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MUSCULOSKELETAL RADIOLOGY

Seronegative spondyloarthropathies: what radiologists should know

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Abstract Inflammatory involvement of the spine and sacroiliac joints is the most peculiar feature of seronegative spondyloarthropathies (SpA), which include ankylosing spondylitis, psoriatic arthritis, reactive arthritis (Reiter's syndrome), enteropathic spondylitis (related to inflammatory bowel diseases) and undifferentiated spondyloarthropathies. SAPHO syndrome may also be considered a SpA, but there is no clear agreement in this respect. Imaging, along with clinical and laboratory evaluation, is an important tool to reach a correct diagnosis and to provide a precise grading of disease progression, influencing both clinical management and therapy. Conventional radiography, which is often the first-step imaging modality in SpA, does not allow an early diagnosis. Computed tomography (CT) demonstrates with a very high spatial resolution the tiny structural alterations of cortical and spongy bone before they become evident on plain film radiographs. Magnetic resonance imaging (MRI) is the only modality that provides demonstration of bone marrow oedema, which reflects vasodilatation and inflammatory hyperaemia. The primary aim of this review article was to examine the involvement of the spine and sacroiliac joints in SpA using a multimodal radiological approach (radiography, CT, MRI), providing a practical guide for the differential diagnosis of these conditions.

Keywords Spondyloarthritis · Spine · Sacroiliac joints · SAPHO · Ankylosing spondylitis

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Introduction

Seronegative spondyloarthropathies (SpA) represent a group of chronic articular inflammatory diseases which differ from rheumatoid arthritis for the typical absence of rheumatoid factor in serum, and have in common several epidemiological, pathological, clinical and radiological features. The positivity for class I human histocompatibility leukocyte antigen (HLA)—B27 is related to a 20-fold increased risk of developing a SpA as compared to the general population [1]. In 2005, it was proposed to divide SpA into five subgroups [2]: ankylosing spondylitis, psoriatic spondyloarthritis, reactive spondyloarthritis (Reiter's syndrome), enteropathic spondyloarthritis (related to inflammatory bowel diseases such as Crohn's disease and ulcerative colitis) and undifferentiated spondyloarthropathies. Regardless of subgroup, the main clinical manifestations of SpA include inflammatory back pain (mainly at night, which worsens with rest and improves with movement) caused by sacroiliitis or inflammatory involvement of the lumbar and/or distal thoracic spine; peripheral arthritis (often oligoarticular and asymmetric); enthesitis and extra-skeletal manifestations, such as uveitis [3]. With the development of more extensive and flexible criteria by

the European Spondyloarthropathy Study Group [3], the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) may also be considered a SpA, even though there is no general agreement in this regard. SAPHO syndrome and SpA have in common many clinical and laboratory features, primarily seronegativity for rheumatoid factor and inflammatory involvement of the axial skeleton, despite only a weak association with HLA-B27 antigen having been identified for the SAPHO syndrome. The incidence of SpA varies, depending on the examined populations, from 0.2 to 1.9 %; males are more affected than females, with an age of onset between the second and third decade of life [4]. There is a tendency to familial aggregation, including nonhomologous aggregation (members of the same family may be affected by different forms of SpA). In SpA, the most characteristic targets of the autoimmune process are entheses, anatomical structures made up of fibrous or fibro-cartilaginous tissue, which provide anchorage for tendons and ligaments to the bone surface [5, 6]. Enthesitis is accompanied by the appearance of small erosions in the cortical bone, typically surrounded by subcortical reactive osteosclerosis (osteitis), which can often prevail over bone reabsorption; in the later stages osteoproliferation leads to the ossification of ligaments, tendons and joint capsules, and, eventually, to ankylosis [6, 7].

Ankylosing spondylitis

The incidence of ankylosing spondylitis, the archetype of SpA, is between 0.1 and 2 %, and the age of onset is less than 30 years in 80 % of patients. Men are more affected than women [8]. The classic form (primary or idiopathic) must be distinguished from the secondary one, which can appear during the course of psoriasis or enteropathic arthritis [9]. Involvement of the axial skeleton includes sacroiliitis, spondylitis, spondylodiscitis and interapophyseal arthritis.

Sacroiliitis is the earliest alteration, followed by the involvement of the thoracic–lumbar spine. Involvement of the cervical spine is almost always late, and it can occur even 20 years or more after disease onset [5, 10]. Sacroiliitis affects both the synovial (antero-inferior) and ligamentous (postero-superior) aspects of the joint, presenting, in most cases (80.2 %), bilateral and symmetric distribution [10].

