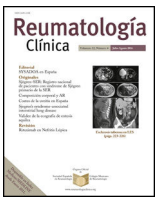
Reumatol Clin. 2018;14(6):334–338

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Original Article

Recurrent Multifocal Osteomyelitis in Children: Experience in a Tertiary Care Center☆

Ana Belén Ariza Jiménez,[a,*] Esmeralda Núñez Cuadros,[b] Rocío Galindo Zavala,[b] Leticia Núñez Caro,[a] Gisela Díaz-Cordobés Rego,[c] Antonio Urda Cardona[a]

[a] UGC Pediatría, Hospital Materno-Infantil de Málaga, Málaga, Spain
[b] Unidad de Reumatología Pediátrica, Hospital Materno-Infantil de Málaga, Málaga, Spain
[c] UGC Reumatología, Hospital Regional Universitario de Málaga, Málaga, Spain

ARTICLE INFO

Article history:
Received 21 December 2016
Accepted 6 April 2017
Available online 19 September 2018

Keywords:
Nonbacterial osteomyelitis
Chronic recurrent multifocal osteomyelitis
Children
Pamidronate
Tumour necrosis factor α inhibitor therapy

ABSTRACT

Introduction: Chronic recurrent multifocal osteomyelitis is a rare aseptic bone inflammation that affects paediatric patients. Its management and treatment have not yet been standardised.
Methods: Retrospective, descriptive study of patients under 14 years of age diagnosed with chronic non-bacterial osteomyelitis (CNBO) in a tertiary hospital. We included patients diagnosed over the last 6 years (2010–2015) who met the Jansson criteria. The clinical and radiological characteristics of CNBO were analysed, as was the outcome after different therapeutic options.
Results: We report 12 patients, with a mean age of 11 years (±1.6 standard deviation [SD]) and female predominance (10:2). The mean number of foci was 3.5 (±2.2 SD). The most common locations were ankle (58%), clavicle (50%), sternum (33%) and hip (25%). The mean disease duration was 10.5 months (±10.3 SD), and the median time to diagnosis was 2.38 months (range 0.17–16). Bone scintigraphy detected asymptomatic foci in 33% and we detected lytic lesions in 50% through magnetic resonance imaging. Biopsy was performed in 60%; 2/12 (16%) were associated with inflammatory disease and 1/12 (8.3%) later developed lymphoma. In all, 58% received antibiotic therapy with little response, 100% anti-inflammatory agents, 50% systemic corticosteroids, 41.6% methotrexate/pamidronate and 16% anti-tumour necrosis factor (TNF) α. The mean duration of treatment was 14.8 months (±12.4 SD) and 66% had recurrences. Currently, 83% are in clinical remission without treatment.
Conclusions: When CNBO is refractory to treatment with anti-inflammatory drugs, intravenous pamidronate can be an alternative. Anti-TNF drugs can be considered in patients who fail with pamidronate, as can agents associated with other autoimmune conditions.

Osteomielitis multifocal recurrente en niños: experiencia de un centro de tercer nivel

Palabras clave:
Osteítis no bacteriana
Osteomielitis multifocal crónica recurrente
Niños
Pamidronato
Tratamiento antifactor de necrosis tumoral alfa

RESUMEN

Introducción: La osteomielitis multifocal crónica recurrente es una inflamación ósea aséptica poco frecuente en pediatría cuyo abordaje y tratamiento no está estandarizado.
Métodos: Estudio descriptivo retrospectivo de menores de 14 años a quienes se diagnosticó osteomielitis crónica no bacteriana (OCNB) en un hospital de tercer nivel. Se incluyeron los pacientes diagnosticados en los últimos 6 años (2010-2015), y que cumplían los criterios de Jansson. Se analizaron las características clínicas y radiológicas, y su evolución tras las diferentes opciones terapéuticas.

☆ Please cite this article as: Ariza Jiménez AB, Núñez Cuadros E, Galindo Zavala R, Núñez Caro L, Díaz-Cordobés Rego G, Urda Cardona A. Osteomielitis multifocal recurrente en niños: experiencia de un centro de tercer nivel. Reumatol Clin. 2018;14:334–338.

