Chronic non-bacterial osteomyelitis (CNO) in childhood and adolescence – a disease with many faces

Die Chronische Nicht Bakterielle Osteomyelitis (CNO) im Kindes- und Jugendalter – eine Erkrankung mit vielen Gesichtern

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ABSTRACT

Background Chronic non-bacterial osteomyelitis (CNO) is a chronic inflammatory skeletal disease that affects particularly children and adolescents and is often diagnosed with a delay. With whole-body MRI, early diagnosis of this disease is possible in many cases. Since children and adolescents frequently present with non-specific complaints for outpatient radiological diagnosis, every radiologist should have basic knowledge of this complex clinical picture.

Materials In this review the basics and current findings regarding the disease are discussed. Unusual courses are also presented.

Results and Conclusion With knowledge of the radiographic and MR tomographic characteristics of the mostly multifocal bone lesions, the diagnosis of CNO can be reliably made in many cases. In particular, the early use of whole-body MRI plays an important role. Thus, therapeutic delays and resulting complications and the number of unnecessary biopsies for diagnosis can be reduced.

Keywords:

- Chronic non-bacterial osteomyelitis is a chronic inflammatory skeletal disease, especially in children and adolescents. The incidence has long been underestimated
- The location of the lesions, especially in metaphyses and metaphyseal equivalent regions, as well as the distribution pattern of the clinically often occult lesions are decisive for diagnosis
- Whole-body MRI plays an important role in the diagnostic workup as it reveals the characteristic distribution pattern of the lesions and helps to confirm the diagnosis
- Differentiated radiological diagnosis can reduce the number of biopsies and reduce long-term complications of the disease by early diagnosis and initiation of therapy

ZUSAMMENFASSUNG

Hintergrund Die Chronische Nicht Bakterielle Osteomyelitis (CNO) ist eine chronisch-entzündliche Skeletterkrankung insbesondere des Kindes- und Jugendalters, die häufig erst verzögert diagnostiziert wird. Mit Hilfe der Ganzkörper-MRT ist eine frühzeitige Diagnose dieser Erkrankung in vielen Fällen möglich. Da die Kinder und Jugendlichen initial häufig mit unspezifischen Beschwerden im ambulanten Bereich zur radiologischen Diagnostik kommen, sollte jede/r Radiolog/in grundlegende Kenntnisse zu diesem komplexen Krankheitsbild besitzen.

Methode In dieser Übersichtsarbeit werden die Grundlagen und aktuellen Erkenntnisse zur Erkrankung diskutiert. Auch ungewöhnliche Verläufe werden vorgestellt.

Ergebnisse und Schlussfolgerungen Unter Kenntnis der röntgenologischen und MR-tomographischen Charakteristika der meist multifokalen Knochenherde ist die Diagnose einer CNO in vielen Fällen zuverlässig möglich. Dabei spielt insbesondere der frühzeitige Einsatz der Ganzkörper-MRT eine wichtige Rolle. Dadurch können Therapieverzögerungen und sich daraus ergebende Komplikationen vermindert und die Anzahl unnötiger Biopsien zur Diagnosefindung reduziert werden.

Introduction

Chronic non-bacterial osteomyelitis (CNO) is an aseptic inflammatory skeletal disease that occurs especially in children and adolescents and is triggered by autoinflammatory mechanisms [1]. The symptoms are often nonspecific and the time between symptom onset and diagnosis is 12 months or longer in large studies [2–4]. Radiology is a starting point in the diagnostic workup of unclear musculoskeletal symptoms. Imaging plays a key role in the diagnosis of CNO since characteristic findings can be considered at an early stage thus setting an important course for further diagnostic workup and treatment of the patient. Since affected children and adolescents are often primarily seen in outpatient settings that are not specialized in pediatric radiology, knowledge of this disease on the part of radiologists is extremely important. The last couple of years have shown that CNO is much more common than previously thought and an incidence in the range of that of infectious hematogenous osteomyelitis has been described [5]. This can also be attributed to radiology since the increased use of whole-body MRI makes it possible to detect specific distribution patterns of CNO, thus allowing definitive and early diagnosis [6, 7].

The morphological features of CNO visible on imaging are discussed in greater detail in the following review and the current diagnostic developments are presented. Unusual disease courses are also shown and important differential diagnoses and the value of histological confirmation of the diagnosis are discussed. The goal is to inform the reader that this disease must be considered in the differential diagnosis of unclear changes in bone in children and adolescents to avoid unnecessary treatment delays or invasive diagnostic procedures and resulting complications.

Basic information

Definition

CNO is not a new disease. It has probably been around as long as there have been infectious bone diseases. Radiological, clinical, and histopathological descriptions of plasma cell osteomyelitis and chronic sclerosing osteomyelitis of Garré are at least reminiscent of non-bacterial osteomyelitis [8]. The term „diffuse sclerosing osteomyelitis of the mandibula“ also refers to non-bacterial osteomyelitis in a characteristic location of CNO. There are significant clinical-radiological overlaps with infantile cortical hyperostosis, known as Caffey-Silverman disease [9, 10].

The first description of CNO is attributed to the Swiss pediatrician and radiologist Andres Giedion, who reported subacute chronic symmetrical osteomyelitis in four children in 1972 [11]. In 1978, Probst coined the term „chronic recurring multifocal osteomyelitis (CRMO)“ because of the course of the disease which is usually already chronic at the time of diagnosis, the multifocality, and the recurrence tendency. This term is still established today [12].

Since the disease can also be unifocal and occur only once, the term CRMO has been replaced by the more general term CNO in recent years [13]. The term NBO (non-bacterial osteitis) is currently also used [14]. Due to the highly variable clinical and visible morphological findings, the diagnosis of CNO is a diagnosis of exclusion with respect to other inflammatory and tumorous skeletal diseases.

Etiology and pathogenesis

CNO is sterile bone inflammation triggered by autoinflammatory mechanisms. Pathophysiologically, an imbalance between pro-inflammatory and anti-inflammatory cytokines is assumed. The elevated level of pro-inflammatory cytokines like IL1, IL6, and TNF α results in activation of osteoclasts and consequent bone absorption [15, 16]. Similar changes in bone are also seen in rare monogenetic autoinflammatory diseases like Majeed syndrome or a congenital IL1 receptor antagonist deficit (DIRA) [17, 18]. This and the observation that chronic inflammatory diseases involving various organ systems are present in up to 50 % of first or second-degree relatives of patients indicates a genetic origin of CNO [13].

