Chronic non-bacterial osteomyelitis in children: Presentation, diagnosis, outcomes, quality of life

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Abstract

Purpose

Chronic non-bacterial osteomyelitis is a chronic sterile inflammatory condition of the bone. We aimed to describe the clinical and radiographic findings of patients and to evaluate their response to therapy and quality of life.

Methods

This cross-sectional study included 18 patients whose clinical, radiological features and outcomes were reviewed retrospectively. The quality of patients' life after treatment was compared to healthy controls by using the Pediatric Quality of Life Inventory 4.0.

Results

The median age of disease onset was 12 (IQR 10-14) years and 11 (61.1%) patients were male. The median follow-up duration was 15 (IQR 12-22) months. The persistent form of chronic non-bacterial osteomyelitis was the most common pattern in 15 (83.3%) patients and a recurrent pattern was defined in 3 (16.7%) patients. The lesions were multifocal in all patients and 15 (83.3%) patients had symmetric distribution in whole-body magnetic resonance imaging. The most common sites of arthritis were the knee and sacroiliac joints.

Methotrexate was used in 16 (88.9%) patients as first-line therapy. However, some patients were unresponsive to first-line therapy and needed tumor necrosis factor-α inhibitors (55.6%) and bisphosphonates (16.7%). We observed remission in only 4 (22.2%) patients and 3 (16.7%) patients were unresponsive. The patients had a significantly poorer quality of life than controls (p=0.005).

Conclusions

Chronic non-bacterial osteomyelitis is an insidious disease that requires detailed analysis for diagnosis and whole-body magnetic resonance imaging is an effective tool for diagnosis. Despite the advanced treatment, patients with chronic non-bacterial osteomyelitis have a poor quality of life.

What Is Known?

- Chronic non-bacterial osteomyelitis is a rare inflammatory bone disease that requires immunosuppressive treatments.

- The lack of awareness about the insidious-onset bone pain of CNO has contributed to underdiagnosis and reporting

What Is New?

- Whole body magnetic resonance imaging is a promising functional tool to diagnose of chronic non-bacterial osteomyelitis without delay and to follow up patients.

- Despite potent treatments, patients with chronic non-bacterial osteomyelitis may have poorer quality of life.

Introduction

Chronic non-bacterial osteomyelitis (CNO) is a chronic sterile inflammatory condition of bone that usually occurs in childhood and adolescent [1, 2]. The etiology and pathophysiology of CNO are not yet clear. Both genetic and environmental characteristics contribute to the underlying sterile bone inflammation that is probably osteoclast-mediated. This sterile osteomyelitis can present as sporadic or as a part of monogenic autoinflammatory diseases like Majeed syndrome or deficiency of interleukin 1 receptor antagonist. The common tendency of nomenclature for sporadic form is chronic recurrent multifocal osteomyelitis (CRMO). In rare cases, the sporadic form can be unifocal at diagnosis or monocyclic. Moreover, CNO is an umbrella term defining a clinical spectrum, including mild, unifocal, self-limited types and severe, multifocal, recurrent types. The other special terminology for patients with skin involvement and sterile osteomyelitis is SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) [2, 3]. In addition, CNO may show extra-osseous manifestations such as skin, joint and intestinal involvements. These manifestations are usually psoriasis, acne, palmoplantar pustulosis, inflammatory bowel disease, and enthesitis-related arthritis [2].

Patients with CNO present with insidious bone pain, normal physical examination, and rarely systemic features like fever, and weight loss. Bone biopsy, bone scintigraphy, and magnetic resonance imaging are used for diagnosis. However, recent studies have supported the use of whole-body magnetic resonance imaging (WB-MRI) in the diagnosis of clinically suspected cases of CNO and monitoring of the progression of the disease. The WB-MRI provides information about the distribution of bone lesions, arthritis, and soft tissue involvements. Furthermore, the WB-MRI aids in the differential diagnosis of conditions such as malignancy and infection [2, 4, 5].

Generally, children with CNO have effective therapy alternatives and appear healthy, but in some cases, growth retardation, poor quality of life can be observed [2, 6].

The aim of this study was primarily to describe clinical features, radiographic findings, and treatment options of CNO patients in a single referral center. The second aim was to compare the quality of life of patients with healthy controls.

