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Evolution of bone lesions in adults with chronic nonbacterial osteitis (CNO): A long-term follow-up study

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ABSTRACT

Objectives: Chronic nonbacterial osteitis (CNO) is a rare disease characterised by sterile bone inflammation. Little is known about the evolution of bone lesions, especially for the adult variant of the disease (adult CNO). We therefore aimed to characterize the radiologic course of adult CNO.
Methods: We conducted a cohort study among confirmed adults with CNO, treated at the Dutch national CNO referral centre between 1992 and 2023. Imaging reports from the first-performed radiological scan (baseline) to the last available scan (end of follow-up) were systematically reviewed for lesion location and radiologic features (sclerosis, hyperostosis, erosions, ankylosis). Incidence rates (IRs) for new lesions, progression, and regression of existing lesions were estimated using the Poisson method. Kaplan-Meier curves were used to visualize cumulative incidence, and Poisson regression models assessed associations between patient characteristics and the outcomes.
Results: The study included 182 adult CNO patients with a mean follow-up of 6.1 ± 5.2 years, treated with nonsteroidal anti-inflammatory drugs or cyclooxygenase-inhibitors and/or intravenous bisphosphonates or tumour necrosis factor alpha inhibitors. The most common pattern was sole involvement of the anterior chest wall (84 %). IRs per 100 person-years were 4 (95 % CI 3–5) (new lesions), 7 (6–9) (progression), and 1 (0.3.-1) (regression). Among patients with anterior chest wall involvement only ($n = 147$), one person developed a lesion outside this area (IR 0.3 (0.06–1)). At 2 years, cumulative incidence of new lesion development and progression were 2 % (0–5) and 7 % (3–10), increasing to 11 % (5–17) and 29 % (20–36) at 5 years, and 36 % (23–48) and 56 % (43–64) at 10 years. No associations were found between clinical characteristics at baseline and these outcomes.
Conclusions: The development of new bone lesions in treated adult CNO patients is typically confined to previously affected regions, primarily the anterior chest wall. Progression of structural changes occurs in the majority of patients after longer follow-up. These findings can be used for prognostic counselling, and suggest that routine whole-body imaging may not be necessary for most patients during follow-up.

Key messages

1. In treated adults with CNO, the development of new bone lesions during follow-up is almost exclusively limited to areas already affected at baseline. Distant new lesions are rare.

2. The progression of structural changes is more common, particularly over extended follow-up periods, with 36 % of patients experiencing progression within 5 years and 56 % within 10 years.

3. These findings suggest that routine whole-body imaging may be unnecessary for most adult CNO patients during follow-up, as new lesion development outside of initially affected regions is uncommon.

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Introduction

Chronic nonbacterial osteitis (CNO) is a rare and complex autoinflammatory disease characterized by sterile bone lesions. Historically, the condition has been referred to by various names, but a recent international consensus has standardized the term "CNO" for patients with sterile bone inflammation. CNO affects children and adults, leading to pain, impaired mobility, and decreased quality of life in both age groups [1,2]. In children, the long bones are primarily affected, whereas adults typically present with lesions in the anterior chest wall (ACW). Additional lesions can also occur in the vertebrae, mandible, pelvis, or peripheral skeleton. Both paediatric and adult CNO can be associated with other autoinflammatory conditions, such as palmoplantar pustulosis, psoriasis, and inflammatory arthritis [3–5].

Diagnosing CNO is challenging and often delayed, with an average lag of five years [6]. To confirm the diagnosis, either magnetic resonance imaging (MRI) or computed tomography is commonly performed [7]. Early stages of the disease are marked by bone marrow oedema, osteolysis and increased isotope uptake on nuclear imaging, whereas secondary changes include hyperostosis, sclerosis, erosions, and soft tissue calcifications and ankylosis [8–10]. Because adult patients usually have years of symptomatic disease before their first imaging, these advanced changes are considered more typical and expedite diagnosis.

Current CNO treatment is largely based on expert opinion, as randomized trials are lacking or pending [11]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-inhibitors (COXIBs) are the most common, and recommended first line treatment [7,12] but second-line treatments like intravenous bisphosphonates or tumor necrosis factor alpha inhibitors (TNFi) are often needed for disease control [7,13].

One of the key challenges in managing adult CNO is the lack of data on the disease's course. While paediatric CNO tends to have a recurrent, multifocal pattern, clinical experience suggests that adult CNO is more stable and confined to initial regions of involvement [14–16]. However, this has not been validated by robust natural history data. Previous studies have shown an increase in the number of osteitis foci over time, but these studies were limited by small sample sizes and less detailed imaging techniques [17]. This study aims to fill this gap by investigating the development of new lesions, as well as the progression and regression of existing lesions in adult CNO. The findings will not only enhance patient counselling but also inform clinical practice, improving imaging strategies, treatment decisions, and monitoring approaches.

