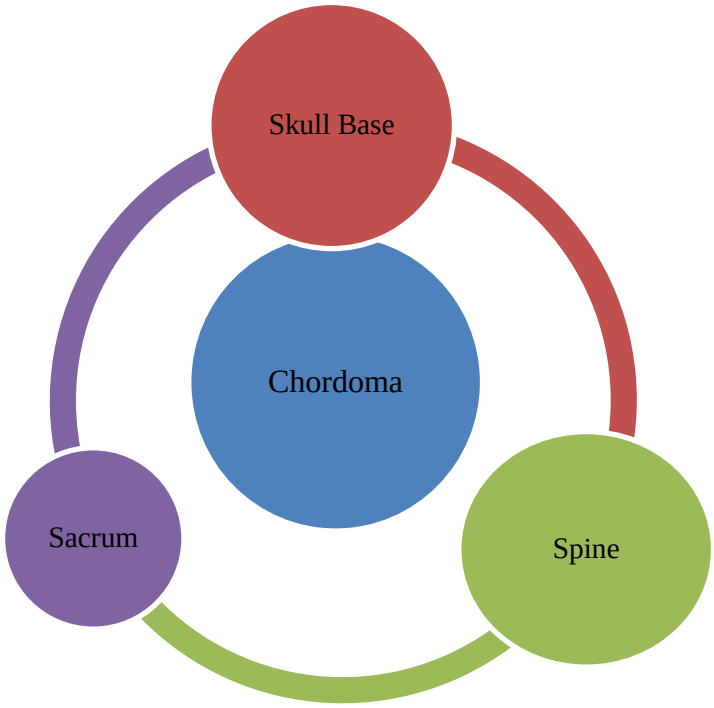

Fig. 2: Different locations of chordoma

Pathogenesis of Chordoma:

The pathogenesis of chordoma has not been fully elucidated (Sun et al., 2015). However, molecular biology studies have revealed the role of brachyury in the development and progression of chordoma cells. Additionally, researchers are identifying signaling pathways that are associated with chordomagenesis. Chordomas are developed from remnants of the notochord (Chauvel et al., 2005; Williams et al., 2013), and notochord cells express characteristic genes. Brachyury is a transcription factor encoded by T, which is a member of the T-box gene family. The T-box genes express a family of transcription factors. Brachyury plays an important role in the formation and differentiation of posterior mesoderm and the development of notochord development in the embryo (Barresi et al., 2014; Herrmann et al., 1991; Showell et al., 2004). Vujovic et al. (2006) revealed that brachyury acts as a specific marker for the notochord and tumors derived from it (Vujovic et al., 2006). Similarly, the role of differential expression of brachyury was reported in chordoma (Romeo and Hogendoorn, 2006). In other studies, this gene has also been recognized as a biomarker that plays a key role in the development of chordoma, and it is also being evaluated as a therapeutic target (Nibu et al., 2013). Presneau et al. (2011) demonstrated the chromosomal aberrations causing gain of the T locus were found associated with sporadic chordomas and expression of this gene plays a key role in *in-vitro* proliferation of chordoma cells (Presneau et al., 2011). Shalaby et al. (2011) reported the role of epidermal growth factor receptor (EGFR) in chordoma pathogenesis (Shalaby et al., 2011). Histologically, notochordal tissue is suggested behind the development of chordomas. Genomic studies also identified recurrent mutations in PI3K signaling pathways and chromatin remodeling genes (Desai et al., 2024).