Epidemiology and clinical picture

CNO is primarily a disease in children and adolescents. The average age of patients is 10 years and girls are affected almost twice as often as boys [2, 19]. The incidence of 0.4 per 100 000 children per year in Germany calculated in 2011 is certainly currently significantly higher [20]. This is due among other things to the advances in diagnostic imaging and the increasing use of whole-body MRI.

Patients usually present with bone or joint pain that often occurs at night. The general condition of patients is usually good. Fever or B-symptoms are rare [21].

Changes in laboratory findings are also nonspecific. Signs of mild inflammation like an elevated ESR, mild leukocytosis, or a slight elevation in CRP can be present as a single change but do not correlate to disease activity and disease extent. In up to 20 % of cases, associated chronic inflammatory diseases of the intestines and skin or rheumatic diseases are observed [2, 4].

In rare cases, CNO can also occur in adults. Compared to adolescents and children, mucocutaneous comorbidities are described more frequently in adults [2]. SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) belongs to this group of diseases in the broadest sense and is considered by some authors to be the adult form of CNO [22].

Treatment and course

CNO treatment is largely based on anti-inflammatory medication to inhibit the inflammatory reaction, to alleviate the patient's clinical symptoms, and to prevent complications. The treatment of first choice is non-steroidal anti-inflammatory drugs, with naproxen being most commonly prescribed in children and resulting in a clinical and visible morphological improvement in over 50 % of cases [23, 24]. In severe cases, glucocorticoids can be additionally used short-term. If clinical symptoms persist or findings worsen, various second-line therapeutic agents like sulfasalazine, methotrexate, TNF α blockers, or bisphosphonates are used [4, 21]. The latter has high therapeutic efficacy particularly in the treatment of vertebral lesions [25].

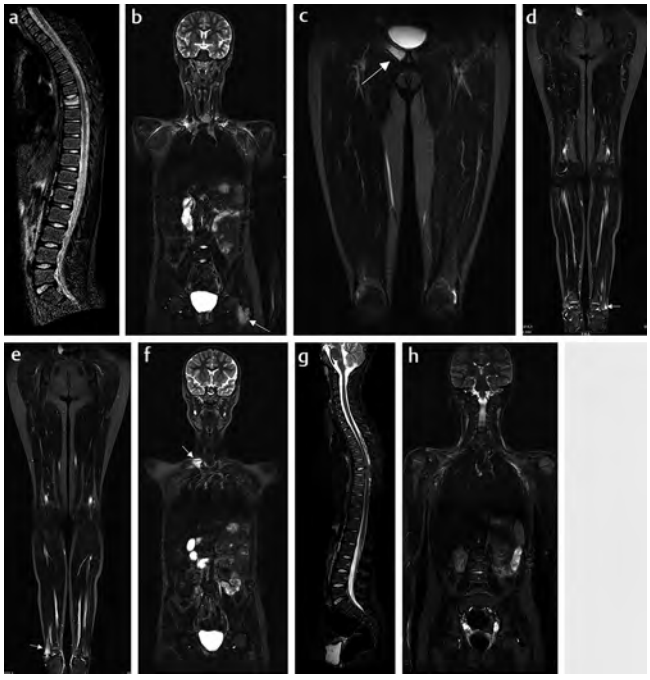
Diagnostic imaging

In the case of chronic or recurrent bone pain, a detailed patient interview and basic laboratory tests are often followed by localized imaging focused on the location of the main symptoms. Imaging-based diagnosis of CNO is the result of the combination of typical changes in bone in characteristic locations that can be found at multiple locations in the skeletal system. Many of the lesions found in addition to the main lesion are clinically asymptomatic so that whole-body imaging is often initially not considered due to the unifocal clinical symptoms, thus resulting in delays in diagnosis and treatment [3, 19]. Therefore, it is decisive for the diagnostic procedure to consider a possible diagnosis of CNO in the case of characteristic local changes and to perform whole-body MRI in the next step to verify the diagnosis on imaging (▶ **Fig. 1**).

Whole-body MRI technique [26]

Whole-body MRI is an important diagnostic component for the diagnosis of CNO [27]. Primarily coronal STIR sequences are needed to detect bone lesions. Due to the prognostic importance of vertebral lesions, the examination protocol should always also include a STIR sequence of the entire vertebral column in sagittal slice orientation [28, 29]. Additional T1-weighted sequences can be helpful in the evaluation of bone marrow changes, for example in the differentiation between hematopoietic bone marrow and a true CNO lesion [30]. However, this greatly increases the examination time. It is usually not necessary to administer contrast agent [31]. There is not yet any meaningful data confirming the superiority or diagnostic benefit of diffusion imaging with respect to CNO [32].

The small bones in the hands and feet must be able to be visualized and evaluated. The hands can be positioned next to the body as well as on the abdomen or under the buttocks [32]. CNO lesions in the foot bones, primarily the calcaneus and talus, are significantly more common than in the skeleton of the hand [33]. Differentiation from physiological bone marrow changes occurring in adolescent foot bones is often difficult here [34].



▶ **Fig. 1 a–h** 10-year-old girl experiencing back pain for several weeks. Acute presentation due to onset of new pain during respiration after physical activity. History of pain in both ankles for months. MRI of the spinal column with recent fracture of T7 (**a**). Based on the patient's history and the vertebral fracture, whole-body MRI was performed and showed further lesions in the left proximal femur adjacent to the trochanter apophysis (→ **b**), in the right pubic bone adjacent to the symphysis (→ **c**), in both distal fibular metaphyses (→ **d**, **e**), and in the right medial clavicle (→ **f**). Due to the distribution pattern on imaging, CNO was diagnosed and antiphlogistic treatment was initiated. Follow-up MRI 4 months later showed complete regression of the bone marrow edema in the vertebral body (**g**) and femur (**h**). The patient is now symptom-free.

