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Chondroma/Chondrosarcoma of the Spine

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Chondromas and chondrosarcomas are rare primary spine tumors. These mesenchymal, cartilage-forming neoplasms comprise a heterogeneous group of benign and malignant tumors. Unlike most other sarcomas, a chondrosarcoma's grade has prognostic significance. The treatment of choice is complete en bloc resection, as conventional chemotherapy and radiotherapy are ineffective.

Chondroma

Epidemiology

Chondromas comprise approximately 5% of all primary bone tumors [1]. These cartilaginous tumors mainly occur in the small bones of the hands and feet, but every bone is susceptible. Chondromas rarely affect the spine, and fewer than 4% originate within the vertebral column [2]. Chondromas have been noted to arise from a muscle tendon or synovial sheath [2]. Men are twice more likely to have a chondroma than women, and lesions typically present between the third and fifth decades of life [3].

Pathophysiology

Chondromas can be labeled according to their site of origin. This includes the medullary cavity (enchondroma) and the cortical surface (periosteal chondroma) [4]. Enchondromas tend to produce an expansile growth pattern, whereas periosteal chondromas are exophytic. Any part of the vertebra can be affected, including the spinous process, lamina, pedicles, and body. A review of three cervical chondromas revealed exclusive involvement of the posterior elements, although other series have reported a more generalized distribution within the vertebra [5]. The thoracic region may be slightly more susceptible to chondromas than other regions of the spine [2].

Evaluation of the patient

Patients presenting with spinal chondromas typically complain of local tenderness at the site of the tumor. There may be a palpable mass present, because the tumor expands into the surrounding paraspinous tissues [1]. Chondromas are slow-growing tumors, and neurologic symptoms and signs may develop gradually. A radiculopathy or myelopathy can result from direct neural compression [2]. Chondromas have caused widening of the neural foramen and impingement of the exiting nerve [4]. Occasionally a pathologic fracture occurs in the affected bone. In a review of 11 chondroma patients, Gaetani and colleagues [5] noted that the mean duration of symptoms before diagnosis was 13.8 ± 3.4 months.

Chondromas usually occur as isolated lesions. The presence of multiple chondromas suggests the presence of a multiple chondromatosis syndrome, namely Ollier disease or Maffucci syndrome [6]. These are rare conditions that present with multiple chondromas in childhood. Their etiology is unknown, although multiple somatic mutations may have a role in development [7]. Multiple chondromas occur throughout the skeleton,

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causing skeletal deformities, limb-length discrepancies, and pathologic fractures. Maffucci syndrome is differentiated from Ollier disease by the presence of cutaneous hemangiomata [8].

Compared with patients who have an isolated tumor, the chondromas in Ollier disease or Maffucci syndrome have a much higher risk for undergoing sarcomatous degeneration. This risk may be as high as 25% [9]. Although the incidence of malignant degeneration for isolated chondromas is low, it is impossible to predict which patients are at risk. All patients require a careful assessment and should undergo complete resection if possible. A (9;12)(q22;q24) translocation has been associated with the malignant degeneration of a chondroma [10].

Imaging

The features of a chondroma on plain radiography may be subtle, and a CT scan is usually necessary to visualize the pathology. A plain film may demonstrate a well-circumscribed, lytic lesion without reactive sclerosis [1]. Local deformity may occur, and the neural foramen may be wide if the tumor is intraforaminal [4]. A CT scan on a bone setting reveals a radiolucent, erosive lesion. Cartilage appears as regions of low attenuation on CT scan. Stippled patterns of calcification may be present [11]. An MRI is useful to help distinguish between benign and malignant lesions [5]. An enhancing cartilaginous tumor on MRI is more likely to be consistent with a chondrosarcoma [2]. Rarely these tumors erode through the dura and mimic an intradural lesion. Radiologically differentiating between a chondroma and a low-grade chondrosarcoma can be challenging.