Methods

This study was approved by the Science Committee associated with the department of Internal Medicine (mandated by the Medical Ethical Review Board) of the Leiden University Medical Center. Written consent was obtained from included from all participants referred >2018, and waived for those referred ≤2018. We adhered to the STROBE guidelines for the reporting of observational studies (see S1) [18].

Study design

This was a single centre cohort study performed at the LUMC Centre for Bone Quality. This centre is the national expert and referral centre for adult and paediatric CNO, and therefore hosts a cohort of nearly all Dutch patients. Adults with confirmed diagnosis of CNO referred between 1992-March 2023 were included. Awaiting validated diagnostic criteria sets for adult CNO, diagnosis at our centre is made in a multidisciplinary evaluation with endocrinologists, radiologists, nuclear medicine physicians and other disciplines if indicated. Diagnosis of CNO is primarily based upon the combination of chronic inflammatory bone pain at typical skeletal sites, accompanied by imaging characteristics such as bone marrow oedema, sclerosis and hyperostosis on CT or MRI. Exclusion criteria were (i) patients with indefinite diagnosis of CNO and (ii) patients lacking baseline and/or follow-up scans.

At the initial evaluation, patients undergo imaging with technetium-99m-labeled hydroxymethylene diphosphonate ([^{99}mTc]Tc-HDP) bone scintigraphy combined with whole-body single photon emission computed tomography (SPECT-CT). Since 2020, whole-body sodium fluoride positron emission tomography ([^{18}F]NaF-PET/CT) has also been used. During follow-up, whole-body nuclear imaging ([^{99}mTc]Tc-HDP or [^{18}F]NaF-PET) is typically performed at 1, 2, 5, and 10 years, or more frequently if clinically indicated. This nuclear imaging is routinely paired with local CT scans of the areas affected at baseline, with whole-body CT added when new areas of increased uptake are detected on nuclear imaging. Treatment at our centre usually consists of NSAIDs/COXIBs, and if clinical symptoms persist, second-line treatments like intravenous bisphosphonates (mainly pamidronate) and TNFi are considered.

Data collection

All data were collected from electronic health records. Data items included demographics (age, sex, BMI, intoxications) and clinical characteristics (age at diagnosis, diagnostic delay, additional inflammatory features, other comorbidities). Treatment type and duration was collected, and classified as first-line treatment of NSAIDs/COXIBs only, or first-line treatment with second-line treatments such as intravenous bisphosphonates and TNFi at some point during follow-up.

Imaging data were extracted from radiological reports. The reports in this study consisted of both free-text narratives and reports formatted with a systematic scoring approach. For the free text reports, it was assumed that features were absent if not reported at all (neither as present nor as absent). Baseline (start of follow-up) was defined as the moment of the first scan that can structurally characterise CNO lesions. Qualifying scans were either CT (performed for the vast majority of patients) or MRI. A lesion was defined as hyperostosis, sclerosis, erosion, osteolysis or ankylosis at a skeletal site as reported by the radiologist. A new lesion was defined as the appearance of one or more of these features in a previously uninvolved bone or in a new location within a bone that was already affected at baseline. Progression was defined as an increase or new onset of hyperostosis, sclerosis, erosion, osteolysis, or ankylosis at a baseline lesion site. For example, if sclerosis was present at the medial clavicle at baseline and hyperostosis developed at the same site during follow-up, this would be classified as progression rather than a new lesion. Similarly, regression was defined as the decrease or disappearance of features at a baseline lesion site. In-depth details on the evaluation of radiologic CNO features at our centre, including definitions of hyperostosis, sclerosis, erosion, osteolysis, and ankylosis, are documented elsewhere [8]. In case radiology reports were inconclusive or contradictive of preceding reports, the images and report were reviewed independently by CJW and ATL. With differing scores or uncertainty, a third review was conducted by ANC.