Materials And Methods

This cross-sectional study included patients who had been diagnosed with CNO or SAPHO syndrome before 18 years; by pediatric rheumatologists between January 2017 and December 2020; with a follow-up of at least 6 months. All procedures were conducted according to the principles of the Declaration of Helsinki, and human and animal rights.

The demographic characteristics, clinical features, patient and family history, extra-osseous organ involvements, the laboratory, radiological and pathological findings, and therapeutic strategies of patients were reviewed retrospectively. The regional and WB-MRI were reevaluated by pediatric radiologists to determine the number and distribution of bone lesions, joint, and other systems involvement.

Definitions

There is no globally accepted criterion for CNO. In this study, the patients were accepted to be in *remission (responsive)* if they had:

- normal c-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR),
- clinically improved known bone pain and no new inflammatory bone pain,
- resolution of marrow edema and no new lesions on WB-MRI.

This definition of remission in CNO was derived from the criteria of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) for treatment failure in CNO [7].

If the clinical, inflammatory, and radiological findings remained unchanged or worsened, the patient was defined as *unresponsive* to treatment. The others with decreased pain, inflammatory markers, and/or radiological findings were accepted as *partially responsive* to treatments [7].

In addition, the definitions for CNO were *unifocal* for a bone lesion in one location, *multifocal* for multiple bone lesions, p*ersistent* for bone inflammation of over 6 months without remission, and r*ecurrent* for bone inflammation of over 6 months with flares [8].

Moreover, there was a new suggested classification pattern for CNO according to the distribution of bone marrow lesions. The main distinctive hallmark was the presence of tibial or clavicular lesions and CNO was classified as a "*tibio-appendicular multi-focal pattern*" or a "*claviculo-spinal pauci-focal pattern*" [2].

In this study, some cases had both or none of these patterns and they were classified as "*the others*".

Well-being and quality of life

A visual analogue scale (VAS) was used to define the intensity of bone pain and global well-being by patients and pediatric rheumatologists at diagnosis and the last visit. Also, the quality of patients' life at the last visit was compared to healthy controls by using PedsQL4.0 which is a self-reported questionnaire including 4 parts (physical, emotional, social, and school life), and 23 items. The range of scores is between 0 and 100; higher scores indicate better quality of life [9, 10]. Each patient was matched to a healthy control and there was no gender and age difference between groups. Healthy controls were chosen from the patients without chronic disease who attended the pediatric outpatient clinic for regular examination.

Statistical analysis

Statistical analyses were done by using Statistical Package for social sciences (SPSS) software version 22. The categorical variables were determined as number and percent. The quantitative variables were evaluated using the Shapiro-Wilk test and histogram to define whether they were normally distributed. Non-normally distributed variables were presented with median and interquartile range (IQR) values. The differences were analyzed between categorical data by using the Chi-square test, between non-parametric independent groups by Mann-Whitney U test, and between non-parametric dependent parameters by using Wilcoxon Rank Sum Test.

Results

This study included 18 CNO patients and 11 (61.1%) patients were male. The median age at diagnosis was 13 (IQR 11–15) years, while the median age of disease onset was 12 (IQR 10–14) years. The median delay time of diagnosis was 9 (IQR 3–15) months and the median follow-up duration was 15 (IQR 12–22) months. The main characteristics, treatments and outcomes were in Table 1 for each patient.

Table 1
The main characteristics and outcomes for each patient.