Pathology and genetics

Grossly, chondromas resemble lobules of firm, mature cartilage [2]. These tumors are well-circumscribed from the adjacent bone. Regions of grittiness signify mineralization of the matrix. Chondromas are typically small tumors, and a diameter greater than 7 cm in diameter is suggestive of malignancy [12]. Histologically they are comprised of neoplastic chondrocytes dispersed within an abundant hyaline or myxoid background. The tumor cells may be arranged in sheets or rows that alternate between regions of relative hypo- and hypercellularity. The tumor cells are small and do not exhibit cellular pleomorphism or nuclear atypia [13]. Multinucleated cells are rare, and mitoses are absent. Foci of calcifications may be present. It is of critical importance to histologically examine the entire specimen, because sarcomatous cells may occupy just a fraction of an otherwise benign tumor [9,14].

Although cytogenetic aberrations may not be detectable for some tumors, nonrandom genomic abnormalities have been linked to chromosomes 4, 5, 6, 7, 12, and 15 [15]. Monosomies of chromosomes 9, 19, and 22 have been reported, as have 12q13-15 rearrangements [16,17]. An (8;17)(q23;p13) translocation was observed in one patient [17]. Other genomic abnormalities include alterations of chromosomes 6 and 11 [18]. Most chondromas grown in cell culture, however, do not exhibit chromosomal aberrations [16]. This is in contrast to chondrosarcomas, which consistently demonstrate complex mutations. c-Myc oncogene amplification and polysomy 8 has been associated with malignant transformation of a chondroma into a dedifferentiated chondrosarcoma [12,19].

Treatment

The management of chondromas is surgical. Resection is used to establish a histologic diagnosis, prevent sarcomatous degeneration, and preserve neurologic function [2]. A CT-guided biopsy should be performed with reservation, because sampling errors may lead to the false-positive diagnosis of a benign tumor [9,14]. This is because of the tumor's cytoarchitecture; a malignant focus may be isolated to just a small region of the neoplasm. In general, a complete excision of the lesion is recommended [1]. The entire specimen should be histologically examined for areas of malignant degeneration. Following complete resection of a chondroma, the recurrence rate is less than 10% [2].

Chondrosarcoma

Epidemiology

Chondrosarcomas are malignant cartilage-forming tumors. Chondrosarcomas are extremely rare; the number of spinal chondrosarcomas registered at the M.D. Anderson Cancer Center over a period of 43 years numbered only 21 [20]. Chondrosarcomas comprise 7% to 12% of all primary spine tumors and account for 25% of primary malignant spine neoplasms [9,21]. There is a clear male predilection, with a ratio of 2 to 4:1. The age at diagnosis is usually between 33 and 51 years, which varies depending on the chondrosarcoma subtype [21]. Chondrosarcomas can

occur anywhere along the mobile spine, although there is a bias toward the thoracic spine. Up to 60% of tumors arise in the thoracic region, and the remaining lesions are asymmetrically divided between the lumbar spine (20%–39%) and cervical spine (19%–20%) [22].

Presentation

Chondrosarcomas have an indolent growth pattern, and symptoms may present gradually. The most common symptom is focal pain [20]. Neurologic deficits are common, which can manifest as a radiculopathy, myelopathy, or cauda equina syndrome [23]. Up to half of all patients have a neurologic deficit at the time of presentation [22]. A palpable mass may be present in the neck or back as the tumor expands outward from the posterior elements.

Pathology

The World Health Organization (WHO) defines chondrosarcomas as mesenchymal, non-meningothelial tumors [13]. A grading system is used by the WHO that ranges from low-grade (grade I) to high-grade (grade IV) tumors. The grade is based on histologic features, such as tumor cellularity, nuclear atypia, stromal content (ie, chondroid or myxoid), and mitoses. The WHO grade is one of the most important prognostic features of a chondrosarcoma [22]. The 10-year survival for a grade I chondrosarcoma is 90%, which declines to 65% to 80% for grade II tumors. The 10-year survival of a high-grade chondrosarcoma is 30% to 40% [22].

Grade I chondrosarcomas closely resemble chondromas, and it may be difficult to differentiate between these two entities on pathology. Both of these tumors resemble mature cartilage on microscopy. Distinguishing features of low-grade chondrosarcoma include invasion or entrapment of surrounding tissues, penetration of the bony cortex, and a prominent myxoid stroma [9]. Grade I chondrosarcomas may have calcifications that coalesce to form discrete islands of bone. The neoplastic cells are small and exhibit little nuclear atypia. Mitoses are absent [24]. The presence of a predominantly myxoid stroma increases the tumor grade to grade II. A grade II lesion also exhibits a relative increase in cellularity as compared with grade I tumors and demonstrates greater nuclear pleomorphism. Mitoses may rarely occur in grade II lesions [22].

