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Adult chronic non-bacterial osteitis (CNO): An illustrated CT-based radiological guideline

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A B S T R A C T

Chronic non-bacterial osteitis (CNO) is a rare chronic auto-inflammatory bone disease. In adults, it primarily affects the axial skeleton, especially the anterior chest wall, followed by the spine and the mandible. Whole Body-MRI (WB-MRI) or computed tomography (CT) combined with nuclear imaging are the preferred imaging techniques for the diagnosis and monitoring of adult CNO. However, WB-MRI has several important limitations when addressing adult CNO, due to the difficult evaluation of bone marrow edema in areas of marked sclerosis.Extensive sclerosis is one of the most important radiological manifestations of the disease, together with hyperostosis, calcification of capsules and ligaments, ankylosis, erosions, and secondary degenerative changes, all easily assessable with CT, which also represents a technique available in the majority of hospitals and countries.CNO disease course is generally chronic, relapsing and remitting over time. For the evaluation of the disease activity, CT alone is insufficient, but it can be combined with sodium fluoride-18 positron emission tomography/computed tomography ([18F]NaF-PET/CT), which gives multiple advantages and strongly correlates with clinical disease activity, qualifying the imaging tool as a disease-monitoring instrument.This manuscript provides a comprehensive overview of characteristic CT features of adult CNO in different "target" locations of the axial skeleton, thereby helping to differentiate them from pitfalls, providing guidance in the (early) detection of the disease.

1. Background

1.1. Clinical Settings

A consensus disease definition has been recently developed after expert consensus recommendations and the term "chronic non-bacterial osteitis" (CNO) is proposed to describe adults with sterile bone inflammation [1].

Chronic non-bacterial osteitis (CNO) is a rare chronic auto-inflammatory bone disease affecting both pediatric and adult population. CNO is an umbrella diagnostic term that encompasses the spectrum of several clinical and radiological osseous manifestations, affecting one in a million patients [1–3]. The spectrum was previously called "chronic recurrent multifocal osteomyelitis" (CRMO) in children, and "Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis" (SAPHO) syndrome in adults. Another distinguished CNO subtype in adults has been described [3] localized in the sternum, clavicles and upper ribs, and was also descriptively referred to as sternocostoclavicular hyperostosis (SCCH). CNO/SCCH contrasts with CRMO in its localization in the axial skeleton and adult onset, whereas CRMO is mostly a pediatric and axial/peripheral disease and differentiates from full SAPHO due to frequent absence of synovitis and cutaneous manifestations [1,3].

The terms CRMO and SCCH are no longer in use, and therefore CNO is applied in this manuscript, which thus involves sterile bone inflammation [1].

The disease has a predilection for the female sex (60 %–73 %), the typical age of presentation falls within the range of 29–46 years [1,3,4] and in adult CNO the major manifestations are osseous [1]. Adult CNO primarily affects the *axial skeleton*, specifically the anterior chest wall (ACW) in up to 78–96 % of cases, however the spine and the mandible may be involved [1,3–5]. These osseous locations are therefore considered "target sites" of the disease. On the contrary, the appendicular skeleton is rarely involved in adult CNO, although common in pediatric patients [6]. Extraosseous manifestations of the disease although

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uncommon may be seen and encompass cutaneous manifestations such as palmoplantar pustulosis (PPP) and other inflammatory disorders, such as Crohn's disease/ulcerative colitis in rare cases and arthritis, including sacroiliitis and arthritis of the sternoclavicular (SC) or temporomandibular (TM) joints [1,3,5,6].

The clinical presentation of the disease is variable. The most prevalent symptom of adult CNO is anterior chest pain and swelling, reported in 89 % and 95 % of the cases, respectively [1,3,4]. Pain elsewhere in the body has been reported for the shoulder (53 %) and back (40 %), though with much more variety [4].

Although adult CNO disease course is generally chronic, inflammatory disease activity may vary over time and may be relapsing and remitting, eventually leading to a chronic state with potentially debilitating symptoms. Left untreated, CNO can have long-term effects such as reduced chest wall mobility due to hyperostosis with or without ankylosis, fractures in ribs and spine [1,3–6], chronic pain, neurological and psychosocial problems [1,3,7,8], in rare cases venous obstruction [9], and also secondary thoracic outlet syndrome due to hyperostosis/ankylosis with compression of the neurovascular structures in the upper thoracic outlet.

The evaluation of the disease activity is currently highly challenging from the clinical point of view, as biochemical markers of inflammation are only increased in a minority of patients. In the absence of validated diagnostic criteria, adult CNO may be identified upon a high degree of clinical suspicion in combination with characteristic radiologically-proven osseous manifestations. Due to this, imaging is necessary to establish the diagnosis. In addition to that, imaging could be used as a disease-monitoring instrument too. Therefore the role of radiologists is key in adult CNO [1,4].

In this article, we will exclusively address the osseous manifestations of adult CNO from a radiologist's perspective.

1.2. Imaging examinations

Whole-body MRI (WB-MRI) has been established as the imaging technique of choice for the diagnosis and monitoring of pediatric CNO [10–12]. This is due to its ability to show osteitis (areas of bone marrow edema on MRI) in the appendicular and axial skeleton, without extensive sclerosis, unlike in adult CNO. Also, radiation and nuclear medicine (NM) examinations should be avoided in pediatric population.

For adult CNO, a recent *meta*-analysis [4] and expert consensus recommendations [1] have shown a lack of unanimity within the scientific community in elucidating which is the best diagnostic test for diagnosis and monitoring of the disease. The use of different imaging techniques in adult CNO is not standardized and varies tremendously between centra and countries.

Analogous to the guidelines in children, WB-MRI is nowadays used in many centra for diagnostic and disease monitoring of adult CNO. However, WB-MRI has several limitations when addressing adult CNO. In a more general technical sense, MRI is challenging especially when assessing the chest wall due to motion and breathing artefacts [13,14] and it is unable to ensure the necessary anatomical detail required since some manifestations of the disease may be subtle (areas of sclerosis-hyperostosis or soft tissue calcifications) and therefore difficult to assess by MRI. In addition, bone marrow edema, representing areas of inflammatory activity on MRI with a high signal intensity on the T2 weighted imaging sequences with fat suppression, is difficult to depict within areas of marked sclerosis, iconic manifestation of adult CNO, due to "T2-blackout artefact". This characteristic makes it very difficult, if not impossible, to assess inflammatory activity of the disease by means of qualitative and quantitative diffusion weighted imaging (DWI) analysis too [15].

Current literature extensively describes radiographic features of adult CNO [16–19]. Apart from the previously named core features of (osteo)sclerosis, hyperostosis, and bone marrow edema (MRI term), adult CNO is characterized by calcification of ligaments, ankylosis, erosions, and secondary degenerative changes like narrowing of the articular space and osteophytes formation. Interestingly, these latter lesser-known features are difficult to assess with MRI and straightforward with CT (especially in the ACW). All these considerations should be contemplated in necessary future dissertations when addressing the preferred diagnostic and monitoring radiological test for adult CNO.

Therefore, we consider, based on our extensive experience in the diagnosis and management of patients with adult CNO in The Netherlands, that CT represents an excellent technique in Adult CNO assessment.

Computed tomography (CT) is an accurate imaging technique in "established" adult CNO with the required detail (especially when assessing the ACW). CT enables 3D reconstruction too and it represents a technique available in the majority of centra and countries, easy and fast to perform. Nevertheless, CT alone has some limitations too since it is not enough to show areas of bone inflammation (osteitis) prior to the presence of structural abnormalities such as sclerosis or hyperostosis ("pre-radiological" phase of the disease), just as it will not be able to monitor properly the course of the disease or during therapy. These limitations can be solved by combining the CT with functional nuclear medicine techniques. CT will thus provide exquisite information about the expected structural abnormalities, and nuclear medicine functional techniques will provide the functional information that CT lacks overcoming many of the obstacles that we face with MRI for this purpose in adult CNO.

