Chondrosarcoma in Childhood: The Radiologic and Clinical Conundrum

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ABSTRACT

Less than 10% of chondrosarcomas occur in children. In addition, as little as 0.5% of low-grade chondrosarcomas arise secondarily from benign chondroid lesions. The presence of focal pain is often used to crudely distinguish a chondrosarcoma (which is usually managed with wide surgical excision), from a benign chondroid lesion (which can be followed by clinical exams and imaging surveillance). Given the difficulty of localizing pain in the pediatric population, initial radiology findings and short-interval follow-up, both imaging and clinical, are critical to accurately differentiate a chondrosarcoma from a benign chondroid lesion. To our knowledge, no case in the literature discusses a chondrosarcoma possibly arising secondarily from an enchondroma in a pediatric patient. We present a clinicopathologic and radiology review of conventional chondrosarcomas. We also attempt to further the understanding of how to manage a chondroid lesion in the pediatric patient with only vague or bilateral complaints of pain.

CASE REPORT

Our patient, a 10 year old male, first presented with vague bilateral leg pain. At the time only knee radiographs were taken and he was diagnosed with Osgood-Schlatter syndrome. When he returned to our pediatric clinic 7 months later with continued bilateral hip and knee pain, hip radiographs (figure 1) were taken. These radiographs demonstrated a round, 8 mm lesion in the proximal left femur with a thin sclerotic border and no definite internal matrix. The differential included a simple bone cyst, intraosseous lipoma, enchondroma or sequestrae from infection or osteoid osteoma.

A contrast-enhanced MRI of the left hip (figure 2) was obtained 3 weeks later to further evaluate the bilateral hip pain. It demonstrated a centrally located, well-circumscribed T1WI hypointense, T2WI hyperintense lesion in the proximal left femur with near-complete enhancement versus more peripheral enhancement; a distinction which was difficult to definitively resolve secondary to the smaller size of the lesion. The differential considerations included a bone cyst, enchondroma, and low-grade chondrosarcoma. A bone scan was recommended to help differentiate between the possible benign (bone cyst or enchondroma) or malignant (chondrosarcoma) differential considerations.

The nuclear medicine bone scan (figure 3) revealed no obvious abnormal uptake in the area of concern. In light of the negative bone scan and nature of the patient's pain (vague, intermittent, and bilateral) the lesion was thought to represent a benign process (enchondroma or simple bone cyst), and no further work-up was pursued.

2 years 8 months after the initial work-up (hip radiographs, MRI, and bone scan), the patient presented to the ER with severe left hip pain. The patient reported that shortly after beginning to run he felt a painful "pop," in his left hip
**Title:** Chondrosarcoma in Childhood: The Radiologic and Clinical Conundrum

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**Dates Covered:** 00-00-2012 to 00-00-2012

**Abstract:** Radiology Case. 2012 Dec; 6(12):32-42

**Security Classification:**
- Report: unclassified
- Abstract: unclassified
- This Page: unclassified

**Distribution/Availability Statement:** Approved for public release; distribution unlimited

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which caused him to fall to the ground. Radiographs (figure 4) demonstrated a fracture through the previously seen bony lesion which had now grown to 3.5 cm in maximum transverse dimension.

Both a CT (figure 5) and MRI (figure 6) of the left hip performed one day later demonstrated a pathologic fracture complicated by an avidly enhancing bony mass. Chondromyxoid fibroma and fibroxanthoma were the two proposed differential considerations.

An ensuing biopsy demonstrated "normal bone surrounded by well-differentiated, neoplastic cartilage (figure 7)" and "bi-nucleated chondrocytes (figures 7 and 8)" consistent with a low-grade chondrosarcoma. A staging CT was negative for evidence of metastatic spread. One week later the patient underwent wide surgical excision of the mass, and the proximal left femur was reconstructed with a metal rod (figure 9). The final histologic diagnosis was a 3.6 cm low-grade (Grade 1) conventional (central) chondrosarcoma. The patient's latest annual CT follow-up remains negative for recurrence or metastatic spread.