Grade III and IV lesions are increasingly cellular and pleomorphic compared with lower-grade tumors. The neoplastic cells are often multinucleated with prominent nucleoli. There are at least two mitotic figures per 10 high-power fields [22]. As the cellularity increases, the amount of background substance decreases. This produces a soft, friable tumor in contrast to the hard cartilaginous matrix of a low-grade lesion. It is vital to histologically examine the entire tumor, because pockets of high-grade tumor may reside within a low-grade chondrosarcoma [25]. The higher the grade, the more likely that metastases occur; grade I chondrosarcomas do not metastasize, whereas 70% of grades III and IV tumors do [22].

In addition to a WHO grade, chondrosarcomas are classified into several subtypes based on stereotypic histologic features [9]. Subtypes include the conventional, mesenchymal, clear cell, and dedifferentiated categories. The tumor's origin (ie, primary or secondary etiology), imaging features, pathology, and immunohistochemistry profile is unique to each subtype.

Conventional chondrosarcomas comprise 80% to 90% of the chondrosarcoma subtypes. Almost all of these tumors are low grade, and less than 10% are grade III or IV lesions [26]. These are lobulated tumors that demonstrate lytic extension into the surrounding bone. Low-grade conventional chondrosarcomas may produce a stroma resembling mature cartilage, similar to that of a chondroma [25]. Calcifications may be present. Conventional chondrosarcomas can arise from normal bone (a primary chondrosarcoma) or from a pre-existing benign cartilaginous or osseous tumor (a secondary chondrosarcoma) [24]. Conventional chondrosarcomas originate from within the medullary cavity or cortical surface. These tumors are reactive to vimentin and S-100, which are often reactive in other low-grade chondrosarcoma subtypes [9].

Dedifferentiated chondrosarcomas occur in the setting of malignant degeneration of a conventional, low-grade chondrosarcoma [27]. This manifests histologically as an abrupt shift in the microscopic appearance of the lesion. Specimens demonstrate a clear demarcation between the low- and high-grade areas [26]. Dedifferentiated chondrosarcomas are notoriously aggressive and have a 5-year survival rate of less than 10%. Distal metastases are frequent [28]. These tumors may also harbor foci of neoplastic tissues resembling other sarcomas, including osteosarcoma, leiomyosarcoma, rhabdomyosarcoma, or malignant fibrous histiocytoma. These regions

have an immunoreactive profile indicative of the neoplasms' embryologic origin [22].

Similar to dedifferentiated chondrosarcomas, mesenchymal chondrosarcomas are comprised of two separate cell populations. Low-grade chondrocytes are interspersed among small, undifferentiated neoplastic cells [29]. These bimorphic collections lack the clear margins of dedifferentiated chondrosarcomas [30]. Which cell type predominates varies among specimens. In some instances, the undifferentiated small cells may express desmin and myogenin, suggestive of a skeletal muscle lineage [29]. Caution must be used when interpreting a CT-guided biopsy of a mesenchymal chondrosarcoma: a sample of low-grade tumor may lead to the incorrect diagnosis of a conventional chondrosarcoma. A patient who has a mesenchymal chondrosarcoma has a poor prognosis with a 5-year survival rate of 50% [22].

The final chondrosarcoma subtype, the clear cell chondrosarcoma, is characterized by dense collections of neoplastic cells that have abundant cytoplasm. This cytoplasm is rich in glycogen and strongly PAS-positive [31]. Each cell shares a discrete border with its neighbors. Lobules of cells are dispersed among bony trabeculae, and foci of conventional chondrosarcoma may be present. Necrosis can sometimes occur. These tumors are immunoreactive to S-100 [31]. In general, clear cell chondrosarcomas have a better prognosis than the mesenchymal or dedifferentiated chondrosarcomas [32].

