The involvement of the spine in psoriatic arthritis

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ABSTRACT

Although different classification criteria have been developed for psoriatic arthritis (PsA) and spondyloarthritis (SpA), a clear distinction is still not always possible in daily practice. In addition, clinical examination of patients initially diagnosed as PsA due to peripheral symptoms and skin lesions may also show inflammation in the axial skeleton causing inflammatory back pain, stiffness and changes on imaging including sacroiliitis, spondylitis and syndesmophyte formation, similar to what is known from ankylosing spondylitis (AS), the prototype of SpA. However, and in contrast to patients with AS, the long-term radiographic progression of patients with axial disease in PsA seems to be rather independent from spinal mobility. If axial symptoms predominate, diagnosis and classification can be made as axSpA – with or without psoriasis. Furthermore, also the role of HLA-B27 appears to be different in patients with PsA. Overall, the most data about axial involvement in SpA come from AS and axSpA studies, while data about the axial involvement in PsA is limited.

Finally, there are no approved therapies for treatment of axial PsA at present, despite significant clinical morbidity. In recent years, anti-TNF therapies have revolutionised the management of axSpA. The new GRAPPA treatment recommendations have given specific management advice for patients with axial involvement based on literature from AS and axial SpA.

This review aims to give an overview of the existing evidence, the clinical and imaging presentation, and therapeutic consequences of axial involvement in patients with PsA.

Introduction

Psoriatic arthritis (PsA) is considered part of the spectrum of spondyloarthritis (SpA). Current classification criteria for axial and peripheral SpA on one side (ASAS) and PsA (CASPAR) on the other side are largely overlapping (1, 2). Since this overlap can be found in many patients, there has been debate about how to best handle this issue. The approach that has been taken in the last decade by clinical studies is to follow the clinically most important symptom – *e.g.* predominantly axial or peripheral. Thus, in studies designed for approval for biologic therapies the ASAS or the New York criteria (3) for axSpA or ankylosing spondylitis (AS) have been used and for PsA the CASPAR criteria.

Overall, up to 50% of patients with PsA also have inflammation in the axial skeleton causing inflammatory back pain, stiffness and changes on imaging including sacroiliitis, spondylitis and syndesmophyte formation (4). However, this condition includes also patients with no or few axial symptoms, and, in contrast to patients with AS, the long-term radiographic progression of patients with axial disease in PsA seems to remain largely independent from spinal mobility (5). If axial symptoms predominate, diagnosis and classification can be made as axSpA – with or without psoriasis. Other authors have included all patients with psoriasis and axial symptoms under the term axial PsA – but there are currently no internationally accepted definitions for this (5). Nevertheless, since psoriasis is such a strong clinical marker, similar to chronic inflammatory bowel disease and HLA B27, spinal involvement in PsA is of clinical interest, especially in the context of axSpA.

While imaging of sacroiliac and spinal inflammation in axSpA can be reliably performed by magnetic resonance imaging (MRI) (6), conventional radiography is still the method of choice to identify erosions and new bone formation in the axial skeleton (7). An interesting question is whether radiographic findings in patients with SpA and psoriasis with axial symptoms are

any different from those without axial changes. Unilateral rather than bilateral sacroiliitis and parasyndesmophytes rather than syndesmophytes have been described in this regard (8). Furthermore, the role of HLA-B27 appears different in patients with PsA (6). The prevalence of HLA-B27 in patients with peripheral arthritis and psoriasis is only a little higher than in the general population. However, the prevalence of HLA-B27 positivity is increased in patients with clear axial disease but not to the same degree as patients with AS without psoriasis (9, 10).

One difficulty in studying axial involvement in PsA is that the number of studies in this area is limited, and most data come from AS and axSpA studies (11). However, since spinal changes may develop in the absence of sacroiliac involvement, the available data may not cover the entire spectrum of involvement (12, 13). This matter has recently also been documented by MRI in non-radiographic axSpA (nr-axSpA) (14).

This review aims to give an overview of the existing evidence, the clinical and imaging presentation, and therapeutic consequences of axial involvement in patients with PsA.

Prevalence of clinical spinal symptoms in PsA

A typical clinical feature of spinal involvement in patients with inflammatory diseases is inflammatory back pain (IBP). Such spinal involvement has been well researched in AS (15), but less in PsA. IBP is considered in patients who have chronic back pain for over 3 months, wake up at night, and the pain improves rather by exercise than by rest (16, 17). Typically it has an insidious onset at a younger age than mechanical back pain.

