Abstract

Chronic Non-Bacterial Osteitis (CNO) is a rare auto inflammatory bone disorder that results in a spectrum of bone lesions. While the pathophysiology of CNO is not well understood, recent studies have shown a derangement on inflammatory markers (such as TNF-α, IL-6, IL-20, IL-10 and IL-19). Patients are usually young females and present with localized pain. Since this presentation is nonspecific, a delay in diagnosis and appropriate treatment may occur. Workup shows that patients have normal to moderately elevated inflammatory markers like ESR and CRP. Bone biopsies may be done if the diagnosis is indeterminate and are negative for infectious etiology. Initial imaging usually consists of radiographs at symptomatic sites. Lesions start as osteolysis lesions and progress to sclerotic lesions. Lesions are most commonly found in the metaphyseal region of the long bones. If initial imaging studies are negative, then localized MRI is done to look for bone marrow edema. Whole body MRI and bone scan are often used to assess for silent lesions. First line treatment consists of NSAIDs. Second line agents include corticosteroids, TNF-α antagonists, methotrexate, and bisphosphonate. While many patients do well, some patients may unfortunately have persistent symptoms leading to development of arthritis, pathological fractures, limb-length discrepancies, and scoliosis.

Pathophysiology

As opposed to autoimmune disorders which may see a derangement in T cells levels and autoantibody levels, CNO is an auto inflammatory disorder with dysregulation of the innate immune system. While the exact pathophysiology of CNO is not fully understood, recent studies have suggested derangement in various cytokine levels as potential causes for the bone lesions [3-6]. In individuals with CRMO, there was evidence of increased pro-inflammatory markers such as TNF-α, IL-6, and IL-20 and decreased expression of anti-inflammatory markers such as IL-10 and IL-19 [6,7]. Additionally, animal studies showed a link between IL-10 deficiency, increased NLRP3 Inflammasome activity, and bone erosions [8]. Pro-inflammatory cytokines can also upregulate RANKL which leads to increased levels of osteoclasts [9]. Thus, this suggests a possible connection to the cytokine imbalances leading to the bone lesions [6]. Furthermore, there is some thought that certain bacteria like Propionibacterium acnes may act as a trigger for an inflammatory cascade that can lead to CNO in susceptible individuals [10-15]. P. acnes may cause increased activation of the Inflammasome and pro-inflammatory cytokines (such as IL-1β and IL-18) that can potentially lead to the bone lesions [6]. Furthermore, there is some thought that certain bacteria like Propionibacterium acnes may act as a trigger for an inflammatory cascade that can lead to CNO in susceptible individuals [10-15]. P. acnes may cause increased activation of the Inflammasome and pro-inflammatory cytokines (such as IL-1β and IL-18) that can potentially lead to the bone lesions [6]. Furthermore, there is some thought that certain bacteria like Propionibacterium acnes may act as a trigger for an inflammatory cascade that can lead to CNO in susceptible individuals [10-15]. 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Clinical Features/Workup

