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MUSKOLOSKELETAL IMAGING

INVITED REVIEW

Pivotal role of the synovioentheseal complex in the imaging of arthritis and rheumatic diseases

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ABSTRACT

Imaging plays a key role in the diagnosis and management of rheumatic diseases. Although joints and periarticular tissue are commonly involved in rheumatic diseases, entheses further away from joints, such as in the Achilles tendon or plantar fascia insertion onto the calcaneus, as well as skin and subcutaneous tissue, are among other -sometimes overlooked- targets. The link of enthesitis, which describes inflammation at the insertions of ligaments, tendons, or joint capsules, with spondyloarthritis (SpA) was established just before the turn of the century as a characteristic feature based on imaging studies with histopathological correspondence. To highlight the association between enthesitis and synovitis in SpA, the anatomical unit of the "synovioentheseal complex" (SEC) and the concepts of "functional enthesis" and "articular enthesis," apart from the better known "insertional enthesis," were introduced to encompass other inflammatory lesions associated with SpA. Studies from the last two decades revealed the involvement of the SEC in rheumatic and non-rheumatic disorders with different pathogeneses. Although such involvement is sometimes distinctive, it does not necessarily point to a specific diagnosis at other times. Nevertheless, the potential of SEC inflammation in the differentiation of SpA from other forms of arthritis remains important. The purpose of this review was to provide essential information concerning the involvement of the SEC in the diagnosis of rheumatic diseases and arthritis, focusing on imaging characteristics.

KEYWORDS

Arthritis, enthesitis, synovioentheseal complex, magnetic resonance imaging, ultrasonography

Rheumatic diseases, including arthritis, are common and disabling health problems.[1] In the last few decades, the widespread use of disease-specific medications that carry the promise of treating arthritis at earlier phases, before deformities develop, has bolstered the importance of reaching a correct diagnosis.[2] Imaging-based diagnosis in arthritis relies mainly on the distribution across the body of inflammatory soft tissue and bone lesions and structural bone changes.[2] Algorithms using an imaging-based diagnosis of arthritis that historically relied on radiographs, which mostly show chronic lesions at joints and bones, usually prioritize proximal or distal and axial or appendicular skeletal distribution.[3] However, there are many challenging instances in daily practice whereby such distribution-based generalizations simply do not work. The additional information that cross-sectional imaging provides is crucial yet sometimes confusing with distribution-based algorithms or in the case of subtle findings. Therefore, it is imperative for radiologists to know where to look and what to search for on cross-sectional imaging to both identify the presence of pre-radiographic findings of arthritis and attempt to classify the disease. In other words, factoring the characteristic involvement of some specific microanatomic sites, such as "the enthesis organ," which we explain below, may take precedence over the more generalized, distribution-based algorithmic approach to diagnosis, especially when cases that do not conform to the existing algorithms are encountered.

The term "enthesopathy," which describes inflammation at the insertions of ligaments, tendons, joint capsules, or fasciae to bone, was first used in 1966.[4] Although the link between enthesitis and spondyloarthritis (SpA) has been mentioned thereafter in several studies, it

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was just over two decades ago that enthesitis was highlighted as a characteristic feature of SpA in the light of magnetic resonance imaging (MRI).[5,6] Based on high-resolution (HR) MRI and histological studies, microanatomical detailed analyses of enthesis culminated in the concept of the "enthesis organ". The latter not only involves a group of related tissues at the insertional sites across the bones but also encompasses the fibrocartilaginous periosteal or tendinous/ligamentous lining that facilitates the gliding of tendons/ligaments during motion.[7,8] In 2007, to better delineate the association between enthesitis and synovitis in SpA, McGonagle et al.[9] introduced the concept of an anatomical unit dubbed the "synovioentheseal complex" (SEC). According to this concept, the normal fibrocartilage related to an enthesis is critically dependent on the immediately adjacent synovium.[9] Currently, based on studies from the last two decades, it has been established that the SEC is involved in various ways in several rheumatic and non-rheumatic disorders with different pathogeneses, somewhat limiting its value as a discriminating factor favoring rheumatic versus non-rheumatic diseases.[10-17] Nevertheless, the potential of SEC inflammation in the differentiation of SpA from other forms of arthritis remains important, given the differences in the treatment of SpA versus other forms of inflammatory arthritis. The purpose of this review is to provide essential information on SEC involvement in the diagnosis of rheumatic diseases and arthritis, focusing on imaging characteristics.

Main points

- As a major target site of involvement in many forms of rheumatic diseases, the synovioentheseal complex (SEC) needs to be a primary focus on imaging-based assessment of arthritis.
- Although the gross anatomic distribution has long been a primary consideration in the radiography-based differential diagnosis of arthritis, the ascertainment of SEC involvement may be a better approach in target-site prioritization on high-resolution (HR) cross-sectional imaging.
- Entheseal bone marrow edema (suggesting SEC involvement) is more common in spondyloarthritis patients compared with rheumatoid arthritis and osteoarthritis patients.
- Focused or HR magnetic resonance imaging that incorporates new technological advances is the best imaging tool for depicting the entire SEC (i.e., osseous as well as soft tissue components).

The anatomical rationale behind the term "synovioentheseal complex"

Enthesis, which means "insertion" in ancient Greek, refers to the locations where tendons, ligaments, fascia, or articular capsules attach to a bone. There are two types of entheses: fibrous and fibrocartilaginous. Fibrous entheses attach tendons of large muscle bodies directly to a broad surface of diaphysis and metaphyses of long bones, where the bone cortex is thick.[6,12] Fibrocartilaginous entheses, which are the main target of inflammatory lesions in SpA, comprise the majority of entheses in the body. Classic fibrocartilaginous entheses are located often in the vicinity of synovial joints, have a unique composition that allows joint movement, and attach tendons to epiphyseal and apophyseal long bone ends, where the bone cortex is thin.[6,12] In addition to classic fibrocartilaginous enthesis, the concepts of "functional" and "articular" fibrocartilaginous entheses related to inflammatory lesions of SpA have been introduced.[18]

