



High-Grade Chondrosarcoma Arising from Synovial Chondromatosis: Case Report and Review of the Literature

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Abstract

Synovial chondromatosis (SC) is a rare, locally aggressive, benign tumor that presents as a lobulated bundle of hyaline cartilaginous nodules in the joint spaces, sub-synovial tissue, or tenosynovium. SC mainly affects large joints, particularly the knee joint. Although malignant transformation of SC to chondrosarcoma (CS) is possible, only a few cases have been reported. Radiologically, SC can present as an aggressive benign tumor, and adequate tissue sampling is essential for a proper diagnosis in cases of malignant transformation. Insufficient tissue biopsy sampling may miss the transformed malignant areas, resulting in a diagnosis of a benign cartilaginous tumor and inadequate patient management. We report a case of intermediate to high-grade chondrosarcoma occurring in the background of synovial chondromatosis. We also review the current literature on SC and CS and discuss the pathophysiology of the malignant transformation.

Introduction:

Synovial chondromatosis (SC) is a rare, benign condition of unknown etiology in which the synovium undergoes metaplasia, leading to cartilaginous nodules that ultimately break free, mineralize, and even ossify.¹ This occurs without signs of malignant transformation or any direct relationship with trauma or inflammatory processes. The most involved joint is the knee. Patients may be asymptomatic or may present with pain, swelling, and a limited range of motion.¹ Chondrosarcomas (CS) constitute a heterogeneous group of primary bone malignancies characterized by hyaline cartilaginous neoplastic tissue. They are the second most common primary bone malignancy. Most CS are conventional CS; most conventional CS are low- to intermediate-grade tumors (grade 1 or 2) with indolent clinical behavior and low metastatic potential.² These are uncommon tumors, representing 20% of primary osseous malignancies with an estimated incidence of 1:200,000.² Chondrosarcomas are defined histologically by the production of a non-osteoid cartilage matrix by neoplastic cells, with primary CS stemming from sporadic mutations and secondary CS from malignant transformations of benign cartilaginous lesions, such as osteochondromas or enchondromas.¹

Few reports detailing the natural history of synovial

chondromatosis exist, although malignant transformation to SC is recognized as a rare event, with reports estimating the incidence to be 1–5%. It is recommended that any rapid deterioration in the patient's clinical course, including worsening pain or aggressive recurrence, should be regarded as suspicious and treated at, or referred appropriately to, a tertiary hospital familiar with managing these often complex cases. We present the case of a 39-year-old man who presented with chondrosarcoma arising from synovial chondromatosis, and we review the pertinent literature.

Case Presentation:

A 39-year-old man reported right pelvic pain lasting for three years, recently increasing in intensity. The patient is a professional wrestler and reported multiple traumas to both knees. No family history or significant personal history was reported. Imaging studies, including X-rays, showed moderate loss of joint space, popcorn-like calcification in the soft tissue, and lytic changes in the right femoral neck (Figure 1A). MRI studies of the right knee demonstrated a heterogeneously high signal intensity mass on the T2-weighted images and low to isointense signal intensity lobulated mass on both sides of the joint on the T1-weighted images compared to those of the adjacent

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muscles. The images taken after gadolinium contrast administration showed heterogeneous and septal enhancement. Imaging studies were suspicious of a malignant process, and tissue diagnosis was recommended. Biopsy of the mass was not diagnostic, showing only benign cartilaginous proliferation, but the pathology report recommended additional tissue sampling as the findings were inconsistent with the worrisome imaging features. A repeat biopsy with adequate tissue sampling showed a cartilaginous tumor with mixed benign and malignant features. A multidisciplinary tumor board meeting recommended a total right hip arthroplasty.