CT can be combined with bone scintigraphy using technetium-99 m radio-labeled hydroxymethylene diphosphonate ([99mTc]CT-HDP) for this purpose. [99mTc]Tc-HDP/CT (SPECT-CT) visualizes the increased bone turnover resulting from active inflammation, but has some limitations since it continues to demonstrate increased uptake despite clinical remission, suggesting an imprinting pattern [20,21]. With bone scintigraphy, symmetric high uptake in the SCC region was traditionally referred to with the term "bull's head sign", with the manubrium sterni corresponding to the upper skull and the sternoclavicular joints with the adjacent clavicles representing the horns. It was thought to be highly sensitive and specific of CNO, even pathognomonic. However, in recent publications over a relatively large cohort of patients with adult CNO, the sign was only observed in a minority of patients [21], supporting its low prevalence.

Other nuclear medicine technique, such as sodium fluoride-18 positron emission tomography/computed tomography ([18F]NaF-PET/CT), is a valid alternative to SPECT-CT. This technique is nowadays a widely used tool in metabolic bone diseases. Its main advantage is the possibility to quantify bone turnover signals with maximum Standardized Uptake Value (SUV max), which strongly correlates with clinical disease activity in other metabolic bone diseases, thus qualifying the imaging tool as a disease-monitoring instrument [22].

Due to the above described [18F]NaF-PET/CT advantages over [99mTc]Tc-HDP/CT (SPECT-CT) in the assessment of adult CNO, this technique has been established as radiological test of choice in the management of adult CNO in our referral national center. Besides excellent qualitative evaluation of the disease, [18F]NaF-PET/CT is able to provide functional assessment with quantitative parameters too. In CNO, the degree of [18F]NaF-uptake reflects the degree of bone turnover, measured as higher SUV max values in bones, soft tissues and joints [23]. Therefore, [18F]NaF-uptake in CNO lesions may be considered as disease activity biomarker in patients who undergo PET/CT examinations during follow-up (Fig. 1).

However, longitudinal data are still needed to compare the diagnostic accuracy of [18F]NaF-PET/CT, SPECT-CT and whole-body MRI in adult CNO, and to assess their utility as disease monitoring instruments.

The purpose of the article is twofold.

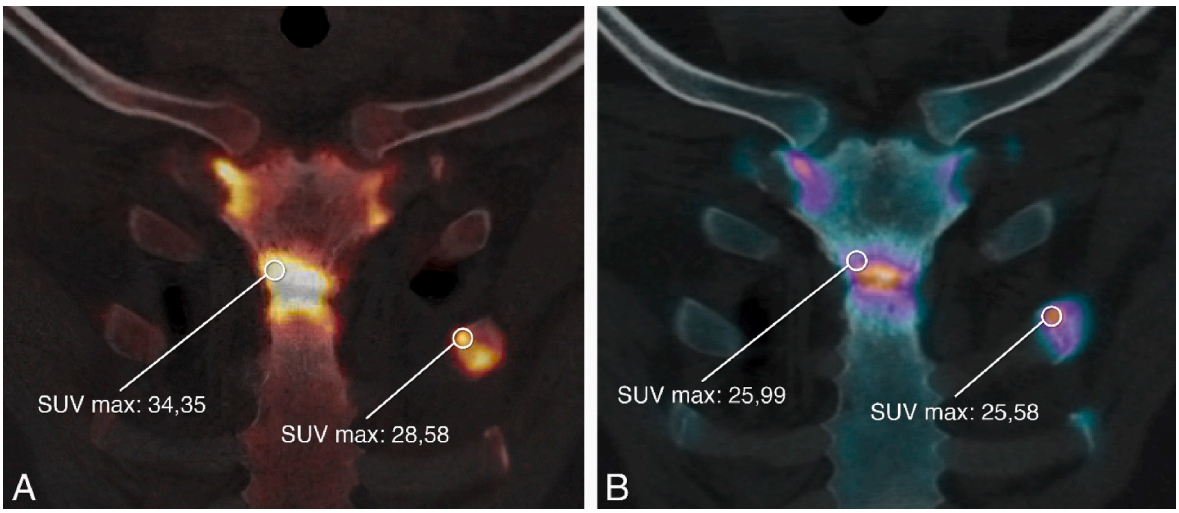

Fig. 1. Two different coronal CT view [18F]NaF-PET/CT-scans of the same patient with adult CNO, performed 6 months apart. A: sclerosis, hyperostosis and erosive changes at the level of the joint between the manubrium and corpus of the sternum, with increased uptake of [18F]NaF at this level, in the manubrium sterni, at the level of the first sternocostal joints bilaterally, and at the 3rd costochondral junction on the left. B: after treatment, radiological features remain stable, although there is an evident decrease in the activity of the disease, as also shown by the decreased SUV max values.

On one hand, to provide a systematic but practical overview of CT-based radiological features typical for CNO in different anatomical locations "target sites", and secondary to provide a practical guidance with a "check list" to help in the systematic evaluation of imaging tests, improving (early) diagnosis and data collection.

For educational purposes, we will first comment on typical RADIOLOGICAL FEATURES of the disease (case-based), their definitions and possible "pitfalls" (differential diagnosis), to move on showing the main LOCATIONS of the disease ("target sites") along with less common locations in a systematic manner.

2. Radiological features of the disease

Taking into account a previous publication [21], imaging diagnostic features for adult chronic non-bacterial osteitis are:

2.1. (Osteo)Sclerosis

Definition: increase in density (localized or generalized) of the bone matrix on CT due to abnormal thickening of trabecular bone. Osteosclerosis is synonymous with sclerosis.

In the context of CNO, we hypothesized that sclerosis is the radiological expression of an (auto)-inflammatory osteitis. In the affected area (s) of the skeleton, pathologically increased bone turnover results in increased formation of osseous tissue that exceeds bone resorption, the amount can vary depending on the stage of the disease. It does not only affect the subchondral bone, like in osteoarthritis (OA), but it may be present at any affected site, as well as away from the subchondral bone.

In a study conducted at our center we found that the most affected region by (osteo)sclerosis was at the level of the first two pairs of ribs (bilaterally in 63 %), followed by the clavicle (unilaterally in 40 % and bilaterally in 60 %) [21], this in accordance with other publications [5], (Fig. 2.A, 2.B, 2.C, and 2.D).

Furthermore, in Adult CNO, bone involvement by sclerosis is usually located in more than one location (non-monostotic disease) [21].

2.1.1. Differential diagnosis

Osteoarthritis (OA): a possible radiological challenge is to distinguish between (osteo)sclerosis in CNO and reactive sclerosis observed in the context of OA. This can be observed in the sternoclavicular (SC) region, around the sacroiliac (SI) region or in the spine. Sclerosis in OA is limited to the subchondral bone, therefore adjacent to the articular surface. Moreover, it is usually associated with other radiological manifestations of OA such as osteophytes, subchondral cysts or asymmetrical narrowing of the joint space. In the spine, reactive sclerosis in the endplates of the spine can be due to disc degeneration, usually associated with narrowing of intervertebral spaces (Modic type 3 changes) and spondylophytes (Fig. 2.E).

Osteitis condensans ilii: benign sclerosis of the ilium adjacent to the SI joint, typically bilateral and triangular in shape (Fig. 2.F). The underlying etiology is unknown but believed to be mechanical stress and imbalance across the SI joints causing a chronic stress response. Supporting this hypothesis, it is most often seen in women who have given birth; however, men and nulliparous women can also be affected [24].

2.2. Hyperostosis

Definition: periosteal bone formation resulting in widening of compact bone of the cortex (cortical thickening) with increase in volume and size of the affected bone (bone hypertrophy).

In the context of CNO, this can be frequently seen in the bones of the sternocostochondral (SCC) region and especially at the medial end of the clavicle, first rib and sternal body. Due to this, the disease was referred in the past as sternocostoclavicular hyperostosis (SCCH), mainly unilateral at presentation, followed by the mandible and the spine [21].

