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SPECIALTY SECTION

This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 21 October 2022

ACCEPTED 06 March 2023

PUBLISHED 21 March 2023

CITATION

Shi X, Hou X, Hua H, Dong X, Liu X, Cao F and Li C (2023) Case report: Child chronic nonbacterial osteomyelitis with rapid progressive scoliosis—an association with disease?
Front. Pediatr. 11:1076443.
doi: 10.3389/fped.2023.1076443

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Case report: Child chronic nonbacterial osteomyelitis with rapid progressive scoliosis—an association with disease?

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Background: Chronic nonbacterial osteomyelitis (CNO) is an auto-inflammatory bone disease that usually develops in childhood. Spinal involvement is a common manifestation of CNO, but it is rare for CNO to lead to rapid progression of scoliosis deformity. Here we present a 9-year-old girl with acute scoliosis with CNO and scoliosis progressed rapidly in 2 months.

Case Presentation: A 9-year-old girl presented bilateral shoulder inequality with pain in the left hypochondrium for 2 months. Standing spinal x-rays showed right convex scoliosis with a 25° Cobb angle. Chest magnetic resonance imaging (MRI) showed that the T8 vertebra was flattened and local bone was destroyed with bone marrow edema. The bone biopsy showed evidence of fibrosis and chronic inflammatory changes with no specific diagnosis. One month later, her scoliosis and bone destruction deteriorated obviously. Thoracic vertebra MRI showed that the T8 vertebra had a compression fracture. ^{99m}Tc-MDP whole-body bone scintigraphy showed intense uptake at T8/9 and the right sacroiliac joint. She was diagnosed with CNO accompanied by rapidly progressive scoliosis. The scoliosis was successfully treated with adalimumab and zoledronic acid, which showed significant improvement after 6 months of follow-up.

Conclusion: Zoledronic acid and adalimumab successfully treated CNO with rapidly progressive scoliosis, but could not prevent vertebral compression.

KEYWORDS

scoliosis, children, autoimmune disease, rapid progress, chronic nonbacterial osteomyelitis, Adalimumab, zoledronic acid

Introduction

Chronic nonbacterial osteomyelitis (CNO) is a rare aseptic and chronic auto-inflammatory bone disease that usually occurs in childhood (1, 2). Clinical manifestations vary in severity from unifocal to multifocal, with chronic recurrent multifocal osteomyelitis (CRMO) being a severe form of CNO (3). The incidence of CNO is unknown, with some surveys suggesting an estimated annual incidence of 4/1,000,000, but the incidence may be grossly underestimated due to the lack of authoritative classification criteria and delay in diagnosis (4). CNO usually presents as insidious bone pain with or without systemic features (4). It commonly affects the metaphyses of long bone, followed by the spine, clavicle and mandible (5, 6). CNO scoliosis is relatively rare and no cases of rapid scoliosis progression have been reported. Here we report a 9-year-old girl with

acute scoliosis secondary to CNO whose scoliosis progressed rapidly within two months and was successfully treated with adalimumab and zoledronic acid.

Case report

A 9-year-old girl presented to the clinic with bilateral shoulder inequality and left hypochondrium pain for 2 months. She had no history of trauma, serious medical problems, or family history of skeletal problems or psoriasis. She developed left hypochondriac pain on 9 June 2022, and two weeks later, her parents found her back curved to the right with skin lesions on both sides of the left lower extremity. The lesions on the inner calf presented as four green bean-sized pustules that partially ruptured, and on the outer side as an oval red squamous patch. Standing spinal x-rays showed a right convex scoliosis with a 25° measured by the Cobb angle method. Chest MRI showed that the T8 vertebra was flattened and local bone was destroyed with bone marrow edema (Figure 1). We biopsied her thoracic vertebrae and skin lesions. She then underwent pathological biopsies of the T8 vertebra and lower limb skin lesions (Supplementary Figure S1). The bone biopsy showed evidence of fibrosis and chronic inflammatory changes with no specific diagnosis. The skin biopsy showed chronic inflammation. Immunohistochemistry results revealed CD207(-), CD1a (-), CD68(focal +), S-100 (-), CD163 (-). One month later, her scoliosis and bone destruction deteriorated obviously, and back pain occurred. MRI of the thoracic vertebra showed that the T8 vertebra had a severe compression fracture (Figure 2A–C). The right sacroiliac joint and T8/9 regions were shown to have intense absorption by ^{99m}Tc-MDP whole-body bone scintigraphy (Figure 2D).

Physical examinations showed normal vital signs and the shoulders were imbalanced, the left shoulder was higher than the right shoulder, and the spinous process of the back was complete to the right. Laboratory assays revealed a slight elevation of C-reactive protein (CRP, 8.41 mg/L, normal range 0–8.0 mg/L) and rheumatoid factor test was negative. Combined with medical history and auxiliary examination, we diagnosed the patient with CNO accomplished by scoliosis.

