



Ustekinumab as a novel treatment of chronic nonbacterial osteomyelitis: a case report

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Background: Chronic nonbacterial osteomyelitis (CNO) is a rare inflammatory disorder that commonly causes bone destruction in the metaphysis of long bones, pelvic and vertebral bones, the clavicle, and the mandible. CNO is often misdiagnosed and underreported. This presentation of debilitating back pain caused by CNO showcases diagnostic challenges and potential for novel therapeutic treatment.

Case Description: A 14-year-old male with Crohn's disease presented with acute, worsening lower back pain and two months of hematochezia after recently stopping infliximab. Physical examination showed sacral tenderness, diffuse erythematous lesions, normal strength and no focal neurological deficits. A T2 hyperintense mass at S4 on magnetic resonance imaging (MRI) was identified. Skeletal survey was negative; however, repeat MRI indicated phlegmon and epidural abscesses suggestive of osteomyelitis. Initial treatments with intravenous cefazolin and oral minocycline were ineffective, leading to interventional radiology (IR) guided S1 biopsy that revealed fibrous tissue without signs of infection. A left L5–S1 laminotomy and microdiscectomy were performed with surgical pathology of the L5–S1 disc showing focal acute inflammation with no evidence of microorganisms, leading to a diagnosis of CNO. Despite surgery, he experienced worsening pain and gait difficulties. After starting Ustekinumab for Crohn's disease, his back pain and mobility significantly improved, and he returned to school. Follow-up MRI showed improvement in the epidural swelling, decreased enhancement of the lumbar and sacral canal extending from L4–S3, and significantly decreased osseous enhancement at S1.

Conclusions: This case illustrates an unusual manifestation of CNO with an S1 vertebral lesion. The initial MRI findings and failed treatment with antibiotics resulted in a diagnostic challenge leading to an invasive workup involving multiple biopsies to rule out infection and malignancy and a subsequent L5 laminotomy and microdiscectomy. The timing of symptom onset following cessation of infliximab suggests a Crohn's flare likely triggered CNO. The soft tissue abnormalities noted on imaging were likely secondary inflammatory changes associated with the vertebral lesion. The resolution of back pain with ustekinumab is in line with other cases of successful resolution of CNO with biologic agents and supports the theory of shared pathophysiology in CNO and inflammatory bowel disease (IBD).

Keywords: Chronic nonbacterial osteomyelitis (CNO); nonbacterial; osteomyelitis; ustekinumab; case report

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Introduction

Chronic nonbacterial osteomyelitis (CNO) is an inflammatory disorder in children that is thought to be caused by a combination of genetics, environmental, and immunologic factors (1-3). If left untreated, it can result in bone destruction that most commonly affects the metaphysis of long bones in the lower extremities, pelvic and vertebral bones, the clavicle, the long bones of upper extremities, and the mandible (4,5).

CNO is a rare disease, with prevalence grossly estimated from 1/2,000,000 to 1/160,000, and incidence between 1/250,000 to 1/1,000,000 (6). The exact incidence of CNO in the United States is not well established due to its rarity and varying diagnostic criteria. However, as CNO is likely underdiagnosed and underreported, the actual prevalence may be slightly higher (7). It can affect children of all ages, with peak onset between 7 and 12 years old (8).

CNO generally presents with insidious onset of bone pain that may be accompanied by swelling, focal tenderness, and occasional warmth over the affected area (9,10). It presents as a spectrum ranging from mild, self-limited focal lesions to chronically active or recurrent multifocal lesions, with the latter referred to as chronic recurrent multifocal osteomyelitis (CRMO) (11). Although it can present as a

unifocal bone lesion, most often in the long bones, clavicle, or mandible (12,13), most patients develop multifocal lesions over time. Although spinal and sacroiliac CNO lesions have been reported, these are more common in adult populations (14) and usually involve multiple vertebral levels (15), with adult populations experiencing continuous multilevel vertebral involvement while pediatric populations tend to have involvement of shorter segments (15,16). Spinal lesions are most often located in the thoracic spine, followed by the lumbosacral spine, and the cervical spine.