* Corresponding author.
E-mail address: micodemas@hotmail.com (A.B. Ariza Jiménez).

Resultados: Se analizaron 12 casos, con 11 años de media (±1,6 desviaciones estándar [DE]), y predominio femenino (10:2). La media de focos fue de 3,5 (±2,2 DE). Las localizaciones más frecuentes fueron: tobillo (58%), clavícula (50%), esternón (33%) y cadera (25%). La media de tiempo de evolución fue de 10,5 meses (±10,3 DE) y la mediana hasta el diagnóstico de 2,38 meses (0,17-16). En el 33% se detectaron focos asintomáticos con gammagrafía ósea y en el 50% lesiones líticas con resonancia. Se realizó biopsia en el 60%; 2/12 (16%) asociaron patología inflamatoria y 1/12 (8,3%) desarrolló linfoma posteriormente. El 58% recibieron tratamiento antibiótico con escasa respuesta, el 100% antiinflamatorios, y el 50% corticoides sistémicos. El 41,6% requirieron metotrexato o pamidronato, y el 16% anti-TNFα. La media de tiempo de tratamiento fue de 14,8 meses (±12,4 DE), presentando recurrencias el 66%. Actualmente el 83% se encuentran en remisión clínica sin tratamiento.
Conclusiones: En OCNB refractarias a antiinflamatorios, el pamidronato intravenoso podría constituir una alternativa terapéutica en niños. Los fármacos anti-TNFα podrían considerarse en pacientes con fracaso a pamidronato, o aquellos que asocien entidades autoinmunes.

Introduction and Objectives

Non-bacterial chronic osteomyelitis (NBCO) is a condition which is characterised by the existence of aseptic bone inflammation. There are different types of this disease with chronic recurrent multifocal osteomyelitis (CROM) being the most serious.[1–3]

CROM is now considered to be a polygenic autoinflammatory disease. It is characterised by the presence of several inflammatory osseous foci (or one associated with acne conglobata) which persists for over 6 months, with the course of the disease alternating between exacerbations and periods of remission.[1,3,4]

The main symptom is pain, usually inflammatory, and may become severely disabling. It may also be associated with general symptoms such as low-grade fever or asthenia. Although it may present in the form of a single focal point, multifocal and symmetrical presentation is more common in most cases,[1,5–8] generally affecting children with a mean age of 8.[1,4] Its most typical location is the metaphysis of long bones and it most frequently affects the femur, the tibia, the vertebrae, the pelvic bones and the clavicle,with a mean of 4 foci.[1,2,5,6,9]

A diagnosis of exclusion is made and particularly in the single focus forms of the disease, where it is necessary to rule out tumour pathology and bacterial infection.[3] For this it may be necessary to order a bone biopsy, although criteria for this referral is not currently well defined. However, it may be associated with autoimmune diseases including inflammatory intestinal disease, or it may form part of syndromic conditions such as the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteomyelitis).[4,10]

Non steroid anti-inflammatory drugs (NSAIDS), systemic corticoids, and biologics may be used as treatment but there are no well-defined guidelines or protocol for their use.[11–13]

In general, it is not a well-known disease due to its recent description[8,10] and it is therefore underdiagnosed. It is thus important to be familiar with its clinical characteristics and the findings of the additional tests to obtain an early diagnosis. Furthermore there is no protocol or consensus regarding diagnosis and standardised treatment on an international level which would facilitate the approach to this pathology.

For all of the above, the main aim of our study was to analyse the clinical, diagnostic-therapeutic and developmental features of the patients with this pathology in follow-up in our centre.

Methods

Retrospective descriptive study of patients under 14 years of age who had been diagnosed with NBCO between 2010 and 2015 in a tertiary level hospital.

Patients diagnosed with CROM in keeping with Jansson's criteria (Table 1) were included and all those who did not meet with these criteria were excluded.

Remission was considered to be the absence of activity for over 6 months and in a well controlled disease the absence of symptoms and relapses.

Relapse was considered to be the reappearance of symptoms after a period of absence of the same symptoms for over a month.

