Chronic Recurrent Multifocal Osteomyelitis with an uncommon presentation and disabling features: A case report

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Case Report

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Abstract

Background: Chronic recurrent multifocal osteomyelitis (CRMO) is one of the auto-inflammatory bone disorders with yet to be determined etiology. Due to overlapping signs and symptoms with other bone involvements, the diagnosis of this disease might take a long period of time and the patients may develop deformities in long-term. Thus, increasing awareness about different presentations of the disease seems beneficial.

Case presentation: A 12-year-old boy was referred to our center with severe back pain in his thoracic vertebrae from 18 months before referral. He had previously undergone two vertebroplasty surgeries due to his kyphosis and had received several courses of antibiotics, which resulted in no improvement in his disabling pain. His physical examination was unremarkable, except for severe thoracic vertebrae tenderness and a mild dextroscoliosis. MRI showed diffuse multiple hypo-signal lesions in thoracic vertebral bodies with slight enhancement, causing compression fractures of T₈, T₁₁ and T₁₂ bodies. Bone scan revealed increased activity in thoracic region (T₇-T₈-T₉-T₁₂ vertebral bodies) and left clavicle. Other differentials were ruled out by bone marrow aspiration, bone biopsy and laboratory tests. His disease showed a favorable response to treatment with Pamidronate, Methotrexate and Indomethacin and he had no relapse in three years of follow-up.

Conclusions: Uncommon presentations of CRMO can be misleading to the specialists and might result in prolonged diagnosis process. Increased awareness among different specialists about such presentations can potentially lead to earlier diagnosis, and timelier and more effective treatment of the CRMO patients.

Background

Chronic recurrent multifocal osteomyelitis (CRMO) is one of the auto-inflammatory bone disorders with still debated etiology. It is the most severe subgroup of chronic non-bacterial osteomyelitis (CNO), which is aseptic, mono- to multi-focal inflammation of the bones (1).

CRMO mostly affects children and adolescents, and the most common age of onset has been reported to be 7-12 years (2). Although the incidence of CNO/CRMO was considered to be low at past, a recent study has demonstrated that the incidence rate of CNO can be comparable to bacterial osteomyelitis (3).

The clinical course mainly includes having chronic recurrent episodes of bone inflammation with symptoms of mild to severe bone pain, mild fever, malaise, and fractures. The most frequent sites for bone lesions are metaphyses of long bones (Tibia and Femur), pelvis, vertebral bodies and the shoulder girdle including clavicle (2, 4). The prognosis of the patients with CNO/CRMO is generally good according to previous studies, and minority of cases will show severe disease in long-term follow-ups (5).

Here we discuss a 12-year-old boy, presenting with severe and disabling back pain and kyphosis as the first presentations of CRMO. This is an uncommon presentation of this disease, and only few cases with such severe symptoms as their first presentation have been reported before.

Case Presentation

Our patient was a 12-year-old boy presenting with severe back pain in his thoracic vertebrae from 18 months before referral. He had developed an abnormal forward bend in his vertebral column after his back pain started, and had problem standing straight due to his pain. The pain was constantly present and did not radiate elsewhere. It was severe and interfered with the patient's daily tasks, such as walking, showering, and etc.

Except the current problem, his past medical history was unremarkable. He was born at term with no birth insults and no anomalies. His growth and development were normal and he had complete childhood vaccination. His current weight was 57 Kg. He did not use any medications prior to the onset of the symptoms. Approximately 18 months ago, he had developed a severe back pain which had gradually become severe and was accompanied with kyphosis. He had 2 vertebroplasty surgeries in the past 1.5 years because of his kyphosis. After each surgery, the pain reduced transiently and restarted after a few weeks. After the second surgery, the pain increased gradually and was extremely severe when he referred to us, to the point that he was not able to stand or even sit upright without support. After his second vertebroplasty, he had received several courses of various antibiotics (including complete treatment for Tuberculosis and Brucellosis regarding his chronic osteomyelitis), and he was under treatment with Linezolid 150 mg and Ciprofloxacin 500 mg twice daily, when he was referred to us. He was also receiving Dexamethasone tablet (0.5 mg three times a day). In his family history, his father previously had erythematous plaques with indefinite diagnosis.

