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The problem in differentiation between psoriatic-related polyenthesitis and fibromyalgia

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ABSTRACT

The recognition of the primacy of enthesitis in animal models of spondyloarthritis (SpA) and the prevalence of clinically occult enthesopathy in psoriatic subjects and of persistent joint pain in psoriatic arthritis subjects that have ostensibly good reduction of joint swelling under biological therapy has highlighted the potential impact of polyenthesitis in psoriatic disease. In daily practice the formal demonstration of enthesitis is challenging due to: the relatively avascular nature of enthesis often leading to the absence of overt clinical inflammatory signs; the frequent lack of inflammatory markers elevation; finally, the limitations of current imaging techniques to provide supportive evidence for inflammation in these areas. Consequently, enthesitis may present as widespread pain indistinguishable from fibromyalgia or may emerge as the dominant feature after successful biological therapy for suppressing synovitis. The unmet needs in the differentiation between fibromyalgia and enthesitis in psoriatic disease subjects are highlighted and critically evaluated in this article.

KEY WORDS: Spondylarthropathies; Fibromyalgia; Chronic pain syndromes; Soft tissue rheumatism; Inflammation; Diagnostic imaging; MRI; Radionuclide imaging; Ultrasonography; Biological therapies

KEY MESSAGES

1) Entheses are avascular, well-innervated structures without gold standard clinical, serum biomarkers, imaging or histological outcomes.

2) There is considerable difficulty in distinguishing between pain from enthesitis or from fibromyalgia.

3) Differentiating fibromyalgia from enthesitis symptoms is crucial in patients failing to respond to treatment.

Introduction and relevant patho-biology

Enthesitis is defined as inflammation occurring in the interface where tendons, ligaments, and capsules attach to the bones. Pain, tenderness and stiffness (with or without apparent swelling) are its main clinical manifestations. Enthesitis plays an important role in the understanding of psoriatic arthritis (PsA) and other forms of spondyloarthritis (SpA) [1, 2]. Several animal models demonstrate that PsA-like disease starts at the enthesis before spreading to adjacent synovium and bone [3-5]. In patients with psoriasis, imaging studies show a high burden of pauci-symptomatic enthesopathy[6]. Psoriatic nail disease, a clinical predictor of future PsA [7], is also strongly linked to local [8] and remote [9] enthesopathy. From a physiological view point, entheses are completely avascular at attachment sites and have a low density of blood vessels in the adjacent ligaments and tendons. Furthermore, entheseal regions are well innervated.

In comparison, synovial tissues are highly vascular and undergo extensive hyperplasia with inflammatory immune cell infiltration with related articular cavity effusions during inflammatory episodes. Because of the different anatomical structure, enthesitis may lead to increased vascularisation (sometimes detectable only through dynamic imaging) (Fig. 1B) and mild swelling of the surrounding soft tissues. In most cases, however, enthesitis occurs without visible signs of clinical inflammation.

SpA-related enthesitis occurs most typically in association with joint swelling when the integral synovio-entheseal complex is involved. In this case it is not clinically possible to distinguish enthesitis from synovitis. Many entheses are placed deep inside the human body and consequently they are not clinically accessible, which undermines the diagnostic process unless considering the use of sensitive and advanced imaging techniques. Histological tissue sampling of entheses as a diagnostic gold standard is also unfeasible. In addition, age- and/or overweight-related changes do occur at entheseal sites (Figure 1, panels C, D) as

degenerative features [10, 11], which may limit the usefulness of imaging, including ultrasound (US) and magnetic resonance (MRI). Finally, another result of the peculiar anatomical structure of entheses is the lack of correlation with acute phase reactants. Following on from these anatomical considerations the specific difficulties that multi-enthesitis poses in differentiating this condition from fibromyalgia are discussed.

Fibromyalgia

Fibromyalgia syndrome (FMS) is a complex chronic widespread pain (CWP) disorder of unknown origin, classified as primary or concomitant to other conditions (e. g. several rheumatic diseases, thyroid disorders, etc.) and has been well reviewed elsewhere[12-14]. The presence of FMS in ankylosing spondylitis (AS) and axial SpA subjects can distort disease activity measures towards more severe activity scores [15-17]. In psoriasis, the prevalence of FMS has been reported ranging between 5.4-8.3% [18, 19], which is higher than that found in the general population [20]. On the other hand, one abstract suggested that up to 93% of FMS subjects may show US signs of enthesopathy[21].

