Review

Chronic Non-bacterial Osteomyelitis in Inflammatory Bowel Disease

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Chronic Non-Bacterial Osteomyelitis in Inflammatory Bowel Disease

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Abstract: Chronic non-bacterial osteomyelitis (CNO), also known as chronic recurrent multifocal osteomyelitis (CRMO), is a rare autoinflammatory bone disease primarily affecting children and adolescents. This review presents a comprehensive analysis of the intricate relationship between CNO and inflammatory bowel disease (IBD), shedding light on shared pathophysiological mechanisms and clinical management. A thorough literature review was conducted, encompassing 24 case reports involving 40 patients. The demographic distribution of patients revealed a near-equal gender ratio, with a median age of diagnosis at 12 years. The diagnosis patterns showed a higher proportion of CNO as the initial diagnosis, while Crohn's disease was more prevalent than ulcerative colitis. The time interval between the clinical presentations varied, ranging from simultaneous detection to a substantial 15-year gap. Treatment modalities included non-steroidal anti-inflammatory drugs (NSAIDs), steroids, aminosalicylates, and biologic agents, such as infliximab, often overlapping in their use, suggesting shared pathophysiological pathways. Both conditions displayed systemic manifestations, and patients often responded well to immunosuppressive medications. The pathophysiology of CNO involves genetic predisposition, cytokine dysregulation, and osteoclast activation. Dysregulated innate immunity results in immune cell infiltration into bones, causing sterile bone lesions. Notably, emerging evidence hints at a potential link between the microbiome and CNO. In contrast, IBD results from imbalanced mucosal immune responses to the intestinal microbiota. Polymorphisms in the promotor region of IL-10, common cytokines, immune cells, and genetic markers indicate shared immunological and genetic factors between CNO and IBD. Both conditions also involve extraintestinal symptoms. This analysis underscores the need for clinical awareness of the co-occurrence of CNO and IBD, especially among pediatric patients. A deepened understanding of the connections between these seemingly distinct diseases could lead to more effective management and improved patient outcomes.

Keywords: CRMO; Crohn's disease; inflammatory bowel disease; osteomyelitis; pediatrics; ulcerative colitis

Introduction

Chronic non-bacterial osteomyelitis (CNO), also known as Chronic Recurrent Multifocal Osteomyelitis (CRMO), is a rare autoinflammatory bone disease that primarily affects children and adolescents. Despite its rarity, CNO can significantly impact the lives of young patients and their families [1]. Inflammatory Bowel Disease (IBD), a group of chronic inflammatory disorders affecting the gastrointestinal tract, is a condition that shares intriguing similarities with CNO. Notably, while IBD primarily involves the gut and CNO affects the bones, there is a growing body of evidence pointing to overlapping pathophysiological mechanisms between these seemingly distinct conditions. Commonalities observed in genetics, environmental influences, microbiome dysbiosis, systemic manifestations, and response to treatment suggest potential shared pathophysiological mechanisms [1]. The primary objective of this analysis is to consolidate and elucidate the information

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surrounding these two medical conditions, shedding light on any discernible patterns, connections, or insights revealed by prior research and to contribute to the existing body of knowledge in the medical field, fostering a deeper understanding of the relationship between CNO and IBD.

Methods

We conducted a search of the Medline-indexed literature on PubMed by combining the following search terms and keywords: ''Chronic Recurrent Multifocal Osteomyelitis'', ''Chronic non-bacterial Osteomyelitis'', ''CNO'', ''CRMO'', ''CRMO and IBD'', ''CNO and IBD'', ''Inflammatory Bowel Disease and Osteomyelitis'', ''Crohn's Disease and CRMO'', ''Ulcerative Colitis and CRMO'', ''Crohn's Disease and CNO'', and ''Ulcerative Colitis and CNO''. We also conducted a supplementary search by examining the reference lists of identified articles for additional papers. Our inclusion criteria encompassed case reports or case series, cohort studies, and clinical studies that investigate the co-occurrence or association between CNO and IBD, as well as articles providing detailed clinical and diagnostic information on patients with both CNO and IBD. We limited our results to English language publications. Exclusion criteria were applied to studies not directly related to the association between CNO and IBD, articles lacking sufficient clinical information, and duplicates or overlapping data. Two independent reviewers performed the initial screening of articles based on their titles and abstracts. Full-text articles were subsequently reviewed to determine their eligibility for inclusion in this literature review. Any differences in judgment were resolved through discussion and consensus.