In a study conducted at our center we found that hyperostosis

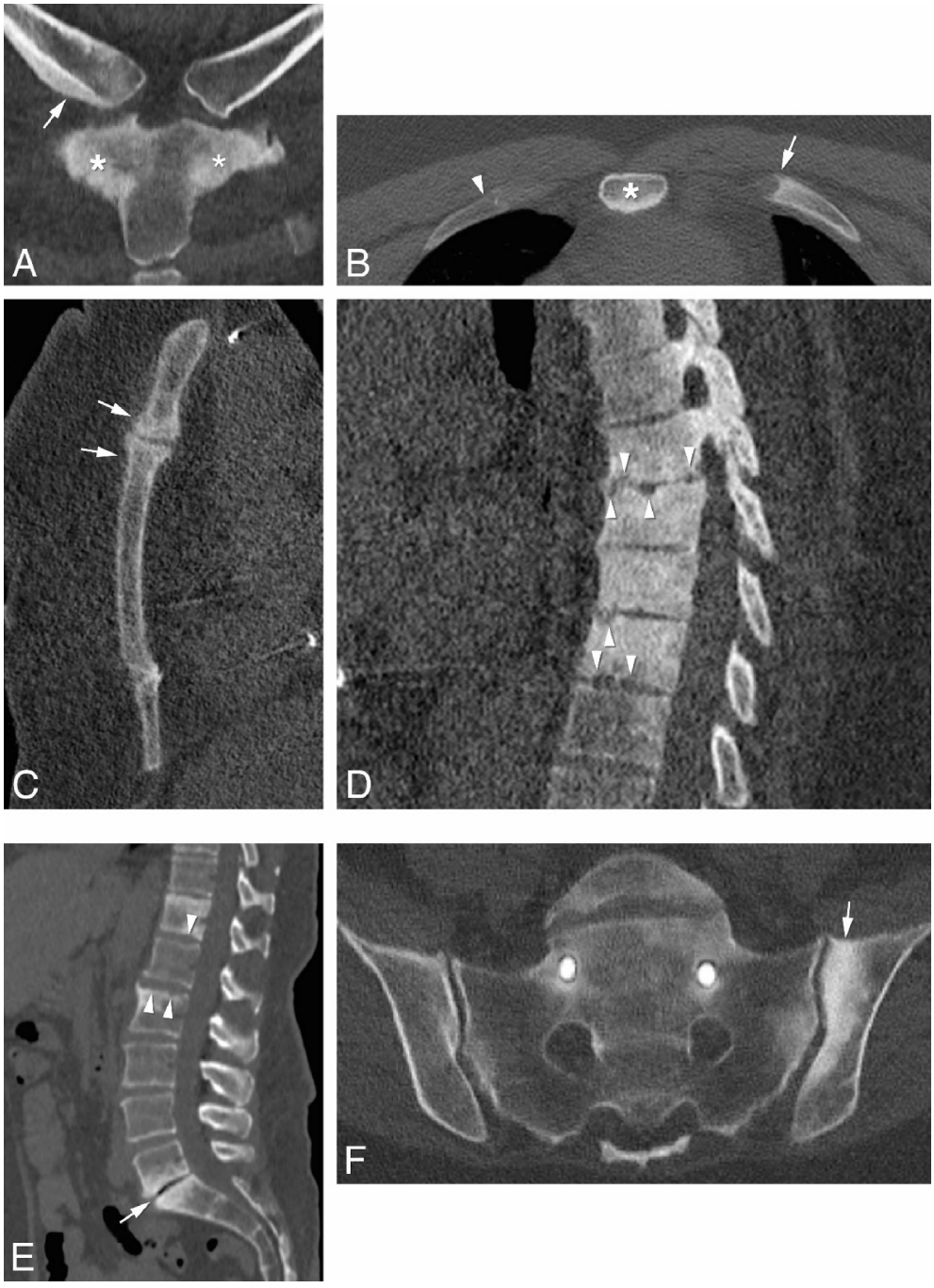

Fig. 2. Examples of common locations of (osteo)sclerosis in adult CNO and pitfalls. A: (coronal CT view) osteosclerosis and mild hyperostosis in the medial end of the right clavicle (arrow), associated with hyperostosis and osteosclerosis of the manubrium sterni (asterisks), at the level of the first costosternal joint bilaterally. B: (axial CT view) osteosclerosis in the anterior right costal arch at the level of the second costochondral junction (arrow) to the left (note comparison to the contralateral rib, normal, arrowhead), and osteosclerosis of the corpus sterni (asterisk). C: (sagittal CT view) osteosclerosis in the sternum at the level of manubrium-corpus joint (arrows). D: (sagittal CT view) osteosclerosis in the thoracic spine (T4-T9), particularly in the vertebral corpora, with erosive changes in the adjacent endplates (arrowheads). E: (sagittal CT view) osteosclerosis with features of CNO in the lower thoracal (T12) and upper lumbar spine (L2) with subtle erosions (arrowheads), concurring with manifestations of osteoarthritis at the level of L5-S1: osteosclerosis limited to the endplates (Modic 3 changes), spondylophytes formation, narrowing of the joint space, and vacuum degeneration in the intervertebral disc (arrow). F: (axial CT view) osteitis condensans ilii is shown (a pitfall), more prominent on the left side (arrow), in a patient with sternal manifestations of CNO. Osteosynthesis material is seen in S1 due to previous spinal fixation.

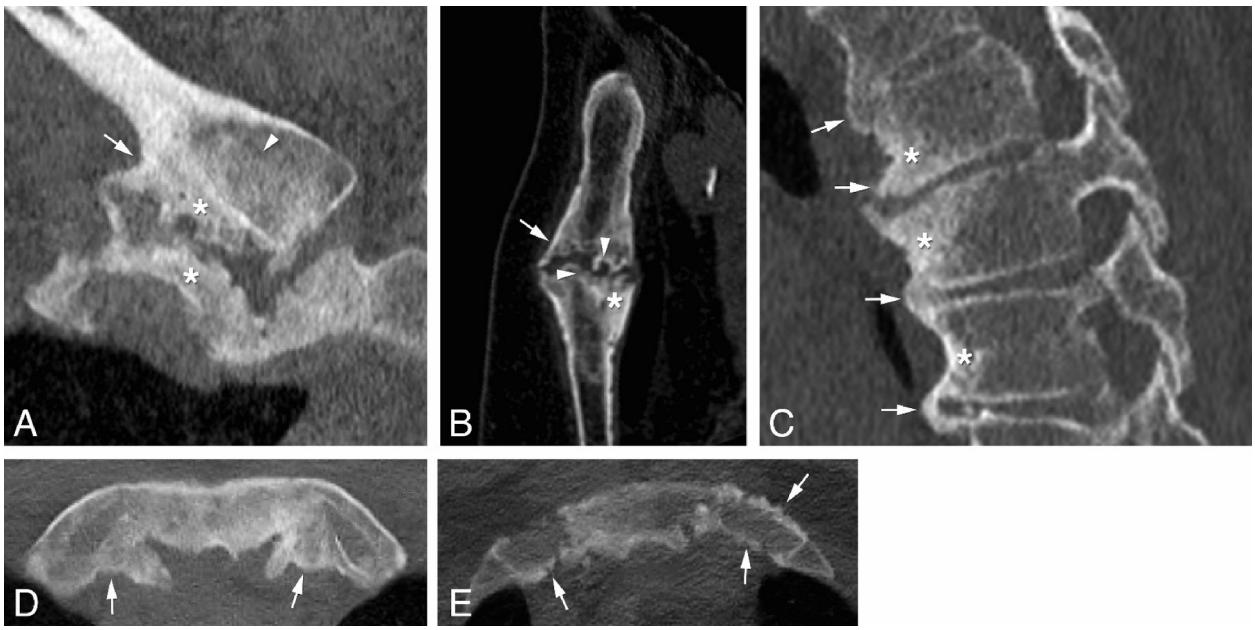

Fig. 3. Examples of common locations of hyperostosis in adult CNO and pitfalls. A: (coronal CT view) hyperostosis in the medial end of the right clavicle (arrow), associated with sclerosis (arrowhead) and calcifications-ossifications of the costoclavicular ligament (asterisks). B: (sagittal CT view) hyperostosis in the manubrium-corpus sterni joint (arrow), together with sclerosis (asterisk) and erosive changes (arrowheads). C: (sagittal CT view) hyperostosis (with at some levels also ankylosis) in the thoracic spine, at the level of the anterior vertebral ligament (arrows), with associated sclerosis in adjacent vertebra (asterisks). This association would not be seen in DISH. D: (axial CT view) example of bridging hyperostosis, with osteosclerosis, and complete ankylosis of the first anterior costosternal joints on both sides (arrows) in CNO. E: (axial CT view) example of bilateral hypertrophic ossifications (common pitfall) affecting the costochondral and sternocostal (SC) junctions of the first rib, more prominent on the left side (arrows). Associated sclerosis of the adjacent sternum is not seen.