Genetics

The cytogenetic abnormalities of chondrosarcomas have not been shown to correlate with outcome [33]. Various nonrandom genetic aberrations occur, and allelic losses occur in almost 70% of tumors [22]. The mutations responsible for the malignant degeneration of a chondroma may occur in a stepwise fashion, including amplification of the c-Myc oncogene. A gain of chromosome 8 may also occur [22,34]. Other genomic mutations include the loss of chromosome 6 and the gain of 12q12, which correlate with high-grade chondrosarcomas [35]. 6q13-21 chromosome aberrations also occur in aggressive tumors [36]. Medullary (central) chondrosarcomas may be diploid, whereas surface (peripheral) tumors may be aneuploid. Dedifferentiated tumors can have a (9;22)(q22-31;q11-12) translocation [34]. Dedifferentiated chondrosarcomas may also overexpress p53 [26]. The addition of chromosome 7 has been associated with high-grade lesions, as have 17p1 alterations [35].

Aberrant platelet-derived growth factor receptor-α (PDGFRα) and PDGFR-β expression may occur in chondrosarcomas [22]. Estrogen hormone signaling, matrix metalloproteinsase-1 expression, histone dysregulation, and methylthioadenosine phosphorylase (MTAP) deletions have also been recently discovered [22]. The blood supply of the tumor may result from vascular endothelial growth factor (VEGF)-A overexpression [22]. Research is underway to explore the possibility of exploiting these proteins and their receptors as targets for novel chemotherapeutics [37,38].

Imaging

The radiologic assessment of chondrosarcomas includes the use of plain films, CT scans, MRI, and bone scans. Specific imaging features can suggest a particular chondrosarcoma subtype [11]. Once a lesion is noted on plain film, a CT scan should be used to define the tumor's location and characterize its growth. These studies often reveal a lytic, destructive lesion of varying density. Alternatively, focal expansion of the bone could occur. A peripheral chondrosarcoma may produce thickening of the vertebral cortex with exophytic extension into the soft tissue [33]. The water content of the cartilage matrix appears as a focus of low attenuation on CT [11]. A clear cell chondrosarcoma may have a rounded, lytic lesion with calcifications and surrounding sclerosis [31]. Dedifferentiated and mesenchymal chondrosarcomas may demonstrate frank destruction of local bone [34]. So-called "ring and arc" calcifications are suggestive of the chondroid matrix of a conventional chondrosarcoma [11].

MRI is useful to assess the extent of soft-tissue invasion. T1-weighted images often demonstrate a hypointense lesion, whereas T2-weighted images are hyperintense. This high-intensity signal results from the high water content of neoplastic cartilage [11]. Mineralization appears as a low signal. Intravenous gadolinium can reveal a peripheral ring of enhancement or heterogeneous enhancement of the entire tumor (Fig. 1). A bone scan often demonstrates increased uptake of radiotracer in the vicinity of the tumor [11].

Treatment

Once a chondrosarcoma is suspected radiologically, the goal should be to excise the lesion as