Fibrocartilaginous entheses, which, in their classical form, serve as a functional unit in the dissipation of mechanical stress at the soft tissue-bone interfaces, are made up of the following subunits: distal tendon, ligament, or fascia; sesamoid and entheseal fibrocartilage of the tendon; fat pads; bursae; synovium; periosteal fibrocartilage; and the bone. This overall arrangement of contiguous structures is also known as the "enthesis organ". The most common fibrocartilaginous entheses that are targeted by SpA are the calcaneal insertions of the Achilles tendon and plantar fascia, and patellar, lateral humeral epicondylar, and greater trochanteric insertions of the quadriceps, common extensor, and hip abductor tendons, respectively (Figures 1 and 2).[19,20]

The term "functional enthesis" is coined to define the fibrocartilage interface between two musculoskeletal infrastructural parts that absorb friction-related stress during activity.[2] In other words, fibrocartilaginous entheses exist not only at the tendon attachment sites but are also found in friction interfaces of tendons versus bones, such as the extensor digitorum tendon and central slip of the extensor tendon crossing over the metacarpal head and the proximal interphalangeal joint, respectively, or the peroneus longus tendon wrapping around the peroneal trochlea of the calcaneus and cuboid (the latter is referred to as the "cuboid pulley") (Figure 3). Other sites of friction interface are pulleys on the volar surfaces of fingers and toes versus the tendon sheaths that they wrap around, whereby finger pulleys show fibrocartilaginous characteristics at their inner gliding layer (Figure 4).[18,21-23]

The "articular" form of fibrocartilaginous enthesis is found in synovial joints that are lined by fibrocartilage as well as hyaline cartilage, such as the sacroiliac joints (SIJs), symphysis pubis, acromioclavicular, temporomandibular, and manubriosternal joints.[18,24-26] Fibrocartilage/hyaline cartilage proportions in some of these joints change during skeletal maturation.[18,24-26] The articular surface at the iliac side of the SIJ consists of hyaline and fibrous cartilage, whereas the

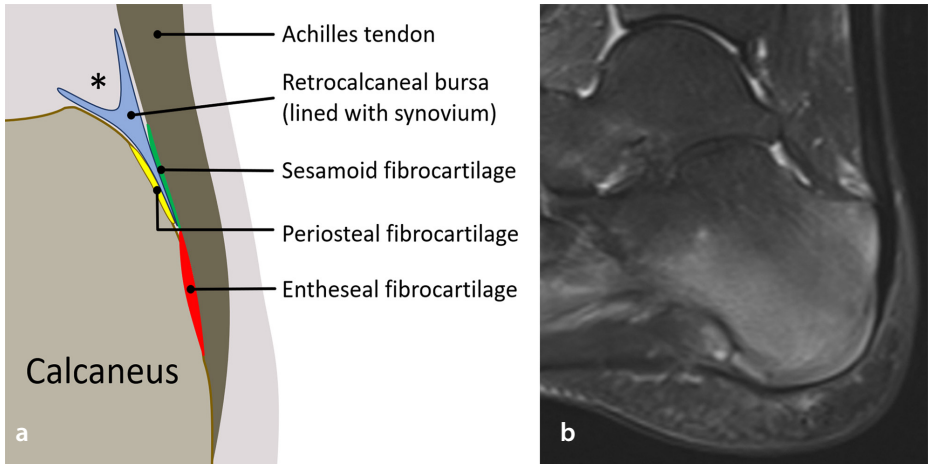

Figure 1. Synovioentheseal complex in a classic fibrocartilaginous enthesis in the ankle. **(a)** Schematic illustration of a midsagittal ankle section through the Achilles tendon shows the synovioentheseal complex including subunits of the entheseal organ: distal tendon, sesamoid (green), and entheseal (red) fibrocartilages of the tendon, periosteal fibrocartilage (yellow) of the calcaneus, retrocalcaneal bursa lined with synovium (blue), and the surrounding fat pad (asterisk). **(b)** Sagittal fat-saturated T2W magnetic resonance image shows Achilles tendon enthesitis as well as insertional plantar fasciitis, which also is a type of enthesitis, in a 16-year-old girl with enthesitis-related arthritis. Note retrocalcaneal bursitis and extensive bone marrow edema related to enthesitis.

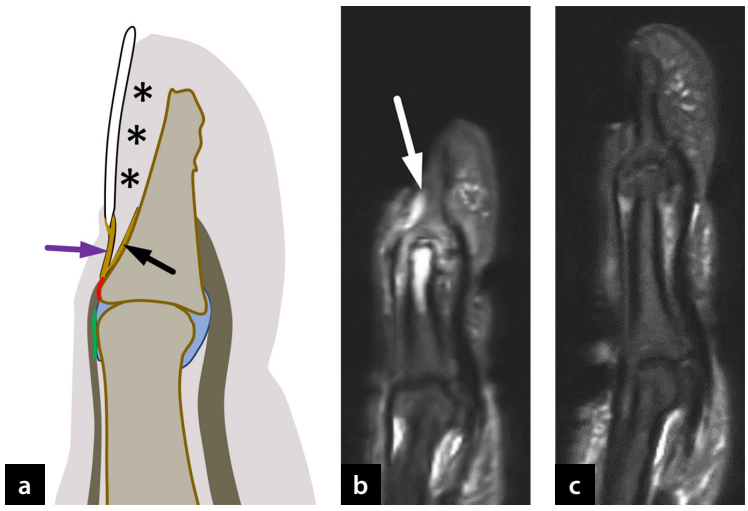

Figure 2. Synovioentheseal complex in the classic fibrocartilaginous enthesis of extensor tendon with its nail root extensions. **(a)** Schematic illustration of a midsagittal distal finger section shows sesamoid fibrocartilage (green) and entheseal fibrocartilage (red) of the extensor tendon with its extensions to the nail root (superficial lamina, purple arrow) and the dorsal distal phalangeal periosteum (deep lamina, black arrow). Asterisks denote the nail bed. **(b, c)** Sagittal fat-saturated T2W magnetic resonance images of the second **(b)** and third **(c)** fingers in a 58-year-old woman with psoriatic arthritis reveal extensor tendon enthesitis of the second finger characterized with peritendinous, nail root, and bed inflammation (**b**, arrow), extensive periarticular osteitis of the middle and distal phalanges and synovitis of the second distal interphalangeal joint in addition to uniform joint space narrowing and mild periarticular bone proliferation. Extensor tendon enthesis, nail root, and bed of the third finger **(c)** are normal.