Statistical analyses

All statistical analyses were performed using R Statistical Software (version 4.3.1; R Foundation of Statistical Computing) using the packages: "Tidyverse", "Epitools", "Survival" and "Survminer" [19]. Patient characteristics are reported as n (%) or as mean with standard deviation or range. Missing data were specified. Incidence rates (IR) of new lesions, progression and regression were calculated with the exact Poisson method, for the total incidence as well as stratified for lesion site and type of progression (all reported in number of cases per 100 years of follow-up, with 95 % confidence intervals). Cumulative incidences were generated with Kaplan-Meier curves. Poisson regression models were used to investigate factors associated with new lesion development or progression, including the presence of additional inflammatory features (arthritis, acne, psoriasis, or PPP), having lesions outside the ACW at baseline, age at diagnosis and treatment type. For the latter, the model

was adjusted for the confounding factors of skeletal distribution pattern and age at diagnosis, as these influence the probability of receiving second-line treatment and may be associated with the outcomes under study. An offset term for follow-up time was included to account for differing observation periods. Bonferroni correction was applied to address multiple testing. Age at diagnosis was additionally stratified in different age groups and the IRs were compared. As sensitivity analysis, IRs were determined in the sample of patients with start of follow-up from ≥2015, as from this point in time, more detailed scanning techniques were in routine clinical use, increasing the likelihood of detecting radiologic abnormalities as compared to scans from < 2015.

Results

Baseline clinical and radiological characteristics

From the 422 patients referred due to suspected CNO between 1992-March 2023, 215 had confirmed diagnosis of CNO and provided written consent for the use of their data. Of these, 33 were excluded due to lack of follow-up imaging, resulting in a total of 182 patients included in the study (Fig. 1). Included patients were mostly female (91 %) and of middle age at diagnosis (43 ± 13 years) (Table 1). Mean follow-up time was 6.1 ± 5.2 years, total amount of person-time was 1107.3 years. 48 % of patients presented with additional inflammatory features, of which PPP was most common (38 %). Patients received NSAIDs/COXIBs (86 %), and bisphosphonates were applied in similar frequency (82 %) at some point during follow-up.

The distribution and types of lesions are depicted in Table 2. On average, 3.4 bones (range 1–13) were involved per patient. The vast majority of lesions were situated in the anterior chest wall, with the sternum affected in 75 %, the clavicles in 68 %, and the upper rib(s) in 67 %. Vertebral and mandibular involvement was less common (10 % and 9 % respectively) and no lesions were seen in the appendicular skeleton. Lesions mostly characterized by sclerosis and hyperostosis, but erosions and more rarely osteolysis were also observed.

New lesions, progression and regression

35 out of 182 patients developed a new lesion at some point during follow-up. The overall IR of new lesions was 3.7 per 100 person-years (95 % CI 2.6–5.2) (Table 3). New lesions outside the anterior chest wall had a lower IR of 0.5 (0.2–1.1) per 100 person-years for the spine and 0.09 (0.002–0.5) for the mandible. In patients with sole anterior chest wall involvement at baseline (n = 153), only one formed a new lesion in the mandible (IR 0.3 (0.06–0.9)). Radiologic progression of existing lesions was more common with an IR of 7.3 (5.6–9.4). Stratifying for type of progression, soft tissue calcification or ankylosis – which represent particularly unwanted outcomes in CNO - were noted with an IR of 2.3 (1.5–3.5) and 1.4 (0.8–2.3) respectively. Radiologic regression of lesions was seen in 7 patients (IR 0.6 (0.3–1.3)).

Table 1
Clinical characteristics of included patients.

Clinical characteristics	Included adult CNO patients (n = 182)	
Sex (female), n (%)	165 (90.7)	
Age at diagnosis (years), mean ± SD	42.8 ± 12.7	Missing n = 5
Age at start of follow-up (years), mean ± SD	43.5 ± 12.8	
Follow-up duration (years), mean ± SD	6.1 ± 5.2	
Diagnostic delay (years)	6.2 (range, 0–30)	Missing n = 15
Body mass index (kg/m^2), mean ± SD	26.3 ± 5.1	Missing n = 29
Additional inflammatory features (any), n (%)	86 (48.0)	Missing n = 3
Pustulosis palmoplantaris	68 (38.0)	Missing n = 3
(Severe) acne	11 (6.2)	Missing n = 5
Hidradenitis suppurativa	2 (1.1)	Missing n = 3
Psoriasis	26 (14.3)	Missing n = 3
Psoriatic arthritis	4 (2.2)	Missing n = 3
Axial Spondylarthritis (axSpA)	4 (2.2)	Missing n = 3
Synovitis/arthritis	11 (6.3)	Missing n = 6
Inflammatory Bowel Disease	2 (1.1)	Missing n = 3
Smoking habit, n (%) (current or past)	104 (60.8)	Missing n = 11
Treatment, n (%) (at some point during follow-up)		
NSAIDs/COXIBs	154 (85.6)	Missing n = 2
Intravenous Bisphosphonates	147 (80.8)	Missing n = 2
TNFi	16 (8.9)	Missing n = 2
Corticosteroids	16 (8.9)	Missing n = 2
csDMARDs	6 (3.3)	Missing n = 2

SD: standard deviation, NSAID's: non-steroidal anti-inflammatory drugs, TNFi: Tumour Necrosis Factor alpha inhibitors, csDMARDs: disease modifying anti-rheumatic drugs.