Results

A comprehensive review of 24 case reports involving a total of 40 patients shed light on the intricate correlation between IBD and CNO [2–25] (Table 1). Among these patients, 22 (55%) were females, and 18 (45%) were males, reflecting a nearly equal gender distribution. The median age of the patients was 12 years, with ages ranging from as young as 9 months to as old as 41 years. The analysis revealed distinct patterns in the diagnosis of CNO and IBD among the study population. A significant majority of patients, numbering 21 (52.5%), received their initial diagnosis of CNO. Conversely, 13 patients (32.5%) diagnosis of IBD proceed the one of CNO. A smaller subset of 5 patients (12.5%) received concurrent diagnoses of both Chronic CNO and IBD. Further delineating the IBD cases, 23 patients (57.5%) were diagnosed with Crohn's disease, while 15 patients (37.5%) presented with ulcerative colitis, while 2 of them (5%) are identified as unclassified IBD (Table 2). This conclusion aligns with the percentages attributed in the review by Costi et al (2023) [26]. The median time interval between the two clinical presentations was 2 years, encompassing a spectrum ranging from concomitant diagnosis to an extended 15-year duration.

Table 1. Summary of case reports and case series identified by systematic literature search.

First author/year	No of patients	Age	Sex	IBD type	Treatment for CNO	Treatment for IBD
Kotilainen (1996) [2]	1	29	F	CD		steroids/aminosalicylates/ azathioprine
Omidi (1998) [3]	1	12	F	UC		steroids
Bousvaros (1999) [4]	6	10	F	UC	steroids	steroids/aminosalicylates/ aminosalicylate enemas
		8	M	UC	steroids/aminosalicylates	steroids/aminosalicylates
		8	F	CD	NSAIDs	steroids/aminosalicylates
		13	F	CD		steroids/azathioprine
		10	M	CD	NSAIDs	steroids/aminosalicylates
		10	F	CD		steroids/aminosalicylates/ MTX
Bazrafshan (2000) [5]	1	12	F	UC	NSAIDs	steroids/aminosalicylates

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Carpenter (2004) [6]	1	9	F	CD	NSAIDs	steroids/6 - MP/ azathioprine/infliximab
Girschick (2007) [7]	1	9	F	CD	NSAIDs	steroids/aminosalicylates/ azathioprine
Bret (2008) [8]	1	29	M	CD	NSAIDs/pamidronate	aminosalicylates/ azathioprine/infliximab
Morbach (2009) [9]	4	12	M	CD		
		15	M	CD		
		15	M	CD		
		10	F	CD		
Kim (2012) [10]	1	41	M	UC	intra-articular steroid injection/pamidronate/ MTX/steroid/NSAIDs	aminosalicylates/colectomy
Audu (2015) [11]	3	9	M	UC		steroids/aminosalicylates
		10	F	CD	NSAIDs/steroids/pamidronate	
		2	M	CD	IVIG/steroids	Enteral feed/ azathioprine/gastrostomy
Christi van Ommen (2015) [12]	1	10	M	CD	NSAIDs	infliximab/azathioprine/ steroids/modulen
Ahmed (2018) [13]	1	11	F	UC	steroids	steroids/aminosalicylates/ azathioprine
Ramraj (2018) [14]	1	16	M	CD		anti-TNF-α
Campbell (2018) [15]	1 (of 5)	11	F	CD	NSAIDs/aminosalicylates/pamidronate/adalimumab	infliximab/MTX
Kołodziejczyk (2019) [16]	1	4,5	M	UC	NSAIDs	steroids/aminosalicylates/ azathioprine/MTX/ adalimumab
De Guerra (2019) [17]	1	15	F	UC	NSAID/steroids	steroids/aminosalicylates/ infliximab
Lorenze (2020) [18]	1	12	F	UC	steroids/MTX	Infliximab
Fujisaki (2020) [19]	1	13	M	CD		steroids/infliximab
Kim (2021) [20]	1	21	M	UC	NSAIDs	steroids/aminosalicylates/ azathioprine
Ng (2021) [21]	1	12	F	UC	zoledronic acid	steroids/azathioprine/ ursodeoxycholic acid
Cantarelli (2021) [22]	1	10	M	CD	adalimumab	adalimumab/infliximab/ CD diet/ MTX
Dushnicky (2021) [23]	7	8	M	UC	NSAIDs	aminosalicylates
		9	F	IBD-U	NSAIDs	steroids
		13	F	CD	NSAIDs	Enteral nutritional therapy/MTX
		9months	M	CD	MTX	sulfasalazine/Adalimumab
		9	F	UC	MTX/Adalimumab	sulfasalazine/Adalimumab
		9	F	CD	Infliximab/ustekinumab	Enteral nutritional therapy/MTX/Infliximab/ Ustekinumab
		12	F	IBD-U	NSAIDs	aminosalicylates/ sulfasalazine/infliximab