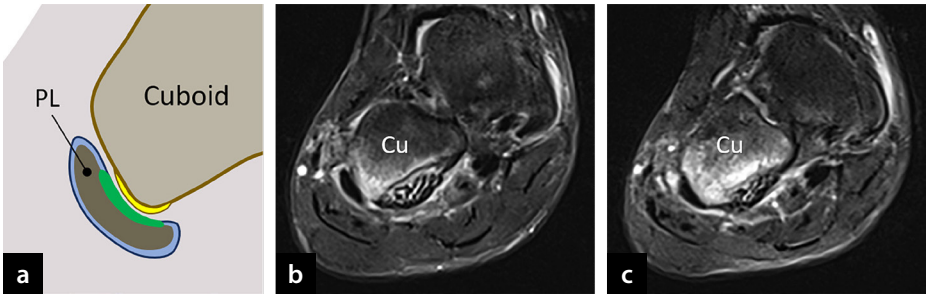

Figure 3. Synovioentheseal complex in a functional enthesis at a tendon–bone friction site. **(a)** Schematic illustration of a midfoot coronal section shows the peroneus longus tendon (PL) enveloped in its synovial tendon sheath. The sesamoid fibrocartilage (green) at the peroneus longus tendon facing the cuboid and the corresponding periosteal fibrocartilage (yellow) at this site constitute a functional enthesis. **(b, c)** Consecutive coronal fat-saturated T1W post-contrast magnetic resonance images through midfoot show functional enthesitis at the cuboid pulley in a 16-year-old girl with enthesitis-related arthritis. Cu, cuboid.

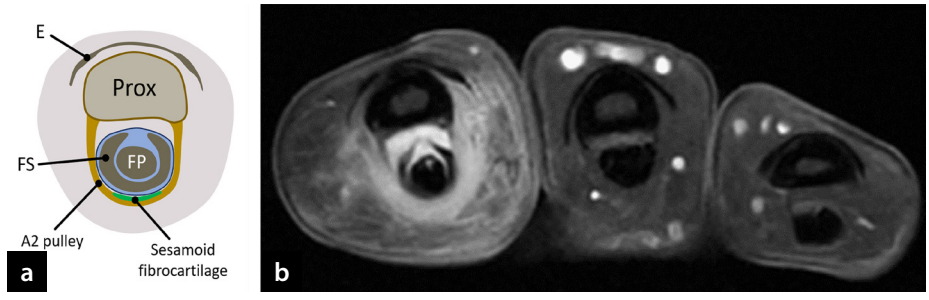

Figure 4. Synovioentheseal complex in a functional enthesis at the finger pulley-flexor tendon gliding site. **(a)** Schematic illustration of a transverse section through the mid-level of a proximal phalanx shows the extensor mechanism (E), proximal phalanx (Prox), superficial (FS), and deep (FP) flexor tendons, which are enveloped in a synovial sheath (blue). Phalangeal insertions of pulleys are classic entheses. The sesamoid fibrocartilage at the A2 pulley (green) facing the flexor tendon group (which is a friction site) is a functional enthesis. **(b)** Transverse fat-saturated T1W post-contrast magnetic resonance image shows functional enthesitis of A2 pulley with accompanying subcutaneous inflammation, dactylitis, in a 34-year-old woman with psoriatic arthritis.

sacral side joint surface is covered exclusively with hyaline cartilage (Figure 5). Articular hyaline and fibrous cartilage blend with the strong fibrous tissue of surrounding ligaments through a transitional zone of fibrocartilage (i.e., fibrocartilaginous enthesis). On the iliac side of the SIJs, the articular hyaline and fibrous cartilage are thinner compared with the pure hyaline cartilage found on the sacral side. At the iliac side, the abundance of fibrocartilaginous components, which are considered to be attacked first in SpA, as well as the relative thinness of the articular cartilage, results in a tendency for erosions in sacroiliitis to occur earlier (and more prevalently) on the iliac (rather than the sacral) side of the joint (Figure 5); progression to the sacral side usually occurs later. Interestingly, but not surprisingly, diskovertebral joints are also considered "articular (fibrocartilaginous) entheses," since disks contain fibrocartilage and are juxtaposed to the hyaline end-plate cartilage of the vertebral bodies (without any synovium involved). It is not coincidental that inflammatory lesions of SpAs tend to involve diskovertebral junctions as well as vertebral corners (classic entheses).[18] A summary of fibrocartilaginous enthesis subtypes and examples of SEC sites across the body are shown in Table 1.

In healthy conditions, the synovial subunit of an enthesis organ lubricates and nourishes the avascular fibrocartilage and provides immunity to enthesis, just as the neighboring bone marrow does when needed. Cytokine-based pathophysiological pathways that drive the disease processes involving the SEC are a prime area of arthritis research.[27,28] However, these are beyond the scope of this review. Any pathological process affecting the enthesis organ, including inflammation, metabolic disorders, trauma, or degeneration, is called "enthesopathy" and may manifest as adjacent synovitis and tenosynovitis or bursitis (Figure 6). However, the microanatomical location of the epicenter of inflammation within a single joint, either the synovium or the entheseal organ, may be different in the early phase of the disease, particularly in cases of inflammatory arthritis. In the later phases, both types of these closely located inflamed structures seem to be affected. This pathophysiologic fact, which is grounded in anatomy, underscores the crucial importance of using HR MRI to detect the epicenter of inflammation in early phases.[2,13,29]