As suggested by patients and experts in PsA, symptoms of back pain reported from many patients with PsA are similar to symptoms reported by patients in AS, including hip/buttock pain, pain that improves with activity and worsens with rest, night pain, NSAID-responsive pain and axial morning stiffness ≥30 minutes (18). PsA patients also may have limited motion and sacroiliac joint tenderness on examination (18).

The presence of IBP in more recent PsA cohorts also is not commonly reported but may be about 15% (19). Even in a cohort of patients with psoriasis and spondylitic lesions on radiographs, IBP was reported in only 19% (20). As more investigation of involvement of the spine in PsA has been reported, an increasing prevalence of asymptomatic spinal involvement has been identified. About one-third of PsA patients have asymptomatic sacroiliitis on imaging (8, 21, 22), and this is more common in women (22).

The importance of psoriasis in the early recognition of patients with axSpA has been recently highlighted by a referral study (15).

HLA B27 status and pathogenesis

In AS, the prevalence of the MHC class one surface antigen HLA-B27 is 85-90%. However, in PsA the prevalence is much lower at 40-50% (9, 10) and varies between subgroups. Overall in PsA, HLA-B27 has been found to be important not only for the susceptibility of PsA with axial involvement but also for determination of clinical features, including earlier onset of psoriasis and arthritis, as well as male gender, but not with severity or extension of the spondylitis, or with functional impairment (23). In one study, no major clinical differences between AS patients who are positive or negative for HLA-B27 have been reported in one study (24). However, an older study indicated an earlier onset, a more severe and prolonged clinical course, higher prevalence of acute anterior uveitis and peripheral arthritis, more frequent family aggregation and male preponderance in HLA-B27 positive patients *versus* a higher prevalence of psoriasis, inflammatory bowel disease, and erythema in HLA-B27 negative patients (25).

Research in early axSpA has shown that the presence of psoriasis and HLA-B27 are associated with different clinical presentations and different imaging findings both in radiography and MRI (26). Preliminary analysis in previous cohorts has suggested a difference in radiographic phenotype in a small number of patients with PsA related to HLA-B27 status (27) but this has not yet been confirmed in a large cohort. It is thought that HLA-B27 in PsA may be associated with a more typical AS-like phenotype of axial involvement and fulfillment of the diagnostic criteria for AS. In contrast, no clear classification criteria are currently available for HLA-B27 negative PsA patients with axial involvement. This matter is particularly important, as new classification criteria, which aim to encompass all axial SpA subgroups (1) rely to a large extent on HLA-B27, potentially excluding these HLA-B27 negative PsA patients.

In general, a positive HLA-B27 finding seems to be associated with the occurrence of bilateral sacroiliitis (23), as well as with spondylitis (28), rendering it more likely to be related to the classic AS phenotype.

Radiographic changes in the spine

Axial disease in PsA was first reported by Wright *et al*., who recognised the frequent sacroiliac changes in patients with PsA compared to rheumatoid controls (29). This study of 99 patients with PsA and 90 RA controls showed a significantly increased incidence of erosion, sclerosis and ankylosis at the sacroiliac joints together with an asymmetry of spinal disease with unilateral changes seen in 21% of patients with sacroiliitis (29).

Overall, only a few studies have assessed the frequency of radiographic spinal involvement in patients diagnosed with PsA. Depending on the classification used, 25%–70% of the patients diagnosed for PsA have been also reported to have such involvement in combination to peripheral symptoms that confirm PsA (30), while early disease cohorts have reported a prevalence of 5–28% of patients with some spinal involvement (27, 31-35) alongside peripheral arthritis. Part of the difficulty to assess radiographic spinal changes is that such changes that can be used for confirmation of the modified New York criteria (3) can take many years to develop (36). Furthermore, degenerative changes tend to become more prevalent with increasing age, and assessment of changes may also lead to false positive evaluations suggesting spinal involvement in PsA. Prevalence of pure axial disease in pa-