Immediately following, the girl has been treated with adalimumab (40 mg once every two weeks) and zoledronic acid (2.5 mg once every three weeks) for six months. We followed up at 3 and 6 months, and the patient's CRP had returned to normal, routine blood and biochemical tests were still negative. The standing spine x-ray and MRI of the thoracic spine (Figure 3 and Supplementary Figure S2) were re-examined and showed significant improvement from before. Meanwhile, we extracted peripheral blood genomic DNA from the patient and her parents and performed whole-exome sequencing, which revealed a variation in the *LAMB3* gene.

After treatment, the girl showed significant improvement in scoliosis, reduction in bone marrow edema and back pain, and improvement in skin lesions (Supplementary Figure S3), although vertebral collapse remained with no significant change.

Discussion

CNO has been characterized for at least 50 years since it was first described by Gideon et al. in 1972 (7). However, there is a lack of internationally accepted diagnostic criteria for CNO, and the classification and diagnostic scores proposed by Jansson et al. are currently the more commonly used criteria (8). As an exclusionary diagnosis, CNO must be distinguished from tumors, infectious osteomyelitis and langerhans cell histiocytosis (LCH), et al. LCH, similar to CNO, can present with osteolytic changes in the vertebra, but the pathology is seen with an abnormal infiltration of Langerhans histiocytes and immunohistochemistry of CD1a/CD207 (+) (9). This girl had no fever and no abnormal blood counts, while bone biopsy and pathology revealed no tumor cells, langerhans cells or bacterial infection. The final diagnosis was CNO with scoliosis, fulfilling the diagnostic criteria for CNO proposed by Jansson et al. (8).

Early reports of spinal involvement in CNO/CRMO were considered rare in the literature, but in the last 20 years there has been a gradual increase with an incidence of approximately 10%–38% (3, 10–13). We reviewed the vertebral involvement of CNO/CRMO patients in the literature since 2000 (Table 1). A PRISMA flow chart of the literature screening process is in the Supplementary Material (Supplementary Figure S4). The relationship between SAPHO and CNO/CRMO in children is unclear, so SAPHO cases were not included (24). We found that the thoracic vertebra were the most commonly affected vertebra, followed by the lumbar, cervical and sacral vertebra, which is similar to the data summarized by S. E. Anderson et al. before 2000 (23). Major vertebral involvement included osteolytic changes (including collapse, compression fractures and complete destruction), kyphosis, scoliosis and bone marrow edema. Scoliosis deformities were seen in 2 studies (16, 20), one of which showed acute scoliosis deformity similar to ours. In contrast to our case, which showed a rapid deterioration within 2 months, his case was very stable, with no significant progression of the scoliosis (20).

In addition to their anti-inflammatory and analgesic effects, bisphosphonates can reduce the development of osteoclast precursor cells and promote the apoptosis of mature osteoclasts (25). So we treated her with zoledronic acid. After 6 months of treatment, the scoliosis had largely improved, but the spinal collapse persisted. In severe spinal involvement, pamidronate may be more effective than zoledronic acid, encouraging bone healing and preventing progression of vertebral compression (10, 26–28). In patients with spinal deformity, the use of a plaster corset to support the spine may also be beneficial (10).

Imbalanced anti-inflammatory and pro-inflammatory pathways are important molecular mechanisms involved in developing CNO. Studies have shown that serum pro-inflammatory molecules (IL-6, TNF- α , IL-1 β) are increased and anti-inflammatory factors (IL-10, IL-19) are decreased in CNO patients (29). The imbalance between pro- and anti-inflammatory cytokines can be restored by TNF- α inhibitors (TNFi) which are recommended as the preferred second-line treatment for patients with associated inflammatory skin lesions