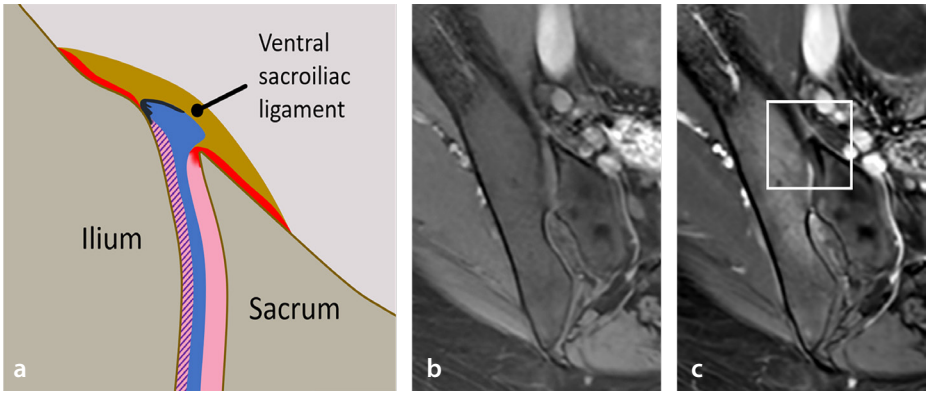

Figure 5. Synovioentheseal complex (SEC) in the articular enthesis at the sacroiliac joint. **(a)** Schematic illustration of an oblique axial section through the distal third of the sacroiliac joint shows entheseal fibrocartilages (red) of the ventral sacroiliac ligament (VSIL) at the sacral and iliac bone insertions and at the transition zone where hyaline cartilage of the sacral side (pink) blend with the VSIL. The articular cartilage on the iliac side is thinner than on the sacral side and consists of a mixture of hyaline and fibrous cartilages (shown shaded in pink and purple diagonal stripes, respectively), and at the joint periphery it merges with the periosteum and is covered by the joint synovium (deep blue). **(b, c)** Transverse oblique fat-saturated T1W pre- **(b)** and post-contrast **(c)** magnetic resonance images (MRI) show linear fibrocartilaginous enhancement at the iliac joint surface with subchondral osteitis and enhancement of the VSIL compatible with active sacroiliitis (the white rectangular box in c roughly corresponds to the area drawn in **a)**. Although the large field-of-view MRI does not distinctively depict each subunit of the SEC, it nevertheless shows the involvement of this complex.

Table 1. Synovioentheseal complex sites across the body

Site	Characteristic	Examples*
Classic fibrocartilaginous enthesis	Tendon, ligament, fascia, or joint capsule attachments to bones	Achilles tendon (Figure 1) Plantar fascia-calcaneus insertion Supraspinatus tendon Extensor tendon's nail root extension (Figure 2) Peroneus brevis tendon-5th metatarsal insertion Collateral ligament-phalanx insertions
Functional enthesis	At friction interfaces where tendons, pulleys, or retinacula wrap around another structure	Cuboid pulley (Figure 3) Extensor tendon-metacarpal head interface Finger pulleys (Figure 4)
Articular enthesis	In synovial joints with a fibrocartilage-as well as hyaline cartilage-lining	Sacroiliac joint (Figure 5) Temporomandibular joint Acromioclavicular joint Sternoclavicular joint

*Please refer to the figures mentioned in parentheses for sample cases.

Imaging approach to the synovioentheseal complex

Radiographs are generally the first-line imaging modality used to assess patients suspected of having arthritis. However, when it comes to enthesitis, radiographs may only reveal late signs of enthesopathy, such as the presence of new bone formation (enthesophytes and syndesmophytes), erosions, and sclerosis (e.g., "shiny corner" lesions of vertebrae). In certain sites, such as the Achilles or patellar tendon insertions, which are surrounded with fat tissue, subtle enthesitis-related soft tissue edema and increased thickness of the tendon may be detectable, especially if a comparative radiograph of the corresponding normal side is available. In terms of differential diagnosis of arthritis, radiographs still maintain their diagnostic yield in structural (i.e., chronic) lesions.[30]

Ultrasonography (US) is particularly valuable for small and peripheral joints, with its widespread availability, lack of ionizing radiation, and HR probes. B-mode and Doppler US (color and power) both depict the morphological features and vascularity of the enthesis and may aid in the diagnosis and treatment response evaluation. According to the Outcome Measures in Rheumatology (OMERACT) US Working Group, US features of enthesitis were grouped into lesions as either active inflammatory (hypoechogenicity, increased thickness with morphologic abnormalities and Doppler activity of the enthesis) or structural (insertional bone erosions, intratendinous calcifications, and enthesophytes).[31] Ultrasound is disadvantageous for large and deep joints and the axial skeleton, where MRI is the preferred modality.

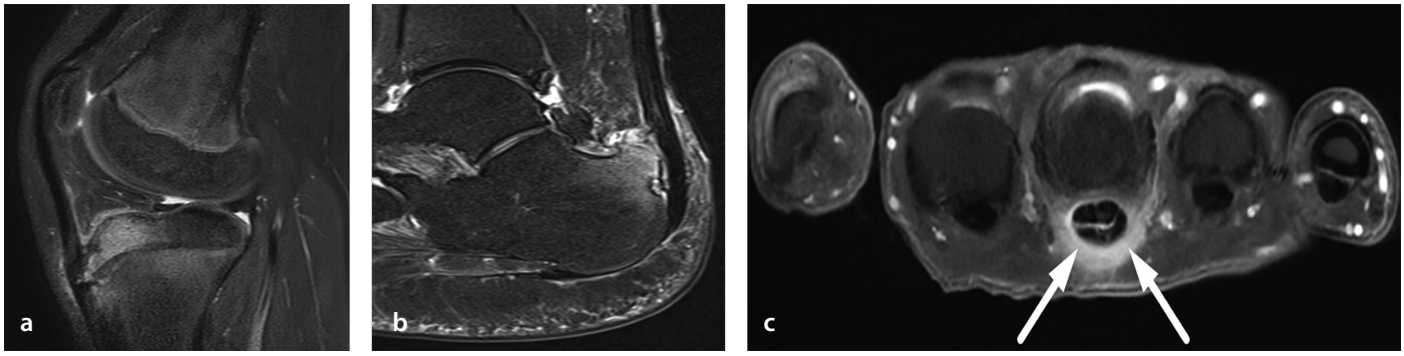

Figure 6. Synovioentheseal complex inflammation in chronic overuse, degenerative, and traumatic injuries. **(a)** Sagittal fat-saturated proton density-weighted magnetic resonance image (MRI) of a 12-year-old boy with Osgood-Schlatter disease, which is an overuse injury, reveals distal patellar tendon enthesopathy characterized by intra- and peritendinous hyperintensity, subcortical bone marrow edema at the entheseal insertion, and deep infrapatellar bursitis. **(b)** Sagittal fat-saturated T2W MRI of a 54-year-old woman with Haglund syndrome shows Achilles tendon enthesopathy characterized by intra- and peritendinous hyperintensity, subcortical bone marrow edema, and erosion at the entheseal insertion, and retrocalcaneal bursitis with Haglund deformity of the calcaneus. **(c)** Transverse fat-saturated T1W post-contrast MR image of a 44-year-old man with a 1-month history of pain following an episode of lifting luggage with a single finger shows traumatic A1 pulley enthesopathy (arrows) with mild flexor tenosynovitis.