Time to development of new lesions and radiologic progression

The cumulative incidence of new lesions and radiologic progression (any type) are visualised in Kaplan-Meier curves (Fig. 2a, b). At 1 year of follow-up, 0.6 % (95 % CI 0.0–1.7) of patients developed a new lesion and 1.1 % (0.0–2.7) showed progression. At 2 years cumulative incidences increased to 2.4 % (0.0–4.8) and 6.5 % (2.7–10.1) respectively. After 5 years, 11.2 % (95 % CI 5.4–16.7) of patients had developed a new lesion and 28.5 % (20.0–36.1) had shown progression. At 10 years, over

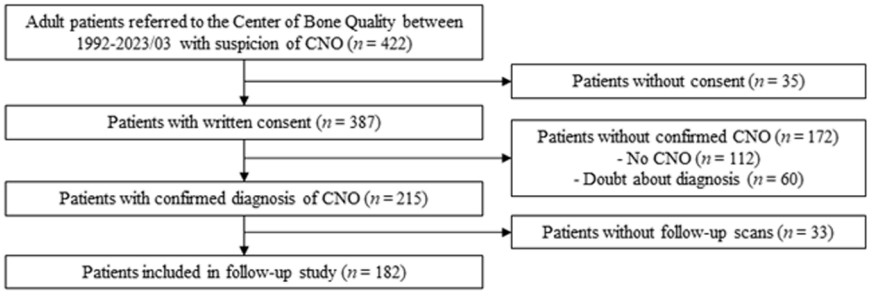

Fig. 1. Flowchart of study inclusion.

Table 2
Radiologic characteristics of baseline lesions.

		Type of lesion				
		Hyperostosis n (%)	Sclerosis n (%)	Erosion n (%)	Osteolysis n (%)	Total n (%)
Site of lesions	Clavicle[a]	68 (37.3)	107 (58.8)	40 (21.9)	16 (8.8)	124 (68.1)
	Sternum	58 (31.8)	123 (67.6)	37 (20.3)	9 (4.9)	136 (74.7)
	Rib [a,b]	83 (45.6)	77 (42.3)	8 (4.4)	5 (2.7)	121 (66.5)
	Vertebra(e)	3 (1.6)	17 (9.3)	2 (1.1)	0 (0)	19 (10.4)
	Mandible	5 (2.7)	11 (6.0)	0 (0)	1 (0.5)	16 (8.8)
	Appendicular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Average number of bones involved: 3.4 (range, 1–13).
Number of bones involved ACW only: 3.1 (range, 0–10).
[a] unilateral or bilateral.
[b] one or multiple.

Table 3
Incidence rates of new lesions, progression and regression (total and stratified for the site of new lesions and for the type of progression respectively). Incidence rates reported as number of cases per 100 person years with 95 % confidence intervals.

	Incidence rates (cases/ 100 person-years)	95 % Confidence Intervals (lower – upper)
New Lesions		
Total	**3.7**	**(2.6 - 5.2)**
Clavicles	1.6	(1.0 - 2.6)
Sternum	0.7	(0.3 - 1.3)
Ribs	1.3	(0.7 - 2.2)
Spine	0.5	(0.2 - 1.1)
Mandible	0.1	(0.002 - 0.50)
Radiologic progression		
Total	**7.3**	**(5.6 - 9.4)**
Hyperostosis	2.4	(1.6 - 3.6)
Sclerosis	3.8	(2.7 - 5.3)
Erosion	0.7	(0.3 - 1.4)
Osteolysis	0	(0 - 0.3)
Soft tissue calcifications or ankylosis	2.3	(1.5 - 3.5)
Secondary degenerative changes	1.4	(0.8 - 2.3)
Radiologic regression	**0.6**	**(0.3 - 1.3)**

a third of the patients had a new lesion (36.4 % (22.9–47.6) and more than half had radiologic progression (56 % (42.5–66.4)).

Patient characteristics associated with new lesions and progression

Patient characteristics that were hypothesised to influence the risk of new lesion development and radiologic progression (i.e. more severe clinical disease course) were analysed using Poisson regression (Table 4). The presence of additional features such as arthritis, acne, psoriasis, or PPP did not show a statistically significant association with the risk of new lesion development (incidence rate ratio [IRR] 1.7, 95 % CI 0.9–3.5) or with progression (IRR 1.6 (0.9–2.7), however, positive association cannot be ruled out given the wide confidence intervals. This was the same for involvement outside the anterior chest wall at baseline, treatment type (first-line versus additional second-line treatment), and age at diagnosis. For age at diagnosis was observed, data were further explored with stratified analysis per age category. Patients diagnosed at ages 30–39 and 40–49 exhibited similar IRs as found for the total patient population (3.6 (95 % CI 1.6–7.1) per 100 person-years and 4.4 (2.2–7.9) respectively. However, patients diagnosed before age 30 had a higher IR of 6.5 (3.2–11.6), while the patients diagnosed at age 50 or later had a lower IR of 1.9 (0.62–4.4; rate ratio of 3.4 (1.1–12.5), $p = 0.02$.