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Goldfarb (2022) [24]	1	5	M	CD	ketorolac	Parenteral nutrition/pulse steroids/infliximab
Mambelli (2022) [25]	1	10	F	UC	salazopirine	anti-TNF-α

6-MP: 6-mercaptopurine; anti-TNF-α: anti tumour-necrosis factor-α; CD: Crohn's Disease; CNO: Chronic Nonbacterial Osteomyelitis; F: female; M: male; MTX: methotrexate; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; IBD: Inflammatory Bowel Disease; IBD-U: Undifferentiated Inflammatory Bowel Disease; IVIG: Intravenous Immunoglobulin; UC: Ulcerative Colitis.

Table 2. Patient characteristics.

Female	22/40 (55%)
Median age (range)	12 (9 months - 41 years)
1st diagnosis CNO	21/40 (52.5%)
1st diagnosis IBD	13/40 (32.5%)
Crohn's disease	23/40 (57.5%)
Ulcerative colitis	15/40 (37.5%)

CNO: Chronic Nonbacterial Osteomyelitis; IBD: Inflammatory Bowel Disease.

Clinical interventions administered for the management of these conditions included various therapeutic options. For CNO non-steroidal anti-Inflammatory drugs (NSAIDs) were administered to 17 patients, representing 42.5% of cases. Biphosphonates such as zoledronic acid was prescribed to a single patient and pamidronate acid was employed in 4 cases, addressing CNO in 19.0% of instances. For IBD, corticosteroids were employed in the management of 24 cases with both CNO and IBD (60%). Aminosalicylates were prescribed for 18 patients (45%) to address both CNO and IBD concurrently. Infliximab was used in 10 cases (25%) as a treatment for IBD or/and CNO and adalimumab was utilized in 5 cases. Additionally, Tumor Necrosis Factor α inhibitor (anti-TNF-α) therapy was administered in two more cases without specifying the specific agent utilized. Azathioprine was also administered to 11 patients (27.5%) for the treatment of IBD. Finally, methotrexate was employed in 10 patients (25%) for the management of both CNO and IBD. In two instances (5%), colectomy was performed as a necessary surgical intervention due to the severity of IBD [5,10]. Additionally, one patient within the cohort was identified as having Takayasu arteritis and received intravenous immunoglobulin (IVIG) therapy, underscoring the complexity of overlapping autoimmune conditions [16]. Different conditions coexisted in several cases, with primary sclerosing cholangitis being the most common in 3 out of 40 cases each [4,8,27], and others such as psoriasis (2/40) pyoderma gangrenosum (1/40) [28], Takayasu arteritis (1/40) [16], and eosinophilic esophagitis (1/40) [11] (Table 3). Furthermore, in the case series by Campbell et al. as well as Dushnicky et al., among other cases, psoriasis is described in the context of managing CNO with Crohn's disease with TNF-inhibitors, specifically infliximab and adalimumab [14,23]. Cantarelli et al. describe the successful treatment of refractory Crohn's disease in combination with CNO in a 10-year-old patient using a combination therapy of infliximab, methotrexate, and Crohn's disease exclusion diet plus partial enteral nutrition, as suggested by Levine et al. [29,30]. It is important to note that in 8 case reports (20%, 8/40), intravenous antibiotics were reported to be used for the treatment of osteomyelitis before arriving at the diagnosis of CNO. In terms of laboratory findings there were no specific autoantibodies noted to be elevated in most cases of concurrent CNO with IBD, except for positive ANCA antibodies identified in 4 case reports [4,8,11,28].

