SAPHO and CRMO: The Value of Imaging

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Abstract

The syndromes synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) and chronic recurrent multifocal osteomyelitis (CRMO) constitute a group of chronic relapsing inflammatory osteoarticular disorders with frequently associated skin eruptions such as palmoplantar pustulosis and acne conglobata and rather characteristic imaging features in the form of osteitis and/or hyperostosis. CRMO predominantly occurs in children/adolescents and SAPHO in adults. Any skeletal site can be involved, and the imaging appearances vary, depending on the patient's age and the stage/age of the lesion. The diagnosis may be difficult if there is no skin disease, but attention to characteristic imaging appearances may help avoid misdiagnosis (e.g., infection and tumor) and thereby unnecessary invasive procedures as well as facilitating early diagnosis and appropriate treatment. This article provides an overview of the radiologic appearances of SAPHO/CRMO and relevant pathogenetic, clinical, and pathologic features to facilitate the diagnosis that often requires an interdisciplinary approach including radiologists.

Keywords
- SAPHO
- CRMO
- osteitis
- hyperostosis
- spondyloarthritis

The syndromes synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) and chronic recurrent multifocal osteomyelitis (CRMO) are rare disorders constituting diagnostic challenges if clinicians and radiologists are not aware of their characteristics.

The acronym CRMO was first coined in 1978 by Björkstén et al[1] to describe the association between multifocal osseous lesions and the dermal disease pustulosis palmoplantaris (PPP) in children and adolescents with a predilection for metaphyses of long tubular bones and the clavicles. However, subsequent studies showed that patients with characteristic osseous lesions do not always have bone and skin lesions simultaneously.[2] Moreover, the number of sites affected can vary greatly, and unifocal involvement, especially of the clavicle, may occur.[3,4] Therefore, the disease entity today is sometimes termed "chronic nonbacterial osteomyelitis."[5]

A wide variety of clinical and radiologic manifestations encompassing skin conditions and osteoarticular disorders in adults have appeared in the literature referred to by different names including pustulotic arthro-osteitis, sternocostoclavicular hyperostosis, and acne-associated spondyloarthropathy. Based on a multicenter survey of 85 patients with osteoarticular disorders associated with PPP or severe acne, Chamot et al in 1987[6] introduced the acronym SAPHO (initially termed *le syndrome acné pustulose hyperostose ostéite*) to bring together the heterogeneous diseases described as a single syndrome. The first initial of the acronym was subsequently altered to synovitis because synovitis may be part of the syndrome.[7] According to Chamot et al[6,7] and other authors,[8,9] SAPHO can be considered an umbrella acronym encompassing several idiopathic disorders sharing clinical, radiologic, and

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pathologic characteristics of the entities just mentioned including CRMO in children/adolescents. This has been widely accepted, although different disorders are then grouped together which can confuse pathogenetic studies.

SAPHO/CRMO can occur at any age but rarely begins beyond the age of 60 years, and there is a slight female predominance.[10,11] Patients usually present with musculoskeletal complaints such as pain, tenderness, swelling, or limited range of motion referable to the skeletal sites involved mainly due to sterile inflammatory osteitis that may or may not be associated with skin lesions. In adults, the main target site is the anterior chest wall followed by the spine and pelvic bones.[9,12] In children/adolescents, the main target site is the long tubular bones followed by the spine and clavicle.[13–15] Diagnosing SAPHO/CRMO is not difficult when typical bone lesions are located in characteristic target sites. However, the diagnosis can be challenging if atypical sites are involved in patients without skin disease.

This article provides an overview of the radiologic appearances of SAPHO/CRMO and relevant pathogenetic, clinical, and pathologic features to facilitate the diagnosis. This often requires a multidisciplinary approach including rheumatologists, pediatricians, dermatologists, orthopaedic surgeons, radiologists, and/or pathologists.

Characteristic Features of the SAPHO/CRMO Spectrum

The spectrum of findings in SAPHO/CRMO includes skin lesions, osteoarticular lesions, involvement of characteristic target sites, nonspecific histopathologic features, and a clinical course marked by relapses and remissions.

Skin Lesions

The skin lesions are neutrophilic dermatoses comprising a heterogeneous but linked spectrum of disorders characterized by perivascular and diffuse neutrophilic infiltrates without evidence of infection. Dermal changes occur in up to 58% of adult patients[16] and in 23 to 80% of children/adolescents.[2] The most common dermatoses in SAPHO/CRMO patients are PPP and acne.[6,11,13,17] PPP is a chronic and recurrent skin condition characterized by 2- to 4-mm yellowish intradermal sterile pustules, erythema, and hyperkeratosis on the palms and soles.[8] Acne as part of SAPHO/CRMO is usually severe and can present as acne conglobata, acne fulminans, and hidradenitis suppurativa. Psoriasis can also be seen in SAPHO/CRMO patients[11,12,18] but often with concomitant PPP[11,19] or in the form of pustular psoriasis. Other rare skin manifestations are pyoderma gangrenosum and erythematous skin lesions as part of Sweet's syndrome.[2,10] Skin lesions may occur before, simultaneously, or after the onset of osteoarticular changes.[12] Thus the absence of concurrent skin lesions does not rule out the possibility of SAPHO/CRMO, and some patients with SAPHO/CRMO lesions may never experience skin lesions.[6,7]

Osteoarticular Lesions

The fundamental component of SAPHO/CRMO is a sterile chronic inflammatory osteitis involving both the cortex and the medullary canal with associated endosteal and periosteal new bone formation and/or hyperostotic and sclerotic periarticular entheseal changes resulting in sclerosis and hyperostosis.[6,7,20]

Involvement of Characteristic Target Sites

The site of disease involvement is age dependent.[9,13] The main target sites in adults are the anterior chest wall followed by the spine and pelvic bones,[9,12] and in children/adolescents the long tubular bones followed by the spine and the clavicle.[13–15] Although patients may present with involvement at a single site,[3] often multiple skeletal foci occur in a synchronously or metachronously.[9,11,13] The multifocal nature of the disease implies the need for a thorough search regarding the presence of subclinical foci.[15,21,22]

Nonspecific Histopathologic Features

The histologic features of osseous lesions are nonspecific and change over the course of the disease. In the initial acute phase, there is predominantly neutrophilic inflammation with edema and osteoclastic bone resorption as well as reactive bone formation, features indistinguishable from bacterial osteomyelitis.[23,24] Later on, there is predominantly inflammation with T cells, a few B cells and plasma cells,[23,25] and in late stages mild chronic inflammation with condensed bone trabeculae and marrow fibrosis.[23,24]

Clinical Course Marked by Relapses and Remissions

The clinical course in both adults and children/adolescents is usually characterized by repeated episodes of active inflammation and remission but may present as single flares or have a chronic inflammatory pattern.[4,10,12,26–28] Involvement of additional sites during the disease course is frequent,[7,10,11,16] but the disease progression, at least in adults, is usually minimal and slow, and SAPHO is not a particularly debilitating disorder.[9,11,12,29]

Low-grade fever may be present during periods with disease activity, especially in children/adolescents, but other systemic manifestations are rare. Biochemical tests are usually of limited value; the white cell count, levels of C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often normal or slightly elevated during exacerbations; other biochemical tests are usually unremarkable.[12] Autoreactive T cells and a high titer of autoantibodies are lacking, and no specific biomarkers have been detected.[30,31] However, high values of acute-phase reactants were shown to correlate with a chronic disease course.[10]

Radiologic Features of SAPHO and CRMO

The imaging needed in patients with suspected or known SAPHO/CRMO depends on the area of disease involvement; choosing the most appropriate imaging strategy is important.

Choice of Imaging Modality

The initial imaging of symptomatic areas in peripheral bones and joints, the spine, and pelvis should be radiography to identify typical findings and exclude differentials, such as

infection and malignancies, as well as provide a baseline for follow-up. It is important to emphasize, however, that radiographs during the first 3 months of the disease course may be normal in up to 80% of patients developing abnormal radiographs at the end of follow-up.[29]

Computed tomography (CT) is the imaging modality of choice for demonstrating the various osteoarticular lesions in the anterior chest wall, especially in adults, because this area may be poorly demonstrated radiographically,[16] and minor osseous changes can be difficult to detect with magnetic resonance imaging (MRI).[13]

MRI using fluid-sensitive sequences such as short tau inversion recovery (STIR) or T2-weighted fat-saturated (T2FS) images may detect bone marrow and soft tissue edema seen at active lesions as increased signal intensity areas with a corresponding decreased signal intensity on T1-weighted images.[9,13,32] Chronic sclerotic bone lesions can appear hypointense on STIR/T2FS and T1-weighted images,[16,32] but episodes of inflammation may also result in fatty metaplasia in the bone marrow appearing as hyperintense areas on T1-weighted images. Postcontrast sequences may be used initially to detect vascularization and increase the morphological evaluation, especially in differentiating lesions from other disorders such as malignancies and infections. However, contrast-enhanced sequences may not be required for follow-up evaluation because STIR/T2FS sequences are highly sensitive in detecting active lesions.[33]

Due to the multifocal nature of the disease, MRI targeted to symptomatic areas may not visualize the whole disease burden. Whole-body MRI (WBMRI) is being used increasingly to detect multifocal bone lesions, both initially and at follow-up.[15,21,33–36] WBMRI may visualize most of the osteoarticular changes of SAPHO/CRMO in one examination, especially when using coronal T1-weighted and STIR sequences in addition to axial STIR images of the whole body supplemented by sagittal sequences of the spine and/or dedicated MRI of inadequately visualized peripheral bone involvement.[28,35–37] WBMRI is valuable for assessing total disease activity as well as for monitoring therapeutic response or the spontaneous course of the disease.[36] This radiation-free assessment of the entire body by WBMRI is particularly important in children/adolescents where repeated follow-up is often necessary because clinical remission does not necessarily mean radiologic remission.[36] Supplementary whole-body diffusion-weighted imaging seems promising, especially for differentiating inflammatory from malignant lesions;[38] however, the value in monitoring the inflammation has yet to be determined.

Whole-body bone scintigraphy or single-photon emission computed tomography using technetium 99m-labeled diphosphonate is also highly sensitive for detecting multifocal bone lesions because both active and chronic subclinical inflammatory lesions show increased tracer uptake.[22,39] But the disadvantage of technetium 99m scintigraphy is the exposure of the patient to ionizing radiation.