Sensitivity analyses

Patients who had their start of follow-up <2015 had a higher IR for

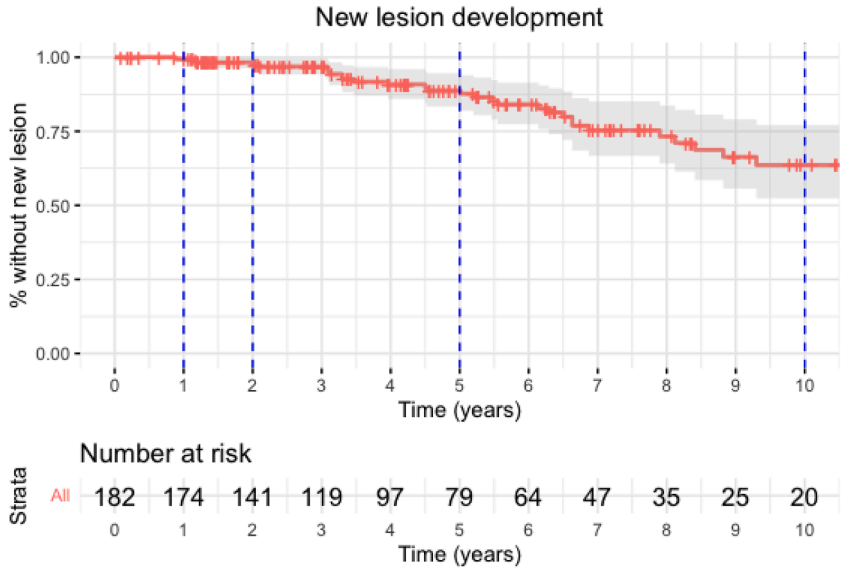

Fig. 2A. Kaplan-Meier curve visualizing time-to-new lesion.

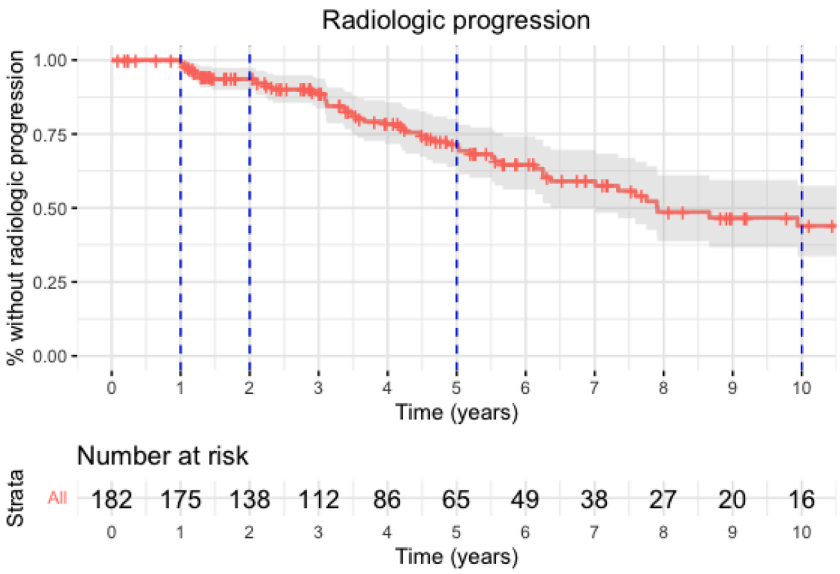

Fig. 2B. Kaplan-Meier curve visualizing time-to-radiologic progression.

Table 4
Poisson regression results to examine patient factors associated with the risk of new lesion development and radiologic progression.