(together with sclerosis) was mainly observed at the level of the first pair of ribs, while in the sternal body hyperostosis was present in 10 % of CNO patients [21], this in accordance with other publications [5,25], (Fig. 3.A, 3.B, 3.C, and 3.D).

2.2.1. *Differential diagnosis*

"Hypertrophic ossification": pattern of ossification affecting the costochondral or costosternal junctions (mainly the first ribs) often described as part of the aging process. This characteristically affects bones of the SCC region, but no associated sclerosis of the adjacent bones may be seen with "hypertrophic ossifications" [21,26,27] (Fig. 3.E).

2.3. *Bone erosions*

Definition: small ill-defined osteolytic lesions without sclerotic margins in the subchondral cortical bone and in the adjacent trabecular bone, due to excessive local bone resorption and inadequate bone formation. They are seen in early-stages as endomedullar bony lucencies, preceding the development of sclerosis and hyperostosis in more advanced stages [21]. The main trigger of articular bone erosions is synovitis in the adjacent joint, which could be found in around 24 % of patients in adult CNO [4,5], especially in the SC joint (Fig. 4.A, 4.B, 4.C).

2.3.1. *Differential diagnosis*

Bone erosions in inflammatory arthropathies: bone erosions, however, are not pathognomonic for CNO and can arise from a variety of causes such as other inflammatory arthropathies (erosive OA, ankylosing spondylitis (SpA), RA, or in the context of crystal deposition disease) [17].

Subchondral bone cysts (in the context of OA-osteoarthritis): lucent bony lesions in the subchondral bone, surrounded by sclerotic margins, associated with other radiological manifestations of arthrosis such as osteophytes, subchondral sclerosis and (asymmetrical) narrowing of the joint space (Fig. 4.D). Subchondral cysts and other manifestations of arthrosis can coexist with typical CNO radiological manifestations due to secondary degenerative changes. These differences are better evaluated by CT than by MRI in the ACW, reinforcing the diagnostic value of CT in Adult CNO.

2.4. *Calcification and ossification of soft tissues*

Definition: calcium salts deposition and ossifications observed in the soft tissues or in the joints (capsule and ligaments), especially at the level of costoclavicular, costochondral or costosternal joints [21]. Severe calcium deposition and bone formation may lead to complete joint ankylosis (Fig. 5).

2.5. *Ankylosis*

Definition: partial or total bony bridges between bones or in a joint.

In the context of CNO, this feature is seen in latter stages of the disease. Chronic local inflammatory changes result in hyperostosis and

Fig. 4. Examples of common locations of bone erosions in adult CNO and pitfalls. A: (axial CT view) erosions in the right SI joint (arrows), with associated sclerosis of the iliac bone (asterisks). B: (sagittal CT view) erosions in the thoracic spine (arrowheads), with diffuse sclerosis. C: (coronal CT view) "kissing" erosions in the medial ends of both clavicles and sternum adjacent to the sternoclavicular (SC) joint (arrows), associated with mild hyperostosis, sclerosis and calcifications of the costoclavicular ligaments (arrowheads). D:(coronal CT view) a case of osteoarthritis of the anterior chest wall (pitfall) shows subchondral sclerosis and osteophyte formation at the level of the proximal ends of the clavicles and manubrium sterni (arrows), with subchondral bone cysts surrounded by sclerotic margins in the left clavicle and in the manubrium sterni on both sides (arrowheads); note that the sternoclavicular joint space on the left side is narrowed and asymmetric, with subtle vacuum phenomena. Additionally, hypertrophic ossifications are present at the first sternocostal (SCo) junctions bilaterally (asterisks), a common pitfall.

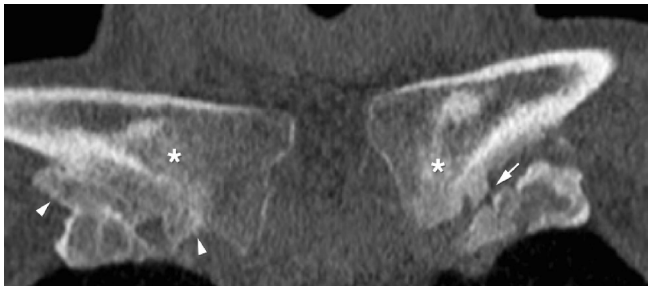

Fig. 5. A case of adult CNO with severe calcification-ossification-ankylosis at the costoclavicular ligaments bilaterally. (Coronal CT view) calcification-ossification on the left side (arrow) and complete ankylosis on the right side (arrowheads) in the costoclavicular (CC) ligaments. The medial ends of the clavicles show sclerosis and hyperostosis, away from the subchondral bone (asterisks).

formation of bony bridges with rigidity of the joint or involved bone structures [21]. Different joints of the ACW can be involved, as will be explained later, as well as the spine and the SI joints [17,18,28], (Fig. 6. A, 6.B, 6.C).

2.5.1. *Differential diagnosis*

Ankylosis of the spine and SI joint in SpA: ankylosing spondylitis has a higher incidence in adult population and affects the axial skeleton too with fusion of the spine and SI joints in advanced stages. The type of ankylosis in SpA is pathognomonic ("bamboo spine"). Bamboo spine occurs as a result of vertebral body fusion by marginal syndesmophytes [28–31]. It is often accompanied by fusion of the posterior vertebral elements as well. This finding is not observed in adult CNO (Fig. 6.D).

Congenital fusion of the joints: manubriosternal and sternoxyphoidal joint fusion can be partial or complete and may be a normal anatomic variant. Complete fusion can be seen at a young age. It is important to distinguish it from pathological fusion seen in inflammatory arthritis (e.