FMS is associated with abnormalities in pain processing in the central nervous system [12], although no specific abnormalities have been found in peripheral nociceptive systems in the skin and soft tissues of these subjects. In contrast, studies using functional brain imaging techniques [22] suggested abnormal pain processing mechanisms in FMS.

Despite these data supporting the unifying concept of central sensitivity syndrome [14], FMS is mostly a diagnosis of exclusion and there is no gold standard confirmatory test or biomarker [23]. In addition to widespread pain, stiffness, fatigue and non-restorative sleep, patients often complain of other symptoms including paraesthesiae, swelling-like feeling in the extremities of the limbs, cognitive difficulties, headaches, irritable bowel syndrome, interstitial cystitis, and many other autonomic dysfunctions. Such features might be

confounders [24], since PsA shares with other SpA the axial involvement (often associated with fatigue and poor sleeping quality) and/or may overlap with inflammatory bowel diseases (which usually lead to intestinal discomfort). The need to differentiate between functional or organic origin of symptoms requires wider investigations and the need for a multi-disciplinary approach.

The presence on clinical examination of tender points, elicited by palpation at specific sites, was part of the 1990 classification criteria of FMS [25]. Since tender points count is still widely used, the substantial anatomical overlap between these and many entheseal sites [26] may mislead the clinician in one way or the other.

More recently, a revised set of FMS diagnostic criteria has been proposed, excluding tender point examination and including somatic symptoms [27]. A modification of that revision [28] has been validated [29]. Despite this, CWP remains the clinical mainstay of FMS and painful reaction to pressure at discrete body areas often is considered to be suspicious of either FMS or multiple enthesitis.

Enthesitis manifesting as fibromyalgia, a PsA subgroup with multiple enthesitis

Historically, the Moll and Wright criteria for PsA [30] did not encompass any purely enthesitic subgroup. Nonetheless, in their seminal textbook on SpA from 1976, Wright and Moll [31] noted that some patients had bone pain, which we now suspect might have been a peri-entheseal osteitis. The relevance of such a clinical manifestation has been increasingly appreciated following imaging observations and theoretical papers in the late 1990s [1, 32, 33]. Following on these, the CASPAR classification criteria for PsA [34] have fully recognised enthesitis as a typical clinical feature of this disease by including it as one of the three entry manifestations. Lastly, phase III clinical trials in PsA carried out during the last

five years show a higher frequency of assessing entheseal involvement than some earlier studies [35-38].

It has been postulated that there is a PsA subgroup suffering mostly from enthesitis, without associated synovitic manifestations. Obvious examples include costochondritis with related thoracic pain; pain over the spine due to interspinal ligament enthesitis; pain localized in one or few entheseal sites; and, presumably, a syndrome characterised by CWP. Due to a lack of description in medical literature, it is not currently known if a presentation pattern characterized by symmetrical distribution in the sites of insertional pain might provide a clinical clue to genuine primary FMS, while a rather scattered, multi-site distribution of symptoms apparently linked with mechanical stresses (weight, manual activities, and posture) could represent multi-enthesitis.

In the light of the similarities with FMS symptoms and the overlap between many entheseal sites and the classic FMS tender points, such patients can be misdiagnosed as having FMS. To make things more complicated, there is a lack of tools that can reliably demonstrate enthesitis in this subgroup. Also, patients with a somatosensory predisposition to FMS [22] might develop the latter condition in addition to their enthesitis. Conversely, psoriatic patients with primary FMS might perceive as painful mild entheseal inflammation which, otherwise, would be clinically silent. Both situations might represent a co-occurrence of two common conditions or a true PsA-FMS overlap disease. Another possible scenario is that psoriatic patients with synovitis and/or spondylitis may eventually develop secondary CWP. Even in this context, understanding whether the predominant underlying pain is a symptom of multi-enthesitis, FMS or a co-occurrence of both may prove to be difficult. A similar scenario is well recognised in patients with other inflammatory arthropathies such as rheumatoid arthritis or osteoarthritis, where FMS or CWP may develop as a concomitant or superimposed syndrome [39, 40].

Another possible confounding situation is represented by patients with CWP and a genetic predisposition to psoriasis or to SpA. Although these subjects might well have multi-enthesitis, they are likely to be diagnosed as having FMS alone. This reasoning implies that in the case of CWP it is worth looking carefully for factors predisposing to enthesitis, such as familial history of psoriasis, SpA or associated diseases. The therapeutic implications of PsA overlapping with FMS may be relevant in many respects, because data suggest decreased chances of achieving remission in this sub-group[41]. A simplified strategy for dealing with these entangled issues is summarised in Figure 2.