In the early stages, alterations are represented by juxta-articular osteoporosis, superficial erosions and progressive subchondral osteosclerosis, which are first focal, then increasingly extensive (Fig. 1a, b). The erosions tend to appear in the synovial portion of the joint on the iliac side, where the cartilage is thinner [5, 11], but they are often masked by reactive subchondral osteosclerosis (Fig. 1c). As the disease progresses, erosions become more numerous and tend to coalesce, thus resulting in diffuse bone resorption which creates the illusion of an expansion of the joint space. Subchondral osteosclerosis decreases in the following stages, which are characterised by an increase in the fatty content of cancellous bone (post-inflammatory fatty conversion of bone marrow). The osteoproliferative stage is characterised by the development of irregular bony bridges that cross the joint space, reducing its width until complete ankylosis (Fig. 1d). The remnants of the joint space are sometimes visible as a thin sclerotic line on plain film radiographs, which appears hyperdense on CT images [12].

In the light of new and promising treatment options, such as anti-TNF (tumour necrosis factor) α agents, early diagnosis is of great clinical significance. Magnetic resonance imaging (MRI) is the only imaging modality that may provide an early diagnosis, showing bone marrow oedema, which appears hypointense on T1-weighted images and hyperintense on fluid-sensitive STIR (short-tau inversion recovery) or T2-weighted images with fat signal suppression. Gadolinium-enhanced fat-suppressed T1-weighted images can help in the diagnosis by showing contrast enhancement of the subchondral cancellous bone and/or joint space [5, 12]. It has been recently proposed to use diffusion-weighted MR sequences for the early detection of sacroiliitis [13], while other authors [14] have employed ultrasonography with power Doppler to demonstrate joint hypervascularity.

Bone lesions are easily detectable by CT, which also represents the reference standard for the detection of osteoproductive alterations (Fig. 2) [15].

Conventional radiography does not allow for an early diagnosis, but it still represents the most frequently requested radiological investigation to confirm the clinical suspicion of ankylosing spondylitis [1, 9, 16]. The modified New York criteria [17], proposed in 1984, are still a widespread radiographic scoring system, and they have also been applied to CT (Table 1) (Fig. 1). Spinal involvement, which may be earlier, contemporary or subsequent to the onset of sacroiliitis, occurs with greater frequency at disco-vertebral junctions and at the level of interapophyseal and costo-vertebral joints. It includes enthesitis with bone erosion, post-inflammatory fatty conversion of red bone marrow, osteosclerosis and osteoproliferation with ectopic bone formation. The enthesitis of the disco-vertebral junction, which occurs at the level of the anterior and posterior corners of vertebral bodies, is associated with erosions, resulting in the typical "lesions of Romanus". Osteosclerotic foci develop at the site of corner erosions ("bright corners" or "shiny corners"); they progressively enlarge, causing the "squaring" of the endplates