Table 3. Comorbidities.

Primary sclerosing cholangitis	3/40 (7.5%)
Psoriasis	2/40 (5%)
Pyoderma gangrenosum	1/40 (2.5%)
Takayasu arteritis	1/40 (2.5%)
Eosinophilic esophagitis	1/40 (2.5%)

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Discussion

Kahn et al. [31] first described concurrent diagnosis of CNO and IBD. Following that, an expanding body of literature has emerged, including case reports and case series detailing this connection. While most of these reports center on pediatric cases, it is noteworthy that in reported instances, the initial symptoms manifested after individuals reached 18 years of age. CNO particularly affects children, but it can persist in adulthood or present later in life. The average age at diagnosis is 9–11 years [32], but the delay in diagnosis from the onset of symptoms is usually around 1 year [33,34]. The incidence of the disease is estimated to be 0.4 per 100,000 children [33,35]with a slight predominance over females than males [36]. However, in series from India and Japan a male predominance is observed [37]. The actual prevalence of CNO is probably understated in earlier studies due to advancements in imaging and diagnostic methods, as well as the notable surge in noninfectious osteomyelitis case reports and series during the past decade [34]. It can affect all ethnicities, although White Causacian population is most frequently affected [38].

In this comprehensive analysis of 24 case reports, the complex relationship between IBD and CNO, especially in pediatric patients, is emphasized. The demographic distribution reveals a nearly equal gender ratio, with a median age of diagnosis at 12 years. The diagnostic sequence shows a higher proportion of CNO as the initial diagnosis, while Crohn's disease was more prevalent than ulcerative colitis. Additionally, the temporal pattern of diagnosis ranged from simultaneous detection to a substantial time gap of 15 years between the clinical presentation of symptoms. The therapeutic approach encompassed a range of medications, with steroids being the most commonly used in both CNO and IBD cases. NSAIDs, steroids, aminosalicylates, and biologic agents (with infliximab being one of the most prominent) are the most used drugs in the treatment of both conditions. They often overlap in their therapeutic use, suggesting that they may follow a similar pathophysiological or molecular pathway.

The clinical presentation of CNO can vary widely from one patient to another, making it a challenging diagnosis to establish. Common symptoms include focal bone pain and tenderness at the affected sites [32,39]. However, further musculoskeletal symptoms, such as swelling, skeletal deformities, and joint pain, may also be involved. The most commonly affected sites are long bones, particularly the epiphyses and metaphyses, with the femur, tibia, and pelvis being the most frequently involved [40,41]. These symptoms can be intermittent and may occur in flares. CNO can affect multiple bones simultaneously, a phenomenon known as multifocality, or it may involve a single bone. Some patients may also experience multifocal lesions that are gradually diagnosed during their follow-up [42]. Systemic symptoms, such as fever and fatigue, are less frequently observed and may raise suspicion for alternative diagnoses [41,43]. Cutaneous manifestations may also be present, including acne, psoriasis, palmoplantar pustulosis, and pyoderma [41]. Skin involvement is further encountered in the context of the Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) symptom complex, which could be considered as the adult form of CNO [44].