Primary enthesitis diagnosed as FMS

Tumor Necrosis Factor α inhibitors (TNFi) treatment has been particularly successful in the context of AS and PsA. More recent developments target the interleukin-23 and interleukin-17 axis. Since the first clinical trials to test biologics efficacy, the indication to start such therapies in PsA has been poly-synovitis. As mentioned above, however, there is increasing interest in evaluating the effects of biologic therapies on enthesitis [35, 36, 38]. International recommendations for the treatment of PsA [42, 43] suggest biologic therapy for enthesitis, when it is severe enough and not controlled by Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or local steroid injections. There are two noteworthy scenarios, when considering the use of biologics in the context of suspected multi-enthesitis/CWP.

PsA with joint swelling and associated insertional pain

Patients eligible for biologic therapy usually experience significant benefits on signs and symptoms of synovitis when treated with biologics. Improvements in enthesis involving superficial areas (e. g. Achilles' tendon) have been widely observed in clinical practice following the use of biologics. As a result, psoriatic patients suffering from CWP on top of

synovitis who would show a good response after a trial of therapy including NSAIDs, corticosteroids or even biological agents might be assumed to have enthesitis rather than FMS.

Poly-synovitis remitting after the therapy, leaving diffuse insertional pain

When patients with active poly-arthritic PsA are treated with biological drugs, the joint count usually shows dramatic improvements, along with a fall in C-reactive protein levels. In some cases, however, regardless of a successful action in suppressing joint swelling and normalising inflammatory markers, on-going pain seemingly related to the entheses may persist, suggesting a possible concomitant/supervening FMS.

The assessment of such patients largely relies on clinical parameters. Thus far, scarce evidence supports any strategy which would rely only on imaging. Interestingly, one small prospective study [44] showed that 27.3% of subjects with enthesitic SpA had radionuclide scanning and MRI evidence of entheseal inflammation similar to that in patients with definite AS or PsA. Although large case-control and prospective studies are lacking, it is possible to postulate that instead of scanning only discrete insertional areas, the whole-body MRI (wbMRI) technique could better assist in uncovering genuine entheseal inflammation [45] or even detect clinically silent enthesitis [46].

Further, the study of Godfrin [44] and co-workers suggests that a favourable response to non-steroidal anti-inflammatory drugs (NSAIDs) was indicative of SpA in subjects presenting insertional pain, although the participants had not been previously treated with biologics. In general, a significant response to NSAIDs, depot steroid injections or biologics would be expected in genuinely inflammatory underlying cause. In clinical practice, however, decisions on biologics dose adjusting (or intra-class switching/inter-class swapping) is based on a pragmatic and time-consuming approach complicated by the absence of biomarkers (figure 2).

Primary fibromyalgia, misdiagnosed psoriatic arthritis

There are few data in literature on this particular scenario. Given the increased utilisation of imaging and given that age-related changes may occur at normal entheses, particularly in patients with high body mass index (BMI), it is quite possible that patients with FMS may show some degree of entheseal change. Indeed, this was shown to be the case in a study comparing entheseal ultrasound findings in PsA and FMS patients [47]. Such clinically trivial findings could be erroneously ascribed to inflammatory enthesopathy, leading to inappropriate conventional disease-modifying anti-rheumatic drugs (DMARDs) or even biological treatments.

Imaging techniques: supporting evidence when enthesitis is considered

As mentioned in the introductory section, the micro-anatomical peculiarities of physiological entheses make these structures difficult to assess from the imaging point of view. Several techniques are available, or under development, to look for inflammatory lesions in the entheses.

Conventional radiography

This technique has many advantages: it could be considered virtually ubiquitous; time to acquire images is fast and costs are limited. Pitfalls are the implied use of ionizing radiations, the need of readers trained in musculo-skeletal radiology and, above all, the limitation of capturing mostly late-stage lesions (such as large bony erosions and fluffy periosteal bony apposition).