Physical examination revealed severe tenderness over the thoracic spine, from T8 to L1. Range of motion in all directions was limited due to severe pain and the patient could not sit upright without his brace support because of the pain. A mild dextroscoliosis was observed. No present kyphosis could be observed at that time due to his previous vertebroplasty. He was not febrile and did not complain of any constitutional symptoms. Head and neck, respiratory, cardiovascular, abdominal, and neurological exams were unremarkable. No other musculoskeletal involvement or tenderness except for the vertebral column was detected.

Plain vertebral X-ray was done which showed generalized low density of vertebral bodies and the evidences of previous vertebroplasty. Also, superior and inferior endplate irregularity was seen thoracic vertebral bodies. The differential diagnoses until this point were infectious osteomyelitis (especially Tuberculosis and Brucellosis which are prevalent in Iran), leukemic malignancies, Scheuermann's disease, insufficiency fractures, and chronic multifocal osteomyelitis. Laboratory tests showed a mild leukocytosis. Erythrocyte Sedimentation Rate (ESR) was mildly increased (25 mm/hr) and C-reactive protein (CRP) was negative. Moreover, Alkaline Phosphatase (ALP) was increased, along with normal Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT). Wright and Coombs-Wright tests were also negative. Other tests including Calcium and phosphorus levels, Parathyroid hormone (PTH), Uric acid and Lactate dehydrogenase (LDH) were within normal range (Table 1).

Table 1
The patient's laboratory values during hospitalization

Laboratory test			Value	Reference range	Unit
CBC [Ⓜ]	WBC [†]	Total	12.92	4.5 - 11.0	10 ⁹ /L
		Neutrophils (%)	8.13 (63%) ↑	1.5 - 8.0	10 ⁹ /L
		Lymphocytes (%)	3.74 (29%)	1.0 - 4.8	10 ⁹ /L
	Hemoglobin		12.3	12.0 - 17.20	g/dL
	Platelets		372	150 - 450	10 ⁹ /L
Inflammatory markers	ESR		25 ↑	1-13	mm/h
	CRP		2	<10	mg/L
Liver function tests	AST		18	10 – 40	U/L
	ALT		32	7 - 56	U/L
	ALP		382 ↑	44 - 147	U/L
Tests for Brucellosis	Wright		Negative	-	-
	Coombs Wright		Negative	-	-
	2ME		Negative	-	-
Other workups	LDH		374	5 - 850	U/L
	Uric acid		4.3	3.5 – 7.2	mg/dL
	Phosphorus		4.1	2.8 – 4.5	mg/dL
	Calcium		9.8	8.6 – 10.3	mg/dL
	PTH		35	11 - 51	pg/mL
*Complete Blood Count †White Blood Cell					

Three phase Technetium-99m (^{99m}Tc) bone scan was also obtained (Figure 1). The scan revealed increased activity in thoracic region (in T₇-T₈-T₉-T₁₂ vertebral bodies) and mild increase in the left clavicle with no other remarkable abnormalities in the rest of the skeleton. At this stage, the diagnosis of CRMO became more probable regarding clavicle involvement, and according to the consults with pediatric orthopedist and pediatric oncologist, spine MRI, bone-marrow aspiration (BMA), and open bone biopsy were requested and done.

The MRI manifested diffused multiple hypo-signal lesions in upper and middle portions of thoracic vertebral bodies with slight enhancement, causing compression fractures of T₈, T₁₁ and T₁₂ bodies.

Significant collapse fracture deformity was also seen in T₇ with posterior pedicle involvement.