Characteristic locations of CNO lesions

For the differential diagnosis of benign and malignant changes in bone in children, the location of the change in the skeletal system plays an important role. Most inflammatory and tumorous diseases are located in the most metabolically active zone of the bone, the metaphysis. Primary bone growth takes place here and this region is characterized by an abundant arterial and venous network. Metaphyseal-equivalent sites are also metabolically active areas of bone in which inflammation often occurs. Metaphyseal-equivalent regions include areas neighboring cartilage tissue like apophyseal joints and synchondroses [35]. CNO lesions also primarily occur in the metaphyses and in metaphyseal-equivalent regions. Thus, the distribution pattern corresponds to that of bacterial osteomyelitis which is consequently the main differential diagnosis in many cases.

A more precise evaluation of the distribution pattern of CNO lesions shows the following [6, 7, 28]:

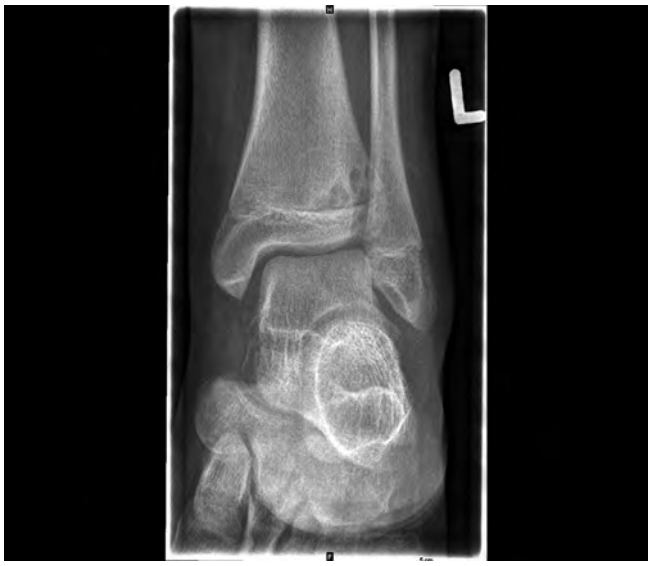
The most common locations are:

- Metaphyses and metaphyseal-equivalent regions of long bones, especially in the lower extremities.
- Metaphyseal-equivalent regions of the skeleton of the pelvis (adjacent to the iliosacral joint, triradiate cartilage, symphysis)
- Spinal column, especially the thoracic spine

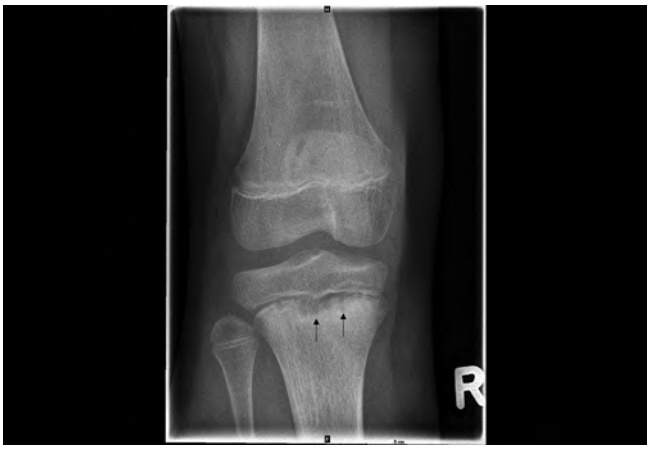
Further typical locations with different frequencies depending on the study

- Medial clavicle
- Mandible
- Sternum, ribs
- Skeleton of the foot and hand

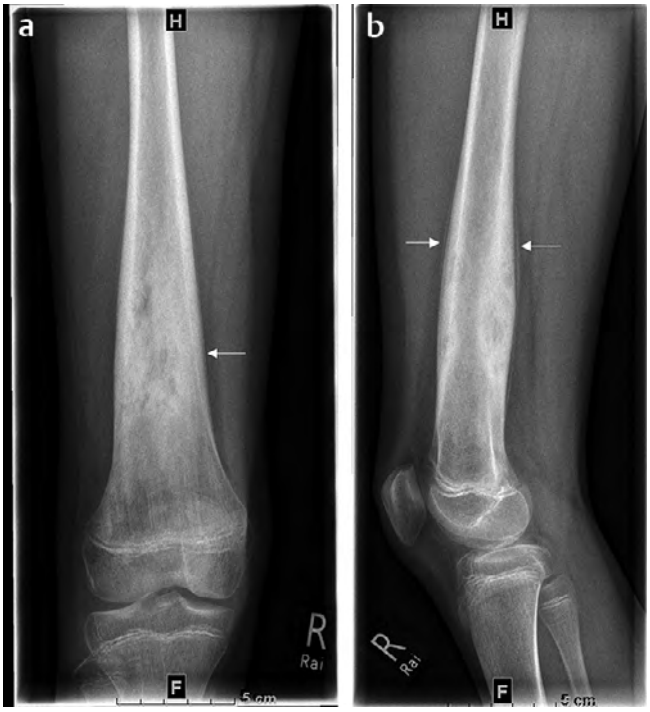
The different frequencies of individual locations may also be an expression of different forms of the disease. A differentiation is made between bilateral symmetrical patterns of involvement, diseases with multiple primarily peripheral lesions or with only a few lesions, and involvement of the clavicle and/or spinal column [36]. However, in our experience, these differences do not play a major role in routine diagnostics.



▶ **Fig. 2** Typical X-ray finding in CNO of the distal tibial metaphysis. ovoid shaped regions of osteolysis with peripheral sclerosis.



▶ **Fig. 3** Pseudo-widening of the epiphyseal plate of the proximal tibia in CNO. Significant increase in sclerosis of the metaphysis adjacent to the defect (→).



▶ **Fig. 4 a, b** CNO verified by biopsy in a patient with chronic leg pain for weeks. Expansion of the distal femoral diaphysis with formation of new periosteal bone, sclerosis, and regions of osteolysis. Lamellar periosteal reaction at the level of the lesion (→).