	Incidence Rate Ratio	95 % Confidence Interval	p-value
New Lesion Development			
Additional inflammatory feature(s) (arthritis, acne, psoriasis, PPP)	1.7	(0.9 - 3.5)	0.1
Lesions outside the ACW at baseline	0.7	(0.2 - 2.3)	0.5
Age at diagnosis	1.0	(0.95 - 1.01)	0.1
Treatment type (additional second line treatment)	0.7*	(0.2 – 2.1)	0.5
Radiologic Progression			
Additional inflammatory feature(s) (arthritis, acne, psoriasis, PPP))	1.6	(0.9 – 2.7)	0.08
Lesions outside the ACW at baseline	1.3	(0.7–2.6)	0.4
Age at diagnosis	1.0	(0.97 - 1.01)	0.5
Treatment type (additional second line treatment)	0.9*	(0.4–2.0)	0.8

*Model adjusted for age at diagnosis and skeletal distribution pattern (lesions outside the anterior chest wall yes/no) at baseline. ACW: anterior chest wall.

new lesions as compared to ≥2015 (4.2 95 % CI 2.8–6.1 versus 2.6 (1.1–5.2)) (data not shown). IR for radiologic progression was similar between these groups (7.2 (5.2–9.8) versus 7.6 (4.8–12)).

Discussion

This study aimed to characterise the long-term radiologic evolution of bone lesions in adults with CNO. We found that new bone lesions are very rare in the first years of follow-up of adult CNO patients treated with first and second-line agents, and occur in only a minority of patients also after more extended follow-up periods (10-year cumulative incidence 36.4 %). This is an important finding, both for patient counselling and for clinical management. It also appears to contrast with what is observed in paediatric CNO, where the formation of lesions in new locations is more common, as also reflected by the name that was historically in use for paediatric CNO; chronic *recurrent multifocal* osteomyelitis (CRMO) [15,20].

When new lesions do develop, they predominantly manifest in the ACW, which is already affected at baseline in most patients. Thus, new lesion formation in adult CNO is mostly regionally confined. Again, this finding contrasts with paediatric CNO, where lesions typically present in a broader distribution both at baseline and during follow-up. In paediatric practice, this broader distribution has led to a preference for whole-body imaging during follow-up to monitor for new lesions [21]. Our data suggest that adult CNO follows a more stable course concerning the sites of lesion involvement. Consequently, whole-body follow-up imaging may not be necessary for most adult patients. This implication could reduce radiation exposure (when imaging modalities other than MRI are used), lessen patient burden, conserve medical resources, and minimize incidental findings.

Radiologic progression of structural changes such as sclerosis, hyperostosis, erosions and ankylosis, however, was found to be more common (cumulative incidence 56 % after 10 years follow-up). This observation aligns with the general understanding of the CNO disease course, which suggests that prolonged inflammation with increased bone turnover leads to secondary changes that gradually accumulate over time [10,22]. To illustrate the changes seen during long-term follow-up of adult CNO patients, we present typical radiological imaging slices at baseline and during follow-up for a female patient in Fig. 3. In this case, and also in our study, the radiologic progression persisted even while on treatment, as all patients were receiving either first-line or second-line therapies based on clinical indications. First-line treatment consists of NSAIDs/COXIBs in maximum approved and tolerated dosage. Second-line treatment includes either intravenous bisphosphonates, primarily pamidronate, administered every three months in a series of three consecutive daily infusions of 30 mg each, or TNFi following dosing schedules similar to those used for axial spondylarthritis. These treatments are among the commonly recommended options for managing CNO. Our findings reveal that despite ongoing treatment, secondary changes continue to progress in a significant proportion of patients. It remains unclear whether this is due to suboptimal disease control in individual patients or if current standard treatments are simply inadequate in fully suppressing bone inflammation or bone turnover. It might also be that changes such as sclerosis and new bone formation may represent normal repair processes, as these changes consistently occur following the resolution of inflammation. This aligns with hypotheses proposed for axial spondylarthritis [23], a disease that shares many features with adult CNO [12]. According to this perspective, radiologic progression during treatment, while potentially undesirable due to its association with impaired mobility, does not necessarily indicate a lack of treatment efficacy.