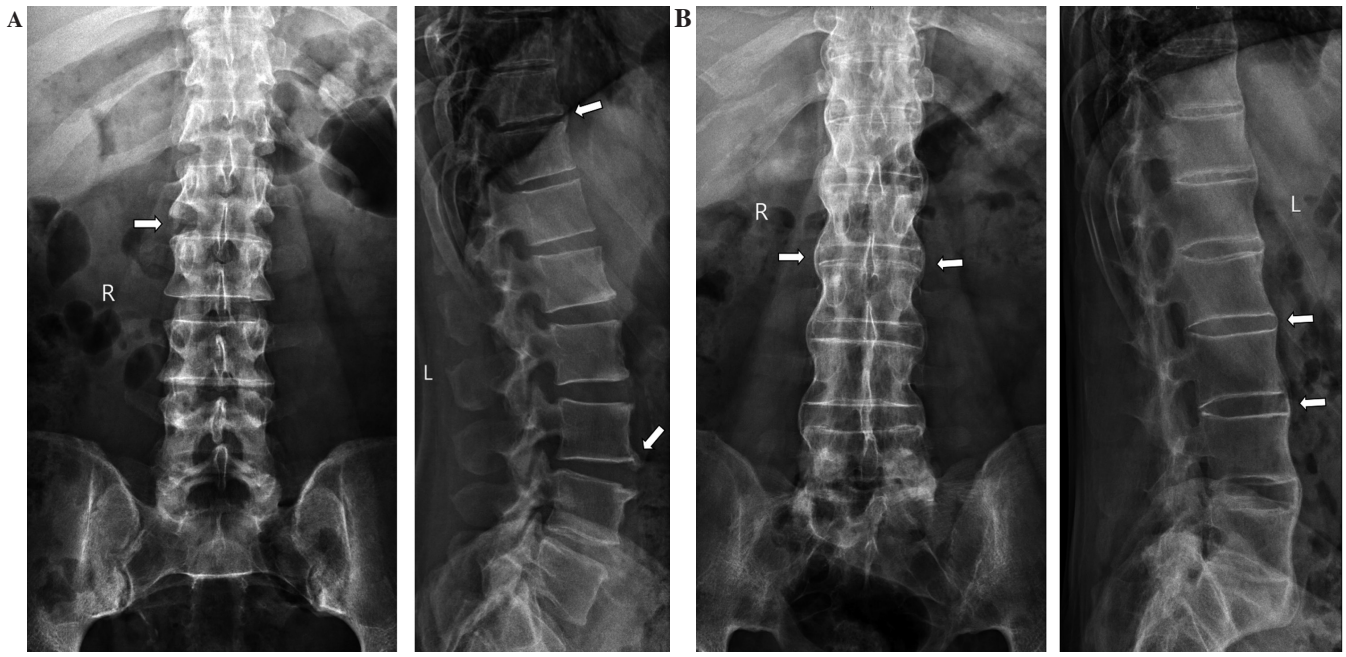

Fig. 1. Example of conventional radiographs of the lumbar spine from a patient with psoriatic arthritis with axial involvement (PsA, Fig. **A**) and ankylosing spondylitis (AS, Fig. **B**) Overall, radiographic evidence of syndesmophytes is less common in PsA than in AS. Spinal disease in PsA is more frequently unilateral, the syndesmophytes show a larger volume, do not follow exactly the course of the anterior longitudinal ligament and do not appear in consecutive vertebrae, as compared to AS.

tients with psoriasis is less commonly reported, with 7–17% (27, 34).

In particular, radiographic evidence of syndesmophytes is less common in PsA than in AS (37). Morphologically, spondylitis in conventional radiographs in PsA patients appears similar to AS but some important differences also are seen in many patients: spinal disease is more often unilateral and the morphology of syndesmophytes also differs from those in AS (38), with syndesmophytes in PsA having a larger volume, not following exactly the course of the anterior longitudinal ligament (showing the so-called 'paramarginal' localisation) and also frequently not appearing in consecutive vertebrae (29, 39, 40) (Fig. 1). Progression of spinal lesions relative to disease duration in PsA may follow a random pattern throughout the spine, rather than a gradual symmetrical extension of disease (38).

Nevertheless, it is unclear whether this finding may represent an important difference in the underlying pathology between axial disease in PsA and AS or a function of the paucity of syndesmophytes in the spine, rather than a true difference in pathology (40).

Radiological changes in the cervical spine have been estimated to occur in up to 70–75% of patients with PsA (41, 42), *i.e.* potentially more frequent than sacroiliitis. Radiologic findings seen in the cervical spine are particularly interesting, as it appears that distinct pathological types may occur. Kaplan *et al.* observed in 1964 that radiological changes in the cervical spine in PsA (and skin psoriasis) bore a closer resemblance to AS than to RA (43). Blau and Kaufman went on to describe two separate patterns of cervical spine disease, either a primarily ankylosing in nature or a rheumatoid-like form of inflammatory cervical involvement (41). This observation was confirmed in an Italian study. However, despite strikingly different radiological features, no difference was reported between the two groups in terms of clinical symptoms (42).

