

Beyond Early Diagnosis: Occult Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous disease involving the skin and nails and different musculoskeletal structures including synovial joints, entheses, synovial sheaths of tendons, and the axial skeleton¹. Therefore, its clinical spectrum is broad and each clinical rheumatological manifestation can occur for a long time in isolation².

PsA should be diagnosed early because the major goals of management, reduction of pain, improvement of function, and inhibition of joint damage, can best be achieved by early intervention³⁻⁶.

For identification of PsA, in either rheumatological or dermatological settings, it seems obvious that the patient must have symptoms and signs of musculoskeletal involvement. A recent study from Germany that analyzed 2009 patients with psoriasis from 13 dermatological hospitals and 129 dermatological private practices showed that in developed countries there is still a significant number of undiagnosed persons with PsA⁷. However, many dermatologists have time restrictions that make it impossible to routinely search for musculoskeletal symptoms. Screening tools to be filled in by the patient in the waiting room or at home have been suggested for identification of these inflammatory manifestations⁸⁻¹¹.

Since the 1970s, it has been recognized that each inflammatory lesion (joint synovitis, tenosynovitis, dactylitis, enthesitis, sacroiliitis, and spondylitis) can develop without symptoms or signs that are recognizable by the patient and the physician. Such patients can be considered to have subclinical or "occult" PsA. Their identification represents a further challenge for rheumatology.

The prevalence of psoriasis in the general population has been estimated to be between 2% and 3%. The estimated prevalence of manifest PsA among patients with psoriasis has varied widely from 6% to 42%. Studies from Sweden and Italy suggest that evident PsA occurs in about one-third of patients with psoriasis^{12,13}. If this is correct, then the prevalence of clinically evident PsA in the general population should be close to 1%. The time lag between the appearance of psoriasis and the onset of specific inflammatory musculoskeletal manifestations can be greater than 20 years¹⁴. During this period, there is a chance to identify occult PsA. The prevalence of occult PsA depends on the kinds of musculoskeletal features searched for and on the imaging methods used.

In 1976, Harvie, *et al* found 8 asymptomatic patients with erosions and mild sclerosis around the sacroiliac joints in pelvis radiographs from among 100 subjects with severe cutaneous psoriasis¹⁵. Using ultrasound (US), De Filippis, *et al* examined Achilles tendons and flexor and extensor ten-

dons of the fingers of both hands in 24 patients with psoriasis¹⁶. Abnormalities not detected at the clinical examination were found in 33% of cases. Subclinical involvement of Achilles tendon in psoriatic patients was also observed by US in 2 other studies^{17,18}. Recently, Gisondi and coworkers investigated the presence of lower-limb enthesal abnormalities by US in 30 patients with chronic plaque psoriasis who had no signs or symptoms of PsA and in 30 controls¹⁹. Results of the examinations were scored according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS). The mean GUESS score was significantly higher in psoriatic patients. Offidani, *et al* used magnetic resonance imaging (MRI) and radiographs to investigate 25 asymptomatic patients with active nummular and/or plaque psoriasis and 12 healthy controls²⁰. Sixty-eight percent of the psoriatic patients showed at least one sign of arthritis (in particular, capsular distension and periarticular bone edema) on MRI. Signs of PsA were detectable in only 32% of cases on radiographs. No arthritic lesions were found in the controls. Two studies also gave evidence that bone scintigraphy is able to reveal subclinical joint disease in more than 70% of subjects with cutaneous psoriasis^{21,22}.

The concept of "occult" involvement in PsA could also be extended to patients already diagnosed with PsA in whom instrumental methods allow identification of more "extensive" disease, such as an axial involvement in patients with only a clinical peripheral arthritis/enthesitis or polyarticular/enthesal involvement in patients with a clinical oligoarthritis/enthesitis.