Several factors are known to be involved in the pathophysiology of CNO. Dysregulated innate immunity results in immune cell infiltration into the bones, subsequently activating osteoclasts and causing sterile bone lesions [12]. One central aspect of the condition is the disrupted balance of cytokines and chemokines within the immune cells. In patients with CNO, immune cells called monocytes show reduced levels of immune-regulating cytokines like IL-10 and IL-19, while displaying elevated levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (IL-8, IP-10, MCP-1, MIP-1a, MIP-1b). This imbalance is partially due to a faulty activation of specific signaling pathways, leading to reduced expression of regulatory factors (Sp-1) that control the production of IL-10 and IL-19. Additionally, this impaired signaling affects histone proteins, which regulate gene expression. This chain reaction results in altered gene expression patterns, further complicating the immune response [6,41].

Another crucial observation is the increased activity of the NLRP3 inflammasome, a complex that triggers the release of the highly inflammatory IL-1β. This molecular imbalance does not just impact the immune system but also affects osteoclasts, cells responsible for bone maintenance. While some individuals with CNO have a clear genetic component or are linked to other autoimmune or

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inflammatory disorders, many cases do not stem from a single genetic mutation. These cases involve a combination of genetic predisposition and environmental factors, making it challenging to pinpoint specific genes responsible for the condition [45]. However, certain syndromic forms of CNO, like Majeed syndrome and deficiency of the IL-1 receptor antagonist (DIRA), have been linked to specific gene mutations (LPIN2 and IL1RN), shedding light on the role of IL-1β in inflammation. It is important to note that these mutations explain only a minority of CRMO cases, and for most patients, the genetic factors predisposing them to the disease remain unclear [46].

Zhao et al. [45] propose a potential link between the microbiome and CNO. Emerging evidence suggests that interactions with these microorganisms may impact immune balance and potentially play a role in disease onset. Animal model research has demonstrated that manipulating the microbiome can prevent osteomyelitis.

Eventually, the pathophysiology of CNO involves a complex interplay of genetic predisposition, cytokine dysregulation, osteoclast activation, and potentially, interactions with the microbiome. While much progress has been made, further research is needed to fully understand the intricate mechanisms underlying this enigmatic condition. While the molecular pathophysiology remains partially understood, it is intriguingly linked to other auto-inflammatory conditions like inflammatory bowel disease (IBD), psoriasis, Wegener's disease, SAPHO syndrome. Chronic Nonbacterial Osteomyelitis (CNO) may manifest several years before the symptoms of the associated disease, the bone remodeling induced by CNO can lead to lasting disability [47,48].

Inflammatory bowel disease (IBD) is thought to result from an imbalanced response of the mucosal immune system to the intestinal microbiota. This dysregulation can manifest as both excessive immune reactivity and inadequate immune responses. Dysregulation of IL-10 is a shared pathophysiological mechanism between CNO and IBD, as polymorphisms in the promotor region of IL-10 have been met in IBD patients [49]. Also, the link between IBD and musculoskeletal manifestations, is well established, indicating a gut-synovial axis [50], while some reports even suggest CNO as an extraintestinal IBD manifestation [17]. Gut immune responses can affect the joints with TNF-α, IL-12 and IL-23 playing crucial roles. TNF-α upregulation is present in IBD, arthritis and CNO, explaining the positive response to anti-TNF-α [23]. IL-12 has been noted as a marker for treatment response in CNO [51]. IL-23 has not been measured in patients with CNO; however, ustekinumab an IL-12/IL-23 inhibitor, showed promise in one patient, prompting further study [23]. Common cytokines and immune cells are implicated in both conditions, as mentioned above, suggesting a shared immunological basis. Also, there is evidence of a genetic predisposition to both CNO and IBD. Certain genetic markers and susceptibility genes have been identified in both conditions, indicating potential shared genetic factors. The NLRP3 gene mutations associated with autoinflammatory syndromes have been found in some CNO patients as mentioned, and similar genetic mutations are implicated in IBD [41]. Both CNO and IBD can have systemic manifestations beyond their primary sites of inflammation. For example, patients with IBD may experience extraintestinal symptoms like joint inflammation (arthritis), skin conditions (psoriasis), and eye inflammation (uveitis). Similarly, CNO can lead to musculoskeletal symptoms beyond bone inflammation [31,47,48]. Furthermore, patients presenting with both CNO and IBD often respond positively to immunosuppressive medications that help control inflammation. Medications such as corticosteroids, immunomodulators, and biologic factors are commonly used in the treatment of both conditions [47,52].