**DISCUSSION**

A chondrosarcoma is a malignant tumor which produces cartilage matrix. A reasonable differential includes enchondroma, giant cell tumor, and a bone cyst. Chondrosarcomas account for up to 27% of all primary malignant bone tumors [1], second only to osteosarcoma in adults [2-4]. Those that arise de novo are called primary. Those that arise from previously benign cartilaginous lesions (i.e. - enchondroma or the benign cartilage cap of an osteochondroma) are secondary. In relation to their osseous location, a chondrosarcoma may be further designated as conventional/central (arising in the medullary cavity), peripheral, or juxtacortical (periosteal). Finally, histologic classifications of a primary chondrosarcoma include intramedullary, clear cell, juxtacortical, myxoid, mesenchymal, extraskeletal and dedifferentiated [1].

A conventional, central (intramedullary) chondrosarcoma is the most common primary subtype. It occurs two times more frequently in males. Most patients present between 40-70 years old with a median age of 45 years. They are uncommon in children [5-6] (as few as 10% occur in children [6]) and are often rapidly fatal in this age group [6]. The overall incidence of all chondrosarcomas is 1 in 20,000 [3]. Patients with Ollier disease, Maffucci syndrome, and Hereditary Multiple Exostosis have a higher incidence of chondrosarcomas, and they generally present at a younger age than those in the general population [4].

95% of patients with a chondrosarcoma report insidious, slowly worsening pain that is most pronounced at night [1, 3-4, 6]. Some demonstrate a palpable soft tissue mass. Occasionally, chondrosarcomas (~20%) present as a pathologic fracture. Due to the vague nature of these symptoms, they are often present for 1-2 years before initial discovery [1] of the malignancy.

Approximately 90% of all chondrosarcomas are primary, central, low-to-intermediate grade, and arise in the shoulder, pelvis or proximal femur [2-4, 7-8]. The femur, (more commonly the proximal portion) accounts for almost 1/3rd of all chondrosarcomas [1]. In relation to the physis, ~50% involve the metaphysis, ~35% involve the diaphysis, and ~15% involve the epiphysis. Albeit rare, chondrosarcomas also arise from the physis of ribs in children [9]. Central chondrosarcomas, as with our patient, are often large lesions more than 4 cm at presentation, with more 50% measuring greater than 10 cm when first discovered. However the extent and size is not always visible on initial imaging studies. Interestingly, a secondary, central chondrosarcoma arising from a pre-existing lesion such as an enchondroma is extremely rare (0.5%) [1-3].

Histologically, as with our patient, a Grade 1 chondrosarcoma is a low-grade lesion demonstrating chondrocytes with small to slightly enlarged, dense nuclei on a back ground of predominantly chondroid stroma. Diploid (or binucleated) cells may be present. These low-grade chondrosarcomas are very difficult to distinguish from enchondromas [1-2].

Increasing cellularity, decreased chondroid matrix, nuclear pleomorphism, and necrosis are features of a higher grade chondrosarcoma. The nuclei enlarge up to 10x their usual size, appear hyperchromatic, and progress from binucleated to vesicular [1-2]. The neoplastic chondrocytes are arranged in lobular cords and clumps which tend to cause the characteristic endosteal scalloping [1].

Radiographically chondrosarcomas present as an expansile, mixed sclerotic and centrally lucent lesion, with a narrow zone of transition, and possible thin sclerotic margin. The sclerotic portion represents the chondroid matrix mineralization [1, 4]. Flocculent calcifications described as "aars-and-rings" are the defining radiographic feature of a chondroid lesion helping to differentiate them from tumors with an "amorphous and cloudlike" osseous matrix. The "aars-and-rings" represent enchondral ossification at the edge of the cartilage lobules. [1].

Most CT features of chondrosarcoma are a more sensitive extension of the radiographic findings. CT accurately defines the intraosseous portion of the tumor, better detects subtle tumor matrix, and adequately delineates soft tissue extension [4]. On CT, the non-mineralized portion of the tumor is hypodense to muscle because of the high water content of hyaline cartilage. The mineralized portion shows the characteristic chondroid "rings and aarc" appearance (70%) [1].

MRI is the preferred imaging modality for assessing a sarcoma involving the bone. This is because of MRI's superior contrast resolution, it ability to determine extent of marrow involvement, and its accuracy at defining soft tissue invasion [10]. In daily practice, MRI is most often used to problem solve as it can help differentiate a benign enchondroma from a low-grade chondrosarcoma. It is also frequently used for pre-
operative planning to define the extent of the chondrosarcoma and thus increase the accuracy of the surgical excision.