In our centre a protocol of procedure has existed since the year 2010 for all patients on wards or in consultation in paediatric rheumatology department with criteria compatible with NBCO. This protocol consists of: initial screening with acute phase reactants, serologies,[14] the Mantoux test and plain radiography of the painful area.[2,3,6–8,15] Once clinical suspicion has been established, in all cases bone scintigraphy was performed with Tc99 for determining the number of inflammatory foci. However, magnetic resonance was used to define the type of lesions detected, as recommended in the literature.[8,16] Afterwards, after a meeting with the multidisciplinary committee, the need for bone biopsy was discussed. Regarding treatment, NSAIDS were used in addition to systemic corticoids, methotexate, pamidronate and anti-TNF in scaled format in accordance with Tables 2 and 3.

After 5 years of experience and the hypothesis that the protocol is useful for diagnosis and disease approach a retrospective review was made of the clinical files of these patients in accordance with the regulations stipulated by the ethics committee of our centre for this end.

The study was not reviewed by an ethics committee although it did comply with the main ethics for data treatment proceeding from the biomedical research with human beings (Geneva 2002).

A descriptive study was conducted of the following variables: gender, age, location, number of foci, symptoms and duration of symptoms, time of evolution until diagnosis, lab results and imaging test results, findings from biopsy, treatment received and duration, number of relapses or recurrences. The results were expressed as percentages in the qualitative variables, as mean and standard deviation in those quantitative variables which followed a normal distribution and as median, interquartile range or range between maximums and minimums in those where it did not. Adjustment to normality of the quantitative variables was measured by the using the Shapiro–Wilk test. Statistical analysis was made with the help of the SPSS v22 package (University of Malaga licence).

Results

Patient characteristics are listed in Table 4. In sum, 12 cases were diagnosed, with a mean age of 11 years (±1.6 SD) and female:male

Table 1
Criteria of Jansson for Diagnosis of CROM.

Major criteria	Minor criteria
Multifocal bone lesions	Good general status
Osteolytic/sclerotic lesion in the radiography	Course of disease over 6 months
Sterile biopsy with signs of inflammation/fibrosis or sclerosis	Lab results normal and raised ESR
Palmoplantar psoriasis or pustulosis	Hyperostosis
	Association with autoimmune or autoinflammatory disease apart from psoriasis and pustulosis

Diagnostic confirmation with two major criteria or one major and three minor criteria.
CROM: chronic recurrent multifocal osteomyelitis; ESR: erythrocyte sedimentation rate.

Table 2
Treatment Protocol for Patient With CROM Used in Our Centre.

1st NSAID[a]	Ibuprofen/naproxen
2nd Systemic corticoids[b]	Oral prednisone 1–2 mg/kg/day for 2 weeks with subsequent progressive reduction
3rd I.V. Pamidronate[c]	1 mg/kg/dose (see Table 3)
4th Biologics[d]	S.c. Adalimumab 24 mg/m^2/14 days and/or s.c./o.r. methotrexate 10–15 mg/m^2/weeks. Other options: infliximab, etanercept

NSAID: non-steroid anti-inflammatory drugs; CROM: chronic recurrent multifocal osteomyelitis.
[a] Administered for the first month or whilst the study is completed.
[b] May be maintained for one month maximum. If new outbreaks occur or there are complications i.v. pamidronate will be administered. This is maintained until symptoms disappear.
[c] On occasions first option may be pamidronate without previous therapy with corticoids.
[d] This is prescribed when the disease is refractory to pamidronate or there is an associated autoimmune disease.

Table 3
Administration Protocol for Pamidronate in Paediatric Patients Diagnosed With CROM Used in Our Centre.

