
Psoriatic arthritis - Pathogenesis and epidemiology

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ABSTRACT

Psoriatic arthritis (PsA), recognised for over 100 years, is common representing the second most frequent diagnostic category after RA and occurring in up to 10% of patients with skin psoriasis. The pathogenic connection between psoriasis and arthritis is not yet clear although our understanding of the mechanisms of disease has progressed significantly in recent years. Factors including immunogenetics, infection, autoimmunity, angiogenesis, trauma and the nervous system are implicated in the pathogenesis of PsA. Organ involvement is largely restricted to the connective tissue of the skin and joints, including both the synovial tissue and sites of enthesal attachment. This restricted inflammatory response suggests that either a common antigen driving the immune response or that antigenic proteins or cells are present at these sites only having migrated there or arising *de novo*. The epidemiology of Psoriasis has been extensively examined since the 1960's, however there have been few large epidemiological studies of PsA. In addition, the lack of diagnostic criteria for the diagnosis of PsA until 1973, and the diffuse clinical manifestations of this condition have hindered meaningful conclusion regarding the epidemiology of this form of arthritis.

Introduction

There are a number of associations between skin and joint diseases, which are usually defined by their clinical characteristics, this includes common infectious and post-infectious diseases and some autoimmune conditions. For over two hundred years there was debate as to the precise nature of the diseases characterized by thick, erythematous plaques of the skin and inflammation of the joints. This association was initially attributed to leprosy and arthritis, PsA as a unified clinical entity in the medical literature was first suggested by Bazin in 1860 and then

later by Bourdillon. The original definition and classification of PsA did not appear until the 1970's however, it was proposed by Moll and Wright based on an extensive clinical experience. It was this initial confusion and failure to agree diagnostic criteria and clearly defined subgroups that has led to problems in pathogenic and epidemiological studies.

Psoriasis (Ps) of the skin affects approximately 2% of the population, it is characterized clinically by hyperkeratotic plaques of skin especially over the elbows, knees, scalp and although it may be more widespread. An associated and potentially disabling arthritis, psoriatic arthritis (PsA) occurs in some individuals with Ps, most estimates suggest between 7-10%, however some series suggest a much higher figure of 40%. Inflammation is not confined to the skin/nails and the joints in PsA, it may also occur in the genito-urinary system, the lymphatics, the uveal tract and the entheses, however systemic vasculitis typical of rheumatoid arthritis (RA) – is not seen in PsA.

Clinical observations

Overall, the clinical evidence suggests that the inflammation of the skin and the joint in PsA are independent, as over 90% of Ps patients never develop an arthritis. Indeed, most PsA patients demonstrate little relationship in the temporal nature or in the severity of their skin and the joint manifestations although there is a higher prevalence of PsA in severe Ps. It is important to recognize that due to predilections for skin lesions to occur in specific sites, Ps may be missed or overlooked by both patient and physician. The distribution or pattern of joint involvement (e.g. asymmetrical joint distribution, dactylitis, DIP joint involvement) is an important clue and should lead to a careful search the interdigital cleft, intertriginous areas, perineum, umbilicus and scalp for Ps lesions. In contrast, the association of nail dystrophic changes

and distal interphalangeal (DIP) joint arthritis is confirmed. Nail lesions such as pitting, horizontal ridging and onycholysis are significantly associated with development of DIP joint PsA (1). Nail disease is found in 67-90% of PsA patients as compared to only 41% Ps patients without arthritis (2, 3). There is a specific relationship of nail dystrophy with DIP disease both temporally and anatomically (2,4), the exact reason for this association is unclear however a vascular or neurogenic mechanism has been suggested. In an important case report, a patient with sensory denervation of one finger secondary to trauma developed severe nail dystrophy and DIP joint PsA in all digits except for the one which had a damaged nerve supply prior to onset of disease (5). It has also been proposed that the close anatomical proximity of the nail bed and the DIP joint, may allow inflammation to spread from one site to another (6).