Case reports have shown the utility of fluorine-18 fluorodeoxyglucose (F^{18}-FDG) positron emission tomography (^{18}F-FDG PET) alone or ^{18}F-FDG PET/CT in differentiating active from healed chronic inflammatory lesions.[40] Currently no major studies have defined the role of ^{18}F-FDG PET/CT in SAPHO/CRMO.

Anterior Chest Wall Involvement

In adults, the anterior chest wall region is the most frequent site for SAPHO lesions.[6,8–11,13] Any area of the region can be involved, but the sternum and the sternoclavicular, manubriosternal, costosternal, and costochondral junctions are the most commonly affected sites.[9,13]

According to the initial description from Japan based on conventional radiography, the osteoarticular changes develop in three stages.[9,13,20] Stage 1 is ossification localized to the area of the costoclavicular ligament; in stage 2, an arthropathy of the sternoclavicular joint develops with osteolytic and osteosclerotic changes of the medial end of the clavicle, adjacent sternum, first rib, and costal cartilage (►**Fig. 1a**); stage 3 is a further progression of osteosclerosis and hyperostosis of these structures with arthritis and potential ankylosis of the adjacent joints (►**Fig. 1e**). This development corresponds to a disease primarily involving entheses, especially at the costoclavicular ligament, and secondarily spreading to the joints and bones. However, changes may also begin in the bones, often in the manubrium sterni, and secondarily spread to the joints and surrounding capsular and ligamentous structures; this is more in agreement with the concept of SAPHO/CRMO (►**Fig. 1b**, **c**). During the course of disease, joint erosions, which are the result of an extension of the adjacent osteitis or a primary arthritis, frequently lead to ankylosis, particularly of the sternoclavicular and sternocostal joints (►**Fig. 1e**, **g**). However, patients often present with changes that have evolved over several years and consist of a mixture of osseous and soft tissue changes (►**Fig. 1**). The diagnosis is then primarily based on the presence of osseous sclerosis and hyperostosis that can be accompanied by enthesopathy including the costoclavicular ligament visible by radiography[20] (►**Fig. 1**).

A detailed delineation of the changes demands CT and/or MRI, especially to detect early changes. CT can demonstrate ligamentous ossification in addition to the extent of potential lytic areas initially as well as sclerosis and hyperostosis occurring later (►**Fig. 1b**, **c**, **f**, **g**). MRI can detect signs of activity in the form of bone marrow edema and/or enhancement (►**Fig. 1d**). Inflammatory involvement of adjacent soft tissue is often present, and voluminous soft tissue may compress or obstruct the subclavian vein causing thoracic outlet syndrome.[11,17,41,42] Furthermore, soft tissue involvement may appear as an aggressive process such as lymphoma or other malignancies.

For decades, bone scintigraphy was used to establish the diagnosis. The so-called bullhead pattern of increased sternocostoclavicular inflammation, with the manubrium sterni representing the upper skull and the inflamed sternoclavicular joint with the adjacent clavicles forming the horns, was considered one of the characteristics of SAPHO.[22]

In children/adolescents, the clavicle is the most common anterior chest wall bone involved. The sternoclavicular and sternocostal joints, as well as the sternum, and ribs are rarely affected,[9,13,41] and ligamentous ossification or bony bridging across the joints has not been described.

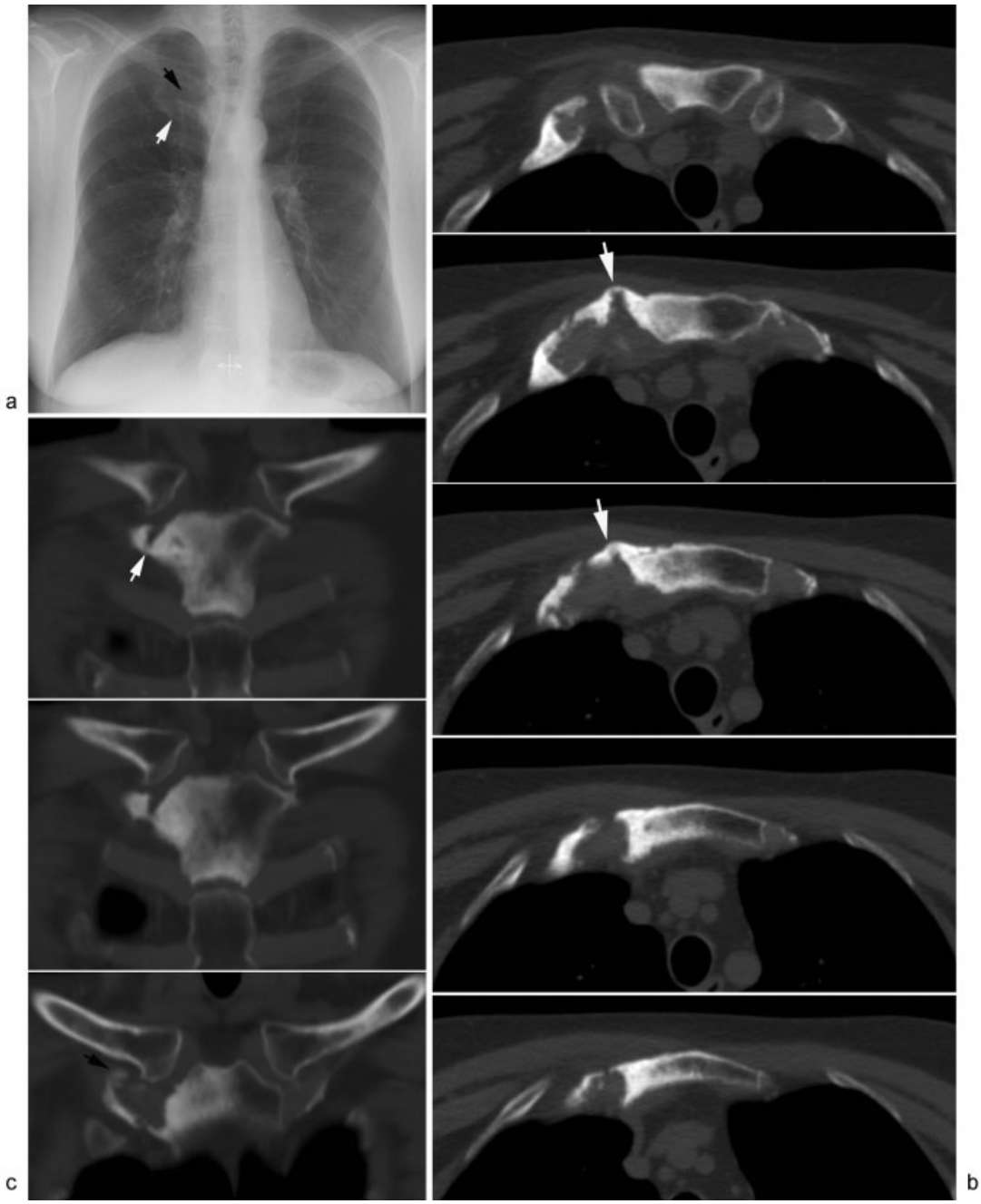
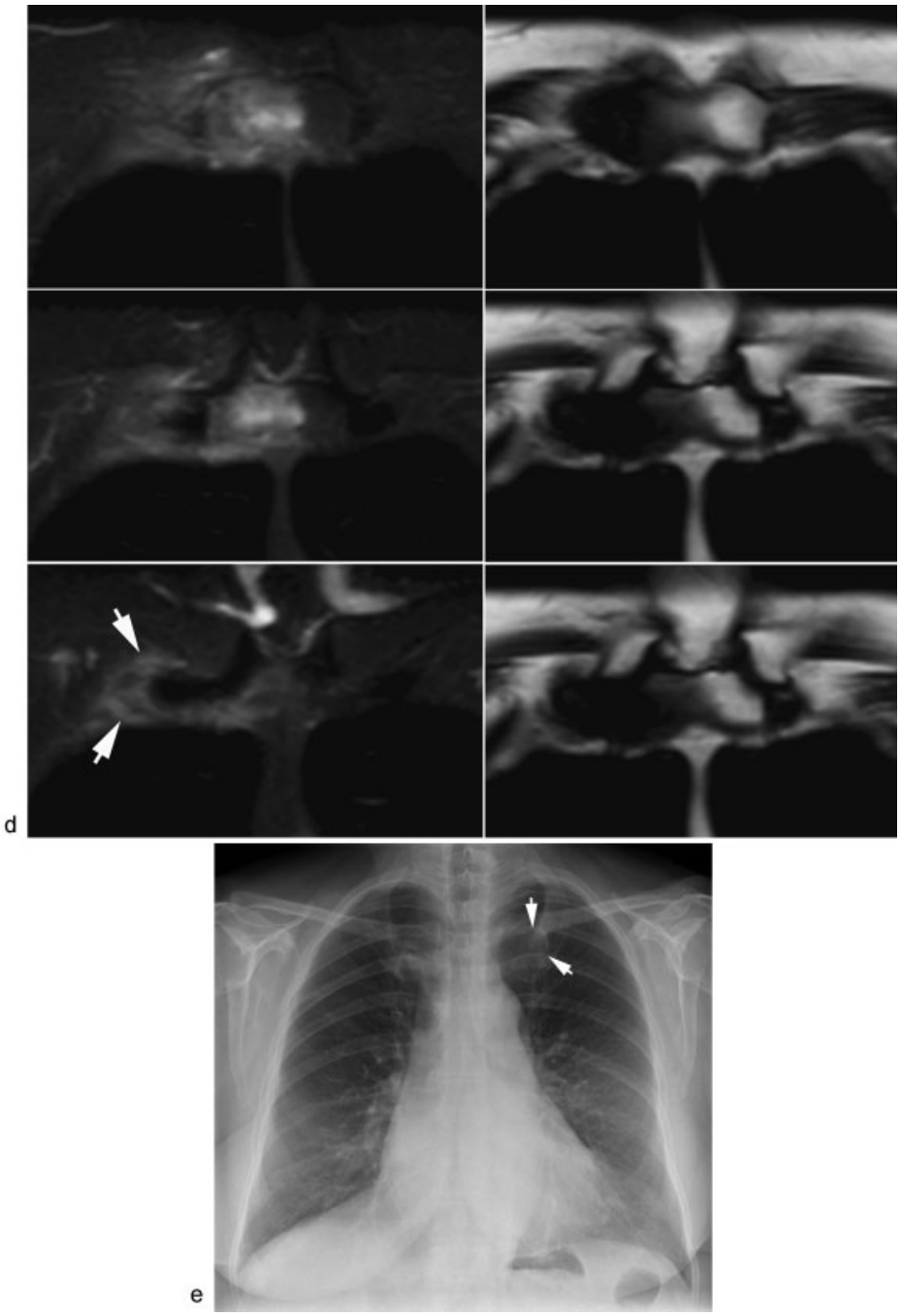