MRI, with its potential to visualize the entire enthesis organ (including its subcortical medullary bone component), is the best imaging modality for enthesitis involving both the axial and peripheral skeleton. An MRI examination to assess inflammatory and structural lesions at entheses should include at least short tau inversion recovery, T2-weighted fat-saturated images, or T1-weighted fat-saturated images with and without gadolinium enhancement.[32] According to the OMERACT Heel Enthesitis MRI Scoring System, MRI features of enthesitis were grouped into lesions as either active inflammatory (intratendinous and/or peritendinous hyperintensity, subcortical bone marrow edema at the entheseal insertion, retrocalcaneal bursitis, and tendon thickening) or structural (insertional bone erosions and enthesophytes).[32] Advancements in hardware and software over the past few decades have enabled HR MRI of small joints, which, in turn, has enhanced understanding of the pathogenesis of psoriatic arthritis (PsA) by providing insights into its microanatomical aspects. HR MRI also enabled the visualization of different types of enthesitis and discrimination of inflammatory arthritis.[2,8,33-36] The term "HR MRI" does not imply employing a specific set of parameters for imaging small joints and body parts. Rather, it describes an attempt to reduce slice thickness and fields of view (by using the most appropriate surface coils and up-to-date software) to such a degree that the signal-to-noise ratio of images and acquisition times remain within an acceptable limit while ensuring patient comfort and compliance.

Since SIJs are an articular enthesis, as explained above, sacroiliitis is a type of enthesitis that manifests itself on imaging as contrast enhancement at the joint capsule and within the articular fibrocartilage (Figure 5). Inflammation may extend continuously from the joint to the pericapsular tendon and ligament attachments.[25] For both active inflammatory and chronic structural lesions of sacroiliitis, MRI is indispensable. Osteitis, which is a cardinal finding of the Assessment of SpondyloArthritis International Society classification criteria for axial SpA,[37] represents an extension of inflammation of articular fibrocartilage to the subcortical bone marrow of the SIJ.[25] Chronic sacroiliitis is characterized by subcortical marrow fat metaplasia, erosions, subchondral sclerosis, transarticular bone bridges, and bone buds.[37]

The developmental process involving SIJs has a bearing on the imaging assessment of SpA in children. The sacrum is formed by the fusion of numerous primary and secondary ossification centers throughout early childhood and adolescence. Predominantly on the sacral side, the metaphyseal-equivalent high signal intensity is typically symmetrical and results from ossifying epiphyseal cartilage and the underlying newly formed subchondral bone, which may be misinterpreted as osteitis. Distinctly in children, the ossifying subchondral bone plate shows partial absence of the cortical black line and frequently appears irregular and blurred at the iliac side of the S1 level, mimicking erosions.[38]

As with sacroiliitis, the imaging assessment of enthesitis in children can also be challenging due to the pitfalls related to the ongoing development of the immature skeleton.[38] In children, entheseal radiographic findings within the bone occur very late in the disease. In particular, enthesophytes are seen less frequently in children than in adults.[39] In evaluating enthesitis in growing children, physiological cortical irregularities at the bone-cartilage interface and the presence of normal intra-/peritendinous vascularity detected by power Doppler US (PD US) pose challenges that are not typically encountered in adults.[40] Nevertheless, a standardized US definition of enthesitis in children is not available, and observers have to resort to a combined assessment of gray-scale and PD US findings while considering these physiological findings.[41]

Depending on the involved anatomical structure, enthesitis in the axial skeleton is grouped as inflammatory lesions of either the vertebral body or the remainder of a vertebra. Anterior or posterior vertebral corner inflammatory lesion, vertebral endplate inflammatory lesion (which is called "aseptic spondylodiskitis"), and thoracic lateral inflammatory lesion (which is at the costovertebral joint) involve the vertebral bodies. Other inflammatory lesions involve the facet and costotransverse joints or spinal ligaments (ligamentum flavum, interspinous, and supraspinous ligaments). All those inflammatory lesions show edema/contrast enhancement of bones and/or adjacent ligaments and/or synovium. In chronic phases of SpA, structural lesions occur, including erosions, focal fat metaplasia and sclerosis of vertebral corners, bone spurs/syndesmophytes at the attachment sites of annulus fibrosus, and ankylosis of vertebrae with bridging syndesmophytes and/or bony fusion across the intervertebral disks or facet and costovertebral joints.[42]

Whole-body MRI, which came of age in the last decade in terms of the extent of practical applications, presents the potential advantage of detecting multiple sites of entheseal involvement in a single imaging session.[43]

Synovioentheseal complex involvement in different forms of arthritis and rheumatic diseases

This section describes the current knowledge of SEC involvement in a wide spectrum of rheumatic diseases. The entities covered here encompass all conditions whereby SEC involvement has so far been described in the literature.

Spondyloarthritis with a highlight on psoriatic arthritis

SpA refers to a group of rheumatic diseases primarily affecting the spine and peripheral joints. PsA is one of the main forms of SpA that affects the skin [psoriasis (PsO)] as well as the joints. The established primary lesion in PsA is enthesitis, reported in 30%–50% of patients with PsA.[30] In contradistinction to other forms of SpA, PsA tends to involve in particular the small joints of the hands and feet, resembling the joint involvement seen in different forms of arthritis, such as rheumatoid arthritis (RA) and osteoarthritis (OA).[2,12,34,44] Although numerous studies utilizing HR MRI and US have identified the SEC as the epicenter of inflammatory lesions in PsA, conflicting results have also emerged suggesting that SEC inflammation may not be specifically linked to PsA.[8,29,33,35,36,44-48]

PsA tends to involve distal interphalangeal (DIP) joints where OA is common, and both of these arthritis forms may present with bone proliferation and inflammation, causing diagnostic challenges.[44] Although inflammatory changes of ligament, tendon, enthesis, and adjacent bone are common both in PsA and OA, HR MRI studies have shown that they are much less prominent in OA than in PsA.[8] In a detailed microanatomical analysis of inflammatory lesions with HR MRI and histology, the epicenter of inflammation in DIP joints is at the extensor tendon enthesis including the nail root, as a part of the enthesis organ, in PsA rather than patients with OA (Figure 2).[33] Nail bed (as well as nail root) involvement with active inflammation has been shown in patients with PsA but without PsO.[34,49] The corollary here is that the nail bed, as well as the nail root, may also be considered part of the DIP extensor tendon entheseal organ, which is a SEC. A re-

cent study comparing PsA with PsO and OA by utilizing US, MRI, and radiography found no imaging variable as a positive predictor for PsA.[44] Nevertheless, the major limitation of that study was patient selection bias, because a considerable number of patients with PsA and PsO had been receiving disease-modifying anti-rheumatic drugs, and this may have caused subdued inflammatory imaging findings.[44]