Microscopic examination showed well-developed benign cartilaginous mass areas consistent with chondromatosis, merging with more cellular areas composed of atypical malignant chondrocytes compatible with chondrosarcoma (Figure 1B). The benign areas showed multinodular cartilaginous proliferation, with clusters of chondrocytes showing minimal atypia and increased cellularity. Focal calcification and areas of endochondral ossification were also identified. These features were diagnostic of synovial chondromatosis (Figure 1C). The malignant areas showed a cartilaginous mass with clones of chondrocytes that presented small bland nuclei and other very cellular areas with prominent cellular atypia, myxoid change, and necrotic chondrocytes eroding and pushing through the bone into the marrow with permeative pattern. These features were diagnostic of chondrosarcoma grade II-III (Figure 1D). Immunohistochemistry studies were not required, and a final diagnosis of unusual chondrosarcoma (Grade II-III) arising in a background of synovial chondromatosis was rendered. The presence of well-identified areas of benign chondromatosis merging with well-defined areas of chondrosarcoma confirmed the given diagnosis. No post-operative treatment was provided. The patient was followed for seven years without evidence of recurrence or metastasis.

Discussion:

Synovial chondromatosis (SC) is a benign neoplastic process that causes several cartilaginous hyaline loose

bodies in the synovial tissue of a joint, tendon sheath, or bursa.³ The nodules may enlarge and detach from the synovium, creating free-floating loose bodies in an affected joint.⁴ The disease was first described by Leannac in 1813; however, its current description was not applied until 1958 by Jaffe.⁵⁻⁶ The knee and the hip are the most common sites affected by synovial chondromatosis. This condition affects adult males more often, with a mere 2:1 ratio compared to their female counterparts.³

Patients between 30 and 50 are commonly affected by this condition and usually present with localized pain, stiffness, and swelling.¹ Diagnosis is made based on the stage at the onset of symptoms. Early disease needs magnetic resonance imaging (MRI) to detect cartilaginous nodules, but radiographs can detect nodules throughout a joint space or tendon sheath for the late stage of the disease. A rare complication of synovial chondromatosis is malignant transformation to chondrosarcoma. As for SC of the hip, treatment options include open or arthroscopic surgical removal of loose bodies with or without synovectomy and conservative management.⁷⁻⁸ However, arthroscopic removal of loose bodies provides a more definitive result as there can be no significant improvement or decrease in the risk of recurrence with conservative management.^{1,8} A total hip replacement may be preferable for older patients due to hip joint osteoarthritis, but a synovectomy for evacuation of loose bodies is recommended for younger patients.⁹ Currently, no non-surgical alternative treatment is advocated for managing synovial chondromatosis.⁴ In addition, it is extremely rare for synovial chondromatosis to malignantly transform into chondrosarcoma, as it tends to occur in patients with long-standing disease and recurrences.¹⁰ A retrospective study investigating outcomes of hip arthroplasty for management found that the 15-year disease-free survival rate was 89% compared to a mean recurrence rate of 7.1% after arthroscopic removal of loose bodies and synovectomy.¹¹ Up to 23% of cases of primary synovial chondromatosis have been found to recur locally even after appropriate surgical debridement.¹² Finding the benign recurrences is

where the challenge lies. The histological findings in SC are variable, but the degree of cellularity is generally striking. The Cartilage is hypercellular with plump hyperchromatic nuclei and binucleate forms that would be interpreted as malignant if the Cartilage occurred within a bone. Despite the cellularity of chondromatosis, individual chondrocytes often have a definite pattern characterized by arrangement into micronodular clones. Conversely, histological characteristics that support chondrosarcoma include chondrocyte necrosis, matrix myxoid transformation, and loss of chondrocyte micronodularity. The most trustworthy histological indicator is Cartilage, which has penetrated the bone and extended into the bone marrow.¹³