Dose
1st Cycle:
1st day: .5 mg/kg
2nd day: 1 mg/kg (maximum 60 mg)
3rd day: 1 mg/kg (maximum 60 mg)
Following cycles: 2 options:
1 mg/kg 1 dose per month
1 mg/kg/day for 3 days every 3 months
Maximum recommended dose: 11.5 mg/kg/year

Preparation
Dilute in 250–500 ml of SSF
Administer in 3–4 h
Pre-medicate with paracetamol (at least the first doses)

Most common side effects
Flu-like syndrome and bone pain (may be treated with NSAIDS)
Hypocalcaemia and hypophospheremia. Treatment with calcium is recommended if symptoms or ionic calcium is <1 mmol/l
Vomiting and diarrhoea (try rehydration)
Conjuntivitis (apply lavages with saline solution)
Reversible cytopenias
Bone surgery after induction with pamidronate is not recommended. Contraindicated in severe kidney failure and enterocolitis

Follow-up
Extract haemogram, ions (including phosphorous), prescribe calcium/creatinine, vitamin D, baseline liver and kidney function, prior to treatment with pamidronate and after 2nd and 3rd dose.
If calcium/creatinine prescribed >.2 a kidney scan should be performed to rule out nephrocalcinosis.
Administer calcium and vitamin D for maintenance in children with low calcium levels, or reduced vitamin D levels (with normal calcium/creatinine rates) or changes to QTc

NSAID: non steroid anti-inflammatory drugs; CROM: chronic recurrent multifocal osteomyelitis; QTc: corrected QT interval; PS: physiological saline.

ratio was 10:2. It is worth highlighting that 60% of patients were initially diagnosed with infectious osteomyelitis, with diagnosis being reformulated due to persistence of pain, poor radiologic and analytical evolution, and/or the appearance of new foci of osteomyelitis, despite wide spectrum antibiotic treatment.

Although 16.7% presented with a single focus, the mean number of foci was 3.5 (±2.2 SD). The most common locations were the clavicle and ankle (tibia, fibula and astraglus). All consulted for pain. 75% suffered from associated functional impotence and 58% from fever. One case had associated acne conglobata and another an intestinal inflammatory disease, the main symptom of which was abdominal pain. Regarding lab test changes only a slight rise in CRP was noted (median: 18.1 mg/l; range: 3.8–235) and ESR (mean: 53.4 mm/h ± 35.2 SD) in 72% and 63.6% of cases, respectively. In all cases magnetic resonance imaging was performed with the most common finding being medullary oedema and with lytic lesion appearing in 50%. Biopsy was performed in 60% of patients, observing in all of them chronic inflammation and fibrosis. All the patients received NSAIDS, with 50% of them requiring prednisone due to the persistence of clinical symptoms after 4 weeks. 33% of patients required a third therapeutic scale (methotrexate/pamidronate) from relapses after withdrawal from corticotherapy. The case associated with intestinal inflammatory disease and the case associated with acne conglobata were treated with subcutaneous adalimumab, with excellent clinical response. Up until now, no serious secondary effects have been recorded in our patients.

Table 4
Epidemiological, Clinical and Diagnostic, Therapeutic Features of the Sample.

Patient characteristics (*n* = 12)	
Gender (female), n (%)	10 (83.3)
Age (years), mean (±SD)	11 (1.6)
Disease characteristics (*n* = 12)	
Clinical symptoms, n (%)	
Pain	12 (100.0)
Functional impotence	9 (75.0)
Fever	7 (58.3)
Location of focis (n = 37), n (%)	
Lower limbs	19 (51.4)
Clavicle	5 (13.5)
Ribs and/or sternum	4 (10.8)
Hip	4 (10.8)
Spine and/or sacrum	3 (8.1)
Upper limbs	2 (5.4)
Course of disease until first consultation (months), mean (±SD)	10.5 (10.3)
Duration of symptoms until diagnosis (months) median (IQR)	2.38 (4.0)
Results of ancillary tests (*n* = 12)	
Analyses	
Leucocytes, mean (±SD)	10,736 (±3905)
CRP (mg/l), median (IQR)	18.1 (48.0)
ESR (mm/h), mean (±SD)	53.4 (±35.2)
MR, n (%)	
Oedema	9 (75.0)
Cortical thickening	2 (16.6)
Lysis and/or cortical disruption	2 (16.6)
Periostic reaction	2 (16.6)
Infiltration	2 (16.6)
Biopsy (n = 8), n (%)	
Fibrosis	5 (62.5)
Inflammation	4 (50.0)
Necrosis	2 (25.0)
No events	1 (12.5)
Treatments (*n* = 12), *n* (%)	
Antibiotic	7 (58.0)
NSAIDS	12 (100.0)
Corticoids	77 (58.3)
Methotrexate	1 (8.3)
Pamidronate	4 (33.3)
Anti-TNFα	2 (16.7)

NSAID: non-steroid anti-inflammatory drugs; SD: standard deviation; CROM: chronic recurrent multifocal osteomyelitis; RCP: reactive C-protein; IQR: interquartile range; MR: magnetic resonance; TNF: tumoral necrosis factor; ESR: erythrocyte sedimentation rate.