Patient	Sex	Age*	CRP/ESR (mg/dL/mm/h)	Patern	Course	Steroid (weeks)	MTX (months)	Anti-TNF (months)	BPs (months)	Therapy Response	Follow-up (months)
1	M	13	30.4/52	Others	recurrent	No	Yes (16)	Yes (5)	No	partial	16
2	M	13	0.5/20	TAP	persistent	No	No	No	No	partial	7
3	M	17	57.8/24	TAP	persistent	Yes (12)	Yes (10)	Yes (7)	No	partial	12
4	F	12	118/98	CSP	persistent	No	Yes (12)	No	No	partial	26
5	M	11	0.7/12	TAP	persistent	Yes (24)	Yes (15)	Yes (12)	Yes (6)	remission	38
6	F	17	28.6/53	CSP	persistent	Yes (8)	Yes (4)	Yes (3)	No	unresponsive	10
7	F	7	0.5/5	TAP	persistent	No	Yes (9)	No	No	partial	10
8	M	14	27.7/16	CSP	persistent	No	Yes (8)	No	No	partial	20
9	M	12	13.7/10	TAP	recurrent	No	Yes (6)	Yes (3)	No	unresponsive	12
10	M	10	12.2/13	TAP	persistent	No	Yes (7)	No	No	partial	11
11	M	12	13.8/15	Others	recurrent	No	Yes (65)	Yes (20)	No	remission	24
12	F	11	32/20	Others	persistent	No	Yes (6)	Yes (6)	No	partial	12
13	M	4	10/42	TAP	persistent	No	Yes (3)	Yes (21)	Yes (6)	partial	12
14	F	7	3/13	CSP	persistent	Yes (8)	Yes (24)	No	No	remission	29
15	F	15	3/28	Others	persistent	Yes (4)	Yes (6)	Yes (7)	Yes (3)	unresponsive	17
16	F	14	1.5/18	TAP	persistent	No	Yes (9)	Yes (5)	No	partial	13
17	M	10	0.7/6	TAP	persistent	No	No	No	No	remission	22
18	M	16	88/56	CSP	persistent	Yes (8)	Yes (12)	No	No	partial	16

M-Male, F-Female, CRP-c-Reactive Protein, ESR-Erythrocyte Sedimentation Rate, TAP- Tibio Appendicular Pattern, CSP- Claviculo Spinal Pattern, MTX- Methotrexate, TNF- Tumor Necrosis Factor, BPs- bisphosphonates,

* Age of disease onset

Clinical and laboratory parameters at diagnosis

All patients had chronic bone pain and 11 (61.1%) patients were limping on first examination by a pediatric rheumatologist. Joint pain was observed in 17 (94.4%) patients. On physical examination, pain and limitation were present in the joints of 17 (94.4%) patients. Two patients had already been diagnosed with juvenile idiopathic arthritis. As extra-osseous findings, one patient had acne and pustulosis, another had abdominal pain and weight loss.

The persistent form of CNO was the most common pattern in 15 (83.3%) patients. The recurrent pattern was defined in 3 (16.7%) patients.

The median value of CRP was 13 mg/dL (IQR 1.3–30); ESR was 19 mm/h (IQR 13–45) at diagnosis. However, 7 patients had negative CRP and 11 patients had normal ESR values (Table 2).

Table 2
Evaluating inflammatory markers and pain in CNO patients at diagnosis and last visit

	Diagnosis	Last visit	p-value
Median CRP (mg/dL) (IQR)	13 (1.3–30)	0.5 (0.5-7)	0.007*
Median ESR (mm/hour) (IQR)	19 (13–45)	7 (5–16)	0.002*
Median WBC (x1000/mm^3) (IQR)	8955 (6858–11208)	7590 (6898–8193)	0.053*
Median PLT (x1000/mm^3) (IQR)	380500 (307500–408500)	317000 (241500–386750)	0.012*
Median pain-VAS score of patients (IQR)	8 (7-8.25)	2 (0-2.25)	0.001*
Median pain-VAS score of physician (IQR)	7 (6–7)	2 (0–3)	0.001*
CNO-Chronic nonbacterial osteomyelitis, CRP-c-Reactive Protein, ESR-Erythrocyte Sedimentation Rate, WBC-White Blood Cells, PLT-Platelets, SD-Standard Deviation, VAS-Visual analogue scale			
* Wilcoxon Signed Ranks Test			

Bone biopsy in 3 (16.7%) patients and bone marrow aspiration in 11 (61.1%) patients were performed to exclude malignancy. There were no positive bone and blood cultures, and no pus collections in MRIs.

Imaging Findings

All patients had plain radiography of painful areas and two patients had findings in plain radiography. These findings were irregularity and narrowing in the hip joint and height loss in the thoracic vertebral body.