CNO should be considered as a potential diagnosis in a pediatric patient experiencing recurring or constant localized discomfort in the bones or joints of the lower limbs, clavicle, spine, or jaw. Some patients might also experience localized swelling and increased warmth in the affected region. This pain tends to intensify at night, potentially leading to sleep disruption [26]. Laboratory evaluation is necessary to complement the diagnostic process. A complete blood count (CBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) should be routinely performed to assess the possibility of infectious osteomyelitis. It is worth noting that most children with CNO typically present with normal CBC, CRP, and ESR values, although some may exhibit significantly elevated

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CRP and ESR levels. Importantly, there seems to be no discernible link between the number or location of bone lesions and these laboratory findings [38,53].

Imaging plays a crucial role in diagnosing CNO in pediatric patients. Whole-body MRI is commonly regarded as the preferred imaging modality and often considered the gold standard, although it may not be available in all centers. In most cases, patients typically undergo an initial radiographic assessment. Plain radiographs are easily accessible but lack sensitivity. Usual observations include osteolytic lesions surrounded by sclerosis and/or hyperostosis. However, MRI is the preferred choice due to its high sensitivity and the absence of radiation exposure [54]. Findings such as bone edema, sometimes accompanied by periosteal reaction and hyperostosis, as well as soft tissue inflammation, support the diagnosis of CNO [55,56].

In some cases, a bone biopsy in multiple sites is performed in the initial stages of the diagnostic procedure, primarily to exclude infectious agents or malignant syndromes such as leukemia or intraosseous lymphoma. Common histologic findings include acute and/or chronic inflammation, bone marrow fibrosis, and osteonecrosis, while results may return normal [54].

Zhao et al. [55] conducted a survey among pediatric rheumatologists through the Childhood Arthritis and Rheumatology Research Alliance (CARRA) in 2016. The study aimed to determine physicians' approaches to diagnosing CNO. X-ray (89%) emerged as the most commonly used diagnostic imaging modality, followed by regional MRI (78%) and bone scintigraphy (43%). The top three MRI findings considered indicative of active disease were bone edema (43%), periosteal reaction (37%), and soft tissue inflammation (28%). Vertebral compression, fracture, and physeal irregularity were identified as poor prognosis indicators. The Jansson [53] and Bristol [57] criteria, which incorporate the characteristic attributes of CNO, are the prevailing standards for assessment. The Bristol criteria [57] identify the best predictors for CNO. These criteria include a normal blood cell count, symmetric bone lesions, lesions with marginal sclerosis, normal body temperature, lesions located in the vertebrae, clavicle, or sternum, the presence of more than one radiologically confirmed lesion (OR 10.9), and a C-reactive protein (CRP) level equal to or greater than 1 mg/dL. A clinical scoring system for diagnosing CNO based on these predictors ranges from 0 to 63. A score of 39 or higher has a positive predictive value of 97% and a sensitivity of 68%. Jannson et al. [53] support a combination of specific criteria that must be met. The patient must exhibit characteristic clinical symptoms, including bone pain and localized swelling, without significant indications of local or systemic inflammation or infection. Radiological assessment should reveal distinct features on plain X-ray images, such as lytic areas, sclerosis, and new bone formation. Alternatively, using STIR MRI is preferable as it can depict bone marrow edema, potential bone expansion, lytic areas, and periosteal reactions. Additional diagnostic criteria include involvement of more than one bone (or solely the clavicle) and CRP levels below a specific threshold (CRP ≤ 30 g/L). If the disease is unifocal, excluding the clavicle, or CRP levels exceed 30 g/L, the diagnosis can be confirmed through a bone biopsy. This biopsy should reveal signs of inflammation, such as the presence of plasma cells, osteoclasts, fibrosis, or sclerosis. Importantly, the biopsy should be performed without the patient being on antibiotic therapy, and bacterial growth should not be detected.