Another characteristic feature of PsA is dactylitis (or "sausage" digits), which is described in approximately 30%–40% of patients with PsA.[2,30] Studies performed with HR MRI and US have demonstrated that dactylitis is a combination of multiple "digital polyenthesitis," featuring "classic" enthesitis at the collateral ligament and extensor tendons, and "functional" enthesitis at other sites. Functional enthesitis in this context comprises inflammation of the extensor tendons (and/or central slips of extensor tendons) where they cross over bones, abnormal enhancement of volar and plantar plates, microenthesopathy of flexor tendon pulleys/flexor sheaths, and edema/inflammation of the surrounding soft tissue.[35,36,45] Interestingly, although synovitis is the epicenter of inflammation in patients with RA with generalized involvement of hand joints, enthesitis may also be involved. This is because synovitis may spread to involve entheses of collateral ligaments or pulleys, particularly in small joints where anatomic structures are very close (Figure 7).[36] In challenging cases, determining the dominant inflammatory lesion pattern in conjunction with clinical characteristics and diagnostic laboratory tests can help make a decision. Another important differential diagnosis of digital enthesitis is traumatic or overuse injury of tendons or ligaments, whereby history of trauma, localized findings (e.g., isolated pulley enthesitis) without arthritis, and the presence of characteristic bone deformity (e.g., Haglund syndrome) are helpful clues (Figure 6).

Extensive bone marrow edema at the phalangeal or metacarpal diaphyses (away from entheses or subchondral bone) favors PsA over other forms of arthritis (Figure 2).[2] Moreover, hand or feet bone marrow edema in RA and OA tends to be more confined to the capsular attachments and subchondral areas, respectively.[19,50] In large joints, bone marrow edema can be more easily demarcated as entheseal or perientheseal, allowing more sensitive evaluation. Entheseal bone marrow edema (suggesting SEC involvement) is more common in patients with SpA compared with patients with RA or OA. In contradistinction to SpA, both synovitis and perientheseal bone erosions are more prevalent in RA.[46] Although a study has reported conflicting results in this regard,[48] specification of entheseal and perientheseal locations was lacking, and the sample size was relatively smaller.

Erosions, calcifications, and new bone formation are late-stage findings of enthesitis, and the latter is a key distinguishing feature seen in PsA but not in RA. New bone formation in PsA can be in the form of an enthesophyte or of periosteal fluffy appearance. The combination of bone erosion and proliferation at an enthesis gives the characteristic appearance of "mouse ears" on the distal surface of the interphalangeal joint, with frequent involvement of the DIP joints.[2]

In early phases, although asymmetry of sacroiliitis and/or cervical predilection of spinal entheseal inflammatory lesions favor axial PsA involvement, generally there is no additional distinctive feature pointing to a subtype of SpA. However, in late phases, structural lesions show distinguishing characteristics allowing the differential diagnosis of axial PsA and ankylosing spondylitis (AS). Axial PsA presents less with sacroiliitis (which is usually asymmetrical) and more with chunky syndesmophytes, which are predominant at the cervical spine, whereas syndesmophytes in AS are marginal, symmetrical, and well-delimited.[51]

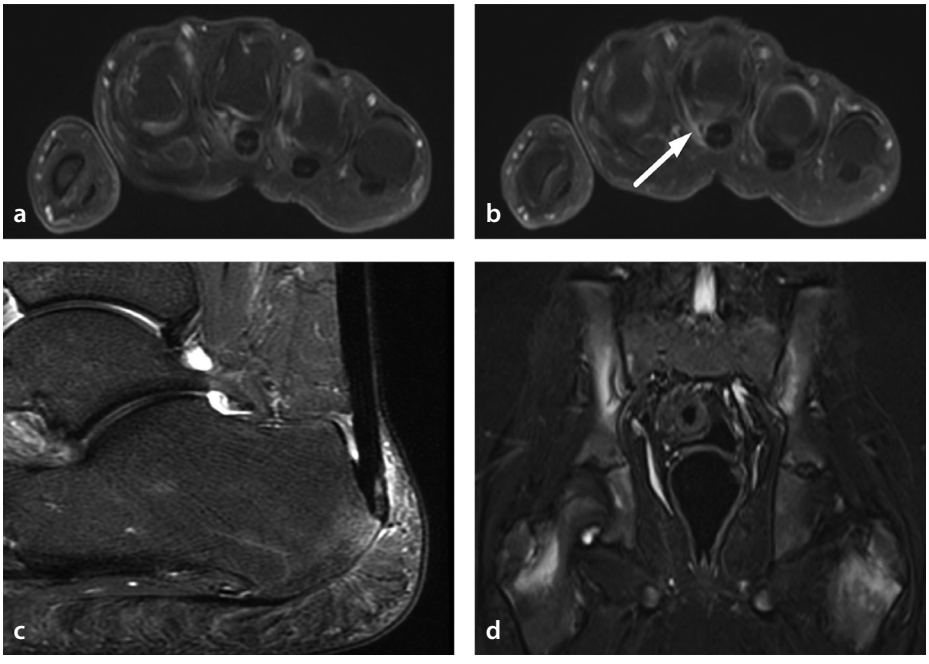

Figure 7. Synovioentheseal complex inflammation in rheumatic diseases other than spondyloarthritis. **(a, b)** Transverse fat-saturated T1W post-contrast magnetic resonance images (MRI) of a 58-year-old woman with seronegative rheumatoid arthritis show mild second through fourth metacarpophalangeal joint synovitis along with A1 pulley enthesitis of the third finger (**b**, arrow). **(c)** Sagittal fat-saturated T2W MR image of a 54-year-old woman with Sjögren syndrome shows Achilles tendon enthesitis characterized by intra- and peritendinous hyperintensity, subcortical bone marrow edema at the entheseal insertion, and retrocalcaneal bursitis. **(d)** Coronal short tau inversion recovery MR image of a 12-year-old boy with chronic non-bacterial osteomyelitis shows bilateral active on chronic sacroiliitis prominent on iliac sides with characteristic periphyseal osteitis at proximal femurs.