Ultrasound scanning

This technique has several interesting characteristics: US scans can provide real-time, dynamic, in vivo imaging of the anatomical sites explored and spot increased vascularity. Further, they can detect erosions more sensitively than conventional radiography; finally, advanced US machines are becoming more compact and cheaper. Interestingly, some research[48] suggests that psoriatic subjects and PsA cases show abnormal vascularity at entheseal level even if asymptomatic, while healthy controls do not. Unfortunately, although in the study by Aydin[48] et al. the increased vascularity was more specific for entheseal inflammation, the sensitivity was low (36%). Furthermore, the same study found that the range of chronic entheseal changes in healthy subjects overlapped the ranges of psoriatic subjects and PsA cases. Such results are in keeping with those from a study[47] concerning FMS subjects. Another pitfall of the US technique is the need of long training necessary for experienced sonographers and the trend to have such professionals mostly available in tertiary centres only. Finally, many entheseal sites are not accessible for US scans or the symptomatic involvement could be excessively widespread to be dealt with in a reasonable amount of scanning time.

Magnetic resonance imaging

wbMRI methods could overcome the difficulties in the assessment of deeply located entheses. Furthermore, such approach allows extensive, multi-purpose scans (assessing several entheses as well as joints) in one single setting. Considering the data from Poggenborg [46] et al., results suggest a remarkable sensitivity of high magnetic field (3 Tesla) wbMRI in detecting even asymptomatic entheseal lesions. Abnormalities detected with 1.5 tesla MRI units seem to have limited correlation with clinical findings [49]. Other MRI techniques like ultra-short echo time (UTE), although not applicable on a whole-body scale, have shown enhanced ability to demonstrate even subtle alterations of entheseal vascularity when compared to conventional MRI and US [50]. Although all the above

progresses are promising, wbMRI and UTE methods are still under development and time-consuming. Furthermore, MRI machines able to deliver that kind of imaging are available mostly in academic centres. Finally, before widespread clinical use, the uncertainties concerning entheseal abnormalities found among healthy subjects [46] still need robust research and clarification.

Positron emission tomography

In rheumatology, positron emission tomography (PET) scans are often used in the assessment of systemic vasculitidies. PET offers metabolic images that can be coupled with computed tomography (CT) scans and MRI. Interestingly, there is evidence of fluorodeoxyglucose uptake at the entheseal sites of psoriatic patients [51]. Despite the small sample dimension of this study, enhanced entheseal uptake was found in 33% of psoriatic subjects. In another study [52], PET scan were abnormal in SpA patients (encompassing one case of PsA), while no uptake was found in healthy subjects or non-rheumatic patients.

Another development of the PET technique in the field of SpA is a radiotracer specific for osteoblastic activity (18 F-NaF PET). Some researchers [53] were able to depict osteolytic/inflammatory lesions and sclerotic/ossifying lesions in axial SpA subjects, a characteristic that could be promising aid in differentiating between FMS and PsA.

Despite these interesting results, the PET technique is not widely available, utilises ionizing radiations (which doses escalate in case of coupling with CT scans) and acquisition time is quite long.

Other considerations

Patients with PsA may be overweight and biomechanical problems may contribute to pain around enthesis as well as to FMS pain. For foot or knee mechanical abnormalities, such as pes planus or genus valgus, attention to podiatry may have a role. These patients also show

strong clinical overlaps with generalised nodal osteoarthritis and spinal degenerative changes. Sleep apnoea, often linked to BMI which is usually elevated in PsA, may contribute to increased levels of pain, although its role in the interplay between CWP and increased body mass is still uncertain [54].

It could be anticipated that patients with non-inflammatory entheseal discomfort may have anxiety and depressive symptoms, which are common in PsA patients as confounding factors [55]. Some evidence suggests that psychological factors can impact the measurement of disease severity [56], although this issue was not specifically addressed in a PsA population characterized by isolated entheseal involvement.

Finally, in a small study psoriasis has been associated with cognitive dysfunctions [57], which might have an effect of pain perception. However, there are no data on this specific issue.

Practical approach to the management of patients with psoriatic disease when enthesitis or fibromyalgia are suspected

When dealing with a psoriatic patient or even with a potentially psoriatic patients (i.e., familial history of psoriasis) who are complaining of CWP, all of the following possible phenotypic patterns should be contemplated in the diagnostic process: i) Multi-enthesitis; ii) FMS; iii) A combination of the two conditions; iv) Other joint diseases.

The presence of long-lasting morning stiffness and a sustained response to a course of steroids would certainly be more suggestive of genuine multi-enthesitis. A higher number of somatoform symptoms [58] would point more towards FMS (figure 3).