Research concerning cellular mechanisms leading to radiographic changes in PsA, suggest that the bulkier form of syndesmophytes may be due to a general pathologically intense osteoblastic activity, which is also known from peripheral disease (40). It is also possible that the cytokine profile released in response to inflammation and/or stress in PsA differs from that found in classical AS, however, this still needs to be studied in controlled studies (44). An alternative explanation is that PsA patients do not suffer from the same degree of reduced spinal mobility due to less frequent affection of the sites where spinal mobility takes place in the spine, like the apophyseal joints in AS (45). Therefore greater mechanical stresses may also result in increased inflammation/repair mechanism activation and additional bone formation.

Finally, quantification of axial involvement in patients with PsA has been evaluated in some studies of patients recognised as having axial PsA (AxPsA). Available scoring systems for radiographic progression used in AS could show a reliable performance also when applied in patients with the diagnosis of AxPsA (46). In addition, a new scoring system has been proposed for assessment of radiologic axial involvement in patients with established PsA (PsA Spondylitis Radiology Index, PASRI, (47)), combining quantification of radiographic changes in vertebral bodies together with radiological involvement in the cervical facet joints. Evaluation in an intial small cohort (47) indicated similarities and differences compared with established scoring systems, but good correlations with anthropometric and patient reported measures. In comparison with

other scoring systems, the overall intra- and interrater reliability was moderate when applied to AxPsA, but PASRI was found to be superior for assessing structural damage in AxPsA (48). However, it remains unclear if these results are due to a distinct pattern of axial involvement in patients suffering primarily peripheral PsA patients compared to those with AS and concomitant psoriasis.

The role of magnetic resonance imaging of the spine in PsA

Traditionally, the diagnosis of sacroiliitis in all of the SpAs including PsA has relied on radiological evidence of disease. However development of radiological sacroiliitis may not occur until 1-9 years after onset of inflammatory back pain (49). In the early 1990s, MRI was investigated as a tool to detect sacroiliitis (5, 50, 51), indicating that bone marrow oedema (BME) can be reliably seen in the SIJ (52) and in the spine (53). BME adjacent to the SIJ also is correlated significantly with histopathological evidence of inflammatory disease (54). MRI is now accepted as a diagnostic tool for axial disease in SpA, including PsA, and is included in ASAS classification criteria for axial SpA (1). Furthermore, MRI is used routinely at this time as an outcome measure to evaluate treatment of axial SpA with TNF blockers (55).

As in many rheumatological conditions, research in AS is increasingly focused on detection of early disease, and lessons from this approach may enhance our capacity to diagnose axial PsA. However, a more precise role of MRI to predict the further course of axial involvement in AxSpA, remains to be elucidated in prospective studies. In a retrospective analysis patients fulfilling the European SpA Study Group (ESSG) criteria were evaluated, independent of their psoriasis status. Patients had to have presentation of early inflammatory back pain and objective inflammatory activity seen as BME in the sacroiliac joints on MRI. Eight years after their initial presentation, 33% had progressed to meet a radiographic diagnosis of AS, as defined by the modified New York criteria. The key predictor of progression to AS was a combination of HLA-B27 positivity and severe sacroiliitis on MRI, with an odds ratio of 8.0 (sensitivity 62%, specificity 92%), while HLA-B27 positivity with very mild or no sacroiliitis on MRI showed an odds ratio for progression AS of 0.4 (sensitivity 23%, specificity 38%) (56).

Although these data support the role of MRI in predicting the further progression of structural damage, they also highlight the need for caution when using particularly in patients with low levels of inflammation or unclear findings. By contrast, axial involvement may be also apparent on conventional radiography or MRI but clinically absent (6). It remains unclear why such changes may occur in the absence of clinical symptoms, and whether these findings represent clinically significant disease that should be treated.

Implications for treatment

At present there are no approved therapies for treatment of axial PsA despite significant clinical morbidity. In recent years, anti-TNF therapies have revolutionised the management of axSpA, where only symptomatic management was previously available. Only one observational trial has evaluated the use of these drugs in axial PsA, but with very promising results (57). Similar observations also were made in patients with AS who did not have psoriasis *versus* those with concomitant psoriasis (58). The principle problem in researching this condition was highlighted by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) who identified the lack of a defined phenotype of axial disease in PsA limiting future prognostic and therapeutic studies (59). The new GRAPPA treatment recommendations have given specific management advice for patients with axial involvement based on literature from AS and axial SpA (60). These recommendations, based on an extensive literature review, strongly recommend the use of non-steroidal anti-inflammatory drugs, physiotherapy and TNF inhibitors. They also give a conditional recommendation for the use of IL-17 inhibitors (where phase III data is in abstract form only) and for IL12/23 inhibitors where a small open label study has suggested some efficacy (60).

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