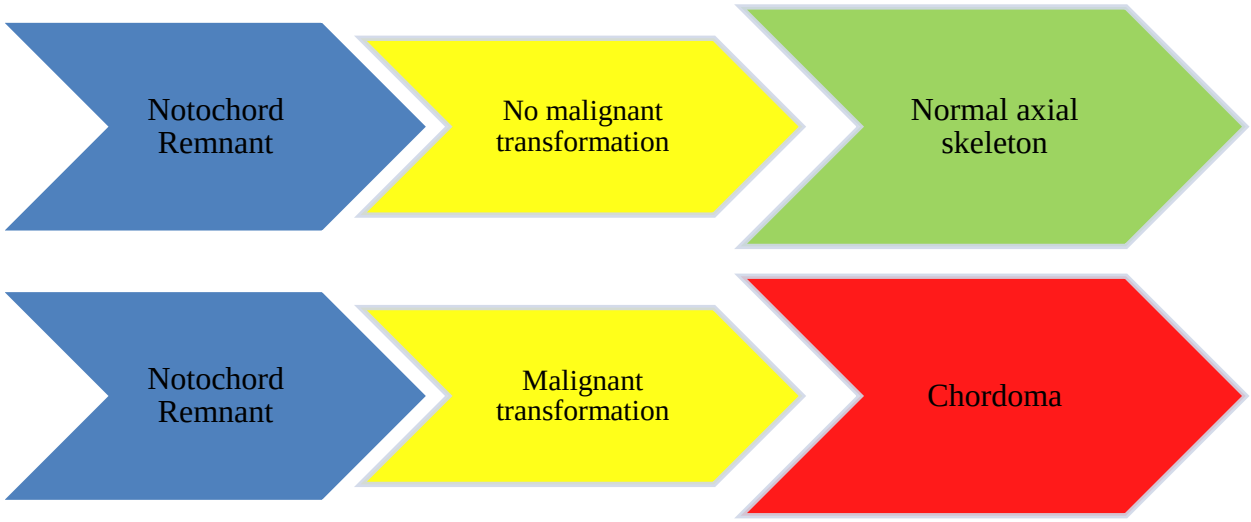

Fig. 3: Development of normal axial skeleton and chordoma from notochord remnant (Sun et al., 2015).

Epidemiology of chordoma:

Chordomas are rare bone tumors developing from remnants of the embryonic notochord. It is also found that elderly males have more incidences of this disease. As per Chordoma Foundation, chordomas contribute approximately 20 percent of primary spinal tumors and about 3 percent of all bone tumors. Bakker et al. (2018) reported that incidence-incidence rates of chordoma are ranged between 0.18 and 0.84 per million individuals per year and the cases also vary between countries and between races. It was also observed that most patients were diagnosed in their late fifties with male predominance (Bakker et al., 2018). Wedekind et al., (2021) reported about 350 incidences of chordoma every year in the USA (Wedekind et al., 2021). It was found that in the USA from 2004 to 2014, a total of 3670 chordomas were identified. Out of these, the common location was cranial (38.7%), sacral (34.3%) and spinal (27.0%) (Das et al., 2020). This study also revealed that in the USA, every year about 0.088 chordoma cases are newly diagnosed per 100,000 individuals, with cranial location being the most common. Including this, men are found at higher risk than women. Another study also reported the overall incidence of extracranial and intracranial chordomas as 8.4 out of 10 million population with a median overall survival of 7.7 years. (Smoll et al., 2013). Ullah et al. (2024) reported that chordomas are more common in white males appearing between the 5th and 6th decades of life. It was also reported that other factors contributing to worse prognosis were American Indian, Asian, Pacific Islander, or Alaska Native races (Ullah et al., 2024).

Risk Factors:

According to the Chordoma Foundation, there are no known lifestyle, dietary, or environmental factors associated with Chordoma (Chordoma Foundation: Chordoma, 2024). Moreover, it is also suggested that Chordoma is developed at random and several genetic factors are associated with chordoma. It is also found that SNP in a gene called brachyury is associated with 95% of chordoma cases. It is also observed that chordomas have been identified in children with a higher incidence having Tuberous Sclerosis Complex (TSC). The mutations in any of two genes involved in the Tuberous Sclerosis Complex (*TSC1* and *TSC2*) may be associated with chordoma (Chordoma Foundation: Chordoma, 2024). Moreover, mutations in the *TBXT* gene are also found to be involved in the development of chordoma (Cleveland Clinic: Chordoma, 2022).