All the cases with diagnostic delay of above 5 months received maintenance treatment with paramidronate or methotrexate, whilst only 16% of patients with early diagnosis required it.

No patient presented with serious sequelae. Only one physeal fusion bridge at right ankle level was detected in one case, without any limitation of associated movement. At present only 16% of patients require treatment for control of symptoms, and these are the patients who require biologics. For those who require pamidronate the treatment may be withdrawn after symptom control (mean 5 months of treatment). In the case of methotrexate treatment was withdrawn after a year of disease inactivity. However, recurrences presented in 66% of cases, and up to on 5 occasions in one. The appearance of a non-Hodgkin lymphoma after 2 years from the CROM diagnosis was notable, when the patient was in remission without treatment.

Discussion and Conclusions

As recorded in our study, non-bacterial osteomyelitis (NO) is a pathology which presents in childhood with pain, swelling, functional limitation and impotence and the disease course results in outbreaks, with patients being asymptomatic when not suffering from them. It may be associated with general symptoms of asthenia, fever or weight loss, with a median of 4 outbreaks annually.[1,5,6,9,17–19]

There is a strong association with autoinflammatory and autoimmune diseases, and in particular with psoriasis, in those subjects affected and their direct family members, which suggests a common psychopathology and supports the idea of a genetic susceptibility component.[2,20,21] In our sample there were 2 cases of associated pathology, including acne conglobata and intestinal inflammatory disease. Both of these had previously been described in the literature. Furthermore, it may form part of the syndromic characteristics such as the SAPHO syndrome, that of Majeed (neutrophilic dermatosis, anaemia, fever, arthralgias and osteomyelitis) and insufficient IL1 receptor antagonist or DIRA (respiratory distress, pustulosis, oral mucous lesions, arthritis and multifocal osteomyelitisl).[4,10]

One of the most controversial points is the diagnostic method to be followed. In our case we applied the diagnostic criteria of Jansson (Table 1)[2,4] for greater precision, but those of Handrick and Bristol[2] are also described in the literature and recently those of Roderick et al.[21] There is thus a need for a combination of clinical, radiological and anatomopathological findings

Once clinical suspicion has been established, and for the differential diagnosis with other pathologies which may present with similar clinical symptoms, certain ancillary tests would be indicated.[5,14,21] In our sample we used analysis, radiography, scintigraphy and/or magnetic resonance.[15,16] Bone scintigraphy with c99 is particularly useful in this pathology since active foci often exist which are not symptomatic and this technique has high sensitivity (around 90%) for their detection.[8] However, given its low specificity (around 75%),[8] the literature recommends magnetic resonance to better define detected lesions.[8,16] In different publications, total corporal magnetic resonance is considered as an alternative but this is not available in all centres for children due to the length of the procedure and its high cost.[16]

Moreover, in the case of lesions under 6-month duration, which are unifocal with an infiltrated or osteolitic infiltrate appearance, it is recommended that a biopsy be carried out.[5,13,15] In our sample this was obtained in 9 patients, due to the short evolution and radiologic findings in the majority of cases.

Regarding therapeutic management the NSAIDS are first line treatment. However, they are only useful for symptom relief, without having any effect on the radiologic image.[8,12,22,23] For this reason, all of our patients were initially treated with NSAIDS (usually naproxen), essentially during the diagnostic process.