Fig. 1 Anterior chest wall involvement in adults. A 63-year-old woman with pustulosis palmoplantaris (PPP) and recurrent pain and swelling in the sternoclavicular region for several years. (**a**) Chest radiograph showing condensation in the region of the right sternoclavicular and first sternocostal joint with certain mineralization/ossification located at the first costal cartilage (white arrow) and possible ossification at the right costoclavicular ligament (black arrow). (**b**) Computed tomography (CT): axial slices from the upper to the lower part of the manubrium and (**c**) coronal reconstructions from anterior to posterior. There is osseous sclerosis corresponding in the right side of the manubrium sterni extending to the manubriosternal joint where there is an uneven joint facet, but the sternal body is normal. There is no involvement of the clavicles, except osteophyte formation, but there is osseous irregularity corresponding to the first right sternocostal joint and hyperostosis of the costal cartilage with a border of homogeneous mineralization including a sclerotic bridge anteriorly (white arrows) and also a slight ossification of the costoclavicular ligament (black arrow). (**d**) MRI of the region as part of whole-body MRI, coronal slices from anteriorly to posteriorly, short tau inversion recovery to the left and T1-weighted images to the right, shows osseous edema corresponding to the manubrium sterni with concomitant edema at the first costochondral junction and the surrounding soft tissue (arrows). Late changes in a 72-year-old woman with PPP and left-sided shoulder pain accompanied by restricted movement for 11 years. (**e**) Chest radiograph shows an ossified mass between the left clavicle and the costal cartilage (arrows). (**f**) CT, coronal reconstruction, and (**g**) three-dimensional reconstructions show pronounced ossification corresponding to the left costoclavicular ligament in addition to partial ankyloses of the sternoclavicular joint.



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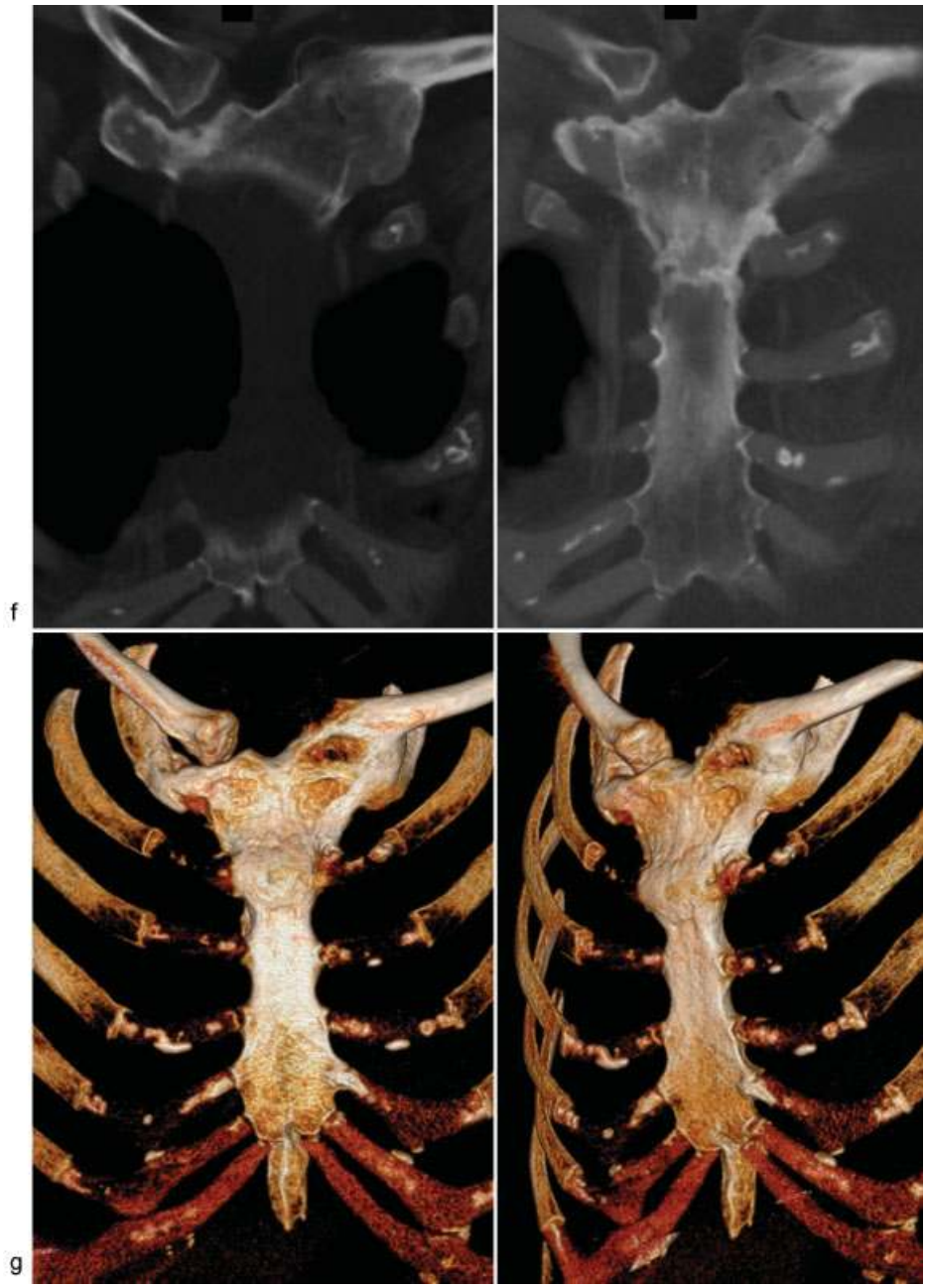
In the early active stages, the radiographic features of clavicular lesions are characterized by lytic medullary destruction in the medial part of the clavicle and periosteal new bone formation, occasionally onion skin–like periosteal changes simulating malignancies, such as Ewing's sarcoma or histiocytosis[3,13,25] (►**Fig. 2a**). At this stage, MRI appearance is nonspecific with bone marrow edema signal on STIR or T2FS images and surrounding soft tissue edema; on T1-weighted images, the lesions appear as a rather homogeneous mass with low signal intensity containing the bone marrow, cortical bone, and the periosteal new bone formation[15] (►**Fig. 2b**, **c**). After the administration of gadolinium contrast agents, a marked somewhat inhomogeneous signal enhancement is seen in both the bone lesions and the adjacent soft tissue,[14,15,25] but there is no delineated soft tissue mass or abnormalities suggesting abscess formation (►**Fig. 2d**).

During periods of remission, the clavicular destruction tends to heal with the formation of sclerosis and the periosteal new bone to organize, sclerose, and fuse with the clavicular bone[3,13–15,43] (►**Fig. 2e**). The course usually implies several exacerbations with new lytic osseous destruction and sometimes periosteal new bone formation, similarly healing with sclerosis. This may result in progressive clavicular sclerosis and hyperostosis.[3,13,43] It can be difficult to detect activity by



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conventional radiography in such hyperostotic and sclerotic bone unless there is periosteal new bone formation. However, MRI can detect this. On both STIR or T2FS and T1-weighted images, an inactive sclerotic clavicular lesion presents with low signal intensity corresponding to the sclerotic bone that can contain scattered areas with fatty metaplasia showing high signal intensity on T1-weighted images. During exacerbations, intraosseous high signal intensity areas and/or surrounding soft tissue edema are detectable on STIR or T2FS images as a sign of disease activity[32] (►**Fig. 2f**, **g**).

The hyperostotic and sclerotic clavicular changes usually persist for several years and gradually extend laterally.[14] Although some spontaneous regression occurs during remissions, complete healing is rare.

Spinal Lesions

In all ages, the second most common site of skeletal involvement is the spine, most frequently located at the thoracolumbar region.[11,44] The spinal manifestations of SAPHO/CRMO can consist of five features that may occur in various combinations: nonspecific spondylodiskitis; osteosclerosis of vertebral bodies; osteolytic lesions with variable degrees of vertebral body collapse, mainly seen in children/adolescents; and in adults, paravertebral ossification in addition to vertebral corner lesions.

Although the earliest inflammatory changes are best observed with MRI, radiography and especially CT appear to be more sensitive for detecting chronic changes such as erosions, sclerotic changes, hyperostosis, and new bone

formation.[45] However, spinal involvement during the course of SAPHO/CRMO may be asymptomatic,[46] and MRI of the spine or WBMRI may be needed to detect asymptomatic changes supporting the diagnosis.[46]

Nonspecific Spondylodiskitis

Inflammatory lesions located at intervertebral spaces conforming to the definition of spondylodiskitis may be the initial manifestation of SAPHO/CRMO[47,48] and may over the years occur at multiple sites in the same patient.