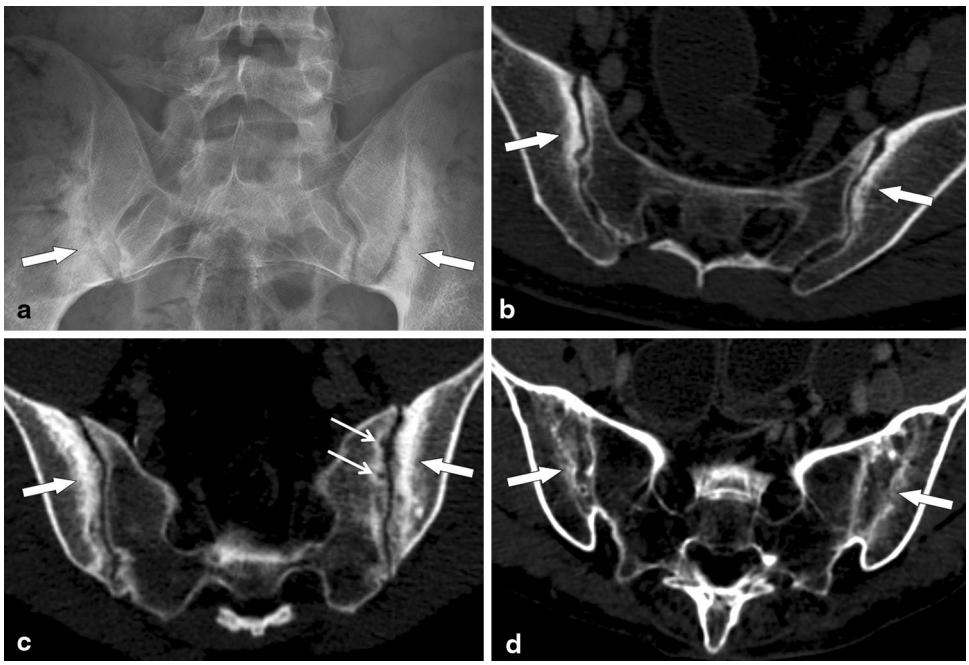

Fig. 1 **a–d** Radiographic and computed tomography (CT) scoring of sacroiliitis by means of the New York modified criteria in four patients with primary ankylosing spondylitis. **a** Anteroposterior radiograph shows bilateral grade 3 sacroiliitis with diffuse subchondral sclerosis involving the iliac (antero-inferior) portion of both sacroiliac joints and widening of the joint space, which is more evident on the left side (*arrows*). **b** Axial CT scan shows bilateral grade 2 sacroiliitis with slight spongiosclerosis, which is more evident along the iliac side of sacroiliac joints (*arrows*). **c** Axial CT scan shows bilateral grade 3 sacroiliitis with dense spongiosclerosis along the iliac side of sacroiliac joints (*arrows*) and some left-sided erosions (*small arrows*). **d** Axial CT scan shows bilateral grade 4 sacroiliitis which is characterised by complete bony ankylosis (*arrows*)

of vertebral bodies, with loss of the normal concavity of the anterior vertebral wall ("square" vertebra or "squaring"). "Shiny corners" are the expression of osteitis and appear hypointense on T1-weighted MR images and hyperintense on T2-weighted images (Fig. 3) [18]. As the disease progresses the shiny corners become hyperintense on T1-weighted images due to the post-inflammatory fatty degeneration of bone marrow. The chronic inflammation at the disco-vertebral junction determines the onset of an osteoproliferative process with formation of syndesmophytes (Fig. 4), which differ from osteophytes in their vertical course and the absence of associated disc degeneration. In advanced stages the ossification of vertebral (longitudinal, supra- and interspinous) ligaments may occur, leading to ankylosis [5, 19].

The presence of symmetric syndesmophytes along the whole spine (cervical spine is the last rachidian region to be involved) leads to the characteristic "bamboo" spine appearance. In about 8 % of patients with ankylosing spondylitis an extensive inflammatory involvement of the intersomatic disc and adjacent vertebral endplates may occur, the so-called Andersson spondylodiscitis [20]. On MRI examination spondylodiscitis is characterised by a diffuse hypointense signal on T1-weighted images involving the intersomatic disc and adjacent vertebral endplates. It appears hyperintense on fluid-sensitive sequences and shows significant enhancement after intravenous administration of Gadolinium-based contrast agents [7, 21]. Ankylosing spondylitis does not preserve interapophyseal joints, where erosions, sclerosis and progressive ankylosis may develop with formation of a continuous bony pillar due to the fusion of the articular processes of adjacent upper and lower vertebrae [9, 11, 22].

Although ectopic bone formation is a typical finding of ankylosing spondylitis, this pathological condition is also characterised by diffuse osteoporosis and low mineral density of bone, with an increased risk of vertebral fractures (Fig. 5) [22].

Psoriatic spondyloarthritis

Psoriatic arthritis, according to the classification proposed by Moll and Wright in 1973 [23], includes five clinical forms, and one of these (i.e. psoriatic spondylitis) is characterised by sacroiliitis associated with spondylitis; its prevalence is estimated to be approximately 38 % in patients with psoriasis [24]. The main features related to axial involvement are: (a) syndesmophytes that differ from those of ankylosing spondylitis (called "non-marginal