CNO is associated with conditions affecting the skin, gastrointestinal (GI) tract, or joints, including inflammatory bowel disease (IBD) and spondyloarthritis/enthesitis related arthritis (ERA) (17,18). Several studies suggest that CNO may represent an extraintestinal manifestation of IBD, or that some individuals have a genetic predisposition to susceptibility to both CNO and IBD (9,19).

The Jansson (20) and Bristol (7) criteria are the most commonly used criteria for clinical diagnosis of CNO. Initial therapy for CNO usually consists of daily nonsteroidal anti-inflammatory drugs (NSAIDs) at standard doses, with up to 50% of patients achieving clinical remission within the first year of treatment (21). For patients with active spinal lesions, use of infliximab with or without bisphosphonate, or bisphosphonate alone, has shown favorable outcomes when added at the start of NSAID therapy. For refractory disease, treatments such as disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor (TNF) inhibitors, and/or bisphosphonates are needed to induce remission and reduce skeletal damage (21,22).

In patients with dual diagnoses of CNO and IBD, treatment approaches often mirror those for CNO alone, with documented responses to NSAIDs, corticosteroids, DMARDs, TNF inhibitors such as infliximab, and bisphosphonates (23). Notably, Dushnicky *et al.* briefly described a patient with coexisting CNO and Crohn's disease who responded to ustekinumab after developing infliximab-induced psoriasis, providing early support for its potential role in this patient population (24). We present this article in accordance with the CARE reporting checklist (available at <https://acr.amegroups.com/article/view/10.21037/acr-25-32/rc>).

Case presentation

A 14-year-old male with a past medical history of Crohn's disease (diagnosed 5 months prior to presentation, and had

Highlight box

Key findings

- This case presents a rare instance of S1 vertebral involvement in chronic nonbacterial osteomyelitis (CNO) with clinical and radiographic improvement following treatment with ustekinumab.

What is known and what is new?

- CNO is an autoinflammatory bone disorder that may be associated with inflammatory bowel disease (IBD) and is typically treated with nonsteroidal anti-inflammatory drugs, tumor necrosis factor inhibitors, or bisphosphonates. Vertebral involvement is uncommon in pediatric patients and may mimic infection or malignancy.
- This case adds evidence that ustekinumab, an interleukin-12/interleukin-23 inhibitor, may provide clinical benefit in select cases of CNO, particularly in patients with coexisting Crohn's disease.

What is the implication, and what should change now?

- Clinicians should consider CNO in pediatric patients presenting with vertebral lesions and gastrointestinal symptoms to avoid unnecessary invasive procedures. Ustekinumab may represent an alternative therapeutic option for CNO in patients with concomitant IBD when traditional therapies are ineffective or contraindicated.



Figure 1 T2-weighted magnetic resonance imaging of the lumbar spine during antibiotic treatment. Posterior extension of soft tissue abnormality from L5–S1 disk space into the ventral canal and left lateral recess, bowing laterally into the foraminal margin. Additional soft tissue abnormality within the ventral epidural space at the levels L5, S1, and extending into the sacral canal. Vertebral flattening along the S1 superior plate, with abnormal marrow enhancement. Impingement upon the thecal sac and left-sided nerve exiting L5 and descending S1.

been on infliximab for 3 months), asthma, iron deficiency anemia, and pathologic T1 vertebral fracture with associated benign lesion at 7 years old, presented to clinic with acute, progressive, midline lower back pain. The pain had been worsening for 2 weeks and was characterized as sharp and intermittent. The pain was described as 9/10 in intensity, worse with movement, refractory to acetaminophen, and only relieved by lying still. Two weeks prior to presentation, he was admitted to the hospital for 1 week in the setting of similar lower back pain. A magnetic resonance imaging (MRI) was obtained, which revealed a 1.1 cm × 0.9 cm × 1.0 cm T2 hyperintense soft tissue mass at the level of S4,

extending from the extradural sacral canal to the posterior sacral osseous elements (*Figure 1*).

Further history revealed the patient had recently discontinued infliximab. Review of systems was significant for 2 months of bloody stool. Physical exam was significant for sacral spine tenderness and pain in the left subscapular region elicited by vertical head movement. Skin examination revealed multiple erythematous scaly lesions on the scalp, trunk, and left lower extremity, suggestive of psoriasis. Upper extremity reflexes were 1+ bilaterally, lower extremity reflexes 2+ bilaterally, and strength 5/5 globally. X-ray of the pelvis showed that sacroiliac joint spaces were maintained; however, no dedicated sacroiliac joint imaging was obtained, and specific provocative maneuvers to assess for sacroiliitis were not documented on the physical exam.