After regional MRIs revealed bone marrow edema and osteitis in commonly affected sites, all patients were first evaluated to exclude infections and malignancy; then they were diagnosed as CNO. In addition, 15 (83.3%) patients had WB-MRI at diagnosis for confirmation. The lesions were multifocal in all 18 patients with symmetric distribution in 15 (83.3%) patients. All patients had bone marrow edema, 6 (33.3%) patients had soft tissue swelling, 1 patient (5.6%) had enthesitis and 13 (72.2%) patients had multifocal arthritis of adjacent joints to bone lesions. The most common localizations of arthritis were; knee in 8 patients, sacroiliac joints in 8 patients, hip in 6 (33.3%) patients, and ankle in 5 (27.8%) patients.

In WB-MRI, a total of 170 lesions were observed and the median number of lesions was 8 (IQR 5–10). The most common sites of lesions were the pelvis (72.2%), sacrum (61.1%), femur (61.1%), tibia (55.6%), and fibula (50%) (Fig. 1). According to the distribution pattern of bone marrow lesions, 9 (50%) patients had the tibio-appendicular multi-focal pattern, 5 (27.8%) patients had the claviculo-spinal pauci-focal pattern. Four (22.2%) patients had both or none of these patterns and they were classified as the others (Fig. 2).

Treatment

In this study, all patients had non-steroid anti-inflammatory drugs (NSAIDs). During the median 15 months (IQR 12–22) follow-up, methotrexate in 16 (88.9%) patients was used as the first-line immunosuppressive therapy. Six (33.3%) patients used steroids as bridging therapy and the median duration of steroids was 8 weeks (IQR 7–15). However, additional advanced treatments were required for some cases. These treatments were tumor necrosis factor (TNF)-α inhibitors in 10 (55.6%) patients and bisphosphonates in 3 (16.7%) patients. The median duration of anti-TNF inhibitor was 7 months (IQR 5–14). Two patients had 6 doses of bisphosphonates and 1 patient had 3 doses.

We observed remission in only 4 (22.2%) patients, one of them was under therapy and the others had completed their CNO therapy. Eleven (61.1%) patients were accepted as partially responsive to CNO therapy but 3 (16.7%) patients were unresponsive. Although one of these unresponsive patients had clinical improvement, newly developed bone lesions were noticed in control WB-MRI and an anti-TNF inhibitor was added to the CNO therapy.

Follow Up

After treatment, CRP and ESR levels on the last visit were significantly lower than the values on diagnosis. In addition, the pain-VAS scores after therapy were significantly better than VAS scores at disease onset (Table 2). Three patients had control WB-MRIs. One patient had radiological remission, another had improvement and the third had an exacerbation in the control WB-MRIs.

During controls, we observed nausea in 2 (11.1%) patients and elevated liver enzymes in 3 (16.7%) patients due to treatment. On the other hand, complications of CNO such as fractures, abscesses, ankylose in the hip, and diffuse skin scar occurred in 3 separate patients (16.7%).

Quality of life

On the last visit, patients were evaluated with PedsQL4.0 to determine their quality of life and they were compared to healthy controls. There was no difference in age and gender between patients and controls. However, the quality of patients' life was poorer than controls (Table 3).

Table 3
The results of the PedsQL4.0 questionnaire and comparing patients and controls

	Patients (n = 18)	Controls (n = 18)	p-value
Mean age (year) ± SD	14.22 ± 3.05	13.28 ± 1.7	0.143*
Sex n (%)			
Girls	7 (19.4%)	7 (19.4%)	0.663**
Boys	11 (30.6%)	11 (30.6%)	
PedsQL4.0 **Mean ± SD**			
Physical functioning	63.93 ± 21.13	88.66 ± 8.08	0.005*
Emotional functioning	74.17 ± 14.78	88.61 ± 9.52	0.002*
Social functioning	83.88 ± 13.67	93.06 ± 8.43	0.044*
School functioning	70.55 ± 17.48	86.39 ± 8.19	0.001*
PedsQL4.0- Pediatric Quality of Life Inventory 4.0, SD- Standard Deviation			
*Mann Whitney U Test ** Chi-square test			

Discussion

This single-center cross-sectional study described a rare autoinflammatory bone disease that was previously accepted as mild and self-limited. We diagnosed 18 patients as CNO in 4 years and over 75% of patients were treated with methotrexate and over 50% of patients needed anti-TNF treatment. Despite these potent treatments, our patients had poor quality of life.