Erosion of vertebral end plates with subchondral sclerosis as part of SAPHO/CRMO may mimic infectious spondylodiskitis, but usually there are some differences. In SAPHO, the lesions are often localized to the anterior or central portions of the diskovertebral junction,[44,46] and the early changes are often confined to one vertebral end plate (►**Fig. 3a**, **b**). The

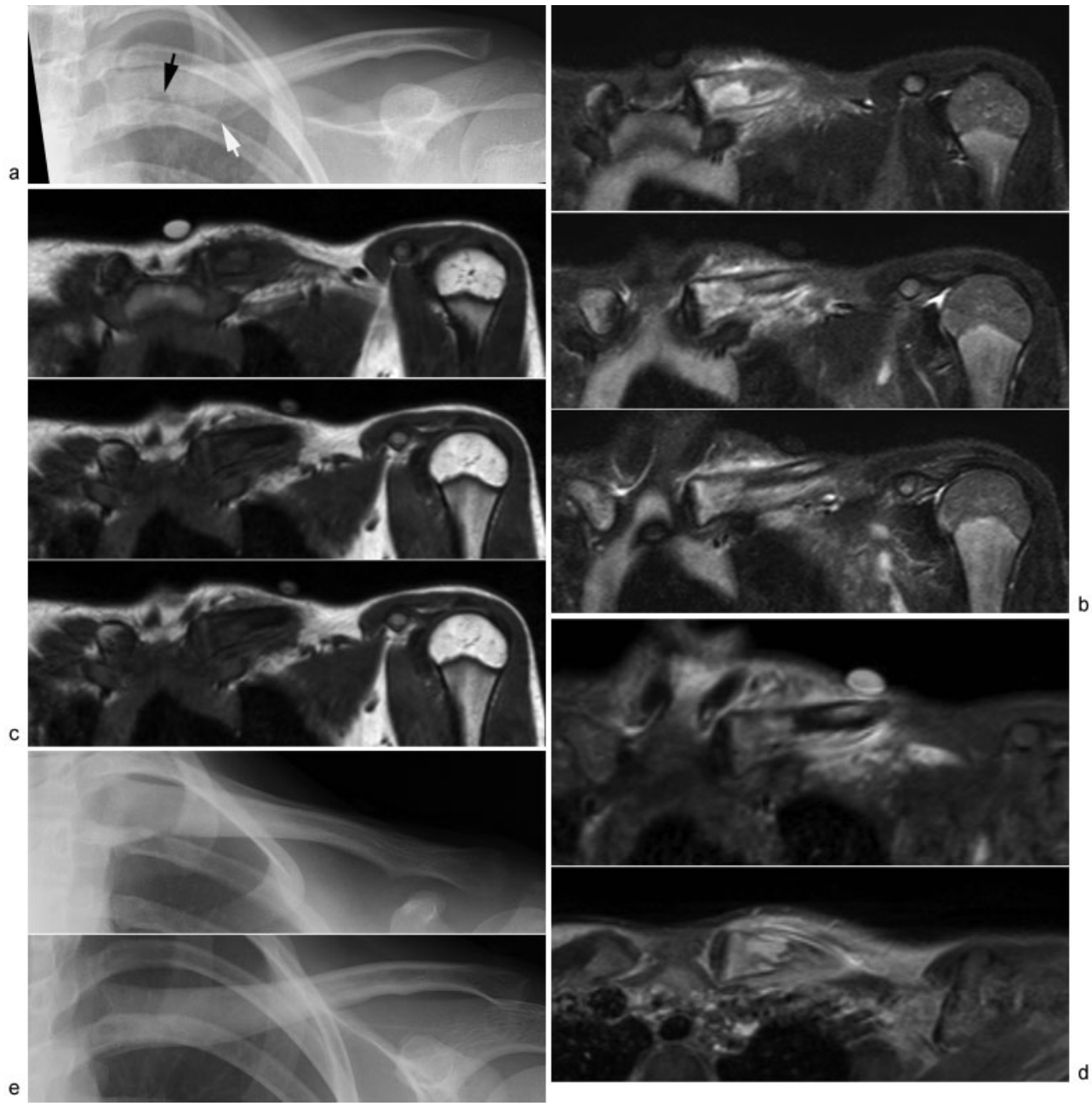
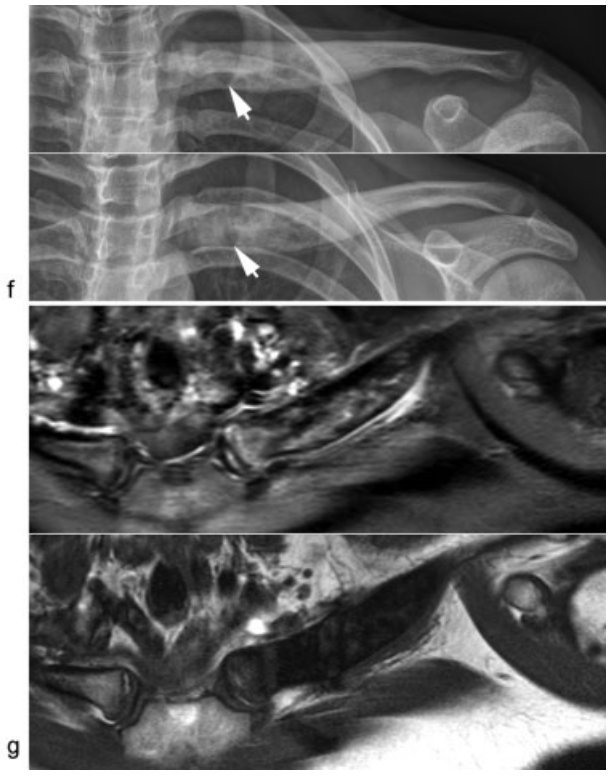


Fig. 2 Clavicular lesions. (**a**) Initial radiography of an 11-year-old girl with pain and swelling at the left clavicle for 2 months. There is lytic medullary destruction in the medial part of the clavicle (black arrow) and periosteal new bone formation (white arrow). (**b**–**d**) MRI shows bone marrow edema signal on coronal short tau inversion recovery (STIR) (b, from anterior to posterior) with surrounding soft tissue edema. (**c**) On coronal T1-weighted images the lesion appears as a rather homogeneous mass with low signal intensity containing the bone marrow, cortical bone, and the periosteal new bone formation. (**d**) T1-weighted fat-saturated postcontrast images, coronal and one axial (at the bottom), show marked inhomogeneous enhancement in both the bone lesion and the adjacent soft tissue with laminar periosteal new bone formation. (**e**) Six months later healing with sclerosis. (**f**) Radiography during an exacerbation 5 years later shows clavicular sclerosis and hyperostosis in addition to small lytic intraosseous areas (arrows) and periosteal new bone formation. (**g**) Supplementary MRI: coronal STIR (upper image) and T1-weighted image show intraosseous edematous areas in addition to soft tissue edema.



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adjacent intervertebral disk space is usually well maintained but can be reduced in height. With time, the changes often spread to both vertebral end plates, and other intervertebral spaces may be involved.

Radiography and CT can detect erosions of the end plates usually appearing with concomitant subchondral sclerosis (►**Fig. 3a**), which can extend to the entire vertebra and sometimes be accompanied by paravertebral ossification resulting in hyperostosis[15] (►**Fig. 3c**).

MRI is able to detect concomitant bone marrow edema that may be focally located at the end-plate erosions or involve most of the vertebral body[9,49] (►**Fig. 3b**, **d**). Normal or low signal intensity in the disk on STIR or T2FS sequences and the absence of disk space enhancement on postcontrast images helps differentiate the lesions from infectious spondylodiskitis. However, the presence of both high signal intensity on T2-weighted images and disk space enhancement can be seen in SAPHO.[44,49] The differentiation of SAPHO lesions from infectious spondylodiskitis may be further complicated if concomitant prevertebral soft tissue swelling is present (►**Fig. 3d**, **e**). However, this is usually < 1 cm thick and not always enhancing.[46] The absence of abscess formation or epidural involvement in SAPHO as well as foci of spondylodiskitis at different consecutive or nonconsecutive spinal levels can aid in the differentiation from infection.[13,44,49] The potential presence of typical vertebral corner lesions in other spinal segments also supports the SAPHO diagnosis[46] (►**Fig. 3b**, **d**). If the differentiation cannot be established by imaging, biopsy of the involved disk space is needed. In patients with SAPHO a chronic nonspecific inflammatory process with mild fibrosis will be revealed, and cultures are classically sterile.[44]

Osteosclerosis

Vertebral body sclerosis is a SAPHO feature mainly seen in adults but occasionally also in children/adolescents. It is probably elicited by osseous inflammation triggered by inflammatory end-plate erosions or occurring in the central portion of the vertebral body.[46]

The sclerotic changes are best visualized by radiography and CT. It can occur in limited areas adjacent to erosive end-plate changes or involve the entire vertebral body ("ivory vertebra")[9] (►**Fig. 3c**). Pure osteosclerosis of one or more vertebral bodies without detectable end-plate erosion may be seen in patients with SAPHO[46,50] and resemble sclerotic metastasis or Paget's disease on radiography and CT. MRI is not of major differential diagnostic value because the occasional involvement of multiple vertebral levels in a noncontiguous fashion may simulate the MRI pattern produced by multiple metastases[46] with edema signal intensity randomly distributed in the vertebral bone marrow. However, concomitant end-plate erosion can aid in differentiating SAPHO lesions from malignancies (►**Fig. 3c**, **d**). High signal intensity on T1-weighted images may also imply fatty marrow metaplasia, seen in SAPHO (►**Fig. 3d**), but it is not a feature of osseous metastases, except in malignant melanoma.

Osteolytic Lesion

The spinal involvement in SAPHO/CRMO may also present as an osteolytic lesion with partial or complete vertebral body collapse without a history of trauma, especially in children/adolescents.[15,26,36,43]

The vertebral lyses and collapse can be detected by radiography and especially by CT with reformatted images,[15] and MRI can demonstrate intraosseous edema during active periods as a sign of osseous inflammation or microfractures causing the osseous collapse[15,36] (►**Fig. 3f**, **g**). The absence of an associated paravertebral soft tissue mass may be important for to distinguish SAPHO/CRMO involvement from malignancy such as Ewing's sarcoma.

In patients with partial collapse, the lesion heals gradually with minor sequelae apart from some degree of kyphosis.[26] In contrast, patients with complete vertebral body collapse (vertebra plana) may develop deformity and occasionally spinal canal stenosis and spinal cord injury.[12,32,51,52] Reconstitution of vertebral height is normally not a feature of SAPHO/CRMO[26] unlike that seen in vertebra plana caused by eosinophilic granuloma.