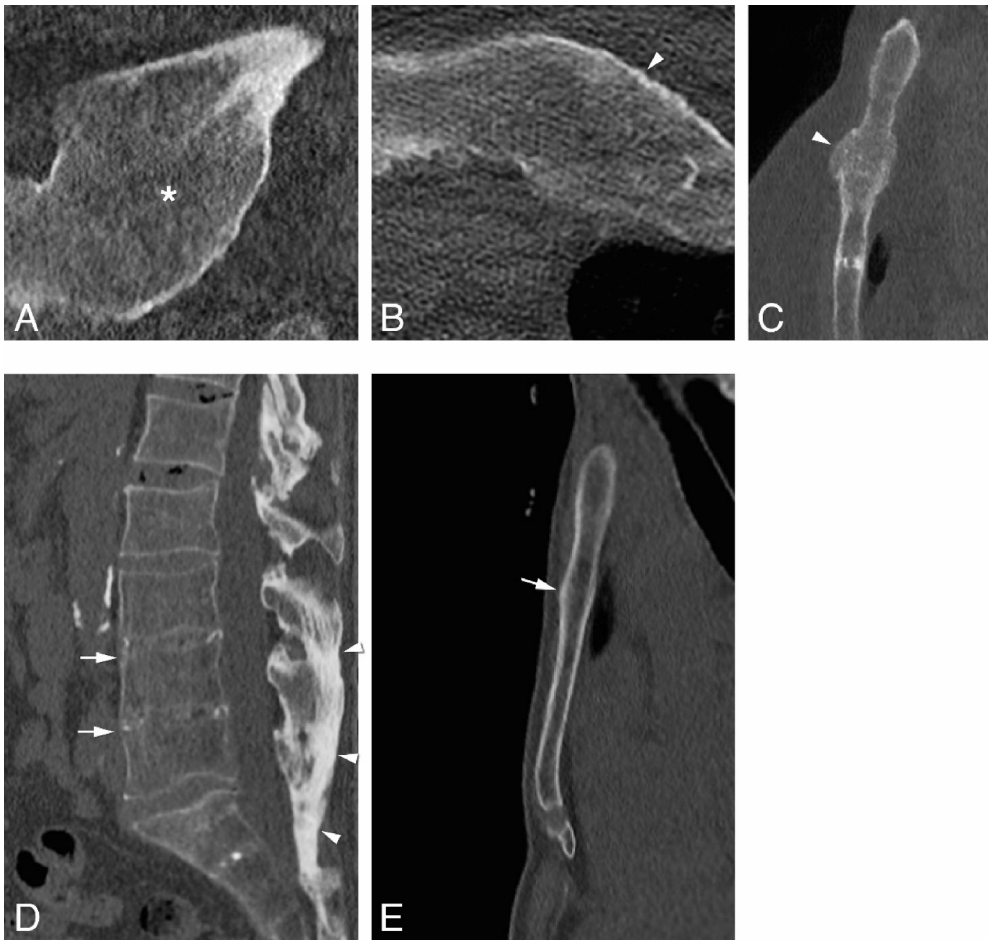

Fig. 6. Examples of common locations of ankylosis in adult CNO and pitfalls. A: (coronal CT view) complete ankylosis in CNO at the level of the left sternoclavicular (SC) joint (asterisk). B: (axial CT view) complete ankylosis in CNO at the first sternocostal (SCo) joint on the left (arrowhead). C: (sagittal CT view) complete ankylosis in CNO at the level of the joint between manubrium and corpus of the sternum (arrowhead). D: (sagittal CT view) case of bamboo spine (a pitfall) in a patient affected by spondylarthritis (arrows), associated also with fusion of the posterior vertebral elements (arrowheads), the latter characteristic is not seen in CNO. E: (sagittal CT view) case of congenital fusion (a pitfall) of the manubrium-corpus joint of the sternum (arrow).

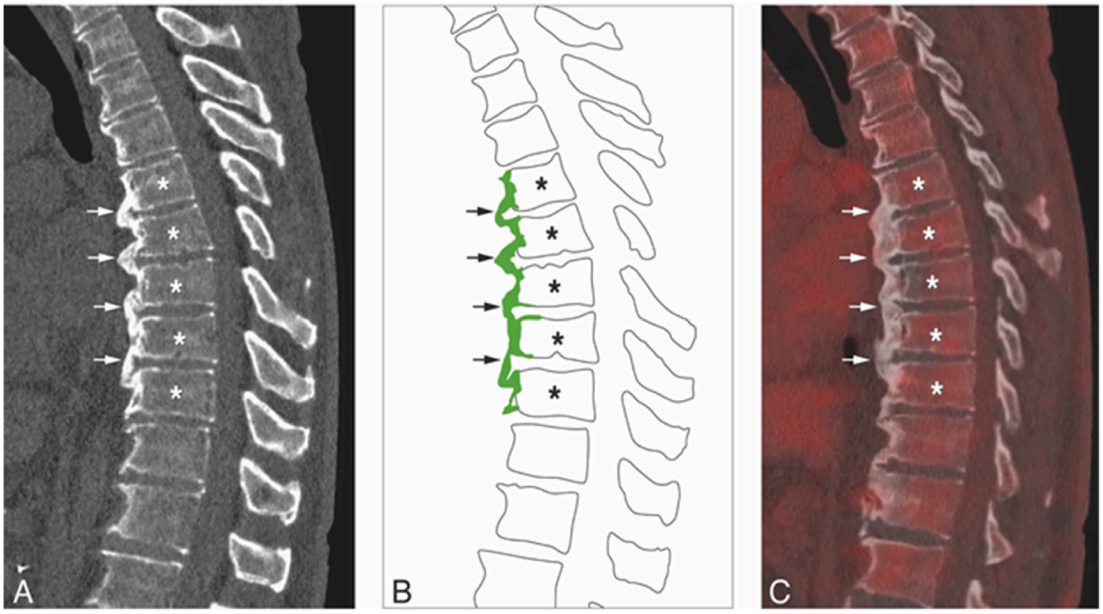

Fig. 7. Diffuse idiopathic skeletal hyperostosis (DISH) or Morbus Forrestier (A), with the corresponding drawing (B) and [18F]NaF-PET/CT fusion image (C) A and B: (sagittal CT view) bone formation along the anterior longitudinal ligament with fusion of the adjacent vertebrae in the thoracic spine.(arrows), which is the most common spinal segment involved in DISH. No associated sclerosis is seen in the vertebrae (asterisk), as typical finding in DISH. C: No increased uptake of [18F]NaF is seen at the level of the bone formation along the anterior longitudinal ligament (arrows) or in the vertebrae (asterisk).

g. SpA) or in Adult CNO. Lack of sclerosis/hyperostosis helps in the differentiation between congenital fusion and secondary fusion in Adult CNO. It is best evaluated in sagittal and oblique coronal planes (Fig. 6.E).

Diffuse idiopathic skeletal hyperostosis (DISH) or Morbus Forrestier: abnormal calcification/bone formation (hyperostosis) of the soft tissues surrounding the joints of the spine, and also of the peripheral or appendicular skeleton. In the spine, there is bone formation along the anterior longitudinal ligament and sometimes the posterior longitudinal ligament, which may lead to partial or complete fusion of adjacent vertebrae. The facet and sacroiliac joints tend to be uninvolved. The thoracic spine is the most common level involved. In DISH no associated sclerosis is seen in the vertebrae [32]. This fact is a fundamental finding to differentiate CNO and DISH (Fig. 7).

In the peripheral skeleton, DISH manifests as a calcific enthesopathy, with pathologic bone formation at sites where ligaments and tendons attach to bone [32].

3. Locations of the disease

As we know now, adult CNO primary affects the *axial skeleton*, and especially the bony structures of the **ACW (anterior chest wall)** region in up to 78–96 % of the cases [3–7,21] (Fig. 8).

3.1. Anterior chest wall (ACW) "checklist"

The main involved locations in the ACW are osseus and can affect the following bony landmarks:

A. Clavicle: Any part of the clavicle can be involved, especially the proximal and, to a lesser extent, the middle segment [21].

"Check" for:

– *(Osteo)sclerosis.*

– *Hyperostosis .*

In a recent cohort study conducted at our center [21], **the clavicle was the second most affected site of the ACW CNO patients (81 %), unilaterally in 40 % and bilaterally in 60 %** (Fig. 9.A and 9.B).

B. Costae: The ribs are frequently affected too, especially the first four pairs [21]. Their involvement can be located both at the level of the sternocostal (SCo) joint(s) (with or without concomitant involvement of the sternum adjacent to the joint), as well as at the level of the costochondral (CC) junction(s)/synchondrosis, or at the level of the costovertebral (CV) joint(s) (see Fig. 8).

"Check" for:

– *(Osteo)sclerosis.*

– *Hyperostosis.*

– *Ankylosis of the SCo and/or CC junction/synchondrosis and/or CV joints.*

In a recent cohort study conducted at our center [21], the **first and second ribs were affected in 69 % of the cases, usually bilaterally** (Fig. 9.C and 9.D). Third and fourth ribs involvement was visualized in 47 % of CNO patients [21].