FMS patients often have pain and tenderness not only in specific points but also in other sites, reflecting the reduction in pain threshold, and in addition always have fatigue and non-restorative sleep. Otherwise, concomitant peripheral and/or axial articular inflammatory

involvement would clearly suggest PsA. Similarly, altered inflammatory markers in the absence of any other possible explanation may be indicative of SpA.

Imaging may be helpful in some cases, although very sophisticated imaging such as wbMRI is usually not available in daily practice. A study of entheseal PDUS showed that a high number of involved sites, a high grey-scale score, a high power-Doppler score in one site, and involvement of typical sites (e.g., the Achilles' tendon) were significantly associated with PsA rather than FMS [59], although the sensitivity of these findings was relatively low. Furthermore, age- and weight-related degenerative changes should always be considered as sources of confounding.

Even if symptoms, sustained versus lack of response to steroids or NSAIDs, laboratory tests, objective findings upon clinical examination, PDUS of the entheses or other imaging may help to point towards multi-enthesitic PsA or FMS, it is always possible that the two conditions coexist as a co-occurrence or overlap disease. In these cases making a correct diagnosis is the first challenge, the second being to dynamically understand which one of the two conditions is the leading cause of discomfort.

Since conventional DMARDs seem to be poorly effective in genuine multi-enthesitis, the absence of response to these drugs is not usually helpful. Conversely, given the acknowledged efficacy of biologics on enthesitis [36, 42, 60], FMS should be reconsidered if there is a lack of response. However, as not all PsA patients with enthesitis improve upon anti-TNFα therapy, the final diagnosis should be based on the integration of all the clinical and imaging findings.

All the above suggests that a holistic approach is needed, both in the initial diagnostic phase and in the long-term management. Agents such amitriptyline, gabapentin, pregabalin, or doluxetine may be used. Although there are no data, it is conceivable that these agents may also have an effect on pain related to the enthesopathy. Of note, it is known that abnormal

innervation of enthesis in the spine contributed to degenerative disc disease. However, there are no data so far on abnormal innervation of enthesis that have previously been inflamed due to a bout of SpA.

Finally, if patients have severe inflammatory symptoms, it may be that a trial of biological therapy and an assessment of response may be the only tool available to differentiate between FMS and multi-enthesitis. This is reminiscent of the use of steroids in suspected normal acute phase response polymyalgia rheumatica, where often a trial of therapy is ultimately used to make the diagnosis.

Conclusions and future directions

There is an increased awareness that psoriatic patients may have CWP. It is difficult to differentiate whether these patients have multi-enthesitis, FMS or both, as the physical examination may be similar and other clinical features need to be taken into consideration. Some points seem noteworthy: i) Early stage enthesitic PsA cases may be diagnosed as FMS if evaluated prior to development of dactylitis and/or synovitis or of musculoskeletal symptoms occur with not apparent psoriasis; ii) Differentiation of the two conditions may be suggested by steroid responsiveness. Lack of benefit or short-lived atypical steroid response may suggest FMS, especially when associated with mood disorders or somatisation; iii) Imaging with PDUS or selected MRI scanning of limited sites of predominant pain, if wbMRI is not available, could be utilised.

Although a comprehensive approach should be helpful, the diagnosis and management may be challenging. On a positive note, patients with entheseal disease with normal x-rays, absence of joint swelling and normal C-reactive protein are unlikely to develop progressive structural damage.

More recent imaging approaches, such as wbMRI scans and F18-Na PET/CT (figure 4), could improve our understanding of the interplay between enthesopathies and FMS. This is an area that warrants further research.