In this study, the median age at onset of the disease was 12 years, the median delay time of diagnosis was 9 months and we observed a male (61%) predominance. In CNO, the peak onset age was 7–12 years and commonly female predominance was reported [2, 11]. The peak onset of CNO in studies from Turkey was between 9 and 10.2 years, and a male predominance was observed in 2 studies [12–14]. Likewise, two studies from India and Chile reported male predominance [15, 16].

Chronic non-bacterial osteomyelitis has no specific clinical features. Bone pain with/without swelling and redness is the main symptom and all of our patients had bone pain without swelling and redness [2, 5, 11].

The main pattern of pain in CNO is reported as alternating and insidious [2]. Another reason for pain and limitation in CNO patients is joint involvement that is adjacent to the osteitis area. We observed joint involvement in 17 (94.4%) patients, and 13 of them had arthritis in MRI [2]. Another study from Turkey reported 17.6% arthritis and 58.8% arthralgia [13]. Limitations and pain in joints are observed in CNO and arthritis is reported up to 40% in studies [16].

Other conditions such as acne, psoriasis, palmoplantar pustulosis, and inflammatory bowel disease accompanying CNO are reported between 4–20% [2, 5, 11]. In this study, one patient had inflammatory bowel disease, and another one had acne and pustulosis as SAPHO syndrome.

Inflammatory parameters at diagnosis in CNO are commonly mildly elevated [2, 5, 11]. Moreover, high values should warn the clinician to check the diagnosis. We observed mildly elevated inflammatory markers except for 1 patient. This patient was accepted as CNO after a detailed evaluation for infection and malignancy. After increasing WB-MRI's use to diagnose CNO, the bone and bone marrow biopsy rates decreased. However, bone and bone marrow biopsy should be performed to exclude malignancy and infection in necessary cases. In this study, bone biopsy was performed in 3 patients and bone marrow aspiration in 11 patients.

After the clinical suspicion of CNO, the painful areas should be imaged with plain radiography and MRI. The plain radiography has poor sensitivity to define bone marrow edema but it is important to exclude fracture and other bone disorders. The study in children reported 15% findings on radiography, such as lytic bone lesions, sclerosis, and hyperostosis [17]. However, the absence of these findings does not exclude CNO and the MRI is necessary to find out CNO. If the regional MRI shows osteitis in metaphyseal regions of commonly affected sites, such as lower extremities, long

bones, vertebrae, clavicles, and mandible, the diagnosis of CNO should be confirmed by the WB-MRI. In this study, 2 (11.1%) patients had findings in plain radiography. At diagnosis, all patients had MRIs and 15 (83.3%) of them had WB-MRIs. All patients had multifocal lesions and the lesion patterns in 15 (83.3%) patients were symmetric in WB-MRIs. The multifocal and recurrent forms of sterile osteomyelitis were severe forms of CNO. The unifocal lesion usually occur in the clavicle and mandible and might have milder symptoms. There was no patient with unifocal lesion and no mandibular involvement in this study. Patients with single and/or milder symptomatic lesions may have been misdiagnosed or underestimated and therefore had no chance to visit a pediatric rheumatologist.

We observed 170 lesions in 18 patients with a median of 8 lesions per child and the most affected bones were the pelvis (72.2%) and sacrum (61.1%). Açarı et al [14] reported lesion sites; femur (67.9%), tibia (57.1%), and pelvic bones (32.1%). Concha et al [16] observed lesions of 21% in the upper limb, 9% in the lower limb, and 36% in the axial skeleton, and the other studies reported sites of lesions under different titles and groups [11–16].

The new classification suggestion for CNO was offered according to the distribution of bone lesions. There were 2 main subgroups according to the presence of tibial and clavicular lesions. These two patterns were called “tibio-appendicular multi-focal pattern” and “claviculo-spinal pauci-focal pattern” [18]. In this study, 9 patients had tibial lesions and were suitable for the tibio-appendicular multi-focal pattern, 5 patients had clavicular lesions and were suitable for the claviculo-spinal pauci-focal pattern. Nevertheless, 1 patient had lesions in both of them and 3 patients had lesions in none of them. As a result, it paused a question mark on whether the new suggested classification criteria covered all types of CNO.