Paravertebral Ossifications

In adults with SAPHO various paravertebral ossifications can occur, best demonstrated by radiography and especially by CT with reformatted images (►**Fig. 3c**), but they may also be detectable by MRI, especially during periods with active inflammation or succeeding fatty metaplasia (►**Fig. 3d**). The ossifications in SAPHO usually consist of nonmarginal and asymmetric syndesmophytes/para-syndesmophytes somewhat similar to the paravertebral ossifications seen in psoriatic spondyloarthritis,[10,13] although often with a more fluffy appearance.[10] In advanced stages, hyperostotic anterior bony bridging can be seen across the diskovertebral

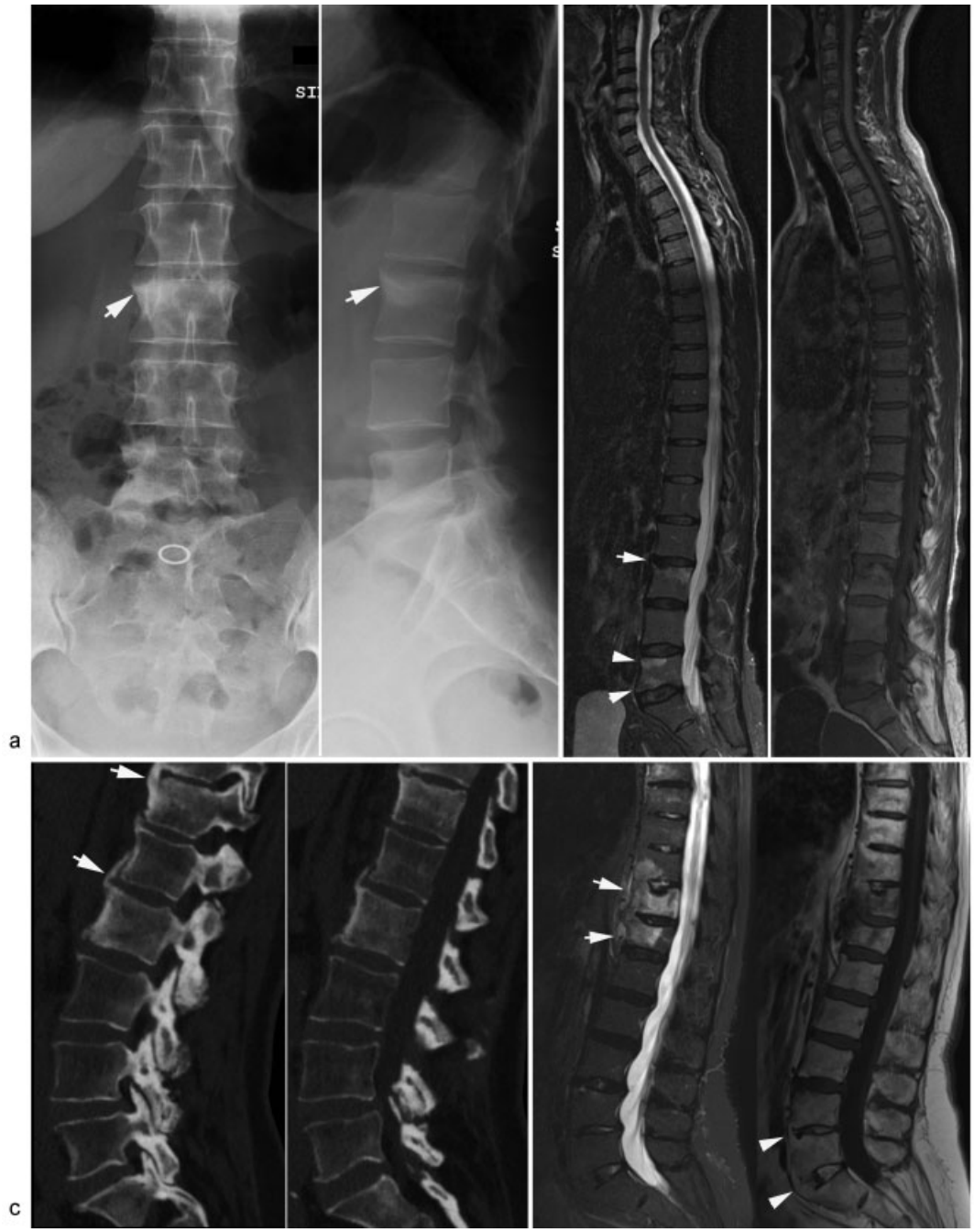

Fig. 3 Spinal lesions. (**a**, **b**) Spondylodiskitis-like changes and corner lesions. (**a**) Radiography of a 43-year-old woman shows irregular upper end plate of vertebra L3 with subchondral sclerosis (arrows) and possible changes at the intervertebral space L5–S1. (**b**) Supplementary MRI, short tau inversion recovery (STIR) to the left and T1 to the right, shows subchondral edema beneath the upper end-plate erosion of L3 in addition to subchondral edema anteriorly in L5 (arrowheads). (**c**, **d**) Osseous sclerosis and paravertebral ossifications. (**c**) Computed tomography of a 60-year-old woman showing osseous sclerosis corresponding to vertebra L2 and the upper part of vertebra T12. Anterior paravertebral ossification extending from the upper corner of L2 to the anterior cortex of L1 and bridging ossification across the intervertebral space T11–T12. (**d**) MRI (sagittal STIR to the left and T1-weighted image to the right), 3 years later shows minimal sequels of the changes at L2 but a pronounced active inflammation in the regions of T10–T12 with paravertebral edema (arrows). Bridging paravertebral new bone formation anteriorly at the intervertebral spaces L4–L5 and L5–S1 (arrowheads). (**e**) Supplementary postcontrast images, sagittal to the left and axial slices to the right, show enhancing paravertebral new bone formation (arrows) but no abscess formation. (**f**) Lytic lesion. MRI of a 13-year-old girl, sagittal STIR to the left and T1-weighted image to the right, shows osseous edema superiorly in vertebral T2 and T3 (arrows) with reduced anterior height of T3 in addition to diffuse edema of the second lumbar vertebra without collapse (arrowhead). (**g**) Vertebra plana in another child (STIR to the left and T1 to the right). There is a wedge-shape collapse of vertebra T9 with osseous edema. (**h**) Supplementary whole-body MRI (coronal STIR to the left and T1 to the right) visualizes concomitant osseous lesions at both knee regions, most pronounced on the right side (arrows).

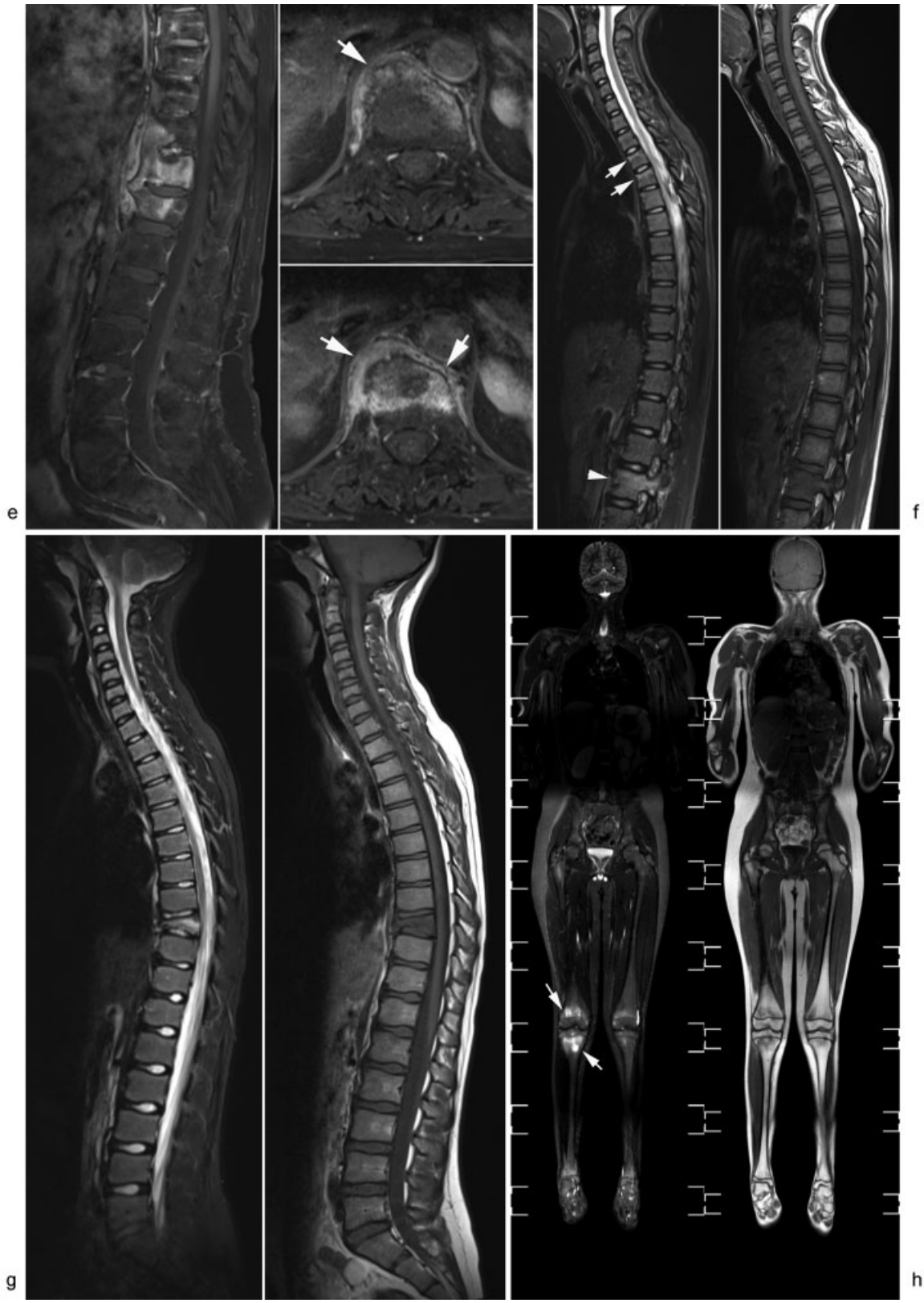

Fig. 3 (*Continued*).

junction at single or multiple levels[10,13] (►**Fig. 3c**, **d**), and subsequent vertebral ankylosis may occur.

Vertebral Corner Lesion

The term *vertebral corner lesion* is used to describe abnormalities at the corner of vertebral bodies visualized by radiography, CT, and/or MRI, encompassing erosion, sclerosis, edema, and fatty metaplasia.[53] It is usually regarded as features of the common forms of spondyloarthritides. Somewhat similar changes, however, can occur in adults with SAPHO.[45]

The early vertebral corner changes in SAPHO are detectable by MRI as areas with edema signal intensity (increased signal on STIR/T2FS and decreased on T1) or contrast enhancement without radiographic changes[44,46,53] (►**Fig. 3b**). Reactive sclerosis occurring later is detectable by radiography or CT and can appear as low signal intensity corners on all MR sequences[46] (►**Fig. 3b**). Postinflammatory fatty metaplasia may occur making the corners hyperintense rather than hypointense on T1-weighted images.[53] These features are similar to those seen in ankylosing spondylitis, but often some imaging differences can facilitate the differential diagnosis.