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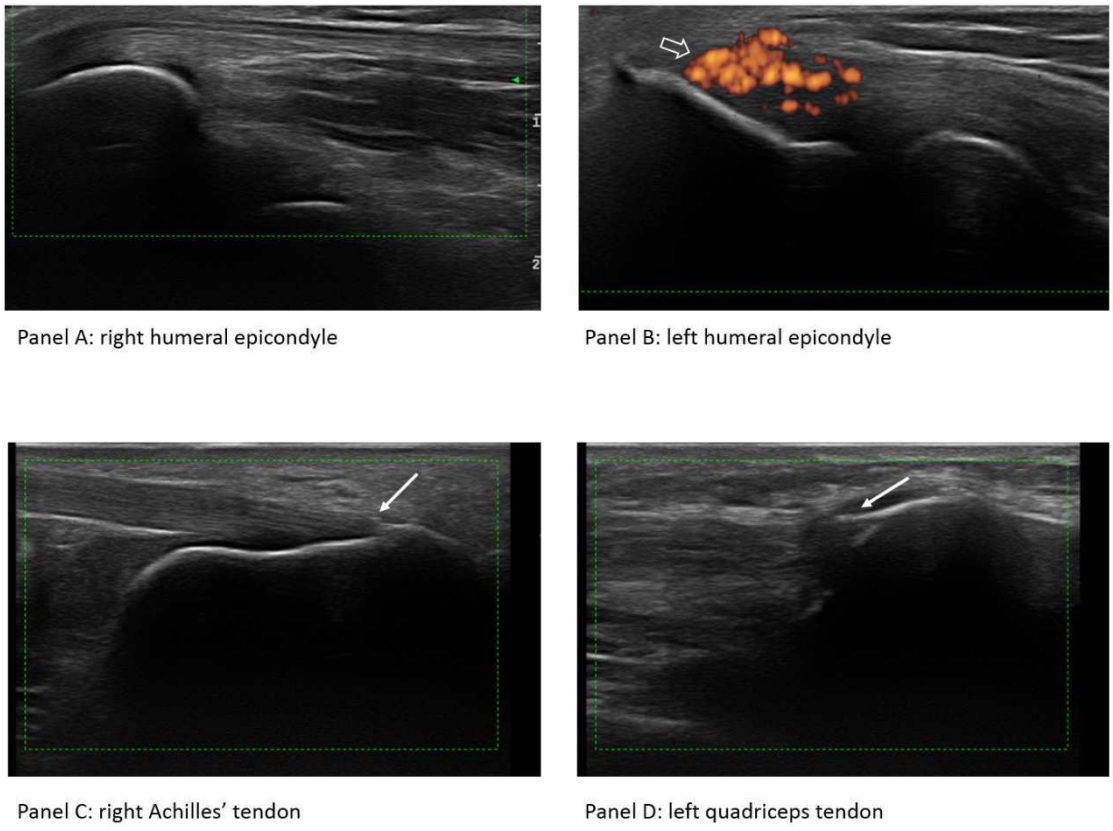
TABLES AND FIGURES

