A LARGE NATIONAL COHORT OF FRENCH PATIENTS WITH CHRONIC RECURRENT MULTIFOCAL OSTEITIS

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Objectives: To document more fully the characteristics of CRMO in paediatric patients, to collect data on the outcomes and management of this disease and to define prognostic factors.

Material and methods: The inclusion criteria were i) patients with a CRMO diagnosis ii) at least one lesion of osteitis confirmed by imaging iii) and beginning before age 18 years.

Results: 178 patients were included (123 females and 55 males) with a mean age at diagnosis of 10.9±2.9 years. Clinical and imaging evolution revealed that only 12/178 (7%) CRMO patients remained with unifocal lesion. We could apply the clinical CNO (chronic non bacterial osteitis) score to 110/178 (62%) patients and bone biopsies would have been avoided in 27 (25%) cases.

At the last medical visit, only 73/171 patients (43%) were considered to be in remission (41% on therapy) after 47.9±38.9 months; 44/171 (26%) patients had sequelae.

Using cluster analysis, CRMO cohort could be separated into three homogeneous phenotypes: the first including males with multifocal form and inflammatory syndrome had the worst prognosis, the second (females with unifocal form, rare clavicular involvement and inflammatory syndrome) had the best prognosis, and the third including females with multifocal lesions and inflammatory syndrome had good prognosis but with the use of more treatment.

Conclusion: This cohort is the largest published CRMO cohort. Clinical evolution and imaging investigations confirm the multifocal pattern of this disease. Three distinct sub-groups of CRMO patients could be distinguished with very different prognosis.

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Introduction

Chronic recurrent multifocal osteomyelitis (CRMO), also known as nonbacterial osteomyelitis (NBO) or chronic non bacterial osteomyelitis (CNO), is an orphan disease (OMIM#259680) and its prevalence is probably underestimated. CRMO was first described in 1972 by Giedon et al. [1]. Recurrent flares of inflammatory bone pain related to aseptic osteomyelitis are the major characteristics of the disease. Some extra-articular manifestations associated with CRMO have been described and include psoriasis [3, 7], palmoplantar pustulosis [2, 5-7], Crohn's disease [2, 5, 8-11], acne [12], and Sweet's syndrome [13, 14]. Although CRMO is considered as benign disease, it can substantially impair quality of life due to persistent symptoms or sequelae [2, 3, 15].

Recently, there has been interest in the clinical, biological and imaging characteristics of CRMO and its natural evolution. Nevertheless, few studies have been published and have included only relatively small numbers of patients [2-6, 15-17]. Results of these studies are consistent regarding sex ratio F:M = 2/1, mean age at onset (10-11 years) and diagnosis (11 years) and number of initial clinical lesions (n=2) (2, 3, 5). On the contrary, results were heterogeneous, in particular concerning outcomes as the sequelae (20% to 46%) or the activity of disease at the last evaluation (18% to 59%) (2, 3, 5).

The pathophysiology remains unknown: some authors classify CRMO as the juvenile form of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) and others as an auto-inflammatory disease. However, recent genetic data [18-23] and the efficacy of anti-ILR1 in Majeed syndrome [24] suggest that CRMO may belong to the vast family of auto-inflammatory diseases with osseous expression (Majeed syndrome, PAPA syndrome, DIRA syndrome). However, anti-IL1 therapy seems not to have the same dramatic improvement in CRMO, probably due to the multifactorial pattern of CRMO [25].

Recently, Jansson et al. constructed a composite score to improve the management of CRMO. This score was designed to decide if bone biopsy was necessary to confirm the diagnosis [26]. We therefore conducted a retrospective national study (1) to document more fully the characteristics of CRMO in paediatric patients, (2) to collect data on the outcomes and management of this disease and (3) to define prognostic factors.

Materials and methods

We retrospectively reviewed medical records of French CRMO patients attending twelve French centres (one in Lyon, Rennes, Brest, Nantes, Nancy, Toulouse, Rouen, Tours, Grenoble and three in Paris) and diagnosed since 1995. This cohort was not a registry with a goal of exhaustiveness, collecting all French cases of CRMO, but the medical records of all patients from each centre were individually reviewed.

In the absence of validated international diagnostic criteria, our inclusion criteria were: at least one lesion consistent with osteomyelitis by imaging techniques in the absence of detectable infection, onset before 18 years of age and a diagnosis of CRMO by local physicians. The exclusion criteria were: onset after 18 years of age and other differential diagnosis (malignancy, infection, enthesitis related arthritis).