Treatment options for CNO encompass various approaches to manage this condition in pediatric patients. In many cases, patients have received antibiotic therapy before an official diagnosis of CNO is made."As the first-line treatment for CNO, NSAIDs are often utilized, with naproxen being the most chosen option [47,58]. NSAIDs can provide significant pain relief and reduce the number of bone lesions seen on MRI within as early as three months. In a recent study, Hedrich et al. documented a group of patients diagnosed with CNO/CRMO who underwent a one-year treatment regimen with naproxen. After this period, more than 50% of the patients experienced a symptom-free state. Nevertheless, it's important to note that only 27% of the patients achieved complete clinical remission, without radiographic evidence of inflammation [59]. However, if children respond inadequately to NSAIDs after this period or if they continue to experience persistent pain and abnormal imaging findings, they are considered NSAID treatment failures, prompting the consideration of second-line treatments. In the absence of treatment guidelines, there is variation in the choice of medications for patients who don't respond to NSAIDs. Rheumatologists often differ in

their selection and dosing of alternative medications. However, consensus treatment plans (CTPs) have been created based on the best available evidence and the practices of North American pediatric rheumatologists [60]. These CTPs are intended to provide guidance for the treatment of pediatric CNO cases that do not respond to NSAIDs or involve spinal issues. Utilizing these CTPs will help future studies determine the most effective treatments [54,61]. These secondary treatments include options such as methotrexate, anti-TNF-α, and bisphosphonates. The choice among these treatments may depend on the severity of the disease, with one or more medications used sequentially or concurrently after NSAID failure. While comparative effectiveness studies have not definitively determined the relative efficacy of these options, retrospective studies suggest that non-biological DMARDs like methotrexate or sulfasalazine may have lower efficacy compared to anti-TNF-α and bisphosphonates. Anti-TNF-α, particularly in the form of monoclonal antibodies, appears to be more effective, especially when patients have additional conditions like inflammatory bowel disease (IBD) or enthesitis-related arthritis. Available data concerning the utilization of anti-TNF-α in the treatment of CNO is relatively scarce [60]. A limited-sized cohort study involving four participants, as documented by Eleftheriou et al., demonstrated a reduction in pain among children with CNO following treatment with infliximab (n=3) and anakinra (n=1), subsequently switched to adalimumab [62]. Combining anti-TNF-α and bisphosphonates has shown promise in providing substantial disease control for CNO patients who do not respond well to NSAIDs. Simm et al. [63] and Miettunen et al. [64] showcased the efficacy of pamidronate in children diagnosed with NSAID-resistant CNO. In Simm's study, over 80% of patients reported pain relief, while in Miettunen's research, more than 90% of patients presented with resolved bone lesions on MRI after six months of pamidronate treatment.

Conclusion

Chronic recurrent multifocal osteomyelitis (CRMO) should be taken into consideration when evaluating inflammatory bowel disease (IBD) patients experiencing unexplained bone pain or displaying abnormal areas of uptake on a bone scan. CRMO could potentially represent an uncommon extraintestinal manifestation of IBD, or it's possible that specific individuals have a genetic predisposition that makes them susceptible to both conditions [4]. The frequency of CRMO diagnosis has increased significantly, a fact also confirmed by the literature. Therefore, vigilance for timely diagnosis and initiation of treatment, as well as awareness of potential coexisting conditions such as IBD, is of great importance for the scientific community. This review serves as a critical foundation for further research and emphasizes the need for heightened clinical awareness of this co-occurrence from pediatricians, rheumatologists, gastroenterologists, as well as, orthopedic surgeons.

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