Juvenile idiopathic arthritis

Enthesitis and sacroiliitis are diagnostic features of juvenile-onset spondyloarthropathies (JSpAs), which make up approximately 20% of all juvenile idiopathic arthritis (JIA). According to the International League of Associations for Rheumatology, JSpAs are classified as enthesitis-related arthritis (ERA) and juvenile PsA. On the other hand, according to the European Spondyloarthropathy Study Group, JSpAs are a separate group of diseases, divided into entities as in adult patients. In the initial stage of the disease, most JSpA cases are classified as undifferentiated-the so-called "seronegative enthesopathy and arthritis syndrome". Differentiated forms comprise four entities: juvenile AS, PsA, reactive arthritis, and arthritis associated with inflammatory bowel disease (IBD).[39,52]

In the early course of the disease, children typically first present with enthesitis and lower extremity peripheral monoarthritis before developing sacroiliitis or spondylitis.[53] The commonly involved entheses are located at the lower extremities, including the

knee, hip, and big toe. Moreover, the tarsal joints and feet exhibit a higher frequency of involvement (Figure 3).[39,52] In patients with ERA, the prevalence of sacroiliitis was reported to be in approximately 75% of patients with pelvic enthesitis. In keeping with these results, it is recommended to add true axial water-sensitive fat-saturated images to the SIJ MRI protocol with a larger field of view to depict the entire pelvis, including the hips, to assess various entheseal sites at the pelvis.[54] Subclinical enthesitis, which may be present in ERA as well as with sacroiliitis associated with familial Mediterranean fever (FMF), can predict disease flare-ups.[55]

Although rare, bursitis can be the sole imaging finding in JIA.[56] The presence of sesamoid fibrocartilage at the Achilles tendon-retrocalcaneal bursa interface is already well known (Figure 1).[6] Bursitis without accompanying overt classic enthesitis, which may be encountered elsewhere in patients with ERA, warrants studies searching for other sesamoid fibrocartilage–bursa interfaces. Bursitis may represent the involvement of the SEC, along with chronic irritation emanating from adjacent tendons gliding over bones (i.e., functional enthesitis).

Rheumatoid arthritis

As the most common form of autoimmune inflammatory arthritis, RA primarily affects the synovium. Although the joint synovium and periarticular bone are the most significant initial targets in RA, the synovium-lined tendon sheaths, bursae, and entheses are also affected.[57] Awareness of the SEC involvement patterns (entheseal vs perientheseal) based on the location of bone edema and erosions may help differentiate RA from other inflammatory arthritis.[46] However, in small joints, the discrimination of such entheseal lesions may be difficult due to the close anatomic alignment of involved structures. Seronegative (for rheumatoid factor and/or anti-cyclic citrullinated peptide) and/or human leukocyte antigen B27 (HLA-B27)-positive patients with RA are the most challenging cases in the early phase of the disease. However, it was shown that HLA-B27-positive patients with RA do not have more pronounced enthesitis than patients lacking this HLA allele.[58]

In studies comparing entheseal abnormalities of PsA and patients with RA with healthy controls, utilizing either US or HR MRI, significantly more entheseal abnormalities in RA were found compared with healthy controls,[29,36,47] regardless of the comparison of results between PsA and RA (although PsA was shown to have more entheseal abnormalities than RA).[36,45] It is likely that RA primarily affects synovial tissue and subsequently involves adjacent structures, such as entheses (Figure 7).

Retrocalcaneal bursitis can occur before or together with Achilles tendon enthesitis in the early phase of RA.[13] This supports the concept proposed by McGonagle et al.[59] that inflammation of the SEC in RA arises from the synovial tissue. Moreover, the interesting recent finding of the presence of isolated Achilles tendon enthesitis without retrocalcaneal bursitis in a subgroup of patients who have already been diagnosed with, and are being treated for, RA,[13] suggests several possibilities. First, enthesitis may be more resistant to RA treatment compared with bursitis. Second, enthesitis may be partially attributed to degenerative changes resulting from damage and deformities caused by RA synovitis. Last, such enthesitis in patients with RA may primarily indicate a reparative process rather than ongoing inflammation.[13] All these observations underline the importance of increased awareness of the SEC on imaging-based detection of involved structures in RA.

Osteoarthritis

OA leads to inflammation and degeneration of various components within the joint, encompassing not only cartilage, cortical bone, and bone marrow but also the joint capsule and ligaments.[60] Studies from the last two decades have shown that enthesitis of ligaments and tendons seems to contribute to early OA as a trigger of further inflammatory changes.[11,61] On the other hand, a recent study challenged the hypothesis that enthesitis is a precursor to OA by revealing a more frequent osseous involvement of the perientheseal (instead of the actual entheseal) regions in patients with OA (as well as those with RA), in contradistinction to the exclusive involvement of entheseal regions (in other words, the SEC) in patients with SpA.[46] Once again, the SEC is at the forefront of investigations into such distinctions.

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is an ossifying enthesopathy characterized by excessive new bone formation in the axial and peripheral skeleton. In the axial skeleton, DISH usually affects the thoracic spine, whereas in the peripheral skeleton, entheseal sites (mainly in the pelvis) are targeted. The condition is regarded as mechanical or degenerative in nature, although local inflammation may also play a role in its development. DISH may be asymptomatic or may manifest as back and cervical pain, dysphagia, pain at peripheral entheseal sites, or limitation of motion of the spine, often mimicking SpA. Although strict radiographic criteria by Resnick and Niwayama[62] have long been used in diagnosing DISH, longitudinal studies have highlighted the need for establishing new criteria to identify it earlier.[63] Kuperus et al.[63] have recently developed and validated criteria for early-phase DISH utilizing computed tomography (CT).