Two definitions for unifocal and multifocal patterns of CRMO were used: the first, the "clinical" definition based solely on clinically painful osseous localisation(s) as stated by the patient before diagnosis; and the second, the "final" definition based on clinical and imaging identification of osseous localisation(s) during all the course of the disease.

The characteristics of CRMO patients were recorded at two periods: the "revealing symptoms" at the beginning of the disease and the "cumulative symptoms" at the last medical visit corresponding to those noted during the entire course of the disease.

Clinical evaluation

The following clinical characteristics were collected: age, sex, age at onset of symptoms, age at diagnosis, the delay before diagnosis, and the clinically painful localization(s). Other features were recorded: presence of fever, local inflammatory signs and personal or familial history of associated disease such as psoriasis, inflammatory bowel disease (IBD), severe acne, palmo-plantar pustulosis, spondyloarthropathy and CRMO. Past and current medications were listed. The effectiveness of NSAIDs was noted when available: NSAIDs were considered as "effective" if the local physicians noted in the medical record that the patient was improved by NSAIDs. Nevertheless, "effective" was subjective and was not a synonym of "remission" or "completely controlled". Finally, remission, as judged by the patient's usual physician at the last medical visit was defined by the absence of pain and, when available, the absence of biological inflammatory syndrome and/or osteitis detected by imaging. The presence of sequelae (localized deformation, vertebral fracture and general growth retardation defined as a body mass index (BMI) under -2 standard deviation i.e. under the 3rd percentile) was noted.

Biological evaluation

Laboratory values collected, as available, for the two different periods were as follows: complete and differential blood count, C-reactive protein (CRP) analyzed according to local laboratory norms, erythrocyte sedimentation rate (ESR) considered as abnormal if > 10mm at the first hour, and the presence of HLA-B27 antigen.

Imaging evaluation

The date, the number and the localisation of lesions in standard radiographs, isotopic bone scans and MRI (magnetic resonance imaging) were collected.

Histological evaluation

Histological results of bone biopsies, when performed, were analyzed: the presence of neutrophils, lymphocytes, sclerosis, bone remodeling and the results of bacteriological cultures (in particular for *Propionibacterium acnes* and *Staphylococcus*) were noted.

Clinical CNO score

Jansson et al. recently developed a score to assist in the diagnosis of CRMO while diminishing the number of unnecessary bone biopsies [26]. The clinical score can range from 0 to 63 (Table 1). We applied this score to evaluate if, retrospectively, CNO score results would have allowed confirming CRMO diagnosis without the result of a bone biopsy.

Statistical analyses

All data analyses were performed using MedCalc® version 9.2.1.0. Data are reported as means (S.D.) for continuous variables and numbers (percentages) for categorical variables. Chi-square tests were used to study differences in frequency and the Student's t-test for comparing pairs of normally distributed continuous variables. P<0.05 was considered statistically significant. In cases of P <0.05, odds ratio (OR) estimates and 95% confidence interval (CI) were calculated.

A multivariate stepwise logistic regression analysis was also performed for all variables identified with p < 0.1 univariately.

For the cluster analysis, we selected ten variables for their relevance to the characterization of CRMO features. The variables were: sex, BMI, the delay of diagnosis, the mono or multifocal pattern, the clavicle involvement, the presence of extra-osseous lesions, a history of familial associated diseases, a CRP > 10mg/l, the use of bisphosphonates and/or anti-TNFα and finally the remission at the last medical visit as defined above. We performed a cluster analysis with R package (R Development Core Team (2005). URL: http://www.R-project.org) based on these significant components using Ward's method. This method groups measures of similarity procedure (minimum within cluster sum of square). The Ward's analysis allows

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detecting homogeneous groups by decreasing the within-cluster variance and increasing the distance between cluster centres.

Results

The "revealing features"

There were 123 female and 55 male (F:M ratio = 2/1) CRMO patients in the study cohort of 178. The mean age was 16.4±4.7 years [range 4-35]. The mean age at onset of symptoms was 9.8±3 years [range 1-17] and the delay before diagnosis was 17.3±24.8 months [range 1-137]. Other characteristics of this cohort of CRMO patients are summarised in Table 2.