Symptoms:

Chordoma is also a growing tumor, and it can press on the spine, brain, and their associated nerves. In some cases, a noticeable lump or mass may be experienced at the site that may lead to pain and nerve problems. The general symptoms include pain and neurological changes. Some activities develop such as; tingling, numbness, visual complications, difficulty in swallowing, and memory disturbance in rare cases (Chordoma Foundation: Chordoma, 2024; Cleveland Clinic: Chordoma, 2022). The clinical representation is based on the anatomical location of the chordoma (Ulici

and Hart, 2022). It is found that patients with sacral chordomas may report urinary and/or bowel dysfunction, neuropathy, and back pain, while clival chordomas may be present with headaches, diplopia, or dysfunction of other cranial nerve (Wedekind et al., 2021).

DIAGNOSTIC METHODS:

The chordoma typically affects individuals of 40-60 age, but these are also reported in young individuals (Tenny and Varacallo, 2023). The diagnosis depends on a variety of factors such as age, chordoma type, chordoma size, and location. Common diagnostic methods include imaging using X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and biopsy. In some cases, positron emission tomography (PET) scans may be used. Delayed months of diagnosis may be observed due to nonspecific symptoms, slow tumor growth, and clinician unfamiliarity with this rare disease (Wedekind et al., 2021). The Chordoma Foundation Medical Advisory Board also suggests that chordoma patients under 35 years of age, or cases with uncommonly fast-growing tumors, have their tumors tested for loss of INI1, by immunohistochemistry or genomic analysis.

Diagnosis by radiographic imaging:

The common imaging techniques used for evaluating the pathological state are CT and MRI. CT demonstrates the destruction of bone while MR imaging is used for soft tissue structures, visualization of blood vessels, and tumor margin from the brain. Chordomas are located more centrally, while most of the chondrosarcomas are present more laterally (Weber et al., 1994). Furthermore, in approximately one-third of cases occasional overlap was also observed (Weber et al., 1994). The chordoma is demonstrated as destructive and osteolytic lesions with associated cortical destruction and extension of soft tissue (Santegoeds et al., 2018). During CT imaging of chordoma, these appear in the form of midline, well-circumscribed, and expandable mass of soft tissue having lytic destruction of the surrounding bone (Barber et al., 2021). The low-density areas may be observed within the mass of soft tissue while analyzed by CT (Barber et al., 2021).

MR imaging is also suggested for both pre and post-treatment studies of intracranial chordoma (Erdem et al., 2003). Chordoma can have variable signal intensity on T1. Classic chordoma demonstrates high T2 signal intensity with heterogeneous hypointensity, which may also be linked with mucous, haemorrhage, and calcification (Meyers et al., 1992; Santegoeds et al., 2018). The presence of haemorrhagic foci or calcification can be further confirmed by other imaging techniques. It is also observed that less differentiated chordoma may exhibit different imaging features. According to the chordoma foundation, the chordoma is visualized efficiently by MRI with T2 weighted imaging.

Diagnosis by histological study:

Chordomas represent an infiltrating, lobulated low-power appearance, where lobules are separated by fibrous bands. Lobules comprise a nest, short chord, and single large epithelioid cells. The nuclear pseudo-inclusions may be observed. Extensive necrosis is also observed (Fletcher et al., 2020; Ulici and Hart, 2022). The Chordoma Foundation recommends the use of trocar CT-guided biopsy for sacral and mobile spine tumors. For skull base tumors, a biopsy is suggested during surgery.

TREATMENT APPROACHES FOR CHORDOMA:

Chordomas have clinical, histological, and radiographic properties. It is difficult to treat chordoma due to its location and recurrence. Improvements in imaging technology have increased the early diagnosis and anatomic localization of tumors. Including this, chordoma is also found poorly responding to conventional chemotherapy and radiotherapy, which is creating challenges to treat chordomas (Barber et al., 2021).