CNO lesions on radiography and MRI

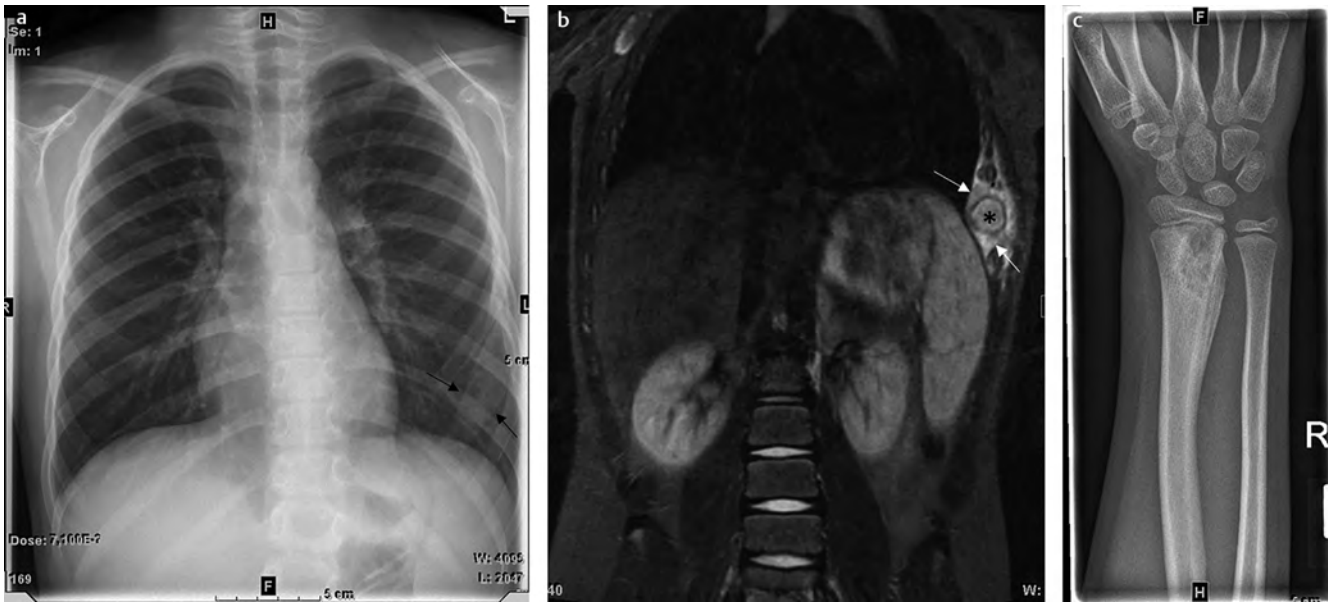
X-ray examination of a clinically relevant region is the first diagnostic step in many cases. It provides initial information regarding a possible underlying disease. Benign and malignant tumors can be relatively reliably categorized based on the morphology on radiography (growth/destruction pattern, periosteal reaction) and the location in many cases. Depending on the body region and duration of symptoms, radiography has various sensitivities with respect to the detection of changes in bone. We see cases again and again in which MRI examination was initially performed and no X-ray examination is available. In the case of a normal MRI finding, a bone pathology can be ruled out with high probability. In the case of a pathological finding, supplementary radiography is still highly important for the differential diagnosis.

CNO in the peripheral skeleton

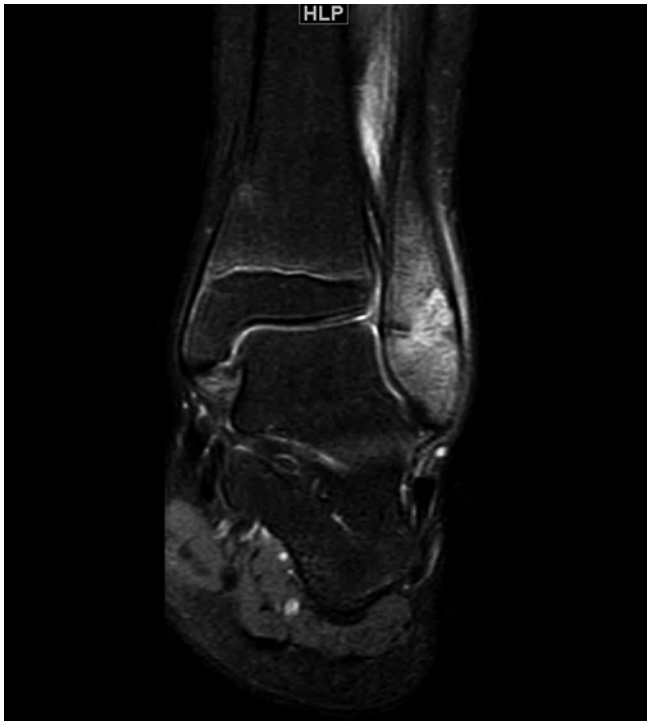
Inflammation-induced osteoclast activation results in osteolytic changes near the joints that have an ovoid or columnar shape. The osteolytic areas are usually surrounded by a sclerotic margin already at the time of diagnosis (▶ **Fig. 2**). The bone absorption near the joint has the appearance of „pseudo-widening“ of the epiphyseal plate [7] (▶ **Fig. 3**). In the chronic stage, sclerotic and hyperostotic changes are primarily seen, the bone is increasingly distended, and the changes extend to the diaphysis [37] (▶ **Fig. 4**).

Depending on the disease activity and extent, periosteal and soft-tissue reactions are also possible. This occurs primarily in the case of involvement of bones with a small diameter [38] (▶ **Fig. 5**). With respect to diagnosis, it can be stated that the indication for biopsy depends on the extent of the changes in bone. The more pronounced the changes in bone, the earlier a biopsy is performed.

MRI is primarily helpful for the detection of clinically or radiologically inapparent lesions. Changes equivalent to bone marrow edema that also become osteolytic lesions in advanced disease are seen in typical locations near the joints. In addition to the typical locations in the metaphyses around the knee joint or ankle, lesions around the apophyses and synchondroses are a very specific sign for of the presence of CNO (▶ **Fig. 1b**). In the case of lesions in the metaphysis, the bone marrow edema can also affect the epiphysis [6, 36] (▶ **Fig. 6**). Purely epiphyseal lesions are rare and are not typical for CNO [32].