If clinical symptoms persisted despite treatment with NSAIDS, treatment with systemic corticoids may be considered for no more than 4–6 weeks. If subsequent to this discontinuity is not possible, biphosphonates are prescribed, and specifically intravenous pamidronate, which has the greatest use from broad existing experience with this drug in paediatrics. In recent years the possibility of directly initiating treatment with pamidronate has been considered if symptoms cannot be controlled with NSAIDS since this would lead not just to fast relief of symptoms but possibly also disease remission. Furthermore, data on the safety of this treatment are increasingly more abundant, with the most frequent side effects in children being flu-like syndrome after the first infusion and electrolyte changes such as hypocalcaemia, hypophosphatemia or hypomagnesemia, all of which are usually asymptomatic.[13,16,24–27] Lastly, in refractory cases to pamidronate, anti-TNF inhibitors could be used as an alternative.[28–30] In our case this treatment guideline was followed, without any notable side effects being recorded (Tables 2 and 3).

According to the literature, the prognosis of these patients is good, with disease duration between 2 and 20 years, and a mean of 4.5 years. It is completely resolved in 73% of cases, without sequelae or new outbreaks, and on occasion even spontaneously.[1–3,6–9] In

our sample we were able to discontinue treatment in 10 patients (83.33%).

On rare occasions there may be complications such as early physeal fusion and lack of growth, degenerative arthrosis, bone deformity and pathological fractures.[19] In our sample, up until now only one case of a physeal bone bridge has occurred.

According to our results, delayed diagnosis and the existence of associated pathology could involve a higher need for scaled therapy and further recurrences. This fact is compatible with what has been published in the literature, since it defends that early diagnosis is related to a more benign course of the disease and the presence of comorbidity with the need for a more intensive treatment.[18,27–30] Furthermore, Catalano et al. relates persistent disease with a number of foci,[19] a fact which is not correlated with our findings.

To conclude, although the spectrum of this disorder is broad, we should suspect it when osteomyelitis is of torpid evolution or new foci appear despite appropriate antibiotic treatment. Biopsy should be reserved for cases of single focus, short evolution or which present data suggestive of malignancy in the ancillary tests performed. NSAIDS remain first line treatment although other alternatives exist, such as pamidronate or anti-TNF agents. We believe that despite sample size, the results obtained with pamidronate in our series allows us to conclude that it is an appropriate alternative when NSAIDS fail.

Delayed diagnosis may lead to higher exposure to diagnostic tests and a need for therapeutic scaling and from there the need for a high level of suspicion.

Recurrences may be related to time of evolution to diagnosis and with the existence of associated pathology. As a result, the establishment of diagnostic therapeutic protocols is needed to help professionals approach this pathology.

Ethical Disclosure

Protection of people and animals. The authors declare that for this research no experiments have been carried out on humans or animals.