On MRI, a chondrosarcoma is low to intermediate signal on T1. Trapped remaining yellow marrow appears as speckles of high T1 signal. On T2WI, it is heterogeneous, but predominately hyperintense (bright). The non-mineralized portion of hyaline cartilage is hyperintense (bright) on T2 owing to the high water content of hyaline cartilage. In contrast, mineralized areas or fibrous septa are hypointense (dark) on T2. Post-contrast sequences demonstrate enhancement of the septa in a ring-and-arc pattern. Areas that do not enhance after contrast administration represent hyaline cartilage, cystic mucoid tissue, and necrosis. Because most chondrosarcomas present as low-to-intermediate grade, contrast enhancement is usually mild, peripheral and septal [1, 4].

While more research is needed, 18FDG PET-CT has been shown to have a high degree of sensitivity (~91%), specificity (100%), and accuracy (~95%) when using Standard Uptake Values (SUV) to predict chondrosarcoma (SUV > 2.0) versus enchondroma (SUV < 2.0) [11]. Approximately 80% of conventional chondrosarcomas demonstrate marked radiotracer uptake on bone scan, although uptake is also seen in enchondromas (~20%) [1].

Differentiating low-grade chondrosarcoma from an enchondroma (table 3)

As previously mentioned, it is highly important to differentiate a low-grade chondrosarcoma (which requires wide-surgical excision) from an enchondroma (which requires imaging and clinical surveillance). But this distinction is not always straight forward. When radiology, and sometimes pathology (due to a non-diagnostic biopsy), are inconclusive; the presence of focal pain is often used as a "tie-breaker," indicating that the lesion is likely malignant. However, localizing pain in pediatric patients is often difficult. When our patient first presented, he complained of chronic pain in both lower extremities mostly around the knees. Radiographs appropriately focused on the area of most concern (knees).

About 7 months elapsed until he returned with complaints of intermittent and bilateral pain which had progressed more proximally; however, it did not limit his daily or extracurricular activities. The clinical findings and hip radiographs, which revealed a lesion which was not aggressive in appearance, favored a benign process. This was further confounded by the MRI, which seemed inconclusive at best. When the patient's bone scan was negative, this added to the growing consensus between pediatrics, radiology, and orthopedics that the lesion was benign.

Pain is the most consistent clinical feature which distinguishes a chondrosarcoma versus enchondroma - and in the absence of a pathologic fracture, an enchondroma is not typically associated with pain or growth [4]. Therefore, regardless of any imaging feature, if pain is present, a chondrosarcoma must be excluded. Chondrous calcifications, loss of tumor definition, cortical breakthrough, and/or a soft tissue mass are generally considered features which favor a chondrosarcoma. However, the latter three generally occur too late in the course of a chondrosarcoma to be reliable indicators that would radiologically differentiate an enchondroma from a chondrosarcoma in a timely manner [1, 6].

Radiographically, the most reliable indicator of chondrosarcoma (75%) over enchondroma (< 10%) in the long bones is the presence of endosteal scalloping more than 2/3rds the cortical width. On MRI, peri-tumoral edema suggests chondrosarcoma over enchondroma. Additionally, intense peripheral, nodular and septal enhancement (both on CT and MRI) suggests chondrosarcoma over enchondroma (which usually only demonstrates peripheral enhancement) [1, 3-4]. A faster rate of dynamic contrast enhancement on MRI may also indicate a malignant lesion [3].

Chondrous calcifications which become more faint and amorphous over serial radiographic studies, often indicate a higher-grade lesion [4]. Lesions greater than 5 cm and those located in the axial skeleton are more frequently chondrosarcomas. Heterogeneous uptake greater than the anterior iliac crest on 99mTc diphosphonate bone scan has also been reported as a feature more consistent with chondrosarcomas [4].