At the time of diagnosis, 124/178 (70%) CRMO patients presented multifocal clinically painful osseous localisations; the mean number of clinical lesions was 2.7±1.8 [range 2-9]. Among the 54/178 (30%) of patients with a clinical single bone localisation, the clavicle was involved for 15/54 (28%). In all, 456 clinical localisations were described before diagnosis, with the lower limbs (47%), pelvis (16%) and clavicles (10%) being the most frequently involved. Mandibular and vertebral localizations were involved respectively in 2% and 8%. The distribution of clinical lesions before diagnosis is detailed in the Figure 1.

Forty patients had clinical vertebral lesions during the course of the disease and 7/40 (17.5%) had vertebral fractures. Comparison of the patients with and those without clinical vertebral lesions showed only significant difference for the use of "aggressive treatments" (27.5% vs 9%, p=0.003).

The number of mandibular lesions was 9/456 (2%) and lesions occurred in 9/178 patients (5%) of which 8/9 were a clinical multifocal form of CRMO. These patients were more frequently male (66% vs 29%, p=0.02) and had more frequently "aggressive treatment" (56% vs 11%, p=1.10^{-4}), but only with bisphosphonates.

Initial extra-osseous manifestations were present in 21/178 (12%) of the patients (6 IBD, 14 palmo-plantar pustulosis, 3 psoriasis and 4 severe acne). For 51/159 (32%) patients, there was a familial history of disease associated with CRMO: psoriasis for 31 cases, spondyloarthropathies for nine cases, IBD for six and CRMO for three.

Laboratory tests showed a high frequency of inflammatory syndrome (n=119, 66%) with high C-reactive protein concentrations in 73/144 (51%) with a mean of 23.6±43.5 and high ESR in 109/127 (86%) with a mean of 37.7±25. Blood cells counts were normal in 82/106 (77%) of patients. The HLA B27 antigen was detected in 6/86 (7%) patients tested and antinuclear antibodies in 9/74 (12%).

The mean number of structural lesions detected by imaging investigations was 3.5±2.9 [range 1-26] with differences between the different imaging techniques: 0.9±1 by standard radiographs, 2.4±1.7 by isotopic bone scan and 3.1±1.3 by MRI.

Bone biopsies were performed in 119/178 CRMO patients. Bacteriological cultures were positive in 11/92 cases with four *Propionibacterium acnes*, and seven *Staphylococcus* isolates (4 were coagulase negative, 1 was aureus and 2 unspecified). These patients with positive cultures were, even so, included in our cohort. Indeed, despite the positivity of cultures, the absence of favourable evolution during and after antibiotics showed that presence of the bacteria was not the cause of symptoms. After bone biopsy, antibiotics were administered to 63/178 (35%) patients. Histological investigations showed that lymphocytes were significantly the most frequent inflammatory cells compared to neutrophils (84% versus 56%, p=4.4 10^{-5}). Lymphocytes and neutrophils were simultaneously present in 37/83 bone biopsies. Patients with only neutrophils on biopsies did not exhibit a more severe or auto-inflammatory pattern (fever, CRP) than patients with lymphocytes in biopsies. Bone remodelling was noted in 38/84 biopsies and sclerosis in 45/83 cases. Regarding the presence of neutrophils, lymphocytes or sclerosis in infiltrate, bone biopsy was respectively performed

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8.9±13.4 months [range 1-86], 9.3±15.4 months [range 1-86] and 9.4±15.4 months [range 1-86] after the onset of symptoms. The comparison between biopsies performed during the first 6 months of symptoms or after showed only difference for the presence of lymphocytes that were significantly more frequent when biopsy was performed after the 6 first months (80% vs 100%, p=0.006) (Table 3 in supplementary file).

CNO score was assessed using the "revealing features" thus at the beginning of the disease, before the diagnosis (i.e. a diagnosis of CRMO made by local physicians) and before bone biopsy. The clinical score for CNO was interpretable for 110/178 patients at this particular time of the course of the disease. The CNO score results would have avoided 27 bone biopsies because 12 patients (score > 39) would have been definitively considered as CRMO even without the result of a bone biopsy and 15 would have been monitored (score between 29 and 38) instead of undergoing the bone biopsy.

The "cumulative features" (At the latest follow-up)

The mean disease duration, between the onset of the first symptoms until the last medical visit, was 47.9±38.9 months. The mean number of clinical (3.6±2.2) and radiological (4.7±3.9) osseous lesions increased during the course of the disease.