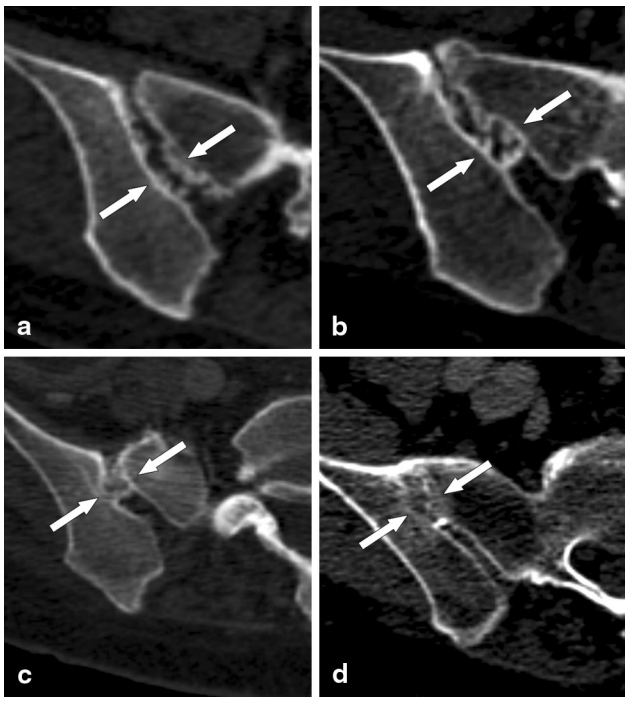

Fig. 2 **a–d** Progressive ossification of the postero-superior ligamentous portion of the sacroiliac joints in four patients with primary ankylosing spondylitis. **a–d** Axial CT images of the right sacroiliac joint show the progressive ligamentous ossification (*arrows*) from early stages (**a**) to the formation of a bony bridge with partial ankylosis of the joint space (**d**)

Table 1 Modified New York criteria for scoring of sacroiliitis

Grade	Radiographic findings
0	No abnormalities
1	Suspicious changes
2	Minimal abnormality—small localised areas with erosions or sclerosis without alteration in the joint width
3	Unequivocal abnormality, with one or more of the following: erosions, evidence of sclerosis, widening, narrowing or partial ankylosis
4	Severe abnormality—complete ankylosis

bulky syndesmophytes" in the English language literature or "para-syndesmophytes" in the Italian literature); (b) involvement of the sacroiliac joints, which may be bilateral and symmetrical, or unilateral (Fig. 6) [25] and (c) sparing or modest involvement of interapophyseal joints.

Syndesmophytes of psoriatic spondyloarthritis are more frequent in the thoraco-lumbar spine and appear as radiopaque elements that are roughly linear or curvilinear, thick, fluffy and parallel to the lateral surface of vertebral bodies and intersomatic discs. They can also tend to coalescence, appearing as a massive osteophytic bone bridge joining two or more contiguous vertebrae, but they rarely

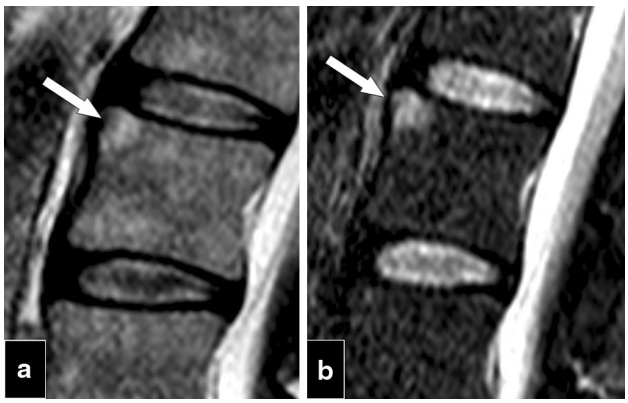

Fig. 3 **a**, **b** 37-year-old man with primary ankylosing spondylitis. **a** Sagittal T2-weighted and **b** corresponding T2-weighted fat-suppressed magnetic resonance (MR) images show a focus of high signal intensity at the antero-superior corner of L1 body (*arrow* in **a** and **b**), which is called "shiny corner". In this early stage conventional radiography usually appears normal

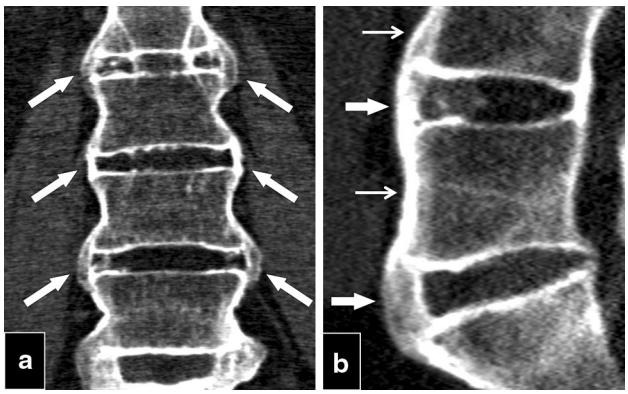

Fig. 4 **a**, **b** 48-year-old man with primary ankylosing spondylitis. **a** Coronal multiplanar reformatted CT image of the thoraco-lumbar spine and **b** sagittal multiplanar reformatted CT image of the lumbo-sacral junction show symmetric and delicate syndesmophytes (*arrows* in **a**, **e**, **b**) and ossification of the anterior longitudinal ligament (*thin arrows* in **b**)