The vertebral corner lesions in SAPHO are most commonly located to the anterior corners and rarely posteriorly,[46] and the extent of adjacent bone marrow involvement is usually relatively large (►**Fig. 3b**), whereas the changes in typical ankylosing spondylitis often are confined to the corner areas.[53] Corner lesions seen by MRI in ankylosing spondylitis probably indicate enthesitis and precede the development of fatty corner lesions as well as the formation of syndesmophytes.[54–56] The corner lesions by MRI in SAPHO are probably also the first stage of a process preceding the development of new bone formation detectable by radiography, but there are usually more voluminous ossifications in SAPHO than in ankylosing spondylitis. Consistent with this finding, the vertebral corner involvement in SAPHO was observed to progress to the adjacent vertebral end plate and/or the anterior cortex of the vertebral body, often accompanied by thickening of the prevertebral soft tissue[46] that may ossify and over time result in pronounced paravertebral ossification covering several intervertebral spaces[46] (►**Fig. 3c**, **d**). Although the voluminous paravertebral ossification can be used to differentiate the changes from those typical for ankylosing spondylitis, similar changes can occur in other forms of spondyloarthritis (e.g., psoriatic spondyloarthritis).

Sacroiliitis and Pelvic Bone Lesions

Adult patients with SAPHO have an increased risk for developing sacroiliitis, usually unilaterally.[16] Therefore, close attention should be paid to the sacroiliac joints. Children/adolescents usually present with inflammatory osseous changes in pelvic bones adjacent to the sacroiliac joint, the triangular cartilage, or the ischiopubic symphysis.[14,15,33,43]

The combination of erosive sacroiliac joint changes and extensive sclerosis of the adjacent iliac or sacral bone is characteristic of SAPHO/CRMO lesions[10,13,17] and helps differentiate it from sacroiliitis in common forms of spondyloarthritis.[1,9,12] Manifest changes are detectable by radiography (►**Fig. 4a**), but MRI may be needed to detect early active lesions and areas of active inflammation in chronic lesions (►**Fig. 4b**, **c**).

The lesions in children/adolescents are similar to those of other bones characterized by initial osteolysis healing with sclerosis and sometimes also hyperostosis.[14] However, early changes may only be detected by MRI (►**Fig. 4c**) (e.g., as part of WBMRI).

Appendicular Skeleton Changes

Peripheral arthritis may occur in adults but usually without structural changes such as erosions.[13]

Long tubular bones represent the most common site of disease in children/adolescents (CRMO).[15] The distal and proximal tibia is most frequently affected, followed by the proximal and distal femur (►**Fig. 5**).[15,21,33,39,57] The fibula, small tubular bones of the feet, humerus, radius, and ulna can also be involved.[39] The metaphyses adjacent to the growth plates or bones adjacent to growth plates at apophyses are the most common locations.[39] However, diaphyseal-metaphyseal (►**Fig. 5f**, **g**), metaphyseal-epiphyseal, and diaphyseal lesions may also occur[15,26,33,43,57] but rarely. Multifocality with a predominance of lower extremity lesions is common at presentation or later in the course of the disease, but monostotic involvement has been described.[15,33,39]

In children/adolescents, the radiographic changes in the appendicular skeleton include osteolysis, osteosclerosis, and periosteal new bone formation[14,15] (►**Fig. 5**). Early in the disease there may be normal or minimal changes by radiography[15] (►**Fig. 5a**, **b**), but when appearing the typical finding is an osteolytic metaphyseal process adjacent to the growth plate surrounded by a thin sclerotic rim (►**Fig. 5a**). During the course, progressive sclerosis often occurs around the lytic lesion producing a mixed lytic/sclerotic picture. If the inflammatory process extends into the cortex, periosteal new bone formation may occur resulting in bone enlargement (►**Fig. 5f**). The healing of such lesions results in a radiographically chronic sclerotic and hyperostotic lesion.[13,15,16,43] Sequestra and abscesses are characteristically absent, but apart from this, the radiographic features are those of a chronic osteomyelitis. The extent of the periosteal reaction depends on both the duration of the disease and the size of the involved bone. It is generally more pronounced in small bones such as the fibula and metacarpals/metatarsals.[43]

MRI is useful to assess the activity and extent of the lesions. In active lesions, MRI typically shows bone marrow edema (hyperintense on STIR/T2FS and hypointense on T1-weighted images)[32] (►**Figs. 3h** and **5c–e**, **g**). Associated periostitis, soft tissue inflammation, and joint effusions adjacent to the bone lesions occurring in pronounced lesions can also be demonstrated by MRI (►**Fig. 5g**). However, due to the increasing use of WBMRI to detect multifocality, many MR-detected lesions only involve bone (►**Figs. 3h** and **5d**, **e**).

Mandibular Involvement

Mandibular lesions predominantly occur in children/adolescents and can be isolated or accompanied by disease at other body sites. The lesions are typically located on the posterior

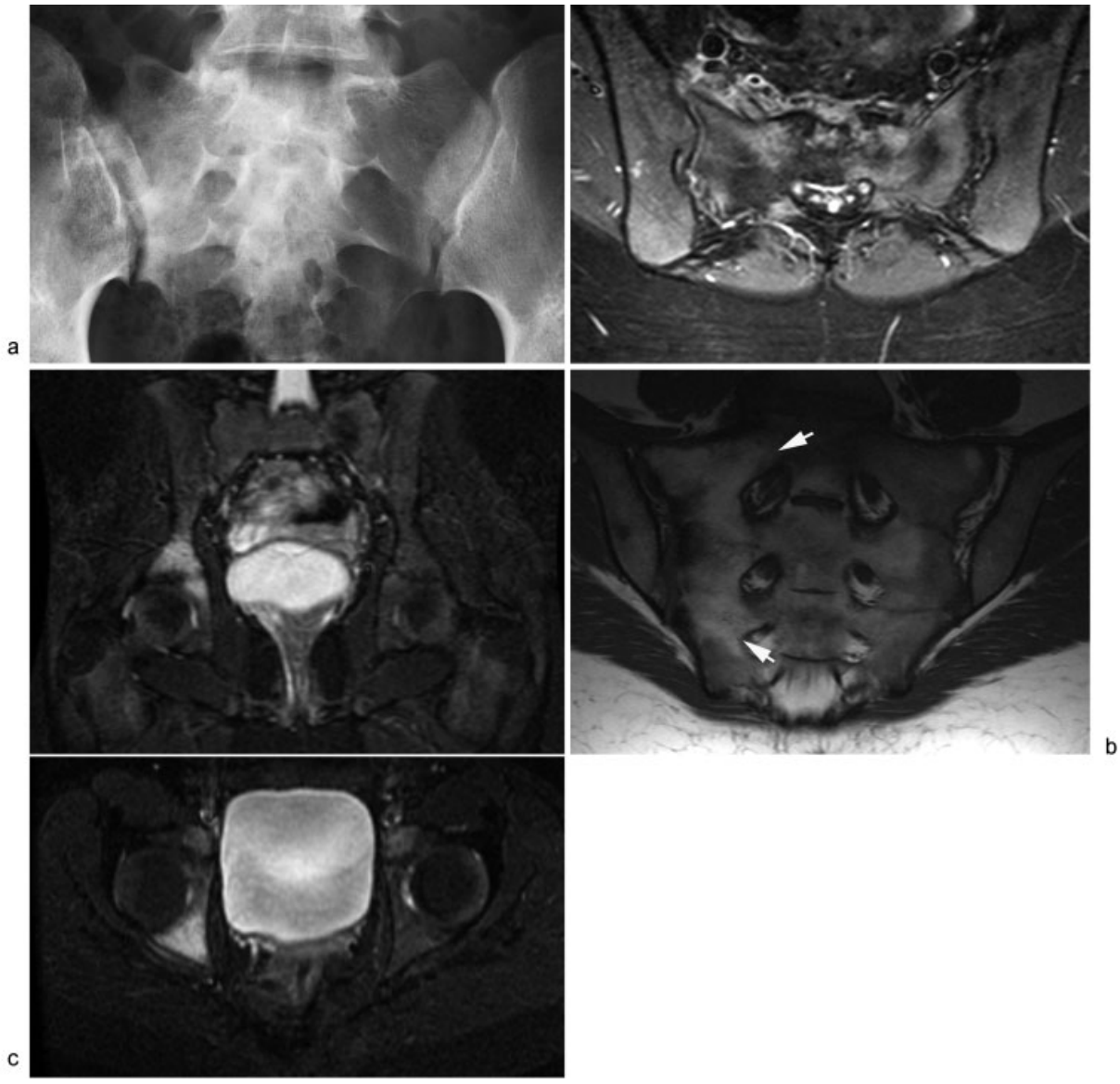

Fig. 4 Pelvic bone lesions/sacroiliitis. (**a**) Radiography of the sacroiliac joint in a 16-year-old adolescent girl shows osseous sclerosis corresponding to the right side of the sacrum with joint facet erosions. (**b**) Supplementary MRI, short tau inversion recovery (STIR) (upper image) and T1 (lower image), shows fatty marrow metaplasia in the right side of the sacrum (white arrows) and inhomogeneous edematous changes on the STIR image in addition to hyperostosis of the right side of the sacrum. (**c**) Early pelvic bone lesions adjacent to the triangular cartilage in a 13-year-old girl, coronal and axial STIR images, show bone marrow edema adjacent to the triangular cartilage. Radiography was normal. The same patient as in ►**Fig. 5a–c**.

mandibular body and ramus,[10,15,16,18,43] and spread to the temporomandibular joint is rare.[58]

In the early stages, mandibular lesions on radiography or CT are characterized by osteolytic lesions with associated variable amounts of periosteal new bone formation causing hyperostosis and a variable degree of sclerosis[43] (►**Fig. 6a**). Over time, increasing sclerosis, hyperostosis, and progressive enlargement of the mandible develop similar to clavicular lesions.[43]

On MRI, active lesions usually demonstrate osseous edema with extensive edematous periosteal new bone formation often accompanied by edema in the adjacent soft tissue but with no detectable abscess formation[16,43] (►**Fig. 6b**). In this stage, the lesions may simulate malignancies just like clavicular lesions. In later stages signal-void sclerosis usually dominates, but edematous and/or enhancing osseous areas occur during exacerbations.