Confidentiality of data. The authors declare that they have adhered to the protocols of their centre of work on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1. Desdoits A, Gandon-Laloum S. Chronic nonbacterial osteomyelitis in children. Pediatr Rheumatol. 2011;9:23.
2. Guillén S, Belda S, Rojo P, Losada B, Ramos JT, Clemente J, et al. Osteomielitis crónica multifocal recurrente. An Pediatr (Barc). 2005;62:573–8.
3. Marrero M, Merino JM, Rodrigo J, Bartolomé MJ, Camino A, Grande C. Osteomielitis crónica multifocal recurrente. An Pediatr (Barc). 2001;54:181–4.
4. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis. Rheumatology. 2007;46:154–60.
5. Padwa BL, Dentino K, Robson CD, Woo SB, Kurek K, Resnick CM. Pediatric chronic nonbacterial osteomyelitis of the jaw: clinical radiographic, and histopathologic features. J Oral Maxillofac Surg. 2016;74:2393–402.
6. Wipff J, Dumitrescu MA, Lorrot M, Kettani S, Faye A, Lacassagne S, et al. Creation of a cohort of French patients with chronic recurrent multifocal osteitis: preliminary results. Pediatr Rheumatol. 2011;9:34.
7. Regueras Santos L, Ledesma Benítez I, Ferrero de la Mano LJ, del Río González E, Fernández Castaño MT. Osteomielitis crónica multifocal recurrente (OCMR). experiencia en nuestro Servicio. Bol Pediatr. 2007;47:136–41.
8. Barral Mena E, Freire Gómez X, Enríquez Merayo E, Casado Picón R, Bello Gutierrez P, de Inocencio Arocena J. Non-bacterial chronic osteomyelitis: experience in a tertiary hospital. An Pediatr (Barc). 2016;85:18–25.
9. Khan MA, Osborne NJ, Anaspure R, Ramanan AV. Clavicular swelling-classic presentation of chronic non-bacterial osteomyelitis. Arch Dis Child. 2013;98:238.
10. Zimmermann P, Curtis N. Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome – a challenging diagnosis not to be missed. J Infect. 2016;72 Suppl.:S106–14.
11. Pardo S, Contreras J, Ballestín J, Rometsch S, Ferrer P, Adell A, et al. Osteomielitis crónica multifocal recurrente. Acta Pediatr Esp. 2014;72:e163–70.
12. Ferguson J, Sandu M. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. Curr Rheumatol Rep. 2012;14:130–41.
13. Handly B, Moore M, Creutzberg G, Groh B, Mosher T. Bisphosphonate therapy for chronic recurrent multifocal osteomyelitis. Skel Radiol. 2013;42:1777–8.
14. Hofmann SR, Kubasch AS, Range U, Laass MW, Morbach H, Girschick HJ, et al. Serum biomarkers for the diagnosis and monitoring of chronic recurrent multifocal osteomyelitis (CRMO). Rheumatol Int. 2016;36:769–79.
15. Khanna G, Sato TS, Ferguson P. Imaging of chronic recurrent multifocal osteomyelitis. Radiographics. 2009;29:1159–77.
16. Fritz J, Tzaribatchev N, Claussen C, Carrino JA, Horger MS. Chronic recurrent multifocal osteomyelitis: comparison of whole body MR imaging with radiography and correlation with clinical and laboratory data. Radiology. 2009;252:250–8.
17. Roderick MR, Ramanan AV. Chronic recurrent multifocal osteomyelitis. Adv Exp Med Biol. 2013;764:99–107.
18. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA, Dedeoglu F, et al. Pediatric chronic nonbacterial osteomyelitis. Pediatrics. 2012;130:e1190–7.
19. Catalano-Pons C, Comte A, Wipff J, Quartier P, Faye A, Gendrel D, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. Rheumatology. 2008;47:1397–9.
20. Cimolai N. Chronic multifocal osteomyelitis: is infectious causation a moot point? J Infect Public Health. 2011;4:157–68.
21. Roderick MR, Shah R, Finn A, Ramanan A. Chronic recurrent multifocal osteomyelitis (CMRO)—advancing the diagnosis. Pediatr Rheumatol. 2016;14:47.
22. Dalgleish S, Smith M, Renshaw P. Chronic recurrent multifocal osteomyelitis: clinical outcome following two different treatment plans with long term follow-up. Ann Paediatr Rheum. 2013;2:95–8.
23. Twilt M, Laxer RM. Clinical care of children with sterile bone inflammation. Curr Opin Rheumatol. 2011;23:424–31.
24. Conejo A, Núñez E, Jiménez JM, Urda AL. Pamidronato: una alternativa terapéutica en osteomielitis crónica multifocal recurrente. An Pediatr (Barc). 2011;75:215–7.
25. Armstrong DJ, Wright SA, Coward SM, Finch MB. Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate. Ann Rheum Dis. 2006;65:976–7.
26. Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. J Pediatr. 2008;152:571–5.
27. Girschick HJ, Zimmer C, Klaus G, Darge K, Dick A, Morbach H. Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated? Nat Clin Pract Rheumatol. 2007;3:733–8.
28. Eleftheriou D, Gerschman T, Sebire N, Woo P, Pilkington CA, Brogan PA. Biologic therapy in refractory chronic non-bacterial osteomyelitis of childhood. Rheumatology. 2010;49:1505–12.
29. De Souza A, Gomes E, Vasconcelos S, de Souza F, Branco AL. Chronic recurrent multifocal osteomyelitis: treatment with a tumor necrosis factor-alpha inhibitor. Turk J Rheumatol. 2012;27:262–6.
30. Ramraj R, Chun C, Marcovici P. Chronic recurrent multifocal osteomyelitis in Crohn's disease — complete resolution with anti TNFα therapy. J Pediatr Gastroenterol Nutr. 2016 [in press].