lead to "bamboo" spine, and remain isolated and asymmetric (Fig. 6) [26]. Unilateral asymmetric distribution and separation from the lateral aspect of the vertebral bodies are the main radiological features differentiating psoriatic syndesmophytes (para-syndesmophytes) from those of ankylosing spondylitis and spondylitis associated with inflammatory bowel diseases. According to de Vlam et al. [27], the morphology of syndesmophytes is related to the degree of functionality of the spinal motion segment in which they develop. The motion segment is the smallest functional unit of the spine and is constituted by two adjacent vertebrae with their surrounding soft tissues. If the interapophyseal joints of this segment maintain a normal mobility, the tensile forces acting on the spine prevent the formation of linear and thin syndesmophytes, and the

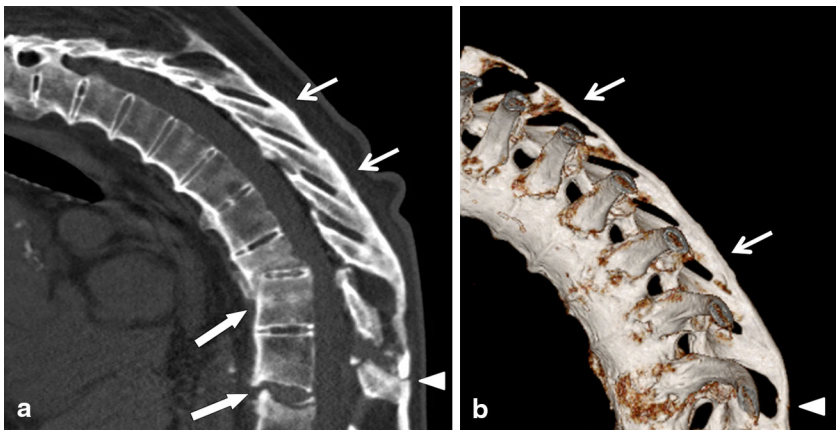

Fig. 5 **a**, **b** Pathological vertebral fracture in a 58-year-old man with ankylosing spondylitis of 21 years' duration after a minor trauma. **a** Sagittal multiplanar reformation and **b** corresponding surface-rendered CT image clearly define the through-and-through fractures (*arrows* in **a**) involving the anterior longitudinal ligament, the intervertebral space, the spinous processes, the inter- and supraspinous ligaments. Note the ossification of interspinous and supraspinous ligaments (*thin arrows* in **a** and **b**) and the fracture line on the latter (*arrowhead* in **a** and **b**)