Among the 54 CRMO patients with clinically unifocal form at the beginning of the disease, the clinical and imaging progression led to a multifocal pattern being detected in 42 patients. Thus, only 12/178 (7%) had persistent unifocal pattern after about 4 years of disease progression (Figure 2). Unifocal and multifocal forms of CRMO were compared using the two definitions of these patterns (Table 1 in supplementary file). Using univariate analysis, initial multifocal patients had less frequent clavicle involvement, a higher CRP concentration ($28.1±49.7$ versus $12.1±16.2$, $p=6.10^{-3}$), underwent fewer bone biopsies, and were more

frequently treated with anti-TNFalpha (TNFα) and/or bisphosphonates (21/124 versus 3/54, p=0.04). Only high CRP level and fewer bone biopsies remained associated with multifocal forms in multivariate analysis. Using the "final" definition, differences between uni and multifocal forms were significant for clavicle involvement (50% vs. 9%, p=4.10^{-6}) and the mean CRP value (24.9±44.9 vs. 7.2±7.6, p=2.10^{-4}) only with univariate analysis. This comparison suggested also tendencies for the "final" multifocal pattern to be more prevalent among males (33% vs. 9%, p=0.08) and to be treated with anti-TNFα and/or bisphosphonates (14% vs. 0%, p=0.06).

Medical treatment, other than antibiotics, was based on non steroidal anti-inflammatory drugs (NSAIDs) as first-line therapy in 173/178 (97%) patients and was effective in 126 patients. Other treatments used were: corticosteroids in 14 patients, methotrexate in 14 patients, sulphasalazine in 21 patients, bisphosphonates in 17 patients, anti-TNFα agents in 13 patients and anti-I1LRa (anakinra) in one patient. For other treatments, efficacy was noted, when available, in 41% (7/17), 37.5% (3/8), 75% (6/8) and 89% (8/9) for sulfasalazine, methotrexate, bisphosphonates and anti-TNFα respectively.

At the last visit, 74/171 (43%) patients were considered to be in remission (seven patients were lost to follow-up after the diagnosis), of which 41% (27/67) remained on therapy. Among patients with active disease (n=97) at the last visit, the rate of patients on therapy was 72% (70/97) but treatment was not specified for all patients (n=18) and some patients had therapy only during painful crises. Sequelae occurred in 44/171 (26%). Seventeen patients with localised bone deformation at the time of diagnosis were considered to be without deformation at the last medical visit. Sequelae included localised deformation (n=26), in particular at the clavicle (n=16), vertebral fractures (n=7) and growth retardation (n=11).

Prognostic factors for persistence of symptomatic disease at the last medical visit are reported in Table 2. The risk of not achieving clinical remission at the last medical visit was

significantly higher for cases for which the delay before diagnosis was longer (22.2±30.6 vs. 11.7±13.5, p=0.003) and a tendency was noted for males (38% vs. 24%, p=0.06, OR=1.9 [0.98-3.7]). None of the other demographic or disease characteristics, including the clinical uni/multifocal pattern of CRMO before diagnosis, were associated with remission. Prognostic factors for the severity of the disease characterized by the use of anti-TNFα and/or bisphosphonates were (Table 2 in supplementary file): male gender (50% vs. 29%, p=0.04, OR=2.4 [1-5.75]) and a multifocal pattern before diagnosis (87% vs. 66%, p=0.04 OR=3.5 [1-12.4]).

Cluster analysis of CRMO cohort

Classification of the 178 CRMO patients using cluster analysis resulted in a dendrogram (Figure 1 in supplementary file). CRMO cohort could be separated into three homogeneous distinct phenotypes which are presented in Table 4. The two first groups were nearly at the opposite whereas the third could be considered as "intermediate".

The first phenotype (n=36) contained male subjects (100%) with multifocal form (97%) with rare clavicle involvement (only 11%) and frequent inflammatory syndrome (CRP > 10mg/l in 72%). The second phenotype (n=56) was composed of females (73%) with unifocal form (80%) and frequent involvement of clavicle (43%) but with low frequency of inflammatory syndrome (26%) and extra-osseous lesion (4%). Finally, the third phenotype (n=86) called "intermediate" was characterized by the following features: females (95%) with multifocal form (91%), inflammatory syndrome (56%), history of familial associated disease (20%), extra-osseous lesion (39%).