The time of onset of skin and joint manifestations of PsA has lead to some confusion which has enhanced the belief of different pathogenic processes. PsA develops in patients with established Ps in 60% of cases. The onset is contemporaneous in 20% and the arthritis manifests before the skin disease in less than 20% (7). The clinical course of skin and joint disease are most often different with flares and remissions occurring with little or no apparent relationship. Only 35% of the patients recognize a link between the activity of their skin and joint features (8). Equally the response to therapy may be dissociated, which can result in significant improvement in one of the two involved tissues but not in both. This apparent paradoxical response to therapy may occur with non-steroidal anti-inflammatory drugs (NSAIDs) and sulphasalazine useful in joint disease, while retinoids, vitamin D analogues and more recently IL-10 administration (9) are useful in treating the skin. Although the therapeutic response to methotrexate, cyclosporin and anti-TNF agents appears to provide a stark contrast with a parallel clinical course being the norm.

The classification of PsA into clinical

subtypes has usually been based on the pattern of joint involvement. Over 90% of cases are polyarticular or oligoarticular in distribution with the former pattern being a little more common (7). Predominant spondylitis with axial disease accounts for 5% of patients and the remaining 5% are a disparate group consisting predominant DIP disease, arthritis mutilans and the synovitis-acne-pustulosis-hyperostosis-osteomyelitis (SAPHO) syndrome. However, clinical phenotype is not permanent, with disease progression the joint pattern may change in particular between poly- and the oligo-articular groups (2, 10). However, the clinical features of these subtypes are diverse which suggests that pathological processes involved are different. Radiographic features may be variable in PsA, with features of new bone formation, such as periosteal reaction or bony ankylosis or bone destruction, with typical erosions or "pencil-in-cup" deformities. Despite these observations no systematic study has examined whether specific immunohistologic, genetic or laboratory parameters or response to therapy account for these clinical and radiographic features. Progress has been limited due to studies of small patient numbers, most of whom have either a polyarticular or oligoarticular joint pattern. Larger scale, multi-center studies are necessary to explore the significance of the variable clinical and radiographic patterns of disease.

Immunogenetic studies

Genetic factors have been proposed in the pathogenesis of both Ps and PsA, initially as a result of observations of familial aggregation in psoriasis (11). A number of genetic loci have been identified, the predominant effect resides within the major histocompatibility complex (MHC). The original association studies of Ps highlighted the HLA-Cw6 locus, with weaker linkage to HLA B13, B17, and the Class II antigen, HLA- DR7. It has been proposed that the class II association reflects linkage disequilibrium between CW6 and HLA -B57, which extends into the MHC class II region (12). In PsA, further associations with HLA-

B27 have been found chiefly in patients with spinal disease, similar to the association with Ankylosing spondylitis, and palmoplantar pustulosis, in addition to associations with HLA-B38, -B39 and HLA-DR4. The association of PsA and HLA B39 has been proposed to identify poor prognosis (10).

It would thus appear from these results that the MHC association with Ps lies close to the HLA-C region while the association with arthritis lies in or close to the HLA-B region.

A significant amount of work has been undertaken to identify which gene or genes contribute to susceptibility for the articular component of PsA and the skin component of Ps, although there has been little advance in identifying such susceptibility genes (13-16). The evidence suggests HLA-C is not itself the susceptibility gene but rather a 170kb sequence centered 100-kb telomeric to it contains a critical susceptibility region. A number of candidate genes which lie close to HLA-C, may also contribute to disease susceptibility. The corneodesmosin gene, initially thought to be a possible candidate is unlikely to be the disease allele but a helix coiled coil rod (HCR) homolog that encodes a protein expressed at high levels in Ps keratinocytes but not in controls, might well be involved. Finally, other MHC and non-HLA genes have been examined. A number of groups have proposed that TNF α -promoter polymorphisms or a linkage disequilibrium gene with TNF α may increase susceptibility to Ps and PsA (17-19). In addition, loci with no identified candidate gene have also been suggested for Ps on chromosomes 4, 6 and 17 (20-22).