Pathogenesis

The pathogenesis of the SAPHO/CRMO spectrum remains unknown, but some hypotheses have been suggested. Initially it was hypothesized that the bone lesions in SAPHO/CRMO are due to infection by a low virulent agent such as *Propionibacterium acnes* that was isolated in bone biopsy specimens from SAPHO/CRMO patients.[59–61] However, *P. acnes* is an aerobic saprophyte that is frequent in the skin and a common contaminant of specimens obtained via transcutaneous biopsies. Moreover, antibiotic therapy is

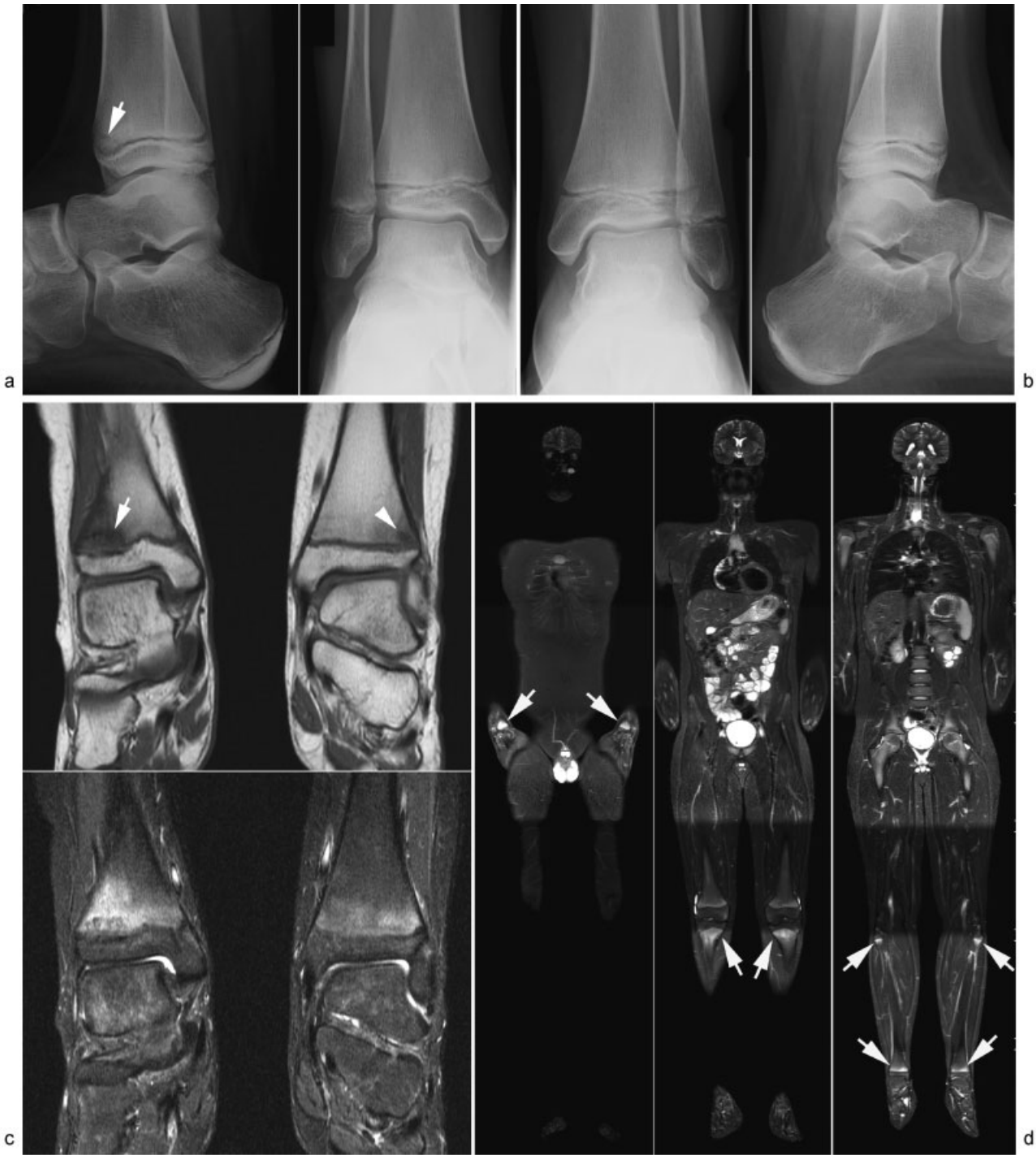

Fig. 5 Tubular bone involvement in children/adolescents. (**a**–**c**) Metaphyseal involvement in a 12-year-old girl (same patients as in ►**Fig. 4c**). (**a**) Radiography of the right ankle and (**b**) the left ankle. There are only minimal changes in the tibial metaphyses best visible on the lateral view of the right ankle (arrow). (**c**) Supplementary MRI, upper image T1-weighted and lower image short tau inversion recovery (STIR), shows characteristic metaphyseal edema with a surrounding rim of sclerosis on the right side (arrow) and a small metaphyseal lesion on the left side (arrowhead). Whole-body MRI in a 14-year-old boy with knee complaint. (**d**) Coronal STIR images from anterior to posterior and (**e**) corresponding T1-weighted images show multiple clinical silent metaphyseal lesions located to the wrist and ankle regions in addition to metaphyseal changes at the knee. The lesions present with high signal intensity on STIR (arrows) and low signal intensity on T1-weighted images. Radiography of the involved areas was unremarkable. (**f**, **g**) Metadiaphyseal involvement in a 9-year-old girl. (**d**) Radiographs showing a mixture of lytic destruction, sclerosis, and periosteal new bone formation. (**e**) MRI, upper image coronal STIR; middle image axial T1, and lower image coronal postcontrast T1-weighted fat-saturated, shows osseous edema and enhancement in addition to surrounding edematous and enhancing periosteum and soft tissue.

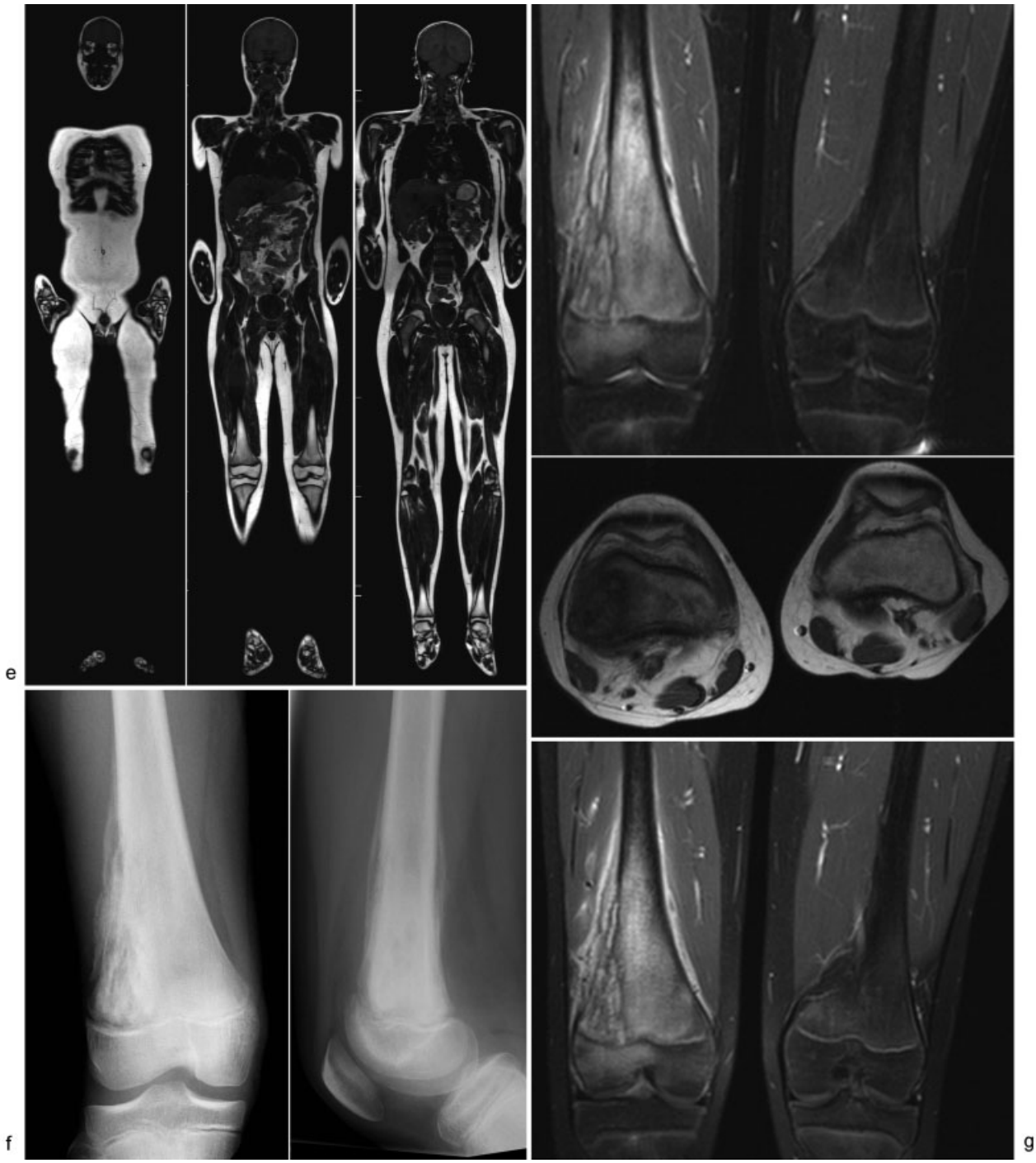

Fig. 5 (*Continued*).

often ineffective.[10,62,63] Nevertheless, this does not exclude microorganisms as an eliciting cause. Interestingly, there have apparently been positive cultures from CMRO-like mandibular lesions in addition to microabscesses by histology.[64] It is possible that organisms requiring a long incubation period were missed by conventional cultures, but supplementary polymerase chain reaction also failed to detect bacteria.[65]