BMA had normal cells with no signs of malignancy and flow cytometry results were normal. Biopsy of the vertebral bone showed chronic osteomyelitis with infiltrations composed of mostly neutrophils, lymphocytes, and some macrophages, with no Reed-Sternberg cells and no granuloma. The results were negative for malignancy and infections (which were ruled out through cultures, and Polymerase Chain Reaction (PCR) testing for Mycobacterium and Non-mycobacterium tuberculosis and Brucellosis).

By ruling out other probable differentials, an autoinflammatory cause for this chronic osteomyelitis was our final diagnosis. With the impression of CRMO, we started the treatment with Non-Steroidal Anti-inflammatory Drugs (NSAIDs)-Naproxen 500 mg tablet twice a day- and 30 mg Intravenous Pamidronate for three consecutive days. Regarding the favorable response to this treatment and partial improvement of the symptoms, our patient was discharged with 15 mg of oral Prednisolone (5 mg TDS), and his NSAID treatment was changed to 75 mg Indomethacin BID.

After six months of follow-up, the patient still complained about moderate back pain and was not in full remission. Therefore, 7.5 mg Methotrexate once a week was added to his medications. The symptoms resided thereafter. Nevertheless, the patient discontinued the medication after a few months, which caused another episode of relapse. Considering the complications of long-term corticosteroid use, Prednisolone was not included in the new regimen, and the treatment was restarted with 7.5 mg Methotrexate weekly, 70 mg Alendronate fortnightly, and Folic acid tablets.

We followed the patient biannually for another three years, during which no more relapses were observed. His Methotrexate treatment was tapered and discontinued during this time. He has been on the treatment with 70 mg Alendronate (every two weeks), Folic acid, and vitamin D3, and has no complaint about any discomfort. There has been no sign of disease activity since.

Discussion

We described a case of CRMO whose final diagnosis and treatment was delayed for over 18 months due to uncommon presentation of his disease. The patient had received several courses of different antibiotics and had two vertebroplasty surgeries prior to his CRMO diagnosis.

First described in 1972 by Giedion et. al.(6), CRMO is an autoinflammatory disease that typically involves children. It affects girls 2-3 times more frequently (7), and its classic presentation is involving the lower extremities (metaphysis of the long bones), spine, pelvis, and clavicle (8). The disease typically affects more than one site; however, at the initial workup the number of lesions might be underestimated due to some of them not having any symptoms (1).

Having described the typical from of CRMO involvement, the disease can manifest a variety of presentations (9). There have been many case reports and case series of patients with atypical involvement (4, 10, 11). For instance, patients with acute vertebral deformities (12), chronic painful

scoliosis (13), and chronic mandible involvement as their only presentation (9). This variety has been considerable, to the point that some studies have proposed classification of CRMO cases into subgroups based on their presented phenotypes, such as spinal or axial versus peripheral form (14, 15).

Spine involvement can be seen in almost 26% of CRMO patients (16). Since presenting only with chronic osteomyelitis of the vertebrae is not a common presentation of this rare disease (1), and there can be other serious conditions causing the symptoms, CRMO was not among the probable differentials for our patient at first. However, after finding clavicle involvement alongside spine osteomyelitis through imaging, CRMO diagnosis became most likely, since the clavicle can be considered a classical involvement site in CRMO (1). Thus, it can be suggested that in similar cases, whole-body imaging can be considered beside other workups. A great example of such imaging modalities is Whole-Body MRI, which has recently been considered the gold standard for CRMO diagnosis, as it is not invasive and does not expose the patient to radiation (1, 9).