The first sub-group had the worst prognosis with a remission rate at 22% despite a high frequency of the use of bisphosphonates and/or anti-TNFα (33%). The second phenotype had the best prognosis at the last medical visit (49% were in remission) despite the infrequency of

use of bisphosphonates and/or anti-TNFα (2%). In the third phenotype, the remission rate was 48% but with an intermediate frequency of use of bisphosphonates and/or anti-TNFα (13%).

Discussion

Our results, collected from the largest published cohort of CRMO patients, provide detailed clinical, biological, histological and demographic data for CRMO during all the course of the disease. Our study: i) identifies, for the first time, three homogeneous sub-groups of CRMO patients with distinct features and prognosis, ii) suggests that the outcome for CRMO patients is not good as already reported, iii) shows that clinical and imaging follow-up for a long enough period confirmed that CRMO is a multifocal disease, iv) suggests that the clinical CNO score may be helpful to confirm CRMO diagnosis without using systematic bone biopsy.

Demographic characteristics, as sex ratio = 2/1 and mean age at diagnosis of 11 years, and clinical data from this national French CRMO cohort shares similarities with those from published studies [2-6]. The delay in diagnosis in our cohort was quite long, 17.3 months (range 1-137), and close to the 18 months described in a previous French study [4, 27, 28]. Comparing the delay before diagnosis before and after 2007 (data not shown), the difference is not significant suggesting that CRMO remains a poorly known disease.

The distribution of painful osseous lesions before CRMO diagnosis in our cohort is consistent with previous data [4, 5] affecting predominantly the lower limbs (47%) followed by pelvis (16%) and clavicle (10%). Vertebral localizations were less frequent (8%) than previously described (14-30%) [4, 5, 16]. However, the number of patients with vertebral lesions (n=40, 22%) and, especially, the risk of vertebral fracture (17.5%) when vertebral lesions occurred has to be considered as high. According to these results, the presence of inflammatory vertebral lesions should lead to consideration of more aggressive anti-inflammatory

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treatments and corset to prevent complications. In patients with mandibular involvement (n=9), data suggest that they were male (66%) needing more aggressive treatments (56%). Nevertheless, these data need to be taken with caution given the small number of patients.

The frequency of personal or familial extra-osseous manifestations as psoriasis or inflammatory bowel diseases already considered as auto-inflammatory conditions [8-14], is consistent with the hypothesis that CRMO belongs to the family of auto-inflammatory diseases. The alternative hypothesis is that CRMO belongs to the group of spondyloarthropathies. The low frequency of HLA B27 (7%) supports the idea that CRMO could have to be closed to non-HLA B27 spondyloarthropathies like enteropathic or psoriatic arthritis [29], psoriasis and IBD being highly associated with CRMO. Another way to address this issue is to consider that spondyloarthropathies may be included in the auto-inflammatory disease spectrum, as suggested by McGonagle in 2006 [30].

Elevated inflammatory markers seem to be frequent in CRMO. In previous studies [2, 5-6, 17] they seemed to be as often elevated as it was in our study. In these studies, CRP and/or ESR was found elevated in 50% to 90% of cases. Our results are in accordance with these results but they should be interpreted with caution taking into account the possible selection bias of the most severe patients needing hospital medical care.

Imaging (isotopic bone scan and/or MRI) is the cornerstone for confirming the multifocal pattern of CRMO. MRI seems to have a better sensitivity (20/38, 52%) than isotopic bone scanning (14/41, 34%) for detecting multiple lesions. This result, consistent with data in the literature [31], is further strengthened by the fact that only 2/38 MRI investigations were whole body MRI. However, no definitive conclusion can be drawn from this retrospective study which was not designed to compare these two imaging techniques head to head.

The definition of the unifocal or multifocal forms of CRMO has not been rigorously defined. Because of this problem, we used two definitions: the "clinical" and the "final" definition.

Irrespective of the definition used, comparisons between unifocal and multifocal forms revealed three main differences between the two forms: CRP values were higher, the clavicle was less frequently involved and the use of anti-TNFα and/or bisphosphonates was more frequent in the multifocal group. The characteristics of patients with "final" unifocal form were: female gender with clavicle involvement and normal biological measures.