▶ **Fig. 5 a–c** CNO of the seventh rib on the left. Expansion of the bone visible on the X-ray image (→ **a**). Pronounced soft-tissue reaction around the distended rib (*) in the adjacent intercostal spaces (→ **b**). Additional lesion in the distal radial metaphysis on whole-body MRI with a osteolysis and formation of new periosteal bone on the radiograph (**c**). To rule out the differential diagnosis of LCH, a biopsy was performed and CNO was confirmed.



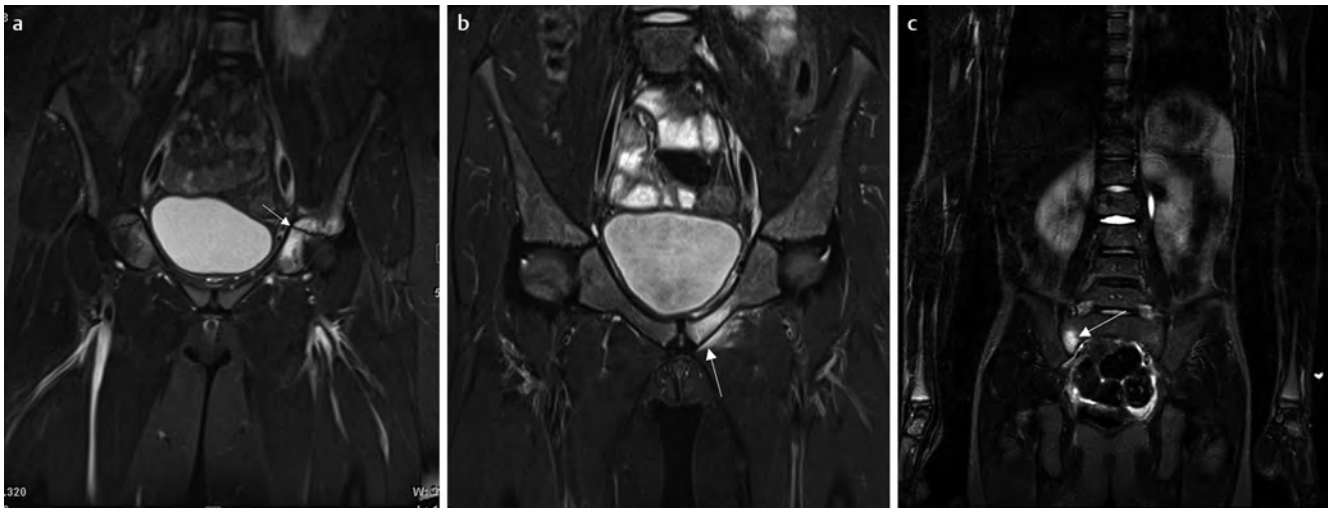
▶ **Fig. 6** CNO lesion in the distal fibular metaphysis. The bone marrow edema surrounding the lesion extends into the fibular epiphysis.

CNO in the skeleton of the pelvis

In addition to the lower extremities and the spinal column, the skeleton of the pelvis is the most affected region in CNO [28, 29, 33]. Radiography tends to play a subordinate role in pelvic lesions since most pelvic lesions are often less clinically symptomatic and are first diagnosed with whole-body MRI [7]. The typical constellation of MRI-positive pelvic findings in a characteristic location with a lack of symptoms is thus primarily decisive for the confirmation of suspected CNO. The typical locations include the metaphyseal-equivalent regions around cartilage structures like the iliosacral joint, triradiate cartilage, or symphysis [7] (▶ **Fig. 7**).

CNO of the spinal column

Inflammatory changes in vertebral bodies are also frequently seen in CNO. In the literature, involvement is reported in up to 30 % of cases with the thoracic spine followed by the lumbar spine being most frequently affected [7, 33, 36]. The spinal column is often the primary symptomatic region, and a pathological vertebral fracture can already be present at the time of initial diagnosis [39]. In addition to impaired growth and axle misalignment of the long bones, vertebral fractures are the main complication of CNO. Therefore, early diagnosis of vertebral body involvement during the initial diagnostic workup is important to prevent fracture by initiating treatment early [7, 33, 40]. MRI shows early signs of edema-equivalent changes in the vertebral end plates. The edema can also extend into the vertebral arch in advanced stages (▶ **Fig. 8**). The necessity to visualize the entire spinal column on whole-body MRI in sagittal slice orientation is derived from the significance of the vertebral body changes for diagnosis and treatment [7].



▶ **Fig. 7 a–c** Typical pelvic lesions in CNO. The lesions are in the metaphyseal-equivalent regions around the cartilage structures. Typical locations around the triradiate cartilage (→ **a**), adjacent to the symphysis (→ **b**), and adjacent to the iliosacral joint (→ **c**) are shown.

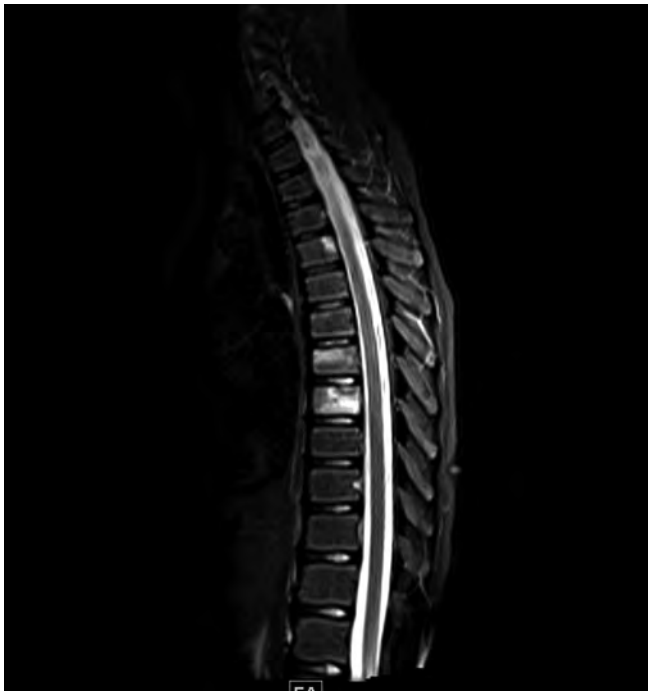
CNO of the clavicle

The medial end of the clavicle is also a classic CNO location and is often the first manifestation of the disease. Patients usually present with unilateral swelling above the medial clavicle with varying degrees of pain. The radiograph shows distension of the bone with sclerosis and circumscribed regions of osteolysis. The changes in the bone can be better visualized on CT. A periosteal reaction is also possible in the advanced stage [33] (▶ **Fig. 9**). MRI shows changes in the shape of the bone as well as increased bone marrow edema and an edematous soft-tissue reaction [7].