According to the studies that report long-term follow-up of the patients, CRMO is generally well-prognosed (1). In a multicenter study following 131 CRMO patients, 82% of them were in remission a few years after treatment and had no relapse (7). Nonetheless, there are some concerns regarding this disease. Definite diagnosis of CRMO is only achievable by ruling out other critical diseases, namely infectious osteomyelitis and malignancies (2). This matter, in addition to its vast range of presentations (explained before) might result in delayed diagnosis of the disease. A study have reported the median time to CRMO diagnosis to be 15 months, with up to 92 months delay for one case (17). Moreover, another study reported a 6-year-old boy in whom symptoms started when he was 2, and it took 4 years to be diagnosed and properly treated (18). A delay in the diagnosis, similar to our case, can lead to the following issues:

First, the patient might receive several prolonged and unnecessary courses of treatment, such as antibiotics (13). In our case, the patient had received various antibiotics, and was on the treatment with Linezolid, which is mostly used for resistant, complicated and hospital-acquired infections (19). Second, the patients might develop deformities during this long period of disease activity without proper treatment (20). In the present case, our patient had developed spinal deformities and had undergone two spine surgeries. Earlier diagnosis can prevent the future cases from experiencing multiple invasive diagnostics (such as biopsies) and treatments, that will most probably have financial and emotional burden on the patients and their family. Another disadvantage of delayed diagnoses is that chronic pain and the impression of having a chronic disease might have psychological impact on the affected children, especially when the disease gives rise to physical deformities (21, 22). This might lead to their depression, anxiety, and consequently, less favorable educational and social function in the school and in future (5, 23). One study reported that even after the remission of their disease, children affected by CRMO had lower health-related quality of life than their healthy peers (24).

CRMO is considered as a rare disease, with estimated incidence of 4 per million children (1). However, as awareness about the disease increased through years, it can be stated that CRMO's incidence has not been much far behind the incidence of bacterial osteomyelitis (3, 25). Thus, the low incidence rate can be

due to underestimation and underdiagnosis of the disease. Nevertheless, the awareness about this disease is still suboptimal, leading to prolonged times to diagnoses (26, 27).

CRMO patients may initially approach or be referred to varying specialists. A case like ours is likely to be seen by an orthopedic surgeon at first because of his kyphosis. Hence, having different specialists, such as orthopedic and general surgeons, radiologists (considering various radiological patterns of the disease mimicking other diagnoses (9, 28)), and rheumatologists, as well as family physicians and general practitioners (as the frontline doctors that visit and refer these patients in the first place) in a close collaboration network is called for. Such interdisciplinary collaboration can possibly establish opportunities to discuss similar cases, and might lead to a timelier diagnosis by increasing the knowledge and awareness about the vast and varied presentations of CRMO.

Conclusions

We described a 12-year-old boy with CRMO whose disease presented with severe and debilitating pain and deformity in thoracic vertebrae, and the diagnosis was made 18 months after his initial symptoms, following two vertebroplasties and numerous workups. Increased awareness among different specialists about such cases can potentially lead to earlier diagnosis, and timelier and more effective treatment of the CRMO patients.

Abbreviations

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Bis In Die (Twice a day)
BMA	Bone Marrow Aspiration
CBC	Complete Blood Count
CNO	chronic non-bacterial osteomyelitis
CRMO	Chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
ESR	Erythrocyte Sedimentation Rate
LDH	Lactate dehydrogenase
MRI	Magnetic Resonance Imaging
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
PCR	Polymerase Chain Reaction
PTH	Parathyroid hormone
Tc	Technetium
TDS	Ter Die Sumendus (Three times a day)
WBC	White Blood Cell

Declarations

Ethics approval and consent to participate

We explained the process of participating in this research article to the patient's parents and written informed consent was obtained from them. The ethics committee of Children's Medical Center, Tehran University of Medical Sciences have approved this study.

Consent for publication

Written informed consent was obtained from the child's parents for the case to be published with all details.

Availability of the materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

S.Sh. drafted the manuscript including introduction, case presentation and discussion, and prepared the table and figure. K.A. contributed in writing the case presentation and discussion and revised the manuscript critically. M.Z. and M.F. contributed in visiting and following up the patient and gathering patient information as well as revising the manuscript. V.Z visited and followed the patient, determined the scientific content and structure of the article, and read and revised the manuscript critically.

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Figures

Figure 1

^{99m}Tc bone scan showing increased uptake in thoracic vertebrae and left clavicle.