SAPHO/CRMO may alternatively be autoimmune disorders triggered by a bacterial or viral pathogen or due to other pathogenetic factors. CRMO may be linked to the group of autoinflammatory diseases (e.g., occurring as part of Majeed's syndrome that is a prototypical autoinflammatory disorder in children/adolescents).[66] The changes in adults may also be linked to autoinflammation.[67] CRMO is often regarded as a pediatric form of SAPHO but could be an independent disease, although it has several similarities with the adult spectrum, and the disease may extend into adulthood, presenting features also occurring in spondyloarthritis.[57] A link to the group of common seronegative

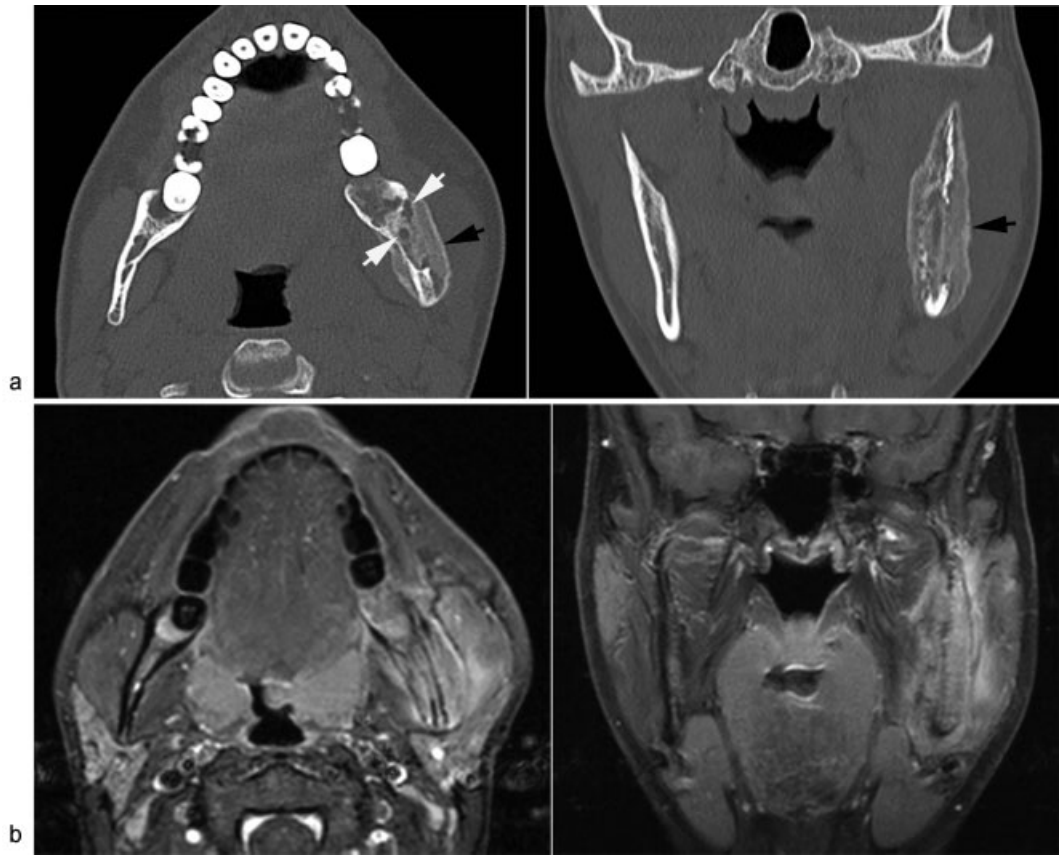

Fig. 6 Mandibular bone involvement. (**a**) Computed tomography of an 18-year-old man, axial slice and coronal reconstruction, showing lytic intramedullary destructions (white arrows) and organized periosteal new bone formation (black arrows). (**b**) MRI, postcontrast T1-weighted fat-saturated, axial and coronal image, shows enhancing bone and periosteal new bone formation in addition to a voluminous and slightly enhancing masseter muscle on the left side.

spondyloarthritides (ankylosing spondylitis, reactive and psoriatic arthritis, and arthritis associated with inflammatory bowel disorders) has been suggested due to the high frequency of axial involvement (spinal lesions and sacroiliitis) and somewhat similar imaging findings. Paravertebral ossification often indistinguishable from that encountered in psoriatic spondyloarthritis and corner lesions somewhat similar to those seen in ankylosing spondylitis occur in SAPHO. The spondylodiskitis feature of SAPHO/CRMO is also equivalent to the aseptic spondylodiskitis occasionally observed in patients with ankylosing spondylitis.[68] Also, a family history of spondyloarthritis-related disorders[69,70] and the occasional association with psoriasis and inflammatory bowel diseases (i.e., Crohn's disease or ulcerative colitis[10,11]) may imply a link to spondyloarthritis.

The relation of SAPHO to human leukocyte antigen (HLA)-B27 has been variable, however. Increased frequency was observed[6,11,12] but is not a constant finding. In two study groups HLA-B27 occurred in only 4 to 5%,[10,71] and the highest frequency of HLA-B27 (18%) was observed in a study group with an equal sex distribution,[12] whereas females predominate in other groups. In juvenile patients, the frequency of HLA-B27 does not seem to differ from the general population.[5] Other genetic factors (the *LPIN2* gene) may play a part,[70] but this has not been fully elucidated.

The current lack of valid knowledge regarding the pathogenesis may be due to the fact that somewhat different disease entities have been pooled together under the SAPHO/CRMO umbrella. In investigations of pathogenetic factors, uniform patient groups are essential. Imaging findings can help by differentiating patients with typical osseous lesions from those having changes attributed to the resampling features of common seronegative spondyloarthritides.

Diagnosis

A clinical and radiographic work-around is often necessary to establish the diagnosis. No validated diagnostic criteria are designed specifically for the SAPHO syndrome, although Benhamou et al[7] proposed these criteria to establish the diagnosis: (1) osteoarticular manifestations of acne conglobata, acne fulminans, or hidradenitis suppurativa, (2) osteoarticular manifestations of PPP, (3) hyperostosis involving the anterior chest wall, spine, or limbs with or without dermatosis, and (4) CRMO with or without dermatosis.

Owing to the lack of diagnostic tests, CRMO often remains a diagnosis of exclusion. However, diagnostic criteria for nonbacterial osteitis (NBO) corresponding to CRMO were proposed by Jansson et al[5] based on major and minor diagnostic criteria. NBO is considered present if two of four major criteria

or one major and three of six minor criteria are present. The major diagnostic criteria are (1) a radiologically proven osteolytic/osteosclerotic bone lesion, (2) multifocal bone lesions, (3) PPP or psoriasis, and (4) a sterile bone biopsy with signs of inflammation and/or fibrosis/sclerosis. Minor diagnostic criteria are (1) normal blood count and good general health, (2) CRP and ESR mildly to moderately elevated, (3) observation time $>$ 6 months, (4) hyperostosis, (5) association with other autoimmune diseases apart from PPP or psoriasis, and (6) grade 1 or 2 relatives with autoimmune or autoinflammatory disease, or with NBO.

These criteria can be used as guidance for both radiologists and clinicians. The radiologist plays a key role in the diagnosis of SAPHO/CRMO because awareness of this entity facilitates differentiation from other diseases that can have similar radiologic features, especially infectious osteomyelitis, bone tumors, lymphoma, metastases, eosinophilic granuloma, fibrous dysplasia, and Paget's disease.[8,16,43] The diagnosis is not difficult when typical bone lesions (sclerosis and hyperostosis) are located in characteristic target sites (anterior chest wall, spine, and sacroiliac joint in adults; metaphyses of long tubular bones, spine, and the clavicle in children), especially if they are associated with PPP or acne. However, the diagnosis can be difficult to establish if the sites of involvement or radiographic findings are atypical, especially if the patients have no skin disease. The diagnosis may then be based on a combination of clinical and radiologic findings. The questioning of the patient about a history of skin disorders has to be detailed because a delay of several years can separate cutaneous and skeletal lesions. In addition, the radiologist needs to obtain previous imaging of other skeletal lesions and/or recommend WBMRI or scintigraphy to reveal subclinical/silent sites of osteoarticular involvement. Detection of multiple lesions without a known inflammatory arthropathy or primary cancer can facilitate the diagnosis. The presence of a scintigraphic bullhead configuration at the sternoclavicular region has been considered one of the characteristics of SAPHO.[22]

In some cases, biopsy may be needed, although the diagnosis cannot be made by histopathology alone, but the biopsy can exclude other diagnoses.[9] Occasionally follow-up may be necessary to confirm the diagnosis.

Treatment

The initial treatment is mainly focused on relief of pain using nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics. This can be sufficient in patients with auto-limited flares.[12,28] In case of severe pain and/or recurrent flares, a low dose of corticosteroids can be used.[12,28] If this fails to control the disease, second-line therapies such as disease-modifying antirheumatic drugs (DMARDs), antibiotics, and bisphosphonates or biological agents are required.[4,10–12,28,70] The use of antibiotics has not shown convincing results, although some patients respond to this therapy.[10,47,62,63] Intravenous bisphosphonates were reported to promote long-term remission in a considerable portion of patients refractory to NSAIDs, and they are especially used in patients with spinal involvement,[4,10,16,19,70] but treatment failures[19] have also been reported. The use of DMARDs such as methotrexate, sulfasalazine, or azathioprine has met with variable results,[5,11] but biological treatment with tumor necrosis factor α has shown promising results.[10]

Conclusion

The clinical presentation of SAPHO/CRMO is heterogeneous with a presenting age range from childhood to middle age and different stages of the disease at presentation creating a spectrum of clinical and imaging features. The diagnosis is not difficult when typical bone lesions are located in characteristic target sites, especially if they are associated with PPP or acne. The general radiologist needs to be familiar with the typical imaging findings because he or she may be the first to suggest the diagnosis. However, the diagnosis can sometimes be difficult to establish and requires an interdisciplinary approach including rheumatologists, pediatricians, dermatologists, orthopaedic surgeons, radiologists, and/or pathologists. It may be necessary to consult dedicated musculoskeletal radiologists and/or clinicians working in tertiary referral centers where a multidisciplinary approach is feasible and may ensure the correct diagnosis without unnecessary biopsies.

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