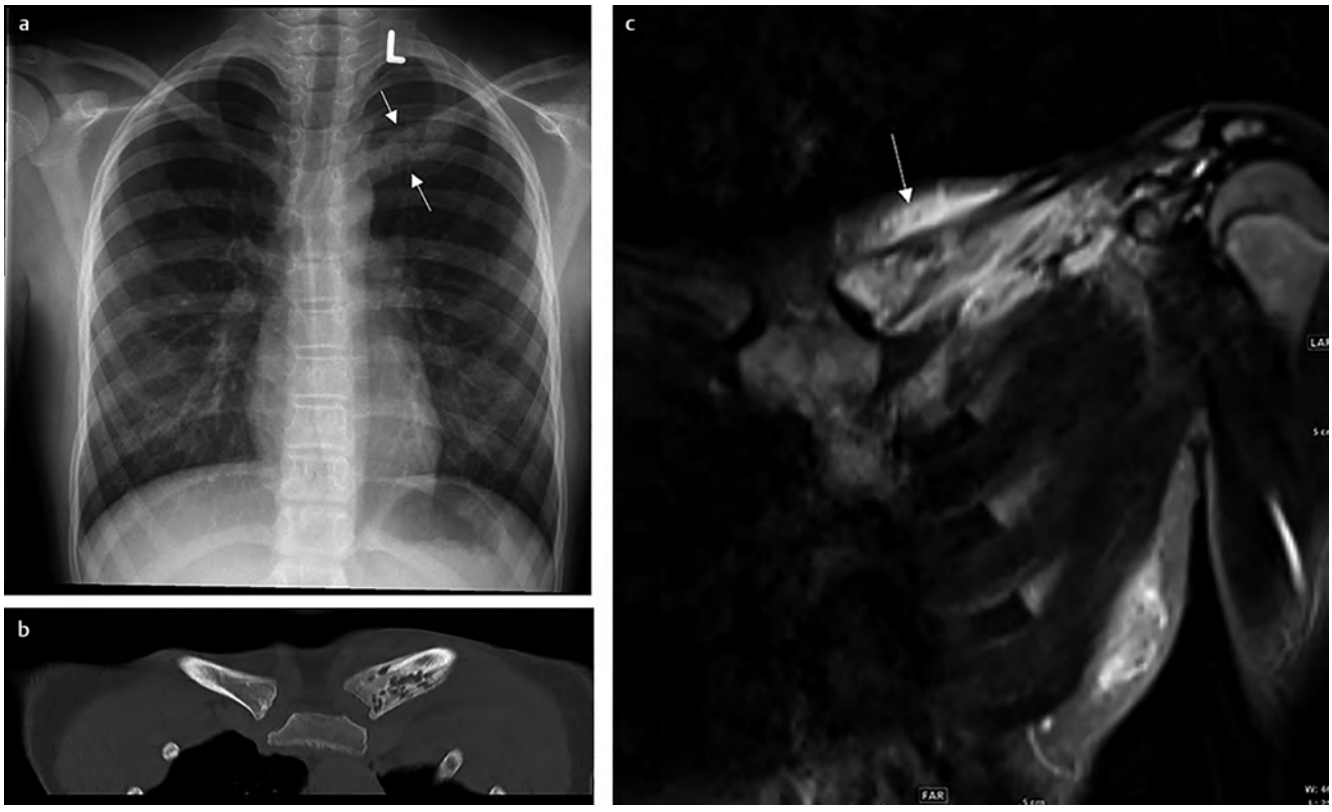
Differential diagnoses

CNO is a diagnosis of exclusion. This means that the potential differential diagnoses must be ruled out particularly in cases in which a biopsy was not performed and the diagnosis is made based solely on imaging. Infectious osteomyelitis including tuberculosis, Langerhans cell histiocytosis, and benign and malignant bone tumors including leukemia and lymphoma are the most common differential diagnoses [37]. In general, infectious osteomyelitis and bone tumors are usually unifocal [41]. The location in bone is not a reliable criterion for differentiation since both bacterial inflammation as well as many tumor diseases are primarily seen in the metaphyses. While subperiosteal abscesses, soft-tissue abscesses, and fistulas are strong indicators of infectious ostemyelitis, intraosseous abscesses can also occur in CNO. However, the typical multiple layers seen in a Brodie's abscess are absent [42] (▶ **Fig. 10**). Aggressive periosteal reactions and soft-tissue tumors are clear indicators of malignant tumor diseases. However, lymphoma or leukemic infiltration of bone can remain primarily limited to the medullary cavity and simulate an inflammatory process [43].