Pathologic differentiation is best demonstrated by evaluating the edge of biopsy sections. If malignancy has been determined, grading can be determined by evaluating cellularity [1-2]. While expression patterns of integrin-linked kinase show promise, no genomic alteration or biomarker is yet able to distinguish enchondroma from chondrosarcoma [12]. Despite this, the genetics of cartilage-producing tumors has produced useful clinical information. Low grade chondrosarcomas demonstrate less low-level genomic imbalances than high-grade chondrosarcomas. Central chondrosarcomas demonstrate more abnormalities of chromosome 9p and extra copies of chromosome 22 compared with peripheral chondrosarcomas. Also, accumulation of p53 has been linked with higher-grade chondrosarcomas and a poorer prognosis [2].

Management and Treatment

It is acceptable to follow an indeterminate lesion, such as ours, with serial cross-sectional imaging at 4-6 month intervals for 2 years, then annually for up to 5 years [1]. However, a high index of suspicion and low threshold to biopsy should be observed for any mass with new clinical symptoms or onset of focal pain [1, 3, 10]. When it has been determined that a tissue diagnosis is indicated, biopsy should be directed to the area of greatest endosteal scalloping which is generally considered the most aggressive portion of the lesion (where the greatest number of tumor foci reside). Also, if a contrast-enhanced CT or MR has been acquired, biopsy may be directed towards the most prominent enhancement, either bone or soft tissue [1].

Abdominal and chest CT’s are highly useful for staging. They accurately detect pulmonary nodules, lymphadenopathy, and metastatic involvement of solid abdominal organs [10]. Newer MR techniques help eliminate metallic artifact in treated patients who have undergone bony reconstruction with
placement of metal hardware; therefore making MRI the most sensitive modality for detecting post-treatment recurrence [10].

There are generally 2 treatment options for a low-grade sarcoma such as our patient, so it is not surprising that the overall 5-year survival rate for all chondrosarcomas, regardless of type, remains 75% and has not changed in the last 3 decades [3].

The preferred treatment in most cases (if possible) is wide surgical excision and reconstruction of the affected bone with graft or metal depending on location and function [1, 3, 13]. To avoid tumor seeding, the biopsy tract is generally resected at the time of surgery. Both prognosis and rate of recurrence correlate directly to the adequacy of the surgical resection. Therefore, surgical margins that are not wide enough pose a real risk of recurrence, often with a higher tumor grade [1, 3]. If the chondrosarcoma cannot be excised, the other treatment option is curettage with thermal ablation (or adjunct chemotherapy). Unfortunately, most chondrosarcomas are resistant to chemotherapy [2, 4]; and many are relatively radioresistant [3].

In retrospect, there are many features of the case we presented which were reviewed. Given the negative bone scan, indeterminate MR, and non-specific nature of our patient's pain, it is very reasonable to suspect that our patient's lesion was initially an enchondroma which later dedifferentiated into a low-grade chondrosarcoma. Thus, this could have been a rare secondary, central chondrosarcoma - made even more rare because it arose in a young adolescent. However, there were also features which suggest that it could have been a primary low-grade chondrosarcoma all along.

It would have been helpful to obtain close interval, serial cross-sectional imaging which would have likely demonstrated enlargement of the lesion. This could have prompted a biopsy and quicker diagnosis, possibly preventing the patient's pathologic fracture. However, social factors including parental hesitancy of subjecting their child to a painful bone biopsy in an otherwise non-aggressive lesion are often difficult factors for the pediatrician to navigate. This is accompanied by the need to coordinate anesthesia for the biopsy and its added, inherent risks. Ultimately, the decision to biopsy should be made after all factors have been weighed, and deference given to the most concerning feature.

TEACHING POINT
If focal pain is present or develops in the area of a known chondroid lesion, it is highly suspicious and biopsy should strongly be considered regardless of its imaging features. Endosteal scalloping greater than 2/3 of the cortical width is highly suspicious and biopsy should strongly be considered even if the patient is clinically asymptomatic. It is reasonable to follow indeterminate lesions with serial, close-interval, cross-sectional imaging at 4-6 months for the first 2 years, then annually for a total of 5 years. This is especially important in a pediatric patient who may not be able to accurately localize their pain.