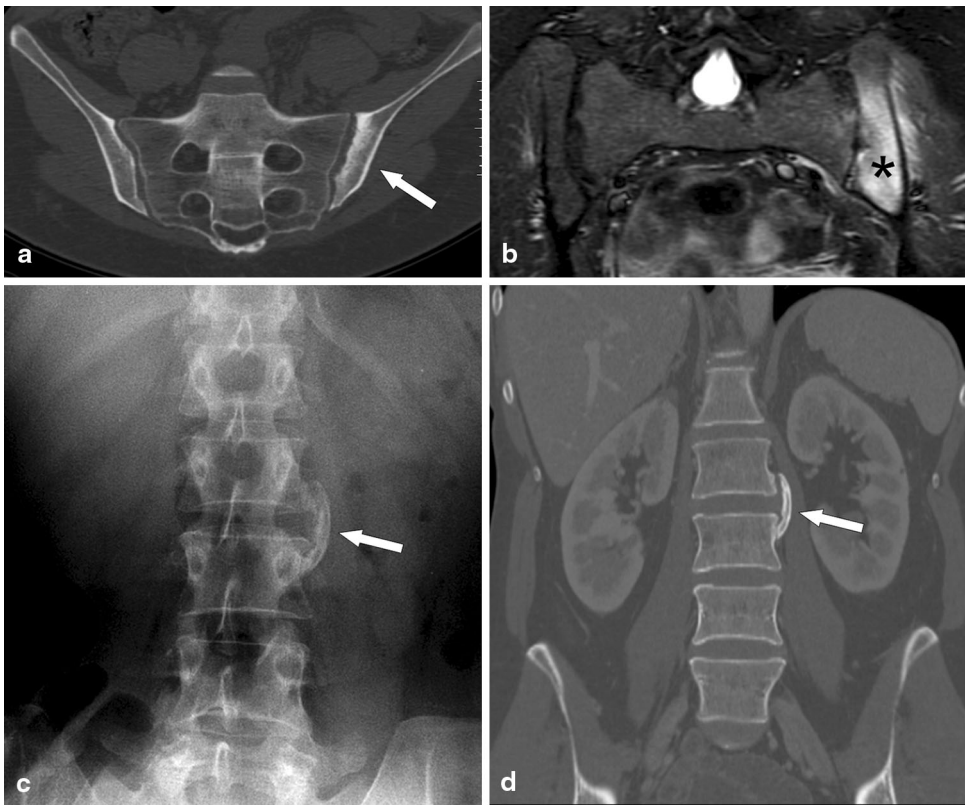

Fig. 6 **a–d** Unilateral sacroiliitis and non-marginal bulky syndesmophyte (para-syndesmophyte) in a 48-year-old woman with psoriatic spondyloarthritis. **a** Coronal multiplanar reformatted CT image shows subchondral bone sclerosis and multiple erosions involving the iliac aspect of the left sacroiliac joint associated with (pseudo-) widening of the joint space (*arrow*). **b** Coronal T2-weighted fat-suppressed MR image demonstrates a large area of bone marrow oedema on the iliac aspect of the left sacroiliac joint (*asterisk*). These findings are typical of active sacroiliitis. **c** Anteroposterior radiograph of the lumbar spine and **d** the corresponding coronal multiplanar reformatted CT image show a left-sided non-marginal bulky syndesmophyte (*arrow* in **c** and **d**); its coarse and wavy appearance is different from the short and thin syndesmophyte of ankylosing spondylitis

paravertebral ossification has a solid and coarse appearance ("non-marginal bulky syndesmophytes", or "para-syndesmophytes"); on the contrary, reduced mobility of the interapophyseal joints leads to the development of thin and linear syndesmophytes. The authors [27] observed a direct relation between ankylosis of interapophyseal joints and the development of thin and linear syndesmophytes (like those of ankylosing spondylitis); on the contrary, they found coarse paravertebral ossification in cases where articular mobility was maintained.

The main radiological findings of psoriatic sacroiliitis, which may also occur in the absence of spondylitis, are: erosions, which are more frequent on the iliac portion of the joint, osteosclerosis, joint space narrowing, and,

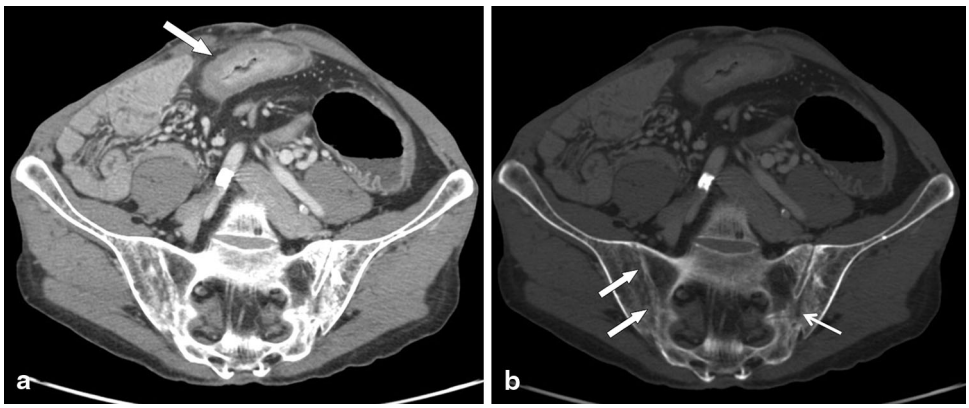

Fig. 7 **a**, **b** 52-year-old man with Crohn's disease and sacroiliitis. **a** Axial CT enterography image shows thickening and mural stratification with mucosal hyper-enhancement of an ileal loop affected by Crohn's disease (*arrow* in **a**). **b** The same axial CT image with bone window shows bilateral grade 4 sacroiliitis according to the modified New York criteria. Note the total bony ankylosis of the right sacroiliac joint (*arrows*) and partial ankylosis (*thin arrow*) of the left sacroiliac joint

rarely, ankylosis [28]. Interapophyseal joints of the cervical spine are frequently involved (in contrast to what happens in the thoraco-lumbar spine), and they may eventually become ankylotic, while anterior atlo-axial subluxation is much more rare [29].