Patients usually have nonspecific clinical findings. They are usually young, female (2:1 female to male ratio) and present with localized bone pain usually in the lower extremities, clavicle, and/or pelvis23. Only about 33% of patients have low grade fevers [13]. There is an association with other autoimmune and auto inflammatory disorders like inflammatory bowel disease (IBD), psoriasis, and palmoplantar pustulosis [14]. Additionally, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome is thought to be a similar, possibly related, condition in which patients have bone lesions along with characteristic skin findings of palmoplantar pustulosis (blistering of the palms and soles). SAPHO patients present as adults rather than children. Workup usually consists of imaging of the symptomatic site and laboratory studies like CBC, ESR, and CRP. Values of the inflammatory markers range from normal to moderately elevated [15,16]. When inflammatory markers and WBC count were severely elevated, there is an increase concern for malignancy or infection [16]. The decision whether to perform a bone biopsy is more varied among practitioners. In a recent study assessing the diagnostic approach pediatric rheumatologist utilize in diagnosing CNO, the clinicians tended to perform bone biopsies when patients presented with solitary bone lesions, constitutional symptoms (fever, weight loss, night sweats), and nocturnal bone pain as they had increased suspicion for malignancy or infection [17]. However, when patients had multifocal lesions in classic sites or had associated conditions like IBD or psoriasis, the clinicians tended to avoid bone biopsy [17]. Additionally created a scoring system to determine whether to obtain a bone biopsy. In this scoring system, Jansson et al. designated a score coefficient to several risk factors such as normal blood cell count: 13 points, symmetric lesions: 10 points, lesions with marginal sclerosis: 10 points, normal body temperature: 9 points, vertebral, clavicular, or subacromial lesion 8 points, radiographically proven lesions ≥ 2; 7 points, and CRP ≥ 1: 6 points [17]. Patients with a score ≥ 39 had a positive predictive value of 97% for CNO, and a score ≤ 28 had a negative predictive value of 97% [17]. Recommended bone biopsy only in the individuals with a single lesion and a score ≥ 28. Score values between 29-38 were indeterminate and require close clinical monitoring [18] also created the Bristol diagnostic criteria based off a cohort study from children diagnosed with CNO at Bristol Royal Hospital for Children to reduce delay in diagnosis [19]. Based on this criteria, CNO can be diagnosed with the 1) presence of typical clinical findings, 2) the presence of typical radiological findings and either 3) >1 bone lesion with CRP <30 mg/L or 4) unifocal disease and/or CRP>30 with negative bacterial growth on bone biopsy [19]. (Figures 1-4).

Image Findings

The most common imaging studies ordered is conventional radiographs (89%), local MRIs (79%), and bone scintigraphy (43%) and whole body MRI (36%) [17]. Therefore, initial imaging consists of radiographs at symptomatic sites. Bone lesions start as osteolytic lesions. Over time, the images develop sclerosis around the osteolytic lesions. Eventually, the lesions may become predominately sclerotic [20]. Bone lesions can occur anywhere throughout the body. However, they tend to have a predisposition to the metaphyseal region of bones (75%) [20]. Additionally, common sites of involvement include the clavicle (34%), pelvis (34%), tibia (31%), and femur (31%) [15]. While there are no pathognomonic imaging findings for CNO, clavicle lesions tend to be strongly associated with CNO as clavicle is usually spared during bacterial osteomyelitis [20].

Another characteristic site for CNO is the mandible, which is seen in approximately 5% of patients [20]. Lytic lesions can cause disruption of the cortical and trabecular bone and subsequent sclerosis can eventually cause enlargement of the mandible. If the initial studies are negative, then localized MRI is done to look for bone marrow edema (decreased signal on T1 weighted images and increased signal on T2 weighted images) [20]. While patients may initially present with a single site of painful bone involvement, studies have shown that patient have, on average, ~3.5 bony lesions [15-21]. To evaluate these silent lesions, bone scintigraphy and/or whole-body MRI are used. Bone scintigraphy uses Technetium 99 m to identify areas of bone remodeling. Thus, bone scintigraphy has been shown to be sensitive to determine clinically silent lesions [22].
Additionally, it can better identify spinal and pelvic lesions that are difficult to assess via X-Rays [22]. Lesions will show initial hyperemia with focal areas of increased uptake on delayed phase images [22]. Bone scintigraphy tends to be more readily available and less expensive than whole-body MRIs [20]. However, whole body MRI has been shown to have improved sensitivity [23]. Therefore, MRI is now being utilized at an increasing rate to evaluate for silent lesions. On MRI, the lesions may be visible along with marrow edema and surrounding soft-tissue inflammations. Whole body MRI use short-tau inversion recovery (STIR) and T1-weighted pulse sequences for evaluation [23,24]. Abnormal lesions have increased signal on the STIR sequence and decreased signal on the T1 weighted sequence [23,24]. Patients are often having follow up imaging to assess for the status of known lesions and to assess for any new lesions [25]. Whole body MRI is recommended, but bone scintigraphy often is done due to increased availability.

**Histopathology**

Bone biopsy shows evidence of inflammation without the presence of microorganisms. Initially, there are increased polymorphonuclear leukocytes, but later stages have increased lymphocytes [26]. Occasionally, bone cultures may be positive for *P. acnes*. However, this is usually considered to be a contaminant rather than a direct bacterial cause of the patient lesions [3-27].