Figure 1. Clinical case: 48-year-old woman, mild psoriasis



Panel A: right humeral epicondyle

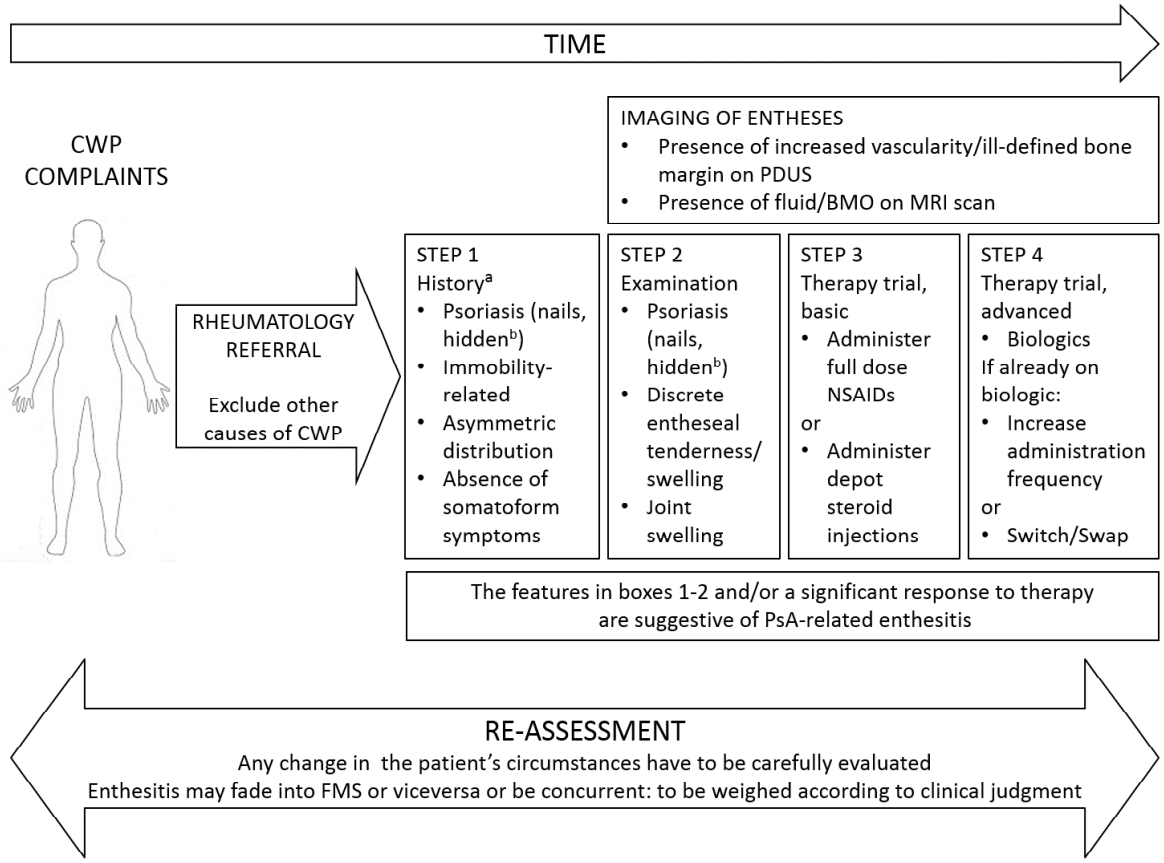
Panel B: left humeral epicondyle

Panel C: right Achilles' tendon

Panel D: left quadriceps tendon

Onset of pain in the elbows and hips, then evolved to widespread musculo-skeletal pain. Other symptoms: moderate-severe fatigue, morning stiffness, sleep disturbances, anxiety. Initial diagnosis of fibromyalgia, paracetamol and duloxetine not effective. Then indomethacin: slight improvement. Enthesitis suspected (see B), sulphasalazine trial ineffective. Biologic treatment: impressive improvement. **A:** enthesis, normal appearance. **B**, empty arrow: presence of power-Doppler signal in the enthesis. **C, D**: thin white arrows indicate enthesophytes.

Figure 2 Features and dynamics related to Chronic Widespread Pain (CWP) assessment.



Anaemia, heart failure, drugs, neoplasms, nutritional factors and endocrinopathies have to be taken into account for differential diagnosis.

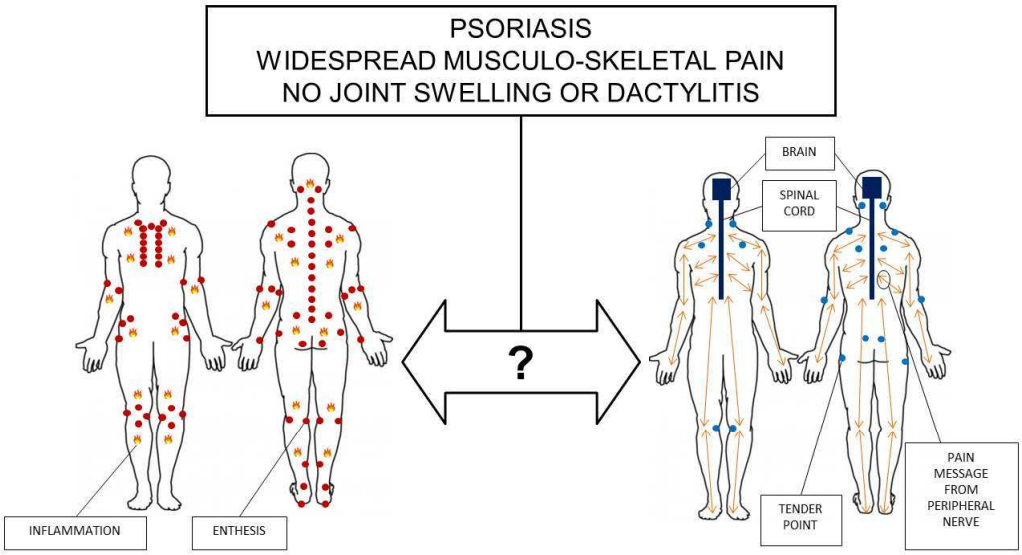
a) Also to be investigated: inflammatory back pain, family history of psoriasis, SpA, inflammatory bowels diseases; check for inflammatory ocular conditions (iritis, uveitis).

b) Located in the natal cleft, umbilicus, auricular ducts.