Despite overlapping imaging features in DISH and SpA, new bone formation and enthesophytes in the spine and the appendicular skeleton are generally thicker and more prominent in DISH. In addition, DISH-related osteophytes in the spine are primarily located on the right and are more horizontal, whereas in SpA they are vertically oriented with no side predilection. At peripheral forms of enthesitis, enthesophytes in DISH are also prominent and show a whiskering pattern, without accompanying erosions and sclerosis. SIJ ankylosis of DISH reveals anterior and/or posterior bridging osteophytes without erosions and sclerosis, different from intraarticular ankylosis and erosions of SpA.[64]

Crystal-induced arthritis

The accumulation of calcium-based crystals in the entheses is arguably the most common underlying factor in systemic enthesopathy[12] and can be easily identified through radiography and/or US. Nevertheless, there is a paucity of research on this subject in recent years. On the other hand, enthesitis related to gout (a monosodium urate-based crystal arthropathy) has been reported.[65] Crystal depositions in gout are found not only in and around joints but also in tendons and entheses, which can be detected by dual-energy CT and US. A recent study utilizing US showed that approximately half of gout patients have entheseal abnormality at their lower extremities, whereby the patellar insertion of the quadriceps tendon was the most common site.[65] Moreover, sacroilliitis as a feature of gout has also been reported in the form of erosions with multilobulated bases (and an absence of subchondral sclerosis).[66]

Familial Mediterranean fever

FMF is the most common autoinflammatory disease that can be associated with SpA,

PsO, vasculitis, Behçet's disease (BD), JIA, and IBD. In addition to episodes of peritonitis, pleuritis, or acute synovitis, a significant number of patients with FMF are found to exhibit enthesitis and sacroiliitis, which are also characteristic imaging findings of SpA.[16,67] Pelvic and lower extremity entheses, particularly the Achilles tendon, are the most commonly reported sites.[67,68] In a recent study, enthesitis was found to be a sign of a more severe FMF phenotype and was associated with other musculoskeletal manifestations that resemble SpA.[67]

Systemic lupus erythematosus

The musculoskeletal system is frequently affected in systemic lupus erythematosus (SLE), whereby enthesitis has also been reported as a manifestation, in addition to arthralgia, arthritis, tenosynovitis, tendon rupture, tendonosis, osteonecrosis, subcortical cysts, osteomyelitis, septic arthritis, and myositis.[69] The distal insertion of the patellar tendon, which features a SEC, is the most frequently affected site of enthesitis in SLE. In comparison with patients with PsA, enthesitis in SLE is rarely associated with US findings of structural damage.[70]

Systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune disease with a complex pathogenesis characterized by fibrosis and inflammation of the skin and multiple internal organs.[71] Ultrasound studies suggest that synovitis is one of the most common findings in SSc, affecting almost half of all patients. In a recent study using US and featuring healthy controls, it was found that 38% of SSc patients exhibited enthesitis of the lateral epicondylar common extensor tendon. Skin thickening and sarcopenia due to myositis and myopathy may serve as risk factors that alter the distribution of mechanical forces on the underlying enthesis and the SEC, thereby contributing to the development of enthesitis.[71]

Sjögren syndrome

Sjögren syndrome (SS) is a chronic autoimmune disease marked by lymphocytic infiltration of the exocrine glands. Diffuse pain is a common feature in SS, and enthesis zones are one of the leading causes of pain in the musculoskeletal system. A US study has shown that the plantar fascia, Achilles tendon, and distal patellar tendon are the most common sites of enthesitis in patients with SS (Figure 7).[72]

Behçet disease

BD is a type of vasculitis with six different phenotypes. A study utilizing US has shown that the arthritis/articular involvement-predominant phenotype features more enthesitis compared with other phenotypes of BD without arthritis (as well as to patients with RA and healthy controls).[10] A recent observational multicenter study found that almost one-third of the juvenile patients with BD who tested negative for HLA-B27 had sacroiliitis revealed on MRI.[17] Although the presence of enthesitis and sacroiliitis in BD suggests an association with SpA, there is no conclusive evidence as yet to include BD in the SpA disease complex.

Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome and chronic non-bacterial osteomyelitis

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and chronic non-bacterial osteomyelitis (CNO) are autoinflammatory diseases. Whereas CNO is characterized by remitting and relapsing bone lesions throughout the body, SAPHO syndrome presents with both skin and osteoarticular lesions.[73,74] CNO predominantly occurs in children/adolescents and SAPHO syndrome in adults. The anterior chest wall bones and joints are the most frequent sites for SAPHO lesions, whereas CNO tends to involve predominantly pelvis and lower extremity long bones, characterized by osteitis of metaphyses and epiphyses (or their equivalents), sometimes with frank involvement of the physes that may cause lifelong deformities.[73,74] In the chronic phase of SAPHO, lesions eventually ossify and cause ankylosis.

In SAPHO syndrome, in addition to subclinical enthesopathy detected with US, axial involvement resembles psoriatic SpA and starts with vertebral corner lesions, such as enthesitis of SpA. In time, corner lesions progress to the adjacent vertebral endplate and/or the anterior cortex of the vertebral body, often accompanied by thickening of the prevertebral soft tissue that may ossify and cause voluminous paravertebral ossification.[73,75] Sacroiliitis may also be seen, usually unilaterally.

Vertebral lesions of CNO may present as inflammatory corner lesions, such as enthesitis, and/or may involve the entire endplate or body, which may eventually collapse. Unlike SAPHO, paravertebral ossification is not expected. Sacroiliitis is another important imaging feature of CNO that was reported in up to 72% of children in a recent cohort (Figure 7).[74] CNO lesions with peripheral enthesitis should raise suspicion of an association with other rheumatic/inflammatory conditions, such as PsA or ERA.[74]

Both in the acute and chronic phases of SAPHO, patterns of chest and vertebral lesions suggest SEC inflammation; however, it is not clear which component of the enthesis organ is primarily involved. Since osteitis is the primary lesion of SAPHO or CNO, secondary involvement of joints and surrounding capsular and ligamentous structures appears more reasonable.

In conclusion, the SEC is a pivotal site in the imaging-based assessment of arthritis and other rheumatic diseases. It should be a prime site of attention in the radiologists' search pattern when performing and interpreting modern imaging techniques. With its capability to show the enthesis organ exquisitely -and in its entirety, including the bone marrow- HR MRI is the most versatile tool for depicting the SEC. Despite their limitations in various aspects, radiography, US and CT are nevertheless also helpful for this purpose, as long as the SEC, with its involvement in rheumatic diseases, is given due consideration. Radiologists need to be familiar with the anatomic properties of the SEC at different locales across the body and its involvement in different conditions, both rheumatic and non-rheumatic.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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