While there has been considerable effort made to identify the genetic basis for susceptibility to Ps, the genetic contribution in PsA appears to be additional to that of Ps and considerable work is required to understand this contribution further. Recent work has pointed to an MHC class 1 chain-related A (MICA)-A9 polymorphism which confers additional relative risk in particular for polyarticular disease in Ps patients who carry Cw*0602 (23). MICA-A9 polymorphism was found in linkage dis-

equilibrium with HLA-B alleles (B*5701, B*3801) (24). These results suggest that the MICA gene or other(s) nearby may be involved in the development of PsA, which supports the hypothesis that different MHC susceptibility genes appear to be associated with Ps and PsA. Genetics studies of PsA are complicated by the diverse clinical phenotypes, and the likely polygenic nature of this disease, so large patient cohorts will be required to unravel the true genetic contribution to disease expression.

Immune mechanisms

Ps skin and PsA synovial membrane (SM), while not identical, share a number of similar pathological features on a cellular and a molecular level. This may seem unusual as the tissues are embryologically derived from distinct origins. Psoriatic plaques exhibit epidermal hyperplasia, inflammatory cell infiltration and vascular abnormalities of papillary dermal vessels. In PsA SM the basic pathological features are mild lining layer hyperplasia (not marked as in RA), inflammatory cell infiltration and abnormal vascularity. Indeed, recent data relating to the pathological features of enthesal inflammation, adjacent to the bone marrow show some similarities also (25). So, inflammatory cell infiltrates and new vessel formation (angiogenesis) are common features to the various sites of involvement in PsA.

The inflammatory infiltrates in both Ps and PsA have been subjected to further detailed investigation. Prominent lymphocytic infiltration is common to skin, synovial tissue and enthesal sites. B-lymphocytes are abundant at all sites, although as Ps and PsA are not associated with high levels of auto-antibody production, the function of these large, focal B-cell infiltrates is not well understood (25, 26). In number, CD4+ T-cells are the most significant lymphocytes seen, outnumbering CD8+ T-cells by 2:1, in inflamed psoriatic skin and synovial tissue. In contrast, CD8+ T-cells are most common, reversing the CD4:CD8 ratio at the enthesal site and in the synovial fluid (25, 27).

Controversy still exists as to the rela-

tive contribution of CD4+ versus CD8+ T-cells to disease pathogenesis in Ps and PsA. The CD8+ T-cells invade the developing psoriatic skin lesion first and reduction in epidermal CD8+ T-cells correlated with clinical improvement in patients treated with lymphocyte-specific therapy (28, 29). In PsA synovial fluid the finding of a dominant CD8+ T-cell infiltrate has led to the proposal that these cells may be driving the immune response in PsA (30). This hypothesis is consistent with the Ps literature, the HLA class 1 association, and the association with HIV infection, which selectively results in CD4+ T-cell depletion, and the incidence and severity of Ps and PsA (31). The recent finding of CD8+ T-cells dominating the infiltrate at marrow sites adjacent to enthesal inflammation further supports the proposal of a primary CD8+ T-cell-driven immune response in Ps and PsA (25). Indeed it is intriguing to speculate that the bone marrow may be the primary route for T-cell recruitment to the site of inflammation, both at the enthesis and also perhaps in the contiguous synovial capsule and cavity.

If Ps and PsA are T-cell-driven, then we hypothesized that T-cell expansion at sites of involvement would be clonal. Recent work has supported this hypothesis. The T-cell receptor (TCR) repertoire in psoriatic epidermal cells showed preferential TCR usage of BV3 and BV13.1 in the CD8+ but not in the CD4+ T-cell population (32). While, in the skin and synovium among and between PsA patients, non-separated T-cell infiltrates showed several homologous amino acid motifs were present (33). Costello *et al*, in studies from our department, have recently extended these observations to the synovial fluid compartment demonstrating the