In our cohort, after a mean disease duration of 4 years, only 74/171 (43%) cases of CRMO were considered to be in clinical remission of which 40% were under treatment. Among CRMO patients with active disease at the last medical visit, 71% remained on therapy but some of them had discontinued treatment. Nevertheless, these results suggest that CRMO may have a poorer prognosis than previous described with more frequently active disease at follow-up [2-6]; note, however, that previous data are scarce and there is no validated or even consensual definition of remission. This argues for the need to identify homogeneous sub-types of CRMO and prognostic factors facilitating case management in order to improve outcomes. The cluster analysis (Table 4) showed three homogeneous sub-groups of patients with distinct prognosis and features. The first sub-group was correlated with the worst prognosis with only 22% of patients at the last medical visit despite the use of anti-TNFα and/or bisphosphonates in one third of patients. CRMO patients of this first sub-group were male with multifocal form and inflammatory syndrome at the beginning of the disease. At the opposite, females with unifocal form, especially clavicle involvement, with normal C-reactive protein had a better prognosis with remission in nearly 50%. These results were globally in accordance with Jansson study [5] that postulated three sub-groups of non bacterial osteitis based on the clinical evolution of patients: acute non-bacterial osteitis (ANBO) patients with complaints lasting not longer than 6 months and with at least one bone lesion, chronic non-bacterial osteitis (CNBO) patients with persistent complaints (without remissions) lasting longer than 6 months, and with at least one bone lesion and finally CRMO patients with

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multiple bone lesions, or one bone lesion plus palmoplantar pustulosis (PPP), and recurrent flares with remissions. The main difference between the two studies was the way to identify sub-groups: in our study, cluster analysis was performed based on patients' characteristics where as in Jansson study this was a postulate. Some features of sub-groups differ depending on the two studies: our results showed differences for gender, inflammatory syndrome and treatments. These differences allowed us to distinguish three homogeneous sub-groups with marked features and prognosis.

Another way to detect patients with poor prognosis is to consider patients who were unable to reach remission or those who needed the use of anti-TNFα and/or bisphosphonates. Results identified the following as poor prognostic factors: male gender, multifocal pattern at the onset and a late diagnosis. These observations highlight the importance of a better knowledge and the need to make the diagnosis early to improve the prognosis. The identification of these prognostic factors has to lead to improved management to prevent sequelae (25% in our study whatever the remission status) which have already been found to be associated with psychological consequences and depression [2, 3].

NSAIDs are undoubtedly the first-line treatment for CRMO and are highly effective, as previously reported [32, 33]. The wide diversity of second-line treatments used [2-6, 25, 34-40] reflects the lack of standardisation concerning the treatment of CRMO, which is a consequence of the absence of controlled and randomised trials. Further studies are needed to evaluate possible treatment strategies.

Bone biopsies were performed more frequently in unifocal pattern (61% vs 81%, p=0.007) because of the necessity to rule out differential diagnoses as malignancy and infection. Although bone biopsies often remained necessary, some CRMO patients could avoid suffering this invasive investigation. To assess this idea, we applied the clinical score proposed by Jansson et al. [26] to our cohort with interesting results. Among the 110 interpretable cases,

bone biopsies would have been avoided for 27 patients. These results suggest that this clinical score may be useful in routine practice for the management of CRMO patients so as to avoid unnecessary invasive investigations.

Our study should be interpreted within its limitations: firstly, it is a retrospective study, and this implies missing data; however, except for data concerning the presence of HLA B27 (n=86) and ANA (n=74), the amount of missing data was not excessive, and did not have large consequences for the validity of our results. Our cohort is not a registry with the aim of being exhaustive. Patients recruited into this cohort were CRMO patients followed in tertiary hospital centres and more severe cases may therefore have been over-represented. However, it is probably this particular sub-group of patients that is at greatest need of adapted management and treatments.

The specific strengths of our study include: i) the identification of homogeneous sub-groups of CRMO patients with distinct prognosis by cluster analysis, ii) the collection of data at two periods which allowed the analysis of the characteristics leading to the diagnosis and the prognostic factors in CRMO, iii) the 4-year follow-up ensures that misdiagnoses were eliminated, iv) the large number of CRMO patients argues for the validity of our results and v) finally, the systematic collection of imaging and clinical evolution findings confirmed that CRMO is, in a large majority of cases, a multifocal disease.

Conclusion

In this large French cohort of CRMO patients, the sub-group of male patients with initial multifocal form and inflammatory syndrome was associated with more severe phenotype and prognosis. Our results also suggest that the clinical course and imaging investigations, especially MRI, are essential to confirm the multifocal pattern of osteitis even in cases that are

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initially, apparently, unifocal. In addition to imaging alone, the clinical CNO score may be useful for avoiding invasive bone biopsies. Although NSAIDs remain the main first-line treatment with efficacy, further studies about treatment strategies taking into account the different phenotypes are warranted.