C. Sternum: The sternum is commonly affected in adult CNO. More specifically, the sternum can be affected by the disease at different levels, requiring its detailed description in the following target (sub) locations: sternum at the level of the sternoclavicular joint (SC), sternum at the level of the sternocostal (SCo) joint as well as sternum in the manubriosternal joint (MS).

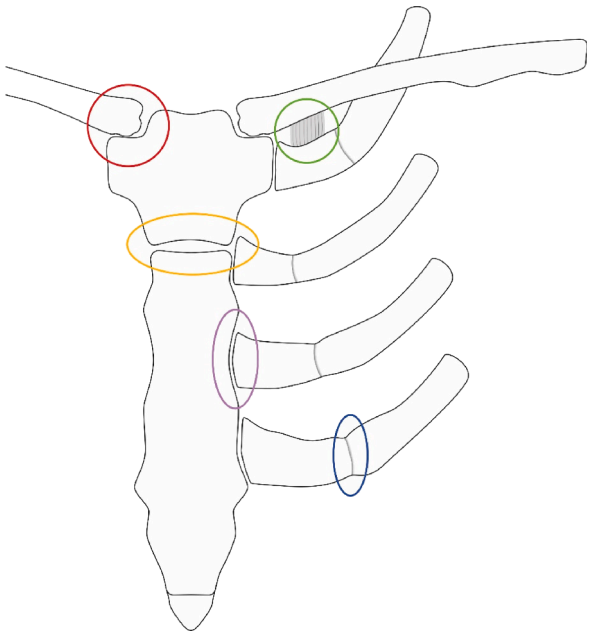

Fig. 8. Schematic overview of the most affected (sub)locations of the anterior chest wall by adult CNO. The sternoclavicular (SC) joints and proximal clavicle (encircled in red), the costoclavicular ligaments (in green), the joint between the manubrium and corpus (MC) of the sternum (in orange), the sternocostal (SCo) joints (in purple), and costochondral (CC) junctions (in blue) are shown. Note that only the first four ribs are shown, as they are the most commonly affected [21]. For approximate percentages of bone involvement of these areas, see text in the article. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

"Check" for:
– *(Osteo)sclerosis.*
– *Hyperostosis.*
– *Ankylosis of the SC, SCo and/or MS joints.*

In a cohort study conducted at our center [21], the **manubrium sterni** was the **most affected site of the ACW in CNO patients (82 %)** (Fig. 9.E and 9.F). The region of the sternal body was visualized in only 54 % of CNO [21]. Sublocations percentage involvement of the sternum (sternoclavicular joint (SC), sternocostal (SCo), manubriosternal joint (MS) has not been further specified to date.

In the ACW, other "extraosseous" manifestations can be seen as part of the disease.

"Check" for:
- *Capsuloligamentous calcifications/ankylosis of the SC (sternoclavicular joint) itself*
- *Signs of arthritis/synovitis of the SC joint, such as soft tissue swelling and presence of erosions in adjacent bone structures*
- *Calcifications/ankylosis of the costoclavicular ligament*
- *Calcifications/ankylosis of the costal cartilages*

3.2. Spine involvement "checklist"

Spinal involvement by adult CNO has been increasingly reported in recent years, sometimes presented in literature as a diagnostic dilemma requiring differential diagnosis with bacterial spondylodiscitis and/or neoplasia. Nevertheless, spine involvement in adult CNO is characteristic [5,16,17,28].

"Check" for:

- *Multilevel-contiguous vertebral (osteo)sclerosis with or without endplate erosions*
- *Paravertebral calcifications/ossification/hyperostosis with or without ankylosis.*
- *Absence of associated paravertebral/intraspinal soft tissue masses or fluid collections. The presence of those will point at a neoplastic process (mass) or an infectious spondylodiscitis (fluid collection).*
- *Absence of calcifications/ossification of the posterior elements of the spine. The presence of those will point out SpA or DISH.*

When the mentioned imaging features are present, confirming in the next step the involvement of other "target sites" allows for reaching the diagnosis of CNO without resorting to invasive procedures. Any segment of the spine can be affected.

In a cohort study conducted at our center [21], the **spine was affected in 23 % of the cases, most commonly at the cervical tract, followed by the thoracic and lumbar spine** (Fig. 10). This percentage should be taken with caution, since not all patients had a complete study of the spine. Therefore the real percentage may be higher.

3.3. Mandibula involvement "checklist"

The clinical presentation of CNO in the jaw is very diverse with the main symptom being recurrent jaw pain and swelling with or without a general fever. Mandibular (not maxillary) involvement by CNO is, from the clinical and radiological point of view, commonly unilateral [5,21].

"Check" for:
– *(Osteo)sclerosis.*
– *Hyperostosis.*
– *Erosions or ankylosis of the temporomandibular joint (TMJ).*

In a cohort study conducted at our center [21], the **mandible was affected in 35 % of the cases, predominantly with unilateral involvement,** sometimes associated with loss of teeth. The mandible involvement by CNO was in our cohort higher than in the literature [25] (Fig. 11).

3.4. Pelvic bones involvement "checklist"

Pelvic bone involvement in the context of adult CNO can be seen, as well as extraosseous manifestations in the region (arthritis/synovitis of the SI joints). Based on literature, 5 % of patients with CNO also have associated involvement of the **sacroiliac (SI) joints** (sacroiliitis), usually unilateral [5], possibly because of overlapping SpA, between 13–52 % [29,33,34]. Sclerosis and hyperostosis are more commonly seen at the iliac part of the joint (Fig. 12).

Fig. 9. Cases of significant involvement of the ACW in adult CNO. A: (coronal CT view) hypertrophy and sclerosis of the right clavicle and of the sternum at the level of the sternoclavicular (SC) joint (arrows); on the left side, severe calcification with complete ankylosis and hyperostosis (asterisk). B: (coronal CT view) prominent bilateral sclerosis, hyperostosis (asterisks) and "kissing" erosive changes (arrowheads) of the proximal end of the clavicles, with moderate calcifications of the costoclavicular (CC) ligaments (arrows). C: (axial CT view) involvement of the costovertebral (CV) joint on the right side, with subtle erosive changes (arrowheads). This represents a less common but classical manifestation of CNO. D: (axial CT view) important sclerosis and hyperostosis of the anterior costal arches on both sides, at the level of the costochondral (CC) junctions (arrows), with associated involvement of the sternocostal (SCo) joints (asterisks). E: (sagittal CT view) important sclerosis and hyperostosis in the manubrium and corpus sterni (asterisks), with partial ankylosis of the joint on the anterior side (arrow). F: (sagittal CT view) significant sclerosis and hyperostosis in the manubrium and corpus of the sternum (asterisks), together with erosive changes (arrowheads).