REFERENCES
**Figure 1:** This is a ten year old male who would be diagnosed 2.75 years later with a low-grade chondrosarcoma. Frog-legged lateral (a) and coned-down frontal (b) radiographs of the left hip demonstrate a faint, round, 8-9 mm lesion (arrowhead) located centrally within the proximal femur. It has a thin sclerotic rim and no evidence of cortical involvement.
Figure 2: This is a 10 year-old male who would be diagnosed 2.75 years later with a low-grade chondrosarcoma. This MR of the left hip took place 3 weeks after the previous radiographs. It demonstrates a round, enhancing, 8-9mm lesion (arrowheads) located centrally in the proximal left femur that is T2WI and STIR hyperintense, and T1WI hypointense. The Philips 1.5 T MR sequences depicted include: Axial STIR (a - top left; supine, TR 3400, TE 81, ST 3), axial T1WI (b - top middle; TR 657, TE 24, ST 3), axial magnified post-contrast T1WI fat-sat (c - top right; 10 cc Magnevist, TR 855, TE 24, ST 3), coronal STIR (d - bottom left; TR 4420, TE 40, ST 2), coronal T1WI (e - bottom middle; TR 604, TE 25, ST 2), and coronal magnified post-contrast T1WI fat-sat (f - bottom right; 10 cc Magnevist, TR 767, TE 25, ST 2)

Figure 3: This is a 10 year-old male who would be diagnosed 2.75 years later with a low-grade chondrosarcoma. Lower extremity, 3 hour delayed PA and AP planar images of a 99Tc-HDP bone scan (a few days after the previous MRI) demonstrate normal musculoskeletal activity without abnormal focal uptake in the proximal left femur (area of concern).
Figure 4: Our patient, now a 12 year-old male, was diagnosed with a low-grade chondrosarcoma a few days after these radiographs. Frontal (a) and frog-legged lateral (b) radiographs of the left hip demonstrate a closed, moderately displaced, pathologic fracture through the [now] lytic lesion (star) in the proximal left femur which has grown to 3.5 cm in maximum transverse dimension. No obvious tumor matrix is visualized.

Figure 5: This is a 12 year-old male who was diagnosed with a low-grade chondrosarcoma a few days after this CT. Oblique sagittal 3D reconstructions (a), coronal (b), and axial (c and d) CT images (1 day after the above radiographs) demonstrate a fracture through the 3.5 cm, hypodense mass centered in the proximal femur. The axial cut superior to the fracture (d) demonstrates endosteal scalloping. The 64 slice CT exam was performed supine with a kVp of 120, mA of 120, ST of 5 for the axial, and ST of 1 for the sagittal and coronal.
Figure 6: This is a 12 year-old male who was diagnosed with a low-grade chondrosarcoma a few days after this MRI. The MR images demonstrate a round, 3.5 cm mass with lobular borders which cause endosteal scalloping greater than 2/3rds the width of the adjacent cortex. It is a STIR hyperintense (bright) mass (star) with extensive adjacent edema (arrowhead). Post-contrast images demonstrate peripheral (c - arrowhead) and central nodular (d - star) enhancement. There is a fracture through the involved proximal femur at the inferior aspect of the mass (d). The Philips 1.5T MR magnet images depicted include: Coronal STIR MRI (a - left; TR 3858, TE 15, ST 5), coronal post-contrast T1WI with fat-suppression (b - middle left; 10 cc Magnevist, TR 715, TE 15, ST 2.91), axial post-contrast T1WI with fat-suppression through the fracture slightly inferior to the mass (c - middle right; 10 cc Magnevist, TR 630, TE 10, ST 3), and axial post-contrast T1WI with fat-suppression (d) through the superior aspect of the mass.

Figure 7: This is a 12 year-old male who was diagnosed with a low-grade chondrosarcoma upon interpretation of this biopsy. Low-powered magnification (20x) of hematoxylin and eosin stains (a) demonstrate normal bone (arrowhead) adjacent to a piece of well-differentiated, neoplastic cartilage (star). 40x magnification (b) demonstrates bi-nucleated chondrocytes consistent with a low-grade chondrosarcoma (arrowhead).
**Figure 8:** This is a 12 year-old male who was diagnosed with a low-grade chondrosarcoma upon interpretation of this biopsy. Medium-power magnification (a) hematoxylin and eosin stains demonstrate lobulated neoplastic cartilage becoming more cellular toward the periphery of the tumor (star). High-medium-power magnification (b) demonstrates a very myxoid chondrosarcoma with some mild cytologic atypia (specifically binucleated chondrocytes, arrowhead).