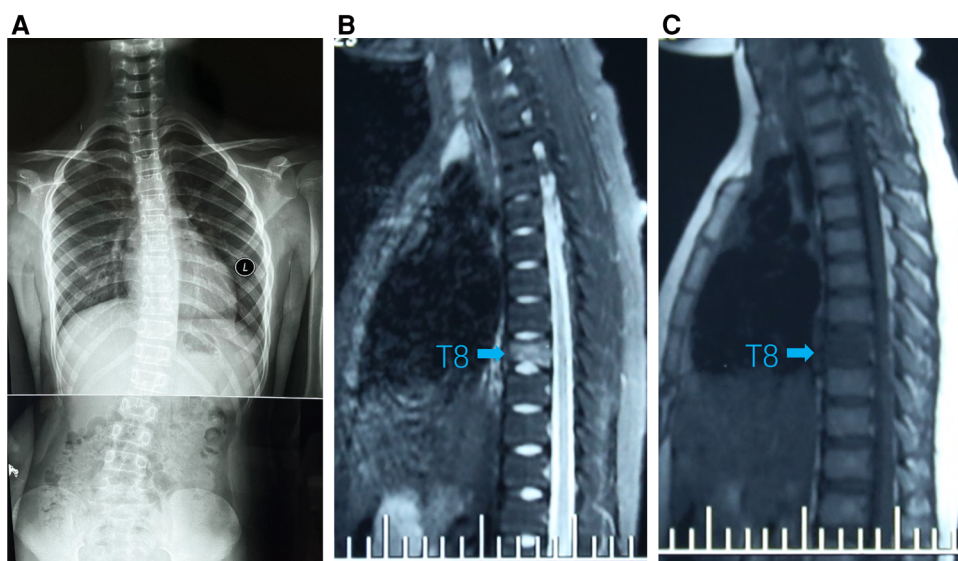


FIGURE 1
 (A) Standing spinal x-rays showed right convex scoliosis. (B) T1-weighted MRI image showed that the T8 vertebra was flattened and local bone was destroyed (arrow). (C) T2-weighted MRI image showed bone marrow edema in T8 vertebra (arrow).

(30). Our patient had pustular lesions on the lower limbs, so we added the TNFi adalimumab. In 2019, the Childhood Arthritis and Rheumatology Research Alliance has developed three consensus treatment plans for patients with NSAID-refractory CNO, including bisphosphonates and TNFi (31).

In this patient, the scoliosis deformity developed rapidly over a 2-month period and resolved after treatment. The images showed a

parallel progression of thoracic spine destruction and scoliosis. It is likely that the spinal destruction and pain from CNO were responsible for the progression of the scoliosis.

There is evidence that CNO may be caused by genetic factors (3, 32). Our preliminary whole exome sequencing results suggest this patient has a *LAMB3* (c.595G > A) gene variant which is a protein-coding gene in exon7. The product encoded by *LAMB3*

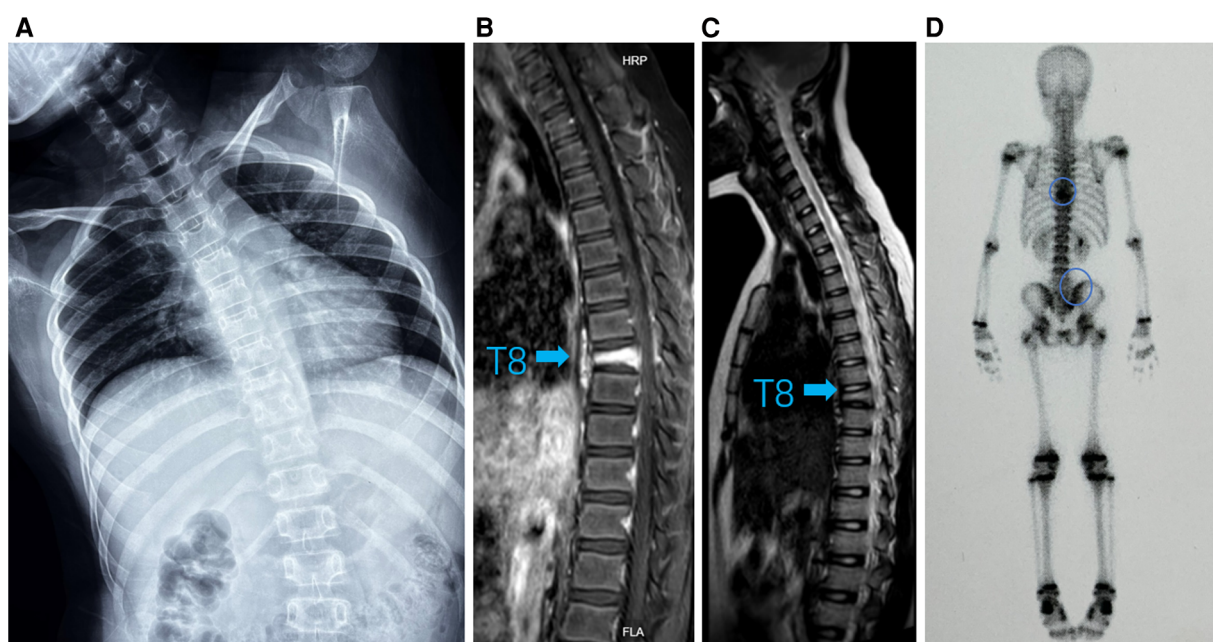


FIGURE 2
 (A) Standing spinal x-rays showed heavier right scoliosis. (B) T1-weighted MRI image and (C) T2-weighted MRI image of the thoracic vertebra showed that the T8 vertebra had a compression fracture (arrow). (D) ^{99m}Tc-MDP whole-body bone scintigraphy showing hot spots in T8/9 and right sacroiliac joint with posterior view (circle).