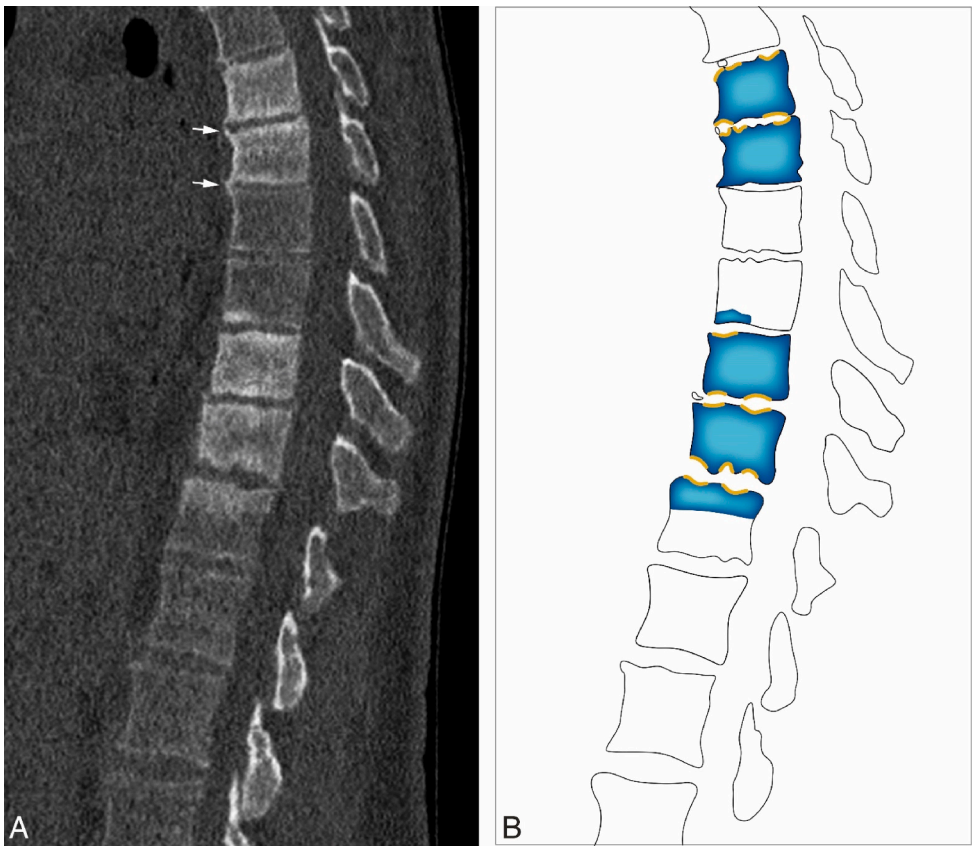

Fig. 10. Multiple sites of involvement of the thoracic spine in adult CNO (sagittal CT view-A), with the corresponding drawing (B). The figures show extensive areas of sclerosis (in blue) with a multilevel-contiguous pattern, with erosive changes in the lower thoracic vertebral bodies (outlined in yellow). Note initial ossification of the anulus fibrosus of the intervertebral discs in the upper tract (arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

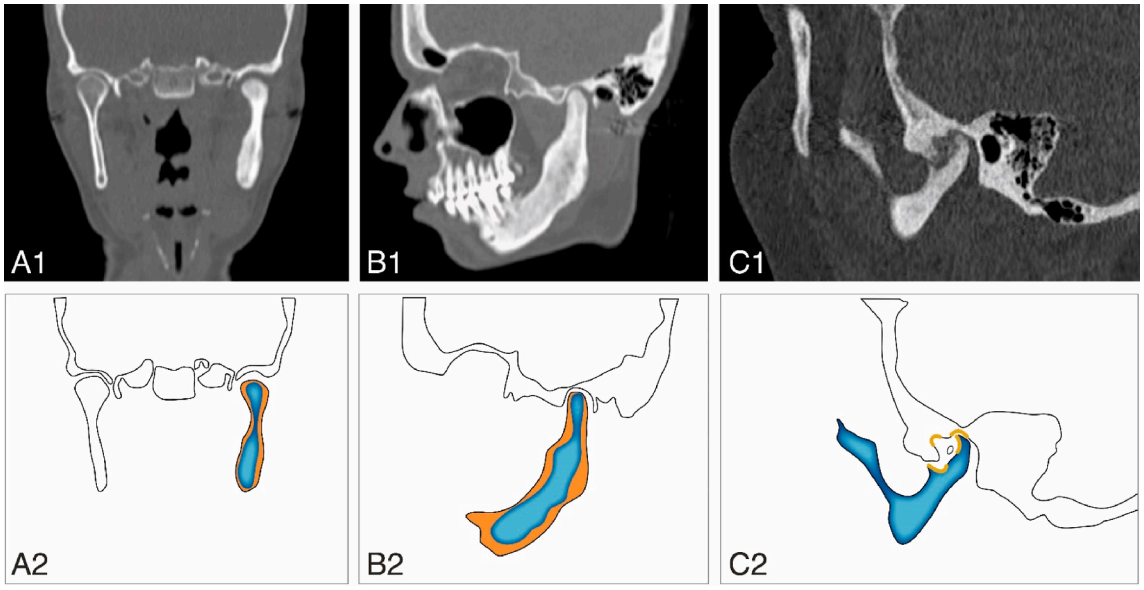

Fig. 11. Cases of involvement of the mandible in adult CNO, with the corresponding drawings. Image A1 and B1 represent coronal (A1) and sagittal (B1) CT views of the same case: the left branch of the mandible shows extensive sclerosis and hyperostosis, depicted respectively in blue and orange in the corresponding drawings (A2 and B2). The third case (image C1 and its corresponding drawing C2), from a different patient, shows erosive changes (outlined in yellow) at the level of the temporomandibular (TM) joint in a sclerotic jaw (in blue) due to osteosclerosis. C1 image represents an oblique sagittal reconstruction of the CT for better demonstration of the erosive changes in the temporomandibular joint. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

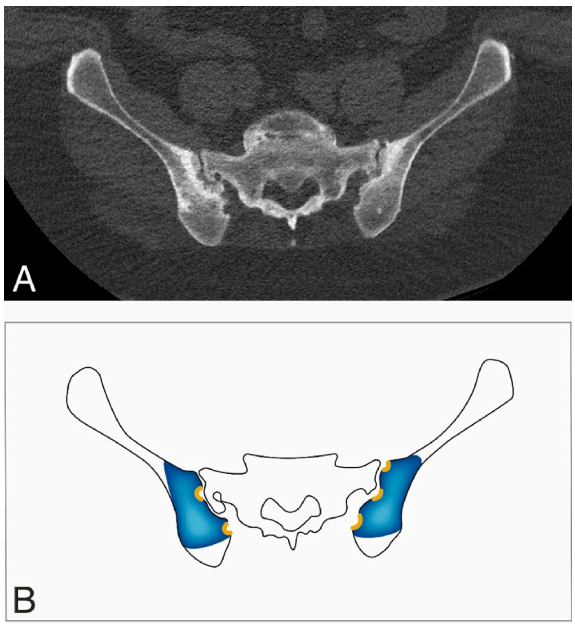

Fig. 12. Bilateral sacroiliitis in adult CNO (axial CT view-A), with the corresponding drawing (B). Figures A and B show extensive involvement of the pelvis with osteosclerosis of the iliac side at the level of the sacroiliac joints (in blue), and erosions bilaterally (outlined in yellow), more prominent on the right side. This pattern of bilateral sacroiliitis is also seen in cases of spondylarthritis (SpA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

"Check" for:
- *(Osteo)sclerosis of the pelvic bones*
- *Signs of arthritis/synovitis of the SI joints*
- *Hyperostosis or ankylosis of the SI joints*

In the cohort study conducted at our center [5,21], the majority of patients showed at least *three or more affected sites in the axial skeleton (74 %)*. When patients have a solitary region affected, the involvement was usually of the clavicle, followed by a rib and the sternum. These data are in accordance with previous studies [6,33–36].

Regarding the general presence of ankylosis, it may occur in some cases and in different locations. It is more commonly seen in costosternal joints, as well as in sacroiliac joints, but it can also affect costochondral junctions and the manubriosternal joint, usually associated with considerable relief from pain [16,25,28].

This leads us to conclude that the clinical symptoms perceived by CNO patients are partly caused by the disease itself, but also partly to other pathophysiological mechanisms like mechanical issues due to secondary arthrosis, with decrease of pain after complete fusion (ankylosis). This further emphasizes the need to search for an imaging technique capable of assessing the status of the disease, but also complications such as OA and/or ankylosis. We point out again CT as an exquisite technique to provide this information [37].

A recent publication have been shown the high prevalence of mixed pain in adult CNO, in which neuropathic and nociplastic pain exist alongside nociceptive inflammatory bone pain [38]. Disease burden in CNO may extend therefore beyond inflammatory activity, highlighting the need for a multifaceted management approach too.