PDUS = power-Doppler ultrasound scan; BMO = bone marrow oedema; MRI = magnetic resonance imaging; NSAIDs = non-steroidal anti-inflammatory drugs; Switch = intra-class change of biologic drug (e. g.: from one tumor necrosis factor α inhibitor to another); Swap =

inter-class change of biologic drug (e. g.: from tumor necrosis factor α inhibition to interleukin 17 axis targeting); PsA = psoriatic arthritis; FMS = fibromyalgia syndrome.

Figure 3 Entheses and tender points: anatomical overlaps and other grey areas.



MULTI-ENTHESITIC PsA

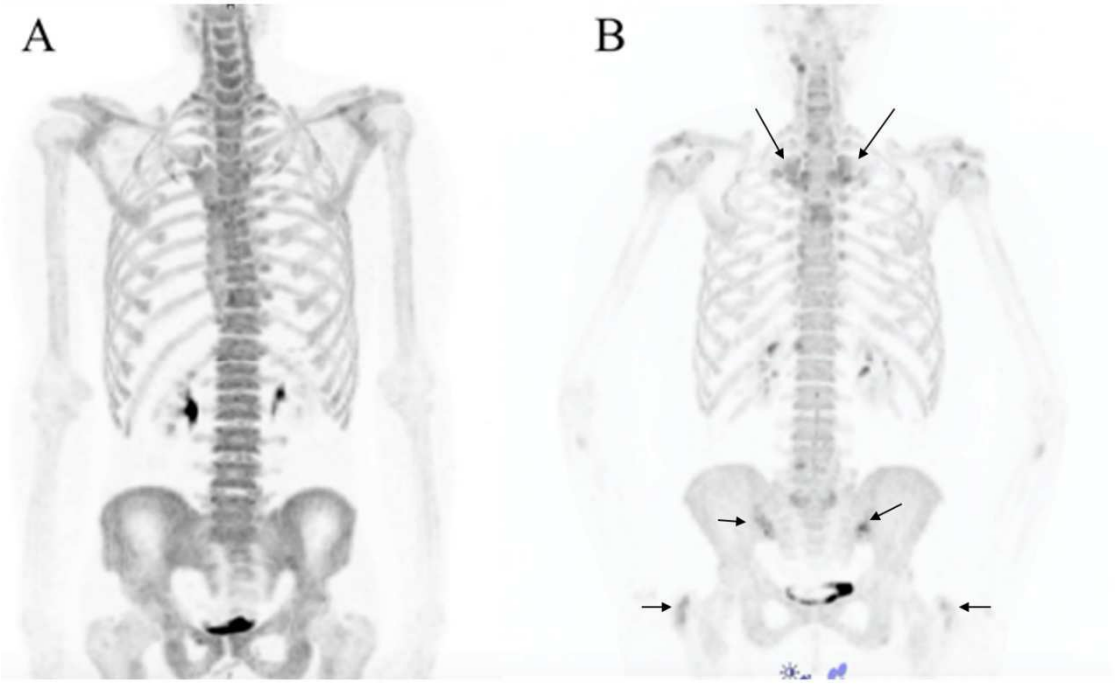
- Stiffness after prolonged immobility
- Anterior chest wall pain
- Heel swelling
- Favourable response to:
  - NSAIDs
  - Biologics
  - DMARDs?

FMS

- Somatoform symptoms:
  - Sleep disturbancies
  - Cognitive impairment
  - Anxiety
  - Migraine
  - Raynaud's phenomenon
  - Irritable bowel
- Indifference to emotional stimulations

Features related to enthesitic psoriatic arthritis (PsA, on the left) and fibromyalgia syndrome (FMS, on the right). The two conditions could dynamically fade into each other over time. Inflammatory markers, like C-reactive protein, may be normal. Sensitive imaging investigations may yield uncertainties.

Figure 4 Clinical case: imaging supporting the clinician. Positron emission tomography scan uncovering enthesitis.



A) 18-F-Na PET of a 55 years old female affected by FMS complaining pain at elbows, shoulders, cervical and low back pain for more than a year. No site of uptake were observed. **B)** 18-F-Na PET of a 51 years old woman, mild psoriasis, affected by widespread musculo-skeletal pain. Initial diagnosis of fibromyalgia, amitriptyline and paracetamol were not effective. The investigation showed an increased uptake at sacro-iliac joints, sterno-clavicular joints, and trochanteric entheses (arrows). The following treatment with indomethacin and sulphasalazine led to significant improvement of symptoms.