Reactive spondyloarthritis (Reiter's syndrome)

The eponym Reiter's syndrome indicates a clinical syndrome characterised by conjunctivitis, urethritis or gastroenteritis, followed by the onset of aseptic arthritis after an interval of 1–4 weeks. The term reactive arthritis, which has only recently been introduced, is related to the pathogenetic theory of this SpA. According to this theory, an infection of the conjunctival, intestinal or urethral-genital mucosa may represent the trigger for a systemic autoimmune reaction which determines an aseptic inflammatory process involving the axial skeleton or appendicular joints. The involvement of the appendicular skeleton is typically represented by asymmetrical oligoarthritis, often unilateral, which shows a predilection for the large synovial joints of the lower limbs [30, 31]. The involvement of the sacroiliac joints is frequent (5–10 % in the early phase, up to 40–60 % in the advanced stages) and has the same radiological features of psoriatic sacroiliitis [30]. Although rare, also spinal involvement has features similar to those of psoriatic SpA. In fact, a typical early finding is represented by coarse syndesmophytes, which are not distinguishable from those of psoriasis and are located most frequently at the level of the lower three thoracic and the upper three lumbar vertebrae. Involvement of the interapophyseal joints is associated with erosions, osteosclerosis and ankylosis, but these findings are less frequent than those observed in ankylosing spondylitis [31].

Enteropathic spondyloarthritis (enteroarthritis)

Enteropathic spondyloarthritis, or enteroarthritis, is related to the two major chronic inflammatory bowel diseases, ulcerative colitis and Crohn's disease, of which they are considered extraintestinal manifestations. Two types of arthritis have been described: peripheral and axial arthritis [32]. Peripheral arthritis is oligoarticular, asymmetrical, often transient and migratory; both large and small joints can be affected, most frequently in the lower limbs [32]. With regard to axial arthritis, the incidence of sacroiliitis varies from 10 to 20 %, while that of spondylitis from 7 to 12 % [33]. It should be remembered that these figures may underestimate the real incidence of axial inflammatory involvement, which may have a subclinical course that eludes diagnosis, being masked by symptoms of bowel inflammation (Fig. 7). In a recent study [34], the review of 221 CT enterography examinations of patients with histologically confirmed Crohn's disease showed a prevalence of sacroiliitis (up to 24 %) higher than that of the other extraintestinal manifestations. Radiological features of both spondylitis and sacroiliitis are closely similar to those of primitive ankylosing spondylitis [35].

SAPHO syndrome

The acronym SAPHO was first used by Charmot et al. [36] in 1987 to indicate the clinical association of synovitis, acne, pustulosis, hyperostosis and osteitis. According to the more widely accepted pathogenetic hypotheses, SAPHO syndrome has been considered a "reactive osteitis", which represents the consequence, in genetically predisposed