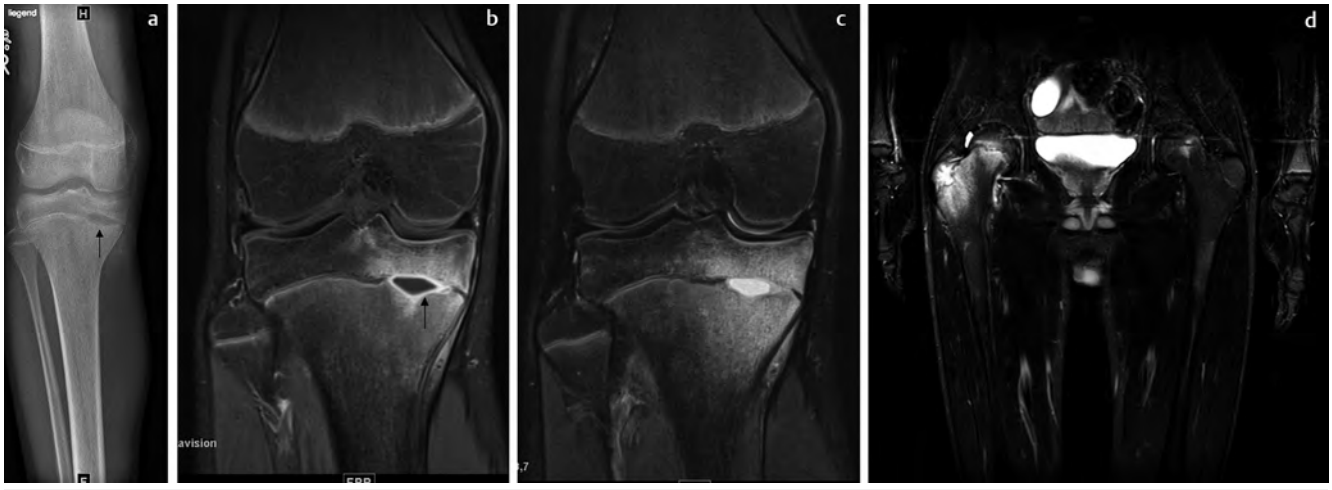
The most important and most difficult imaging-based differential diagnosis for CNO is LCH. Atypical proliferation of dendritic cells in various organ systems is seen in this disease. In the case of isolated bone involvement, it can be difficult to determine a differential diagnosis for CNO. For example, in the case of involvement of the vertebral bodies, the vertebra plana is a typical osseous manifestation of LCH that cannot be differentiated from CNO based purely on imaging [33] (▶ **Fig. 11**). In contrast, differentiation features are the predominant diaphyseal location of LCH lesions on the long bones and the frequent involvement of the skull, which is unusual for CNO. A metaphyseal location and multifocality are suggest the diagnosis of CNO [44].



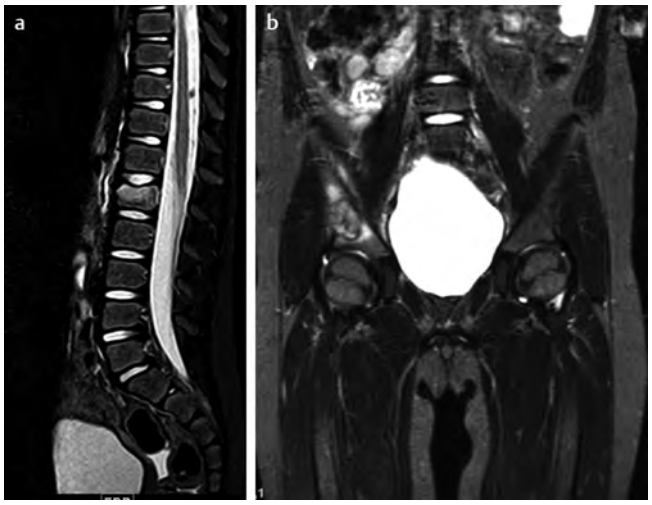
▶ **Fig. 8** Multiple lesions of the thoracic spine in a patient with CNO. Typical band-like bone marrow edema of the cranial and caudal end plates on whole-body MRI.



▶ **Fig. 9 a–c** Left-sided involvement of the clavicle in CNO. The radiograph shows distension of the left medial clavicle (→ **a**). The CT scan of the clavicle shows the typical combination of sclerotic and osteolytic changes as well as distended bone and formation of new bone (→ **b**). The MRI scan also shows pronounced inflammatory soft-tissue changes (→ **c**).



▶ **Fig. 10 a–d** Unusual abscess-like finding in the epiphyseal plate of the right proximal tibia in a 14-year-old male patient, who had been experiencing knee pain for weeks. Pseudo-widening of the epiphyseal plate on the radiograph (→ **a**). Contrast enhancement in the periphery of the fluid collection in the epiphyseal plate (→ **b**) and pronounced bone marrow edema (**c**). Curettage of the lesion was performed with sterile fluid. The patient had a history of severe acne vulgaris for months. Whole-body MRI showed typical additional findings of CNO, for example, adjacent to the right trochanter apophysis (**d**).



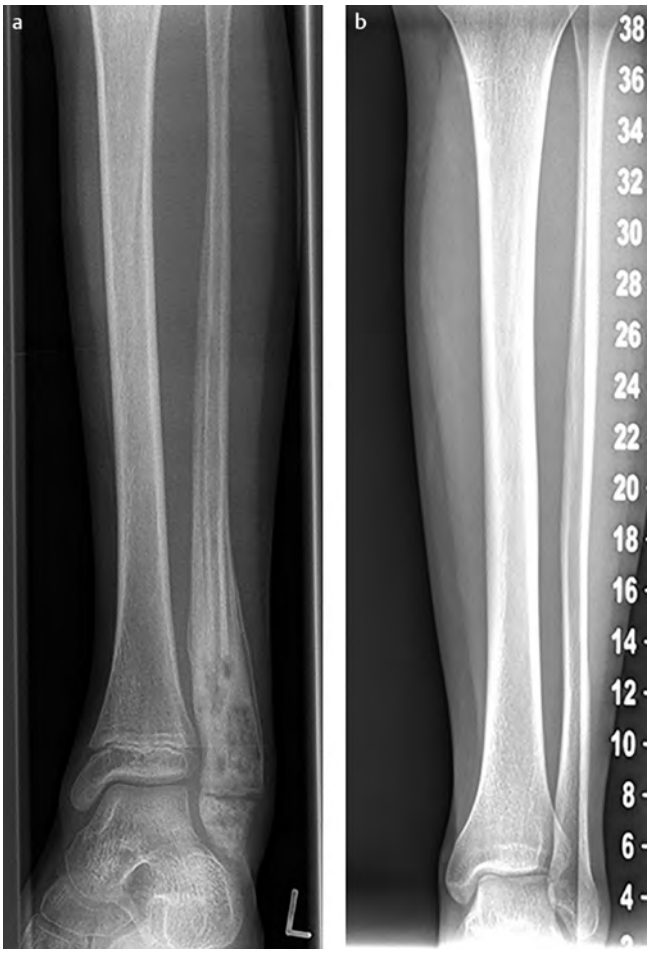
▶ **Fig. 11 a, b** Langerhans cell histiocytosis confirmed by biopsy in a 5-year-old girl who had been experiencing back pain for several weeks. Decreased height and bone marrow edema of L2 on the sagittal STIR image (**a**). Whole-body MRI showed an additional lesion in the right iliac bone consisting of a central lesion with surrounding bone marrow edema.

Follow-up

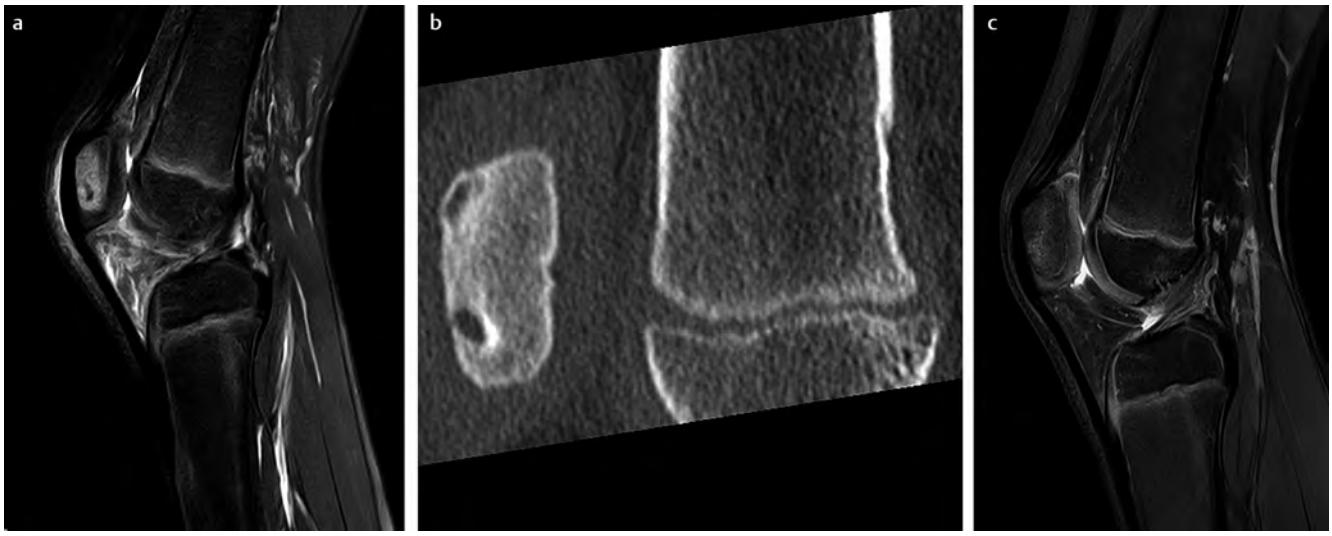
After diagnosis and the initiation of treatment, follow-up is necessary to confirm treatment response. This is important particularly in cases not confirmed by biopsy so that the diagnosis can be reconsidered in the case of a lack of treatment response. In addition to imaging, the improvement of symptoms during treatment indicates that the diagnosis is correct. Therefore, the interval for follow-up imaging should also depend on clinical presentation. In general, we perform the first follow-up MRI examination 6 weeks after the start of treatment. In the further course, follow-up intervals of 3–6 months are usually sufficient. After the discontinuation of medication, radiological follow-up is important to ensure that a recurrence of the disease is detected early [45]. Particularly in the case of pronounced changes in bone with hyperostosis and deformation on imaging, it can take months or even years until the bone changes regress (▶ **Fig. 12**) [31]. As already mentioned, a vertebral fracture is irreversible.

Conclusion and outlook

CNO is a common chronic inflammatory skeletal disease in children and adolescents caused by an excessive inflammatory reaction. Knowledge of the morphological features on imaging has resulted in CNO being diagnosed based on morphological characteristics on imaging findings alone in many cases, thereby significantly reducing the number of biopsies. The increasing use of whole-body MRI has contributed to this significantly since the multifocality in characteristic and often clinically asymptomatic locations can be shown. Therefore, attempts have been made to establish scores to standardize diagnosis. To date, there are primarily clinical scores, which use radiological criteria. In a study by Jansson et al., the radiological criteria > 1 lesion, presence of symmetrical bone lesions, presence of lesions with a sclerotic margin, and location in the sternum, clavicle, or spinal column are used to create a diagnostic score [14]. In a study by Roderick et al., the „Bristol diagnostic criteria“ are proposed for diagnosing CNO. The radiological criteria multifocality and osteolytic lesions with sclerosis and new formation of bone also play a major role here [46]. Purely radiological classifications have only been described to date to evaluate the disease extent and disease activity. The RINBO score (radiological index for NBO) described by Arnoldi et al. is based on whole-body MRI examinations and takes into consideration the number and size of lesions, extramedullary changes like periosteal or soft-tissue reactions, and involvement of the spinal column [29]. Since diagnosis is based on the combination of clinical, laboratory, and radiological parameters, the use of a purely radiological score for diagnosis has not been described to date. However, there are clear indications of CNO on imaging. The decisive step in radiological diagnosis is the early implementation of whole-body MRI to diagnose clinically inapparent but characteristic lesions. In principle, whole-body MRI is indicated for every unclear bone lesion that does not definitively correspond



▶ **Fig. 12 a, b** CNO of the left distal fibula confirmed by biopsy. The initial image showed pronounced expansion of the fibular shaft with formation of new periosteal bone, regions of osteolysis, and bone marrow sclerosis (**a**). Follow-up imaging 6 years later showed complete regression of the changes and remodeling of the bone (**b**).



▶ **Fig. 13 a–c** Unusual case of CNO with primary symptomatic involvement of the patella. The initial examination showed pronounced bone marrow edema of the patella and soft-tissue edema prepatellar and in the Hoffa's fat pad (**a**). Combination of osteolytic changes and sclerosis on CT (**b**). Whole-body MRI (not shown) showed additional characteristic lesions in the pelvis and metaphyses of the lower extremities. Under treatment with naproxen, complete regression of the changes seen on follow-up MRI 4 months later (**c**).

to bacterial osteomyelitis or tumor disease based on symptoms and X-ray morphology (▶ **Fig. 13**). As a result, unnecessary delays in diagnosis that can result in irreversible damage, particularly in the case of involvement of the spinal column can be avoided. A biopsy should be performed particularly in the case of unifocal lesions, lesions with advanced bone remodeling, lesions in atypical locations (e. g., diaphyseal), and a lack of treatment response [46].

Conflict of Interest

The authors declare that they have no conflict of interest.

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