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Table 1: Optimal multivariable logistic regression model for calculating the clinical score for a diagnosis of nonbacterial osteitis

Risk factor	Logistic regression coefficient	p	Score coefficient
Normal blood cells count	4.4	0.002	13
Symmetric lesions	3.4	0.018	10
Lesions with marginal sclerosis	3.29	< 0.001	10
Normal body temperature	3.01	0.011	9
Vertebral, Sternal or Clavicular lesion	2.63	0.002	8
Radiologically proven lesions ≥ 2	2.39	0.001	7
CRP ≥ 1mg/dl	1.93	0.005	6
Total clinical score			63

* Risk factors were included if the regression coefficient was statistically significant (P < 0.05). Score coefficients are the scaled coefficients of the logistic regression values and represent the score compon ent for each risk factor. If the individual does not have the specific risk factor, his or her contribution t o the total clinical score for that characteristic is zero. The total clinical score is the sum of score coeffi cients not equal to zero, with a range of 0–63. OR = odds ratio; CRP = C-reactive protein. This table is adapted from the following article: "*Annette F. Jansson, Thomas H. Muller, Leonhard Gliera, et al. Cl inical Score for Nonbacterial Osteitis in Children and Adults. Arthritis Rheum 2009;60:1152-1159*"

Table 2: Initial characteristics of CRMO patients (n=178)

n (%)	French national CRMO cohort (n=178)
Age (mean±SD)	16.4±4.7
Sex (F/M)	123 / 55
Age at onset of symptoms (years; mean±SD)	9.8±3
Age at diagnosis (years; mean±SD)	10.9±2.9
Delay before diagnosis (months; mean±SD)	17.3±24.8
Nb of clinical localisations per patient (mean ±SD)	2.7±1.8
Clinical unifocal form	54/178 (30%)
Local inflammatory aspect	77/178 (43%)
Arthritis	20/178 (11%)
Fever	36/178 (20%)
Extra-osseous involvement	21/178 (12%)
Family history	51/159 (29%)
Inflammatory syndrome	119/178 (67%)
HLA B27	6/86 (7%)
ANA	9/74 (12%)
Nb of radiological lesions per patient (mean±SD)	3.5±2.9
- Radiographs	1±0.9
- Isotopic bone scan	2.5±1.7
- MRI	3.1±3.3

F: Female; M: Male; SD: Standard Deviation; Nb: Number; MRI: Magnetic Resonance

Imaging; ANA: antinuclear antibodies; HLA : Human Leucocytes Antigen

Local inflammatory aspect corresponded to the presence of tumefaction and/or heat and/or

redness

Table 3: Comparison between CRMO patients with and without remission at the last medical visit

n (%)	Patient without remission (n=97)	Patients with remission (n=74)	p	p*
Age	17±4.4	15.6±4.8	0.9	
Sex (F/M)	60/37	56/18	p=0.06 OR=1.9 [0.98-3.7]	
Age at onset (years)	9.6±3.2	9.9±2.6	0.5	
Age at diagnosis (years)	11.3±3.1	10.6±2.5	0.1	
Delay before diagnosis (months)	**22.2±30.6**	**11.7±13.5**	**p=0.003**	**p=0.04 OR = 0.98 [0.97-0.99]**
Clinical multifocal form	70/97 (72%)	50/74 (68%)	0.5	
Local inflammatory aspect	45/96 (47%)	28/70 (40%)	0.5	
Inflammatory syndrome	65/93 (70%)	50/68 (73%)	0.6	
Extra-osseous involvement	9/96 (9%)	12/73 (16%)	0.2	
Nb of radiological lesions per patient	4.7±3.2	4.8±4.6	0.9	
Biopsies	69/97 (71%)	46/74 (62%)	0.2	
Bisphosphonates	12/97 (12%)	5/74 (7%)	0.2	
Anti-TNFα	**12/97 (12%)**	**1/74 (1%)**	**p=0.007 OR=10.3 [1.3-81.2]**	
Bisphosphonates and/or biotherapy	**18/97**	**6/74**	**p=0.05 OR= 1.3 [0.97-6.9]**	**p=0.03 OR = 0.11 [0.01-0.85]**
Sequelae	27/97 (28%)	17/74 (23%)	0.4	