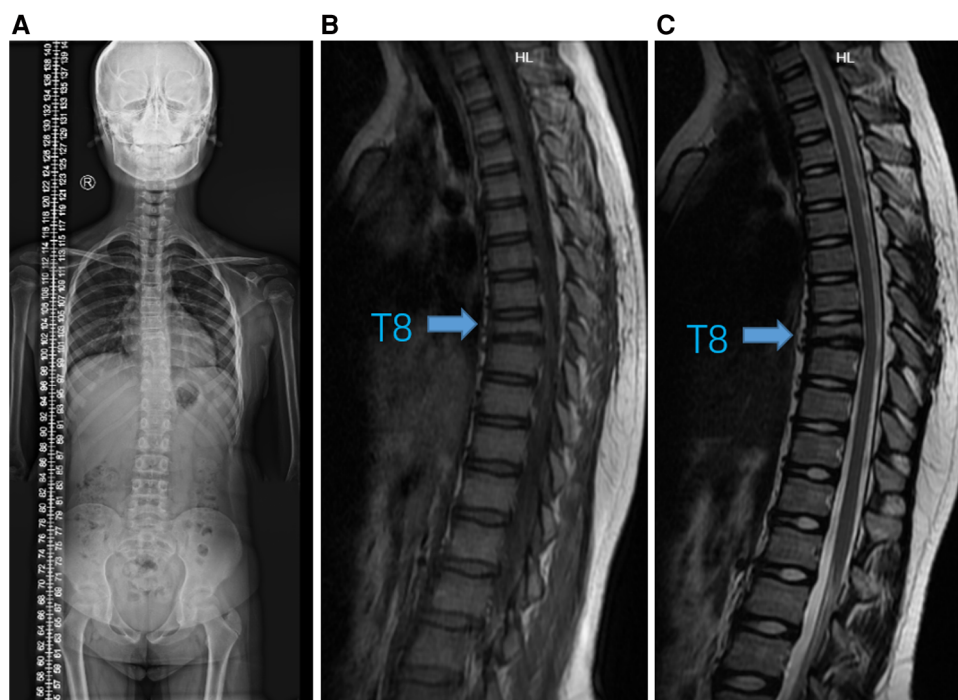


FIGURE 3
Imaging changes after six months of therapy. (A) Standing spinal x-ray. (B) T1-weighted and (C) T2-weighted MRI images showed that T8 vertebra remained stable without progression (arrow).

TABLE 1 Review of CNO/CRMO with spinal lesion.

First author-year	Number of cases	Type of spine lesions	Site of spin involved	Treatment
Sirisha Koneru-2022 (14)	1	bone marrow edema	T8, L1	naproxen
Dheeraj Batheja-2021 (15)	1	Osteolytic lesion	T6-8	bisphosphonates and NSAIDs
Kazuta Yamashita-2021 (16)	1	Osteolytic lesion and bone marrow edema	T4, T7, T11	NSAIDs and pamidronate
C Galeotti-2015 (17)	1	Osteolytic lesion and kyphotic	T5-6	NA
Cheng William Hong-2015 (18)	1	bone marrow edema	T6, T8, S1	alendronate
Shabina Habibi-2013 (19)	1	Osteolytic lesion	NA	pamidronate
Kedar Deogaonkar-2008 (20)	1	Osteolytic lesion and scoliosis	T10, L2-3	NSAIDs
Tony Walls-2006 (21)	1	Osteolytic lesion	T6-7	Ibuprofen
Colleen S Y Chun-2004 (22)	1	Osteolytic lesion	S1	prednisone, alendronate, and naprosyn
S E Anderson-2003 (23)	3	Osteolytic lesion and kyphotic	P1: T4, T6, T8	NA
		Osteolytic lesion	P2: C2-3, T9	NA
		Osteolytic lesion	P3: L3	NA

is laminin beta3 that belongs to a family of basement membrane proteins. Laminin beta3 is a unique component of laminin 332, which is a novel negative regulator of osteoclastogenesis in the bone microenvironment and has an important role in the control of normal bone remodeling (33). We recommend further functional studies to elucidate its pathogenic impact.

In conclusion, we report a case of CNO with rapid scoliosis in a patient who had significant relief of scoliosis after treatment with zoledronic acid and adalimumab, but was failed to avoid vertebral compression. We need to properly identify the spinal involvement of CNO, which can progress rapidly in combination with scoliosis, and develop an individuation therapy.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Fangshan Hospital of Beijing University of Traditional Chinese Medicine. Written informed

consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

CL: contributed to the conception and design of the article. XS and XH: wrote all the contents of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by the National Natural Science Foundation of China (grant no. 82074246) for CL and construction project of clinical key specialty in fengtai district of Beijing for XH.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2023.1076443/full#supplementary-material>.

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