In a small group of Chinese patients with PsA, Thumboo, *et al* found 45% with painless spondylitis that was detectable on radiological examination²³. A significant prevalence of painless axial disease in PsA patients was also confirmed by Queiro and coworkers²⁴. In particular, they described the absence of pain and stiffness in 12 (41.4%) out of 29 patients with radiographic evidence of cervical spondylitis. Scarpa specifically searched for the presence of erosive/destructive changes localized in the discovertebral junction in PsA cases²⁵. Back pain occurred in only 5 patients (41.6%) among 12 showing these kinds of lesions. Considering that plain radiographic changes take time to develop, it is likely that a conspicuous number of subjects with asymptomatic spine/sacroiliac involvement cannot be found with this imaging technique, but only with more sensitive methods such as MRI²⁶. In 2000, we described 2 cases of asymptomatic psoriatic polyarthritis, one belonging to the "mutilans" subset²⁷. In 2003, using radiographs we studied 22 patients with very recent onset of PsA (6 weeks to 3 months)²⁸. Among these, 4 (18.2%) showed multiple bone

erosions. Considering that a PsA course shorter than 3 months is unable to induce joint erosions identifiable on standard radiographs, we outlined the previous asymptomatic course of the disease. More recently, Scarpa, *et al* studied 47 PsA patients and reported that the number of joints and/or entheses showing increased tracer uptake on bone scintigraphy was 3-fold greater, compared to evidence from the clinical data²⁹. US examination confirmed the inflammatory involvement of synovium and/or entheses in all sites was active at the time of bone scintigraphy, but silent at clinical examination. In addition, 7 patients showed joint and/or enthesal erosions on radiographs. Healy, *et al*, studying dactylitic fingers and toes by MRI, observed prominent inflammatory abnormalities in the other digits of the same hand or foot³⁰.

What is the reason for the asymptomatic course? Currently, there are no certain explanations; the most insightful and immediate answer is probably that the inflammation level in occult PsA is below the symptomatic threshold.

Once the concept of “occult PsA” has been recognized, problems begin. Who should be screened? How should the screening be performed? Patients with psoriasis and healthy subjects with a family history of psoriatic disease represent the population to be screened. A periodic US examination of upper and lower limbs for patients with psoriasis could disclose an occult peripheral PsA. Impediments for this approach are (1) the very high number of psoriatic subjects that should be screened; (2) the long duration of these extensive US examinations and their costs; and (3) the scarce availability of experienced US examiners in many countries. Early axial involvement of PsA should be studied by MRI, because it is the most sensitive method to detect inflammatory lesions³¹. The impossibility of periodic MRI examination of spine and sacroiliac joints of all psoriatic subjects appears obvious, even if the new whole-body MRI techniques promise a reduction of examination times and global scanning of inflamed regions. Scintigraphy is less specific and involves exposure to radiation. Laboratory tests offer little help in the search for occult PsA. The inflammatory acute-phase indicators erythrocyte sedimentation rate and C-reactive protein and HLA typing are of little use; the first 2 are often normal in patients with active PsA, and HLA typing has a limited predictive value. In the future, biomarkers able to recognize the musculoskeletal inflammation of psoriatic disease could be useful; so far, only limited data are available about biomarkers associated with diagnosis of PsA³². However, a recent study showed that interleukin 6 (IL-6) was significantly higher in sera of patients with psoriasis and inflammatory joint disease, compared with patients having skin disease only³³. Thus, IL-6 seems a promising biomarker to screen psoriatic patients for presence of occult musculoskeletal inflammation.

As noted, the limitations of screening procedures such as

MRI, US, and biomarkers do not recommend them for daily clinical practice. At this time, the identification of occult forms should be reserved to research settings.

How do we manage the “occult” PsA? Studies on sub-clinical rheumatological manifestations in patients with both psoriasis and PsA have had mainly cross-sectional design. Therefore, no data are currently available on progression of these forms. In particular, we do not know if a clinical asymptomatic entheses and/or joint showing abnormalities by US or MRI will present subsequent structural damage or will normalize spontaneously. In this field of uncertainty no treatment is advisable for occult PsA. Prospective studies are urgently needed to define the natural history of and eventually to establish the correct therapeutic approach to occult PsA.

In conclusion, since the 1970s, reports have disclosed the presence of occult forms of PsA that contrast with the common conception of clinical joint inflammation. Currently, in consideration of the availability of effective drugs for PsA, that is, the anti-tumor necrosis factor agents, early diagnosis has become necessary^{6,34,35}. Future research achievements in the recognition and progression of these occult forms could permit successful management of PsA.

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