The development of novel and effective therapies is positively influencing the control of disease and the quality of patients' lives. Patients with advanced stages of chordoma require systemic treatment (Colia and Stacchiotti, 2017). Multimodality therapy like surgery and spinal cord-sparing radiation therapy may offer good tumor control (Healey and Lane, 1989). The important therapy procedure involves surgery to remove the tumor. For the treatment of chordoma, En bloc resection has been recommended as the gold standard while radiation-based therapy demonstrated both therapeutic and palliative advantages (Colia and Stacchiotti, 2017). Unluckily, even after surgical procedures, local recurrences are also generally observed (Colia and Stacchiotti, 2017; Lebellec et al., 2015). Walcott et al. (2012) also suggested the en-bloc excision with wide margins and postoperative external-beam radiation therapy as the gold standard treatment for chordomas of the sacrum and mobile spine. Chordoma often leads to significant pain and discomfort. To address these challenges, pain management strategies, such as medication regimens and physical therapy, can be incorporated into the patient's treatment plan. Moreover, the provision of comprehensive supportive care, which includes both physical and emotional assistance, plays a key role in enhancing the overall quality of life for chordoma patients. Though, surgery is the main approach for chordoma management, but some advanced techniques are also being used for the

treatment such as heavy-particle beam therapy, targeted molecular therapy, and genetic therapy (Connors et al., 2020). It is also found that molecular targeted therapies such as the use of imatinib may reduce the growth of tumors but more clinical studies and more reports are required to reach a conclusion (Lebellec et al., 2015).

However, research and development related to the molecular pathophysiology of chordoma have identified several pathways that may serve as potential targets for molecular therapy (Barber et al., 2021). It has been suggested that inhibition of products of both T (brachyury homologue) and EGFR genes may be a potential therapeutic strategy (Dei Tos, 2011). Notably, Ghaly et al. (2016) highlighted the addition of EGFR inhibitors with a MET inhibitor as the potential approach for chordoma treatment.

FUTURE DIRECTIONS:

Following the completion of treatment, patients typically require long-term monitoring to rule out any potential recurrence or progression of the disease. Regular imaging procedures, such as MRI or CT scans, are commonly employed to assess the tumor's status and its response to the treatment regimen.

As the driving forces behind the chordoma are not well explored, hence biochemical, molecular, and imaging studies are required to fill the knowledge gap. Including this, imaging may be important in distinguishing between slow-growing and fast-growing lesions, and imaging methods will play a key role in treatment planning and analysis of current treatment strategies. Molecular imaging studies of chordoma with PET-CT are limited but these studies are expected to be crucial in the future (Santegoeds et al., 2018). Furthermore, more molecular studies will provide more insights into understanding the pathogenesis of chordomas and the identification of new targets for the treatment.

CONCLUSION:

Chordoma is an exceptionally rare and complex type of bone cancer originating from residual notochord cells. Moreover, its intricate connection with vital body structures makes treatment challenging. Chordoma manifests through various distressing symptoms, including pain, nerve complications, and other associated issues. The diagnosis involves the use of imaging techniques such as MRI and confirmation via biopsy, as chordoma cells closely resemble notochord cells.

Early diagnosis, appropriate therapies, and comprehensive patient care will result in better outcomes and improved quality of life for patients. The effective management of chordoma may be performed by a multidisciplinary approach. The primary approach is surgery that is aimed at tumor removal without compromising the critical structures. Moreover, innovative techniques like endoscopic surgery are also suggested as less invasive alternatives with enhanced efficiency. Furthermore, radiation may also be used prior or post-surgery. Furthermore, pain management and supportive care play important roles in chordoma management. Though chordoma remains a formidable medical challenge, research outcomes are enhancing the understanding of the disease, and paving the way for efficient treatment approaches.

Conflicts of Interest: No

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