Repeat MRI revealed multiple phlegmons with epidural abscesses, which were ultimately suspicious for osteomyelitis. Skeletal survey was negative. The patient was started on a prolonged course of intravenous cefazolin, with oral minocycline later added for presumed osteomyelitis. However, the patient's pain and function continued worsening, prompting further workup with consideration for malignancy. Interventional radiology (IR) guided biopsy cultures were unrevealing and surgical pathology from the biopsy revealed scant fibrous tissue. Follow-up imaging showed a stable lesion with no improvement post-antibiotics, and repeat S1 biopsy showed fibrous tissue with no definite morphologic evidence of acute osteomyelitis or malignancy.

Due to persistent and severe pain and progressive lower extremity weakness, the patient underwent a left L5–S1 laminotomy and microdiscectomy. Surgical pathology of the L5–S1 disk was significant for fragments of fibrocartilage and soft tissues with focal acute inflammation and reactive changes, with no evidence of microorganisms. At this point, a diagnosis of CNO was made through the Jansson Criteria.

He was discharged post-laminotomy, but readmitted 1 week later with worsening sacral back pain, difficulty walking, and limited activities of daily living. New spinal misalignment with pelvic tilt was noted on exam. Spinal and pelvic X-rays showed diffuse mild osteopenia in bilateral femoral heads. No further imaging or interventions were recommended at this time.

The patient was started on ustekinumab for his IBD. On outpatient follow-up, he reported significant resolution of his back pain and GI symptoms, and had made significant improvements in gait. Repeat MRI showed marked improvement in epidural swelling and decreased osseous

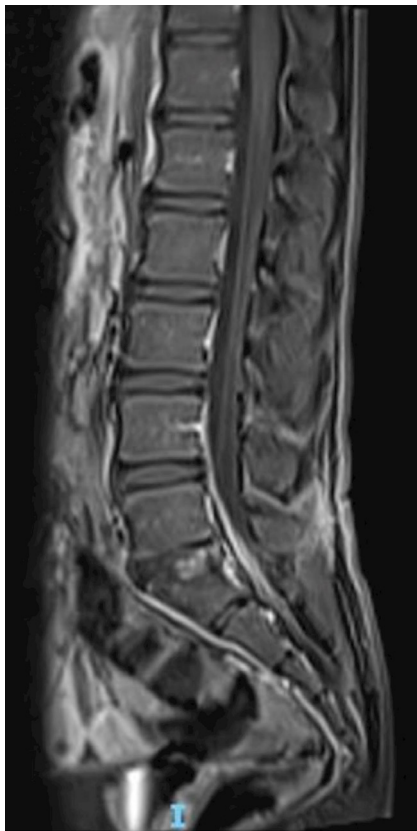


Figure 2 T2-weighted magnetic resonance imaging of the lumbar spine after initiation of ustekinumab. Marked improvement of the epidural swelling and enhancement of lumbar and sacral canal extending from L4–S3. Improved S1 superior endplate abnormality with chronic endplate collapse, mild disk thinning, and decreased osseous enhancement. Post-surgical changes following left L5 laminotomy, including mild enhancement likely due to scarring along the left lateral epidural space at L5–S1.

enhancement (*Figure 2*). Although he experienced a lapse in follow-up that led to an interruption in therapy, ustekinumab was re-initiated with adjusted maintenance dosing. Over the course of approximately 12 months of intermittent treatment, he demonstrated sustained clinical and radiographic improvement. He received outpatient physical therapy for general strengthening after deconditioning due to his prolonged hospital stay and has returned to school.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration and its subsequent amendments. Written informed consent for publication of this case report and accompanying images

was not obtained from the parents of the patient or their relatives after all possible attempts were made.

Discussion

This case represents an unusual manifestation of CNO with an isolated lesion affecting the S1 vertebra in an adolescent. While sacral involvement in CNO has been described, it more commonly affects the sacroiliac joints. In this case, the absence of clinical or radiographic evidence of sacroiliitis—combined with the presence of a solitary vertebral lesion—makes the presentation particularly atypical within the known CNO spectrum.