F: Female; M: Male; TNFα : tumor necrosis factor alpha; Nb : Number
p* is p value using a multivariate stepwise logistic regression analysis
Local inflammatory aspect corresponded to the presence of tumefaction and/or heat and/or redness

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Table 4: Cluster analysis: three distinct sub-groups of patients with CRMO

	Light phenotype n=56	Intermediate phenotype n=86	Severe phenotype n=36	p
Female	73%	95%	0%	2.10^{-16}
BMI	-0,31	-0,48	-0,10	
Delay before diagnosis	14,6	14,6	27,8	
Multifocal form	20%	91%	97%	2.10^{-16}
Clavicular involvement	43%	14%	11%	6.10^{-5}
Extra-rheumatologic	4%	20%	15%	0,02
Familial history	20%	39%	35%	
C-reactive Protein > 10mg/l	26%	56%	72%	0,0002
Bisphosphonates and/or anti-TNFα	2%	13%	33%	0,0001
Remission	49%	48%	22%	0,02

BMI: Body Mass Index expected for age

TNF: Tumour Necrosis factor alpha

Legends

Table 1: Optimal multivariable logistic regression model for calculating the clinical score for a diagnosis of nonbacterial osteitis

Table 2: Clinical and biological characteristics of CRMO patients (n=178) before the diagnosis
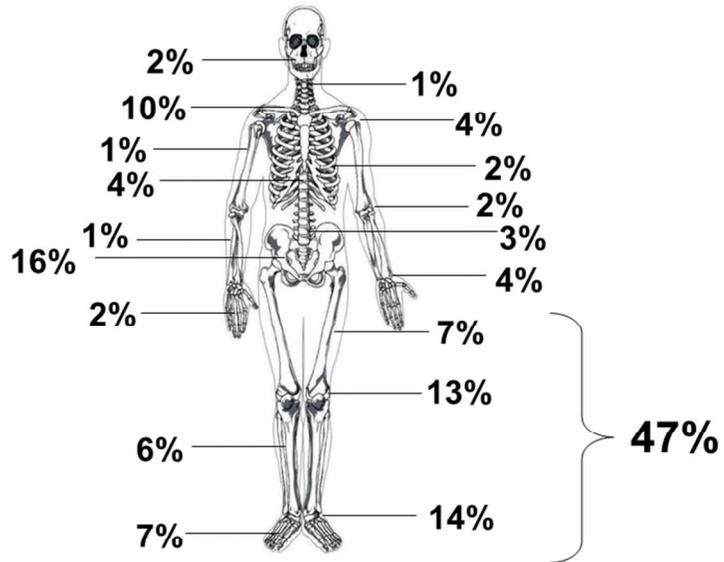
Table 3: Comparison between CRMO patients with and without remission at the last medical visit

Table 4: Cluster analysis: three distinct sub-groups of patients with CRMO

Figure 1: Distribution of clinically painful osseous lesions at presentation

Figure 2: Evolution of the percentage of diagnosis of unifocal and multifocal forms in the French CRMO cohort during the course of the disease.
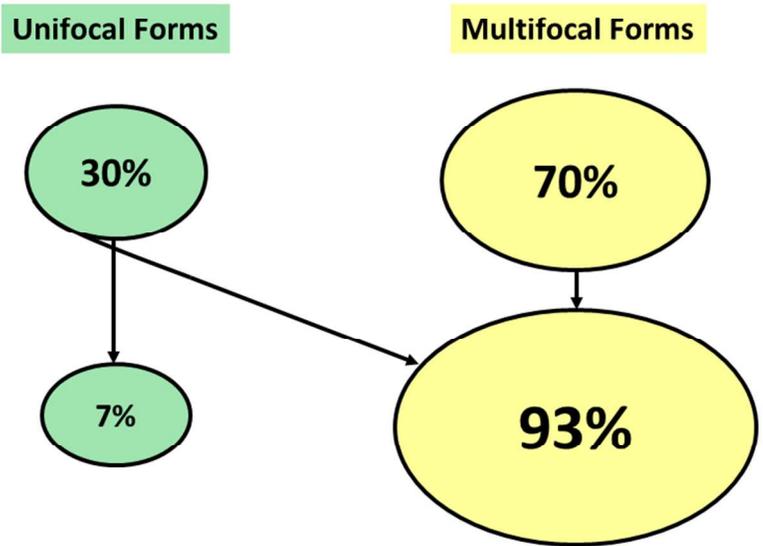
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