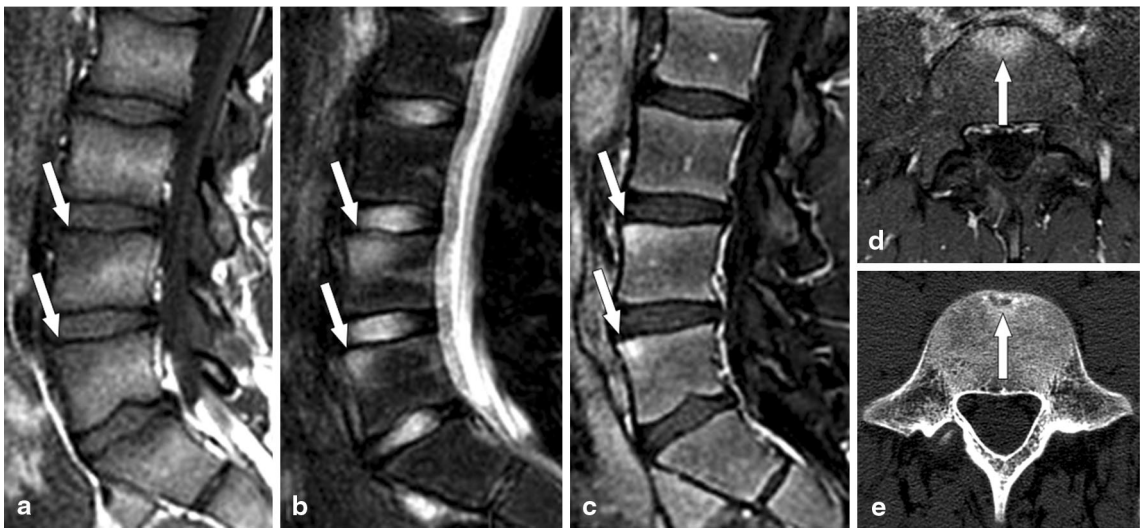

Fig. 8 **a–e** 24-year-old man with palmoplantar pustulosis and low back pain. **a** Sagittal T1-weighted, **b** T2-weighted fat-suppressed, and **c** contrast-enhanced T1-weighted fat-suppressed MR images of the lumbar spine show two signal alterations at the level of the antero-superior corners of L4 and L5 vertebrae (*arrows* in **a**, **b** and **c**). The corner lesions are hypointense on the T1-weighted image, hyperintense on the T2-weighted fat-suppressed image, and enhance after the i.v. administration of contrast material. The L4–L5 intervertebral disc is preserved. **d** Axial T2-weighted fat-suppressed MR image passing through L5 body confirms the corner lesion (*arrow*) and **e** the corresponding axial CT scan clearly demonstrates the corner erosion of the vertebral endplate surrounded by spongiosclerosis (*arrow*)

individuals, of a nonspecific and inadequate immune response, triggered by infection with some microorganisms [37]. SAPHO is currently considered a rare disease with an incidence of 1 in 10,000 individuals, although this figure probably underestimates the real incidence of the disease, because of the wide spectrum of clinical manifestations and the lack of valid diagnostic criteria. The syndrome shows a slight preference for females with a mean age at diagnosis of 28.6 years, and a chronic relapsing and remitting course.

Many clinical features of SAPHO syndrome, including involvement of the axial skeleton and entheses, seronegativity for rheumatoid factor, and the association with some varieties of psoriasis and enteroarthritis, suggest a link with SpA, even if a significant correlation with histocompatibility antigen HLA-B27 has not yet been clearly demonstrated [38]. According to the criteria defined by Kahn et al. [39], SAPHO syndrome should be suspected in patients with pustular skin lesions and musculoskeletal pain caused by an osteoarticular aseptic inflammation. The bone involvement concerns mainly the sterno-costo-clavicular region (70–90 %), the spine (30 %) and the sacroiliac joints (13–52 %) [38]. The imaging findings may vary through the different stages of the disease. In the early phase, osteitis appears as focal osteosclerosis associated with erosive changes of the bone cortex and oedematous thickening of the adjacent soft tissues. Subsequently, hyperostosis (diffuse osteosclerosis with increased bone volume) and synovitis develop. The latter can be primary or secondary to the intra-articular extension of an adjacent osteitis. Synovitis appears more frequently in the sacroiliac joints, where involvement is often unilateral, and in the sterno-cost-clavicular joints [38]. Laredo et al. [40] have demonstrated a prevalent involvement of the anterior vertebral corners of the thoraco-lumbar spine (Fig. 8) [41].

Conclusions

Bone marrow oedema, osteoproliferative changes, erosions and osteosclerosis are the main radiological findings of SpA, and multimodal imaging allows a complete demonstration of the inflammatory lesions in their different stages of progression. The diagnosis of SpA and its treatment must be early to avoid structural damage and functional impairment, and the role of MRI is particularly important for this purpose, especially after the introduction in the clinical practice of new effective drugs such as anti-TNFα. Radiologists, to have a correct diagnostic approach, have to know the patho-anatomical basis of the radiological findings and the main classification and scoring systems for musculoskeletal lesions.

Conflict of interest Francesco Paparo, Matteo Revelli, Alessia Semprini, Dario Camellino, Alessandro Garlaschi, Marco Amedeo Cimmino, Gian Andrea Rollandi, Antonio Leone declare no conflict of interest.

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