As initial treatment, nonsteroidal anti-inflammatory drugs are the first choice for cases without vertebral involvement. A prospective observational pediatric study reported that 43% of patients achieved clinical remission after 6 months and 62% of patients had clinical remission after 12 months [19]. A retrospective study observed relapse in 50% of patients treated with NSAIDs [20]. In this study, all patients had NSAIDs as initial treatment and 2 patients were treated with only NSAIDs. There was no commonly accepted therapy algorithm for CNO, but it was suggested that, if the patients were unresponsive to NSAIDs, the therapy should change gradually to disease-modifying anti-rheumatic drugs (DMARDs: methotrexate) and/or biologic DMARDs (anti-TNF agents) and/or bisphosphonates. Moreover, some patients might need corticosteroids as bridging therapy in a short time and patients with vertebral involvement should be treated rapidly with methotrexate and/or anti-TNF agents [2, 21]. In this study, three patients had bisphosphonate treatment. Two of them had bone destruction and were given bisphosphonate in addition to an anti-TNF inhibitor to reform bone structure. Another one was partially responsive to anti-TNF inhibitor and had bisphosphonate.

In this study, we observed that the quality of CNO patients’ life was influenced negatively, although they were treated effectively. These negative effects of CNO were observed not only in physical activities but also in the social, emotional, and school life of patients. A current study showed similar worsening physical and school functioning in CNO patients by using PedsQL4.0 [6]. Likewise, the same study reported anxiety and communication problems in CNO patients.

The main limitations of the present study were the single-center design and the small number of cases.

Conclusion

CNO is an inflammatory bone disease that can vary from asymptomatic to serious bone deformity. The diagnosis of this insidious disease requires detailed clinical analysis and imaging. The WB-MRI has been seen as an effective tool for the diagnosis and monitoring of CNO. The severe CNO cases should be rapidly treated with advanced therapy to prevent the damage by CNO. Although the CNO patients have clinical improvement under effective treatment, they have a poor quality of life.

Abbreviations

CARRA- Childhood Arthritis and *Rheumatology* Research Alliance

CNO-Chronic non-bacterial osteomyelitis

CRMO-Chronic recurrent multifocal osteomyelitis

CRP-C-reactive protein

DMARDs-Disease-modifying anti-rheumatic drugs

ESR-*Erythrocyte sedimentation rate*

IQR- Interquartile range (IQR

NSAIDs-Non-steroid anti-inflammatory drugs

PedsQL4.0-Pediatric Quality of Life Inventory 4.0

SAPHO-Synovitis, acne, pustulosis, hyperostosis, osteitis

TNF-Tumor necrosis factor

VAS-Visual analogue scale

WB-MRI-Whole-body magnetic resonance imaging

Declarations

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara City Hospital (Date 02.06.2021/No 562).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication

Conflicts of interest All authors declare no conflict of interest.