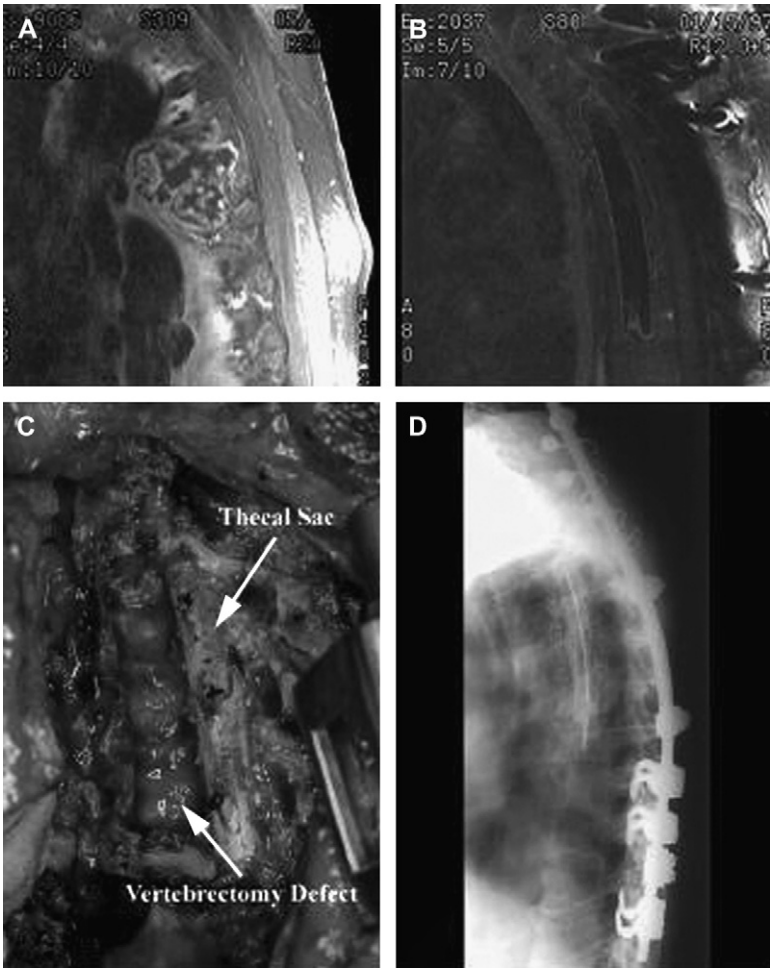

Fig. 1. (*A*) Preoperative T1-weighted with gadolinium MRI showing a heterogeneously enhancing chondrosarcoma of the thoracic spine. (*B*) Postoperative MRI following 3-level vertebrectomy. (*C*) Intraoperative photo of 3-level vertebrectomy from the anterior approach. (*D*) Lateral radiograph of instrumented construct with methylmethacrylate and posterior fixation. (*From* York JE, Berk RH, Fuller GN, et al. Chondrosarcoma of the spine: 1954 to 1997. J Neurosurg Spine 1999;90(1):73–8; with permission.)

completely as possible [28]. These tumors are resistant to conventional chemotherapy and radiation, and their role in treatment is limited. Nevertheless, high-dose radiotherapy or proton beam therapy may slow tumor progression. This may be useful for tumor recurrence and palliation [39,40]. Hypofractionated stereotactic radiation therapy has provided some evidence of a therapeutic response [41]. The long-term results of this treatment are unknown [40]. Novel radiosensitizers may hold some promise for improving the efficacy of these therapies [39].

A complete en bloc resection is the ideal surgical technique for resecting chondrosarcomas (see Fig. 1) [20]. This may be technically challenging to perform, but the use of en bloc vertebrectomy and spondylectomy has been associated with prolonged, recurrence-free survival [42–45]. Local curettage of a chondrosarcoma virtually guarantees recurrence [28]. Complete en bloc resections require careful planning, an experienced multidisciplinary team, and meticulous surgical technique [46,47]. It has been shown that even minor contamination of an en bloc specimen's margins with tumor heralds a worse prognosis [20]. Complete en bloc resections have resulted in recurrence rates of 20% or less, and in some instances survival of 5 years or longer [28]. Percutaneous CT-guided biopsies require careful interpretation. Given the heterogeneity of

chondrosarcoma cytoarchitecture, the false-negative rate for malignancy can approach 24% [14].

Local tumor recurrence portends a dismal prognosis, with more than half of patients dying from the disease in less than 2 years [9,48]. The role for aggressive surgical resection for local recurrence has yet to be defined, although Weber and colleagues [49] achieved a 50% long-term survival in 12 patients treated surgically for recurrent pelvic chondrosarcomas. It remains to be seen if this translates into improved survival rates for recurrent chondrosarcomas of the mobile spine. Although metastases can occur with chondrosarcoma, local recurrence is a stronger negative prognostic factor [48].

Summary

Chondromas and chondrosarcomas are rare primary vertebral column tumors. Chondromas are benign, minimally-cellular lesions that histologically resemble mature cartilage. These slow-growing tumors erode adjacent bone and are lytic on radiographs. Focal pain and progressive neurologic deficits are common presenting symptoms. To achieve long-term local control, these lesions must be completely resected. Rarely a chondroma undergoes malignant degeneration. Patients at risk for sarcomatous transformation include those who have multiple chondromatosis syndromes.

Chondrosarcomas are the malignant forms of these cartilage-forming tumors. Chondrosarcomas are subcategorized by histology and graded using WHO criteria. A tumor's grade is the most important prognostic factor affecting survival. Neurologic deficits are frequently present at diagnosis. Imaging reveals local bone destruction and soft-tissue invasion, especially when the tumor is high grade. Metastases can also occur with chondrosarcomas. These tumors are resistant to adjuvant chemotherapy and radiotherapy. A complete en bloc resection offers the best chance of a prolonged, recurrence-free survival.

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