**Figure 9 (left):** This is a 12 year-old male who underwent resection of a low-grade chondrosarcoma from his proximal left femur with subsequent reconstruction depicted here. An AP radiograph of the proximal left femur demonstrates wide resection of the proximal left femur with interval placement of an intramedullary rod.
Differential Radiographic findings CT/MR findings

Chondrosarcoma Expansile, mixed sclerotic and centrally lucent lesion, usually greater than 1 cm in size, with a narrow zone of transition, variable endosteal scalloping, and a possible thin sclerotic margin. Characteristic arc-and-ring type calcifications (representing chondroid matrix) are often seen. On CT, the non-mineralized portion of the tumor is hypodense to muscle because of the high water content of hyaline cartilage. The mineralized portion shows the characteristic “rings and arcs” chondroid matrix. On MRI, chondrosarcoma is low to intermediate signal on T1. Trapped remaining yellow marrow appears as speckles of high T1 signal. On T2WI, they are heterogeneous, but predominately hyperintense (bright). The non-mineralized portion of hyaline cartilage is hyperintense (bright) on T2 owing to the high water content of hyaline cartilage. In contrast, mineralized areas or fibrous septa are hypointense (dark) on T2. Post-contrast sequences demonstrate enhancement of the septa in a ring-and-arc pattern. Areas that don’t enhance after contrast administration represent hyaline cartilage, cystic mucoid tissue, and necrosis. Because most chondrosarcomas present as low-to-intermediate grade, contrast enhancement is usually mild, peripheral and septal.

Enchondroma Central, metaphyseal lesion often in the hands or feet. There is usually no peripheral sclerotic margin or extensive endosteal scalloping. MRI shows a hyperintense T2WI mass, with low signal intensity calcifications more often in the hands and feet than chondrosarcoma

Giant Cell Tumor Lytic lesion without sclerotic margins which abuts the articular surface of long bones. It usually presents in 20-40 yo patients with closed physes. Calcifications are not usually present. Heterogenous but predominately hypointense on T2WI. Enhancement is variable and heterogeneous.

Table 2: Differential diagnosis table for low-grade chondrosarcoma.
**Table 3:** Clinical, radiological, and pathological features of a benign chondroid lesion versus a low-grade chondrosarcoma.

<table>
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<tr>
<th>Favors Chondrosarcoma</th>
<th>Clinical</th>
<th>Radiological</th>
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<td></td>
<td>Pain</td>
<td>• Endosteal Scalloping &gt; 2/3rds the cortical width</td>
<td>• Increasing cellularity, decreased chondroid matrix, nuclear pleomorphism, and necrosis.</td>
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<td>• Large (&gt; 5 cm)</td>
<td>• The neoplastic chondrocytes are arranged in cords and clumps and become irregular in shape. The nuclei enlarge up to 10x their usual size, are hyperchromatic, and progress from binucleated to vesicular.</td>
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<td>• Intense septal and peripheral enhancement on MR</td>
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<td>• Associated Soft Tissue Mass (late)</td>
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<td>• Cortical Breakthrough (late)</td>
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<td>• Peri-tumoral edema on MR</td>
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<td>Favors a benign chondroid lesion (i.e. – enchondroma, osteochondroma, etc.)</td>
<td>Asymptomatic Small (&lt; 1 cm)</td>
<td>• Small (&lt; 1 cm)</td>
<td>• Normal sized nuclei without nuclear pleomorphism</td>
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<td>• Stable in appearance while undergoing imaging surveillance</td>
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<td>• Located in the hands or feet</td>
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<td>• Minimal or mild peripheral (only) enhancement</td>
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<td>• CT: Computed tomography</td>
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<td>• T2WI: T2 weighted imaging</td>
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**ABBREVIATIONS**

CT: Computed tomography  
MRI: Magnetic resonance imaging  
T1WI: T1 weighted imaging  
T2WI: T2 weighted imaging

**KEYWORDS**

pediatric chondrosarcoma; chondrosarcoma; bone tumor; pediatric

**ACKNOWLEDGEMENTS / DISCLAIMER**

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