**Figure 2**: Patient 2 imaging review.

a. Figure 2A: AP view X-ray of pelvis showing a sclerotic left iliac lesion.

b. Figure 2B: Axial CT demonstrating sclerotic left iliac lesion.

c. Figure 2C: T2 MRI of the pelvis demonstrating left iliac cortical sclerosis and underlying bone marrow edema.

d. Figure 2D: AP view X-ray of the right clavicle showing increased sclerosis. Findings consistent with multifocal CNO in the same patient.

e. Figure 2E: MRI of the clavicle showing cortical sclerosis and bone marrow edema.

**Figure 3**: Patient 3 imaging review.

a. Figure 3A: AP view X-ray of the left hummers showing cortical sclerosis.

b. Figure 3B: Coronal and axial CT scans showing cortical sclerosis with intramedullary calcifications consistent with long staging sclerotic reparative lesion with both endosteal and periosteal components.

c. Figure 3C: 3 phase bone scan demonstrating increased radiotracer activity in the proximal to mid-hummers.

**Figure 4**: Patient 4 imaging review.

a. Figure 4A: One view X-ray showing chronic thickening and mature periosteal reaction.

b. Figure 4B: Axial T1 post contrast demonstrating bone marrow edema and ongoing maturing periostitis.

c. Figure 4C: Axial T1 shows cortical thickening and bone marrow edema.

d. Figure 4D: Coronal T1 demonstrating sclerosis and mature periosteal reaction.
Treatment options

Many patients are started on antibiotics due to misdiagnosis of bacterial osteomyelitis. This can cause unnecessary hospitalization (IV antibiotics) or prolonged oral antibiotic regimens. One study showed that 54% of the patients had received at least one course of IV antibiotics before diagnosis [19]. Not only does this cause an unnecessary medical burden, it delays the appropriate diagnosis and appropriate treatment.

Unfortunately, an evidence based treatment protocol has not been well defined as current treatment regimens are empiric based. Generally, the first line treatment is non steroidal anti-inflammatory drugs (NSAIDs) [3]. Some studies have shown up to 80% success with NSAIDs [28]. However, some studies may contest the effectiveness of NSAIDs as they may not effectively treat the underlying problem. One study showed while there was improved symptom relief and overall reduction in lesions after starting naproxen therapy, 41% of the patients still developed new lesions detected on whole body MRI. More research and randomized controlled trials need to be done to understand the true effectiveness of NSAIDs in treating and preventing new lesions [25].

There is no consensus on second-line agents, but some options include corticosteroids, TNF-α antagonist, DMARDs like methotrexate, and bisphosphonates. Bisphosphonate therapy like pamidronate and alendronate is encouraging and has shown patient improvement especially with mandibular lesions [29-36]. However, the long-term side effects in children have not been well studied, which has somewhat limited increased adoption. Ultimately, treatment is done to improve prognosis and prevent the complications of the bone lesions and provide symptomatic pain relief.

Prognosis

Most patients usually have a good long term prognosis [31]. A study by showed a 78% of patients after 13 years of follow up had a score of 0 measures by the Health Assessment Questionnaire (HAQ) suggesting no physical disability [31]. Another study by showed a HAQ of 0 in 59% of patients [21]. However, the study by also demonstrated that patients had CNO lesion for median of 5.7 years and about 25% of patients had persistent symptoms more than 12 years. Much of the sequelae of CNO depend on the location of the lesions. Many patients end up developing arthritis [25]. Lesions near the growth plate can lead to their premature closure resulting in limb-length discrepancy, which should be treated immediately to minimize morbidity [32]. Pathological fractures can occur when the integrity of the bones is compromised [33]. Lesions in the spine can lead to kyphosis, scoliosis, and up to 40% may develop vertebral fractures [33]. Mandibular lesions can result in paresthesia and their extension to the Temporomandibular joint can lead to trismus [37].

Conclusion

While CNO diagnosis often requires a multidisciplinary approach, general practitioners and pediatricians will often be the first point of contact for many of the patients that suffer from bone pain. Thus, early recognition of CNO by these individuals can lead to prompt treatment with NSAIDs and avoid costly hospitalizations, antibiotics, unnecessary bone biopsies, and improper imaging studies. It can also help prevent more serious complications like limb-length discrepancies and pathological fractures.

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None.

Conflict of Interest

All authors declare no conflict of interests.

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