The soft tissue abnormalities and swelling noted on imaging were likely secondary to inflammatory changes associated with the vertebral lesion. Musculoskeletal abnormalities, including pathologic fractures, are known extraintestinal manifestations of IBD and may present prior to the onset of GI symptoms. However, it is possible that the patient's history of spine fracture with benign biopsy at 7 years old represented an earlier, subclinical manifestation of CNO, rather than a musculoskeletal manifestation of Crohn's disease. Painless CNO lesions may go unrecognized and only become clinically apparent when complicated by fracture or worsening inflammation. The patient may have experienced a period of disease quiescence or ongoing subclinical activity, with symptom exacerbation occurring in the setting of an inflammatory flare associated with newly diagnosed Crohn's disease. This overlapping clinical picture, combined with the unusual imaging findings, made the diagnostic process particularly challenging.

During his hospitalization, initial MRI findings were suggestive of epidural abscesses and infectious osteomyelitis, and his subsequent lack of improvement with antibiotics reinforced concern for an atypical or resistant infection versus malignancy. This led to multiple biopsies and ultimately surgical intervention. In retrospect, earlier use of advanced imaging may have altered the diagnostic trajectory. Whole-body MRI (WB-MRI) is a valuable tool in the diagnostic workup of CNO, as it can detect bone lesions at an early, subclinical stage. In this case, WB-MRI could have assisted with earlier diagnosis of CNO by identifying additional subclinical lesions, and potentially reducing the need for invasive workup. However, WB-MRI was not performed due to limited institutional availability at the time of evaluation. Incorporating WB-MRI into future diagnostic protocols may expedite diagnosis and reduce patient morbidity in similarly complex cases.

Beyond advanced imaging, consideration of the clinical context offers additional insight into the underlying disease process. The patient's symptom onset following cessation of infliximab therapy, along with bloody diarrhea noted on review of symptoms, points to an uncontrolled Crohn's flare potentially triggering the onset of back pain secondary to CNO. His resolution of back pain, along with imaging findings showing decreased epidural swelling and osseous enhancement following treatment with ustekinumab (a biologic agent used for Crohn's disease management) is in line with other cases of successful resolution of CNO with biologic agents (21,25-27) and supports the theories of shared pathophysiology in CNO and IBD.

This case follows a previous report of successful use of ustekinumab for management of CNO in a patient with IBD. Its benefit in CNO may be due to its mechanism as an interleukin-12 (IL-12)/IL-23 inhibitor, blocking IL-12 and IL-23 mediated cell signaling, activation, and cytokine production that contribute to inflammatory immune responses, including dysregulation that has been linked with multiple immune-mediated diseases (28). As cytokine dysregulation has been implicated as a factor in the pathophysiology of CNO, ustekinumab's role in inhibiting IL-12 and IL-23 mediated cytokine production and subsequent downstream effects suggests the mechanism for its efficacy in the treatment of CNO (23).

Conclusions

There are multiple lessons from this case. First, although infliximab and ustekinumab are both Food and Drug Administration (FDA) approved for the treatment of Crohn's disease, infliximab and other TNF inhibitors are included in the consensus treatment plans for CNO (29), while ustekinumab is not. As the patient's symptoms improved and follow-up imaging demonstrated decreased epidural swelling and osseous enhancement following treatment with ustekinumab, this case demonstrates potential for the use of other IBD agents to resolve symptoms of CNO in patients with IBD. Secondly, as CNO is a diagnosis of exclusion of other etiologies of bone pain and inflammation, including infection and neoplasia, it commonly requires rigorous laboratory testing and imaging for diagnosis. However, with increased awareness of this condition, there is potential to decrease the amount of testing to arrive at this diagnosis. Physicians should be aware of this diagnosis when encountering pediatric and adolescent patients with a history of GI symptoms presenting with musculoskeletal pain, to

facilitate prompt diagnosis and optimize treatment. Last, this case illustrates the importance of maintaining a broad differential diagnosis and taking a robust history and review of systems when evaluating patients presenting with pain, ensuring investigation into potential systemic contributors, rather than anchoring into musculoskeletal causes.

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Footnote

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