Comparing first- and second-line treatments and we did not observe

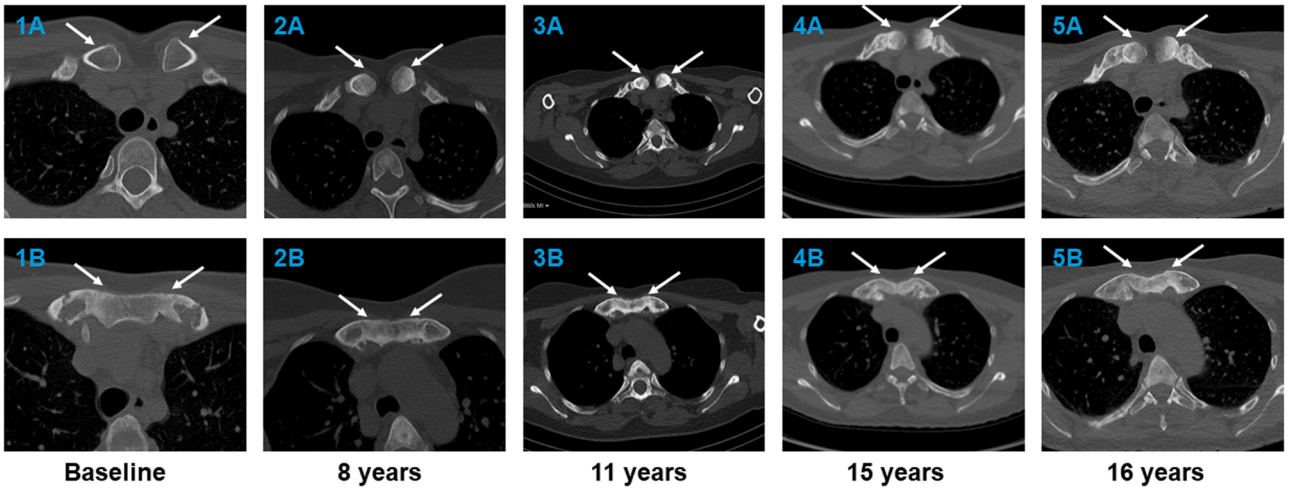

Fig. 3. Axial plane of computed tomography (CT) images from de SPECT-CT of a representative female adult CNO patient visualizing the radiologic progression of anterior chest wall lesions in the context of treatment over time.
Legend: **Baseline:** At baseline, axial CT shows unaffected proximal clavicles (1A), and sclerosis and hyperostosis of the manubrium and costosternal transitions costa 1 bilaterally (1B). NSAIDs/COXIBs were started in maximum approved and tolerated dosage.
8 years: Follow-up imaging after 8 years of NSAIDs/COXIBs with good clinical response. Imaging revealed now mild hyperostosis with sclerosis of the medial clavicles (2A) and progression of sclerosis and hyperostosis of the manubrium and first costosternal transitions (2B). Intravenous pamidronate (3 days of 30 mg, at 3-monthly intervals) was started alongside NSAIDs/COXIBs.
11 years: Follow-up imaging after 3 years of combined NSAIDs/COXIBs and intravenous pamidronate treatment, with poor clinical response. Imaging showed slight progression of sclerosis and hyperostosis at known lesion sites (3A and 3B). Due to lack of clinical response, pamidronate was stopped; NSAIDs/COXIBs were continued.
15 years: Follow-up imaging after 3 years of NSAIDs/COXIBs monotherapy, and one recent cycle of 3 × 30 mg intravenous pamidronate (started because of clinical relapse). The patient reported no clinical response to this cycle of pamidronate, and imaging revealed further progression of sclerosis and hyperostosis at known lesion sites (4A and 4B). TNFi (adalimumab) was started alongside NSAIDs/COXIBs.
16 years: Follow-up imaging after 9 months of TNFi yielding good clinical response. Imaging reveals further progression of CNO features (5A and 5B).

a protective effect of additional second-line treatments such as intravenous bisphosphonates and TNFi against new bone lesions and radiologic progression. This finding may be explained by the fact that, although intravenous bisphosphonates and TNFi are more potent against bone turnover and inflammation respectively, patients in the NSAID/COXIB group had clinical disease control by definition (otherwise, they would have progressed to second-line treatments). This is not necessarily the case for the second-line treatment group, which may contain patients with inadequate disease control. Therefore, both randomized trials are needed to evaluate the unconfounded clinical efficacy of intravenous bisphosphonates and TNFi, as well as additional long-term follow-up data to determine whether these treatments influence the disease course over time. Regardless of these speculations, it is important for clinicians to be aware of the commonness of radiologic lesion progression, as progressive hyperostosis can lead to neurovascular complications, and advancing ankylosis is linked to reduced mobility and function, all of which give poorer patient outcomes [22,24,25].

Given that only a minority of patients develop new lesions and approximately half exhibit radiologic progression after prolonged follow-up, it is important to determine whether baseline characteristics can predict which patients are at higher risk and would therefore benefit from closer monitoring. In this study, we found no significant associations between the presence of additional inflammatory features, having lesions outside the ACW at baseline, and treatment type and the development of new lesions or disease progression, suggesting that patient stratification is challenging. Specifically, patients with additional inflammatory features, such as arthritis or skin involvement, did not show a higher risk for new lesions or progression. This contrasts with findings from a study in children, which suggested that extra-osseous comorbidities were associated with a more severe disease course [26]. Similarly, previous studies have suggested that patients with vertebral involvement at baseline have a more aggressive disease course or exhibit more systemic inflammation [24,25], but our findings did not reveal any significant associations between baseline involvement pattern and new lesion development or disease progression.