Chondrosarcoma (CS) is a bone tumor that originates in chondrocytes. Primary or conventional chondrosarcoma arises in preexisting normal bone and is distinguished from the rarer secondary tumors in preexisting enchondroma, osteochondroma, or other benign conditions.¹⁴ CS is the second most common malignant primary bone tumor after osteosarcoma that commonly manifests in populations 40 - 70 years of age.¹⁵ The most common locations affected are the pelvis, proximal and distal femur, proximal humerus, distal tibia, and scapula. Possible risk factors for CS include patients with inherited gene mutations and genetic disorders.¹⁴ Primary synovial chondromatosis has no potential to spread, even though it might be locally aggressive and have a tendency to recur. For symptomatic primary synovial chondromatosis, partial synovectomy or cartilaginous body removal are the available therapy options. Chondrosarcoma, on the other hand, is a malignant tumor that calls for more intrusive surgery, such as amputation or radical excision, and it has been observed that up to 29% of cases eventually spread to other parts of the body.¹⁶ As a malignant cartilaginous tumor, the primary management for conventional chondrosarcoma is complete surgical resection with a wide margin, as they are generally considered resistant to standard chemotherapy and radiotherapy.¹⁷ Aiming to define a 'wide margin,' a retrospective study that included 341 patients concluded that surgical margins ultimately

determine the local recurrence in all chondrosarcoma grades and that a minimum 4-mm margin should be met to ensure the best prognosis for a cure and local control.¹⁸ Chemotherapy regimens in treating chondrosarcoma typically include some form of a combination of cisplatin, doxorubicin, or ifosfamide, and high-dosed advanced radiation therapies are selective for those with tumors in surgically challenging locations or unexpected positive margins.¹⁹ As for prognosis, Grade I chondrosarcoma lesions are rarely metastasizing and recurring in nature, while Grade III chondrosarcoma lesions have a poor prognosis with the highest recurrence rates.¹⁵ At the 3-, 5-, and 10-year survival rates, respectively, Grade I came in at 96%, 93%, and 88%, Grade II was 82%, 74%, and 62%, and lastly, Grade III was 38%, 31%, and 26%.¹⁵

Differential diagnosis of intra-articular masses may include infectious granulomatous diseases, non-infectious synovial proliferative processes (synovial chondromatosis, lipoma arborescens, rheumatoid arthritis, pigmented villonodular synovitis [PVNS]), vascular malformations, deposition disorders, benign or malignant neoplastic conditions, and miscellaneous conditions.²⁰ Early imaging is essential in the early detection of synovial diseases to avoid the incidence of irreversible joint injury. Conventional radiography, high-frequency ultrasonography (US), and musculoskeletal magnetic resonance imaging (MRI) are used to diagnose synovial lesions and in follow-up. MRI is often done before arthroscopic procedures; management plans are usually based on MRI findings.²⁰ Chondrosarcoma displays diverse histopathology and clinical behavior. Clinical management is exceptionally challenging as they are inherently resistant to conventional chemo and radiation therapy. Therefore, new therapeutic approaches are urgently needed. Recent studies have suggested several promising biomarkers and therapeutic targets for chondrosarcoma, including IDH1/2, COL2A1, and PD-L1.²¹ Preclinical data indicate antitumor activity of IDH inhibitors in chondrosarcoma cell lines. New IDH inhibitors are being tested in early-stage clinical trials to see how well

they work in treating people with advanced solid tumors like chondrosarcoma with an IDH1 or IDH2 mutation. Research conducted in the last few years to clarify the molecular processes that underlie the development of chondrosarcoma has identified several novel treatment targets. While most of these targets showed significant antitumor efficacy in preclinical stages, early-phase clinical study findings have been inconsistent.²¹ Additional research should be done to learn how these molecularly focused candidate therapeutics might help the different types of people with chondrosarcoma. Many molecularly targeted therapeutics are being evaluated in clinical trials for chondrosarcoma patients to provide a more individualized and efficient course of treatment.²² In addition, clinical trials of patients with advanced chondrosarcoma have demonstrated excellent antitumor activity for several molecule-targeting drugs and immunotherapy. Additional research on the processes underlying tumor growth, invasion, migration, and microenvironment is necessary to find novel targets for chondrosarcoma treatment. Developing novel anticancer drugs and immunotherapy through basic research and clinical trials may aid in optimal chondrosarcoma treatments.²¹ In our case, the patient refused to perform any molecular studies.