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Figures

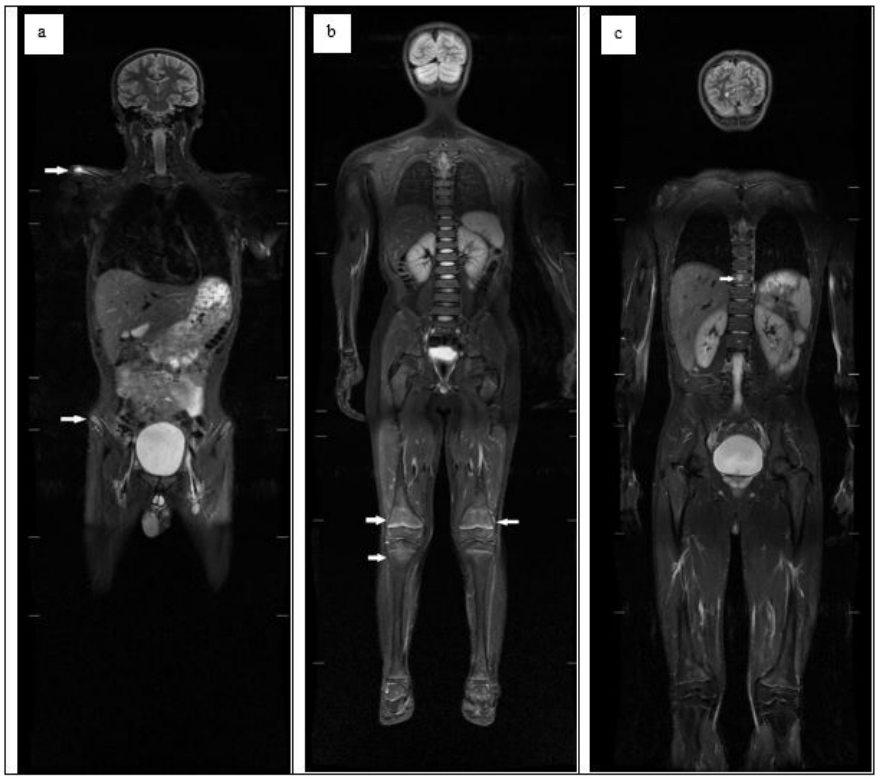

Figure 1

Lesions of chronic nonbacterial osteomyelitis in whole-body magnetic resonance imaging. The arrows show hyperintense signals of bone marrow edema in the clavicle and iliac bone (a), in the tibia and femur (b), in the vertebral body(c)

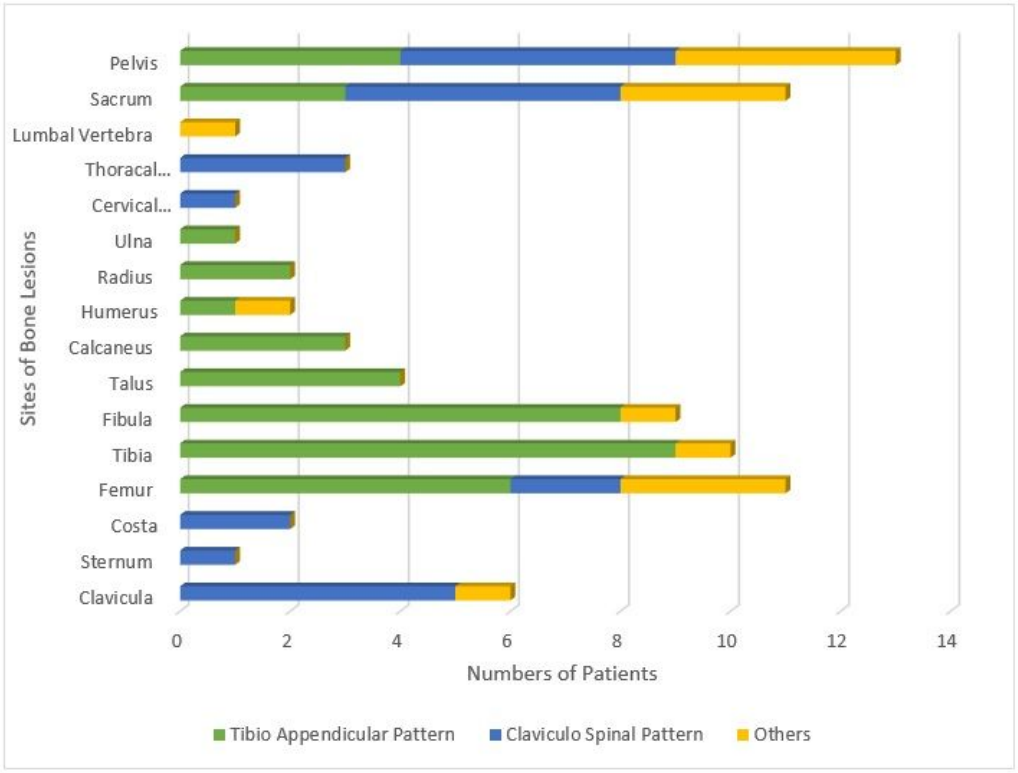

Figure 2

The sites of bone marrow edema per patient and the distribution of bone lesions according to new suggested patterns* of chronic nonbacterial osteomyelitis

* The new suggested classification patterns were for tibial lesion “tibio-appendicular multi-focal pattern”, for clavicular lesion “claviculo-spinal pauci-focal pattern”. The term "others" was used for the cases suited to both or none of these patterns in this study.