Patients diagnosed with CNO before the age of 30 exhibited a significantly higher risk of developing new lesions compared to those diagnosed at an older age. This finding suggests that early onset of CNO may be associated with a more severe disease pattern. Alternatively, it is possible that earlier diagnosis simply identified the disease at a more active stage, prior to the formation of new lesions. In both scenarios, early recognition remains an important clinical objective, as it allows for timely intervention with effective treatment to reduce inflammation and bone turnover, potentially preventing the development of new lesions and limiting disease progression. It also suggests that clinicians should be more inclined to repeat (whole-body) imaging in patients under 30 years old compared to older patients. However, it remains unclear up to what age this approach is advisable.

Strengths of this study include the relatively large patient sample and long follow-up duration. Our studied patient sample also seems representative of the total CNO population, as demographics, clinical manifestations, treatments and the distribution of lesions are in line with previous literature [7,17,27]. However, the interpretation of our findings is constrained by several limitations, primarily because we relied on pre-existing electronic health record data rather than collecting imaging data specifically for this study. Consequently, we had to make certain assumptions based on the available data. Firstly, we assumed non-informative censoring in our analysis. However, we expect that patients who were lost to follow-up mainly were so due to remission or lack of symptoms, while those with ongoing complaints (potentially associated with new lesions or progression), were more likely to remain in follow-up and receive repeated imaging. This may have led to an overestimation of the IRs and likely contributed to the high cumulative incidences observed at the end of the Kaplan-Meier curves. The IRs may have been further inflated due to our assumption that features not reported (either positively or negatively) were indeed absent. With

advancements in scanning techniques and more comprehensive radiology reports over time, some lesions identified in follow-up scans may have been present at baseline but not detected or reported. This is supported by our sensitivity analysis, which showed slightly lower incidence rates for new lesions and progression in patients followed from 2015 onward. Another limitation is that our health records lacked systematic data on the symptomatology of newly detected lesions; we were only able to gather radiological data regarding the development of new lesions, without information on whether these lesions were causing pain. Consequently, it is unclear if the presence of new lesions corresponds to an increase in clinical symptoms. Similarly, we did not collect data on symptom intensity, making it impossible to determine whether the progression of lesions is associated with worsening pain or other clinical manifestations. Lastly, this study carries a risk of bias related to the timing of treatment initiation, even though patients could receive the treatment regardless of whether they had developed new lesions or shown progression. While this reduces the classic form of immortal time bias, there remains a possibility of residual bias if follow-up time before treatment initiation was misclassified as "treated" time. Additionally, the risk of time-dependent confounding cannot be excluded: patients who developed new lesions early during follow-up may have been more likely to receive the treatment sooner, potentially influencing the observed effect of the treatment.

While not within the scope of this study, future research should attend to sacroiliac imaging – preferably with MRI – in adult CNO patients as well. Currently at our centre, sacroiliac MRI is performed only when sacroiliitis is clinically suspected, such as in cases of inflammatory back pain or a family history of axial spondylarthritis. However, sacroiliitis may be underrecognized in CNO due to overlapping inflammatory back pain and osteitis-related pain. Performing systematic sacroiliac MRI in the adult CNO population could provide important insights its overlap with axial spondylarthritis, and improve diagnostic and management approaches.

Nevertheless, the main conclusion remains that the disease course in adult CNO is generally stable with respect to lesion locations and progresses slowly in terms of lesion features. These insights can be applied in clinical practice to better inform patients about their disease prognosis. Patients concerned about the development of new lesions can be reassured that this occurrence is rare, especially in other body regions. However, they should be informed that lesions are more likely to progress than to regress. While predicting which patients are at highest risk for a more severe disease course remains challenging, clinicians should be particularly vigilant with those diagnosed at a younger age. Regarding imaging, our findings support the non-routine use of whole-body follow-up scans; instead, targeted regional imaging, based on clinical indications to assess disease activity or evaluate complications, is generally sufficient.

Statements and declarations

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

The authors declare no competing interests pertaining to the current study.

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This study was approved by the medical ethical review committee associated with the Leiden University Medical Center.

CRediT authorship contribution statement

Anne T. Leerling: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christophe C.J. Weizenbach:** Investigation, Formal analysis, Data curation. **Ana Navas-Cañete:** Methodology, Investigation. **O.M. Dekkers:** Writing – review & editing, Supervision, Methodology. **E.M. Winter:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Elizabeth Martha Winter reports a relationship with Amgen Europe GmbH that includes: consulting or advisory and speaking and lecture fees. Elizabeth Martha Winter reports a relationship with UCB that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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