We would like to conclude by proposing a "radiological checklist" (see link below) with the common locations and CT features of established adult CNO.

This checklist is new and has been prepared by our group as part of a study (still in progress) of patients with CNO followed by [18F]NaF-PET/CT to improve data collection.

Standardized reports will improve reporting and data collections and this will help to improve collaboration between centers for research purposes too.

Additional information on functional data, SUV max registration if a [18F]NaF-PET/CT is performed, can be added to this check list with the purpose of evaluating disease activity at presentation and as a monitoring instrument of metabolic activity of the disease during follow up (Fig. 13).

Interestingly, a very recent study in our cohort (unpublished data) suggests that routine WB imaging may not be necessary for most patients during follow-up [39] reducing radiation exposure (when CT is used), lessening patient burden, conserving medical resources, and minimizing incidental findings. This study may help to define the best follow-up protocol for adult patients affected by CNO.

However longitudinal studies are still needed to evaluate diagnostic accuracy of [18F]NaF-PET/CT in treated adult CNO (with indication of functional information of the disease), and to assess their utility as disease monitoring instrument [40].

4. Conclusion

Adult CNO differs significantly from pediatric CNO in its radiological presentation. Nowadays there is lack of unanimity within the scientific community in elucidating which is the best diagnostic tool for diagnosis and monitoring of the disease.

Understanding the radiological manifestations of the disease in its

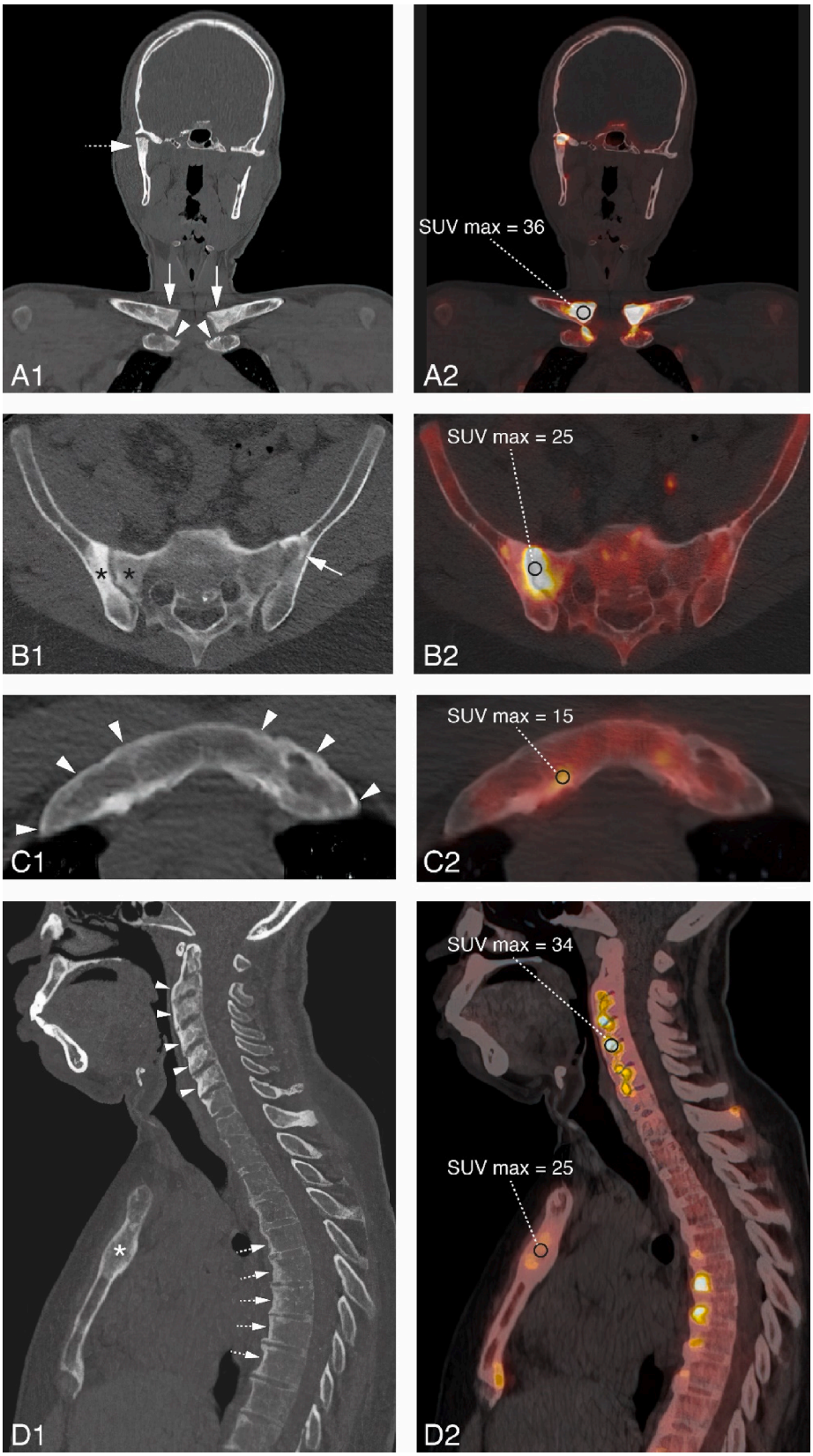

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Fig. 13. CT-scan with its correspondent [18F]NaF-PET/CT fusion imaging in a single patient with typical radiological features of adult CNO at different anatomical locations. A1: (coronal CT view) sclerosis at the level of the proximal clavicula bilaterally (arrows), the sternocostal (SCo)joints bilaterally (arrowhead) and the right mandible (dashed arrow). A2: increased uptake of [18F]NaF at the level of the proximal clavicula bilaterally, the sternocostal (SCo)joints bilaterally and right temporomandibular (TM) joint. Degree of bone turnover, measured as higher SUV max values in bones, is noted at the level of the right proximal clavicle (SUV max = 36). B1: (axial CT view) sclerosis at the level of the right sacroiliac (SI) joint (asterisks), more prominent on the iliac side, and almost complete ankylosis of the left sacroiliac joint (arrow). B2: Uptake with high SUV max values is seen at the level of the right sacroiliac joint (SUV max = 25). No uptake is seen at the left sacroiliac joint. C1: (axial CT view) complete ankylosis at the first sternocostal (SCo) joints and costochondral (CC) junctions bilaterally (arrowheads). C2: mild uptake is seen (SUV max = 15) at the level of the first sternocostal (SCo) joint on the right. D1: (sagittal CT view) multiple sites of CNO involvement of the cervical and thoracic spine (arrowheads and dashed arrows respectively) and complete ankylosis and sclerosis at the level of the joint between manubrium and corpus of the sternum (asterisk). D2: High degree of bone turnover (SUV max values), measured in the cervical spine (SUV max = 34) and in sternum (SUV max = 25) is noted.

adult form will help the scientific community to discern which radiological technique should be imposed as "gold standard" in the future for disease detection and evaluation of therapy response, as well as for detection of secondary complications like secondary arthrosis and ankylosis.

[18F]NaF-PET/CT represents in our opinion an excellent and promising technique for all these purposes, being able to demonstrate structural changes as well as to quantify the disease activity. However, results of longitudinal studies are still needed to evaluate the feasibility of [18F]NaF-PET/CT as biomarker for disease activity and treatment response in adult CNO [40].

This article will help in daily clinical practice by providing a CT-based guidance to radiologists improving (early) disease detection.

The proposed "checklist" form will improve data collection, stimulating collaboration between centers for clinical and research purposes too.

CRediT authorship contribution statement

Ana Navas-Cañete: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Chiara Ricchiuti:** Writing – review & editing, Writing – original draft, Conceptualization. **Anne T. Leerling:** Writing – review & editing. **Frits Smit:** Writing – review & editing. **Kirsten van Langevelde:** Writing – review & editing. **Elizabeth M. Winter:** Writing – review & editing.

Declaration of competing interest

The authors 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2025.111950

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