It can be challenging to distinguish between SC and CS because both conditions present similar patterns of pain, edema, and restricted joint movement. Clinical and radiological criteria have been shown in numerous studies to be ineffective in distinguishing between the two disease processes since there is frequently substantial overlap and no distinguishing characteristic between the two.²³⁻²⁵ Evans et al. reviewed a large orthopedic oncology database in their institution and identified five cases of synovial chondromatosis that developed malignant transformation to chondrosarcoma. With their detailed review of these five cases, they concluded that not all patients with primary synovial chondromatosis require long-term surveillance to monitor for the development of malignant change; however, they recommend that any rapid deterioration in the patient's clinical course,

including worsening pain or aggressive recurrence, should be regarded as suspicious and treated at, or referred appropriately to, a tertiary hospital familiar with managing these often complex cases.²⁶ Given these findings, we encourage cautious monitoring of patients with numerous recurrences of synovial chondromatosis, particularly if the patient's pain is getting worse or if there are any aggressive or unusual imaging characteristics associated with the disease. These patients should be referred to an orthopedic oncologist with expertise in managing these complex cases.

Malignant progression is a rare but potentially devastating complication of synovial chondromatosis. Practitioners should consider it in patients with worsening or refractory pain, or atypical imaging findings. A review of the literature revealed that all cases of synovial chondromatosis progressing to chondrosarcoma were patients with recurrent episodes of the disease over an extended period. This was not the case with our patient, as the initial biopsy revealed the presence of both SC and CS simultaneously. The existence of well-defined areas of benign chondromatosis merging with well-defined areas of chondrosarcoma led us to conclude that the condition had progressed malignantly. It is impossible to say whether SC existed long before the transition to CS. To increase awareness of this phenomenon among pathologists and clinicians, we are reporting this case to add another case of malignant transformation of SC to CS to the small body of literature. We also recommend that patients experiencing rapid deterioration in their synovial chondromatosis, such as worsening pain or an aggressive recurrence, should be treated at, or appropriately referred to, a tertiary hospital experienced in handling these frequently complex cases.

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Figures:

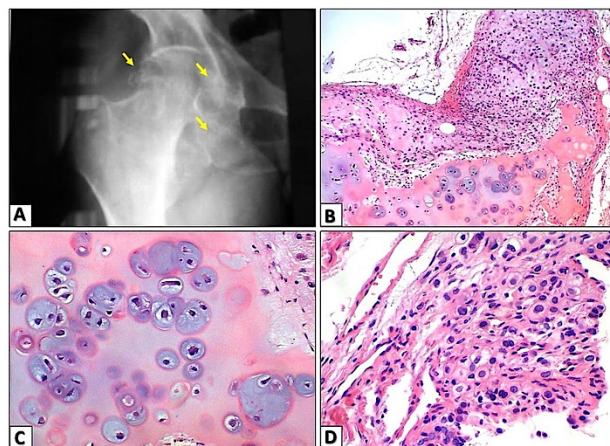


Figure-1: Imaging findings and microscopic examination of the tumor mass

1A: X-ray of the right hip joint showing moderate loss of joint space, popcorn-like calcification in the soft tissue, and lytic changes of the right femoral neck (Arrows)

1B: Intermediate power view showing well-developed benign cartilaginous mass consistent with chondromatosis (lower) merging with more cellular areas composed of atypical malignant chondrocytes consistent with chondrosarcoma (upper). (H&E stain X20)

1C: High power view showing chondromatosis with multinodular cartilaginous proliferation and clusters of chondrocytes showing minimal atypia and increased cellularity. (H&E stain X60)

1D: High power view showing chondrosarcoma displaying clones of chondrocytes that presented small, bland nuclei and other very cellular areas with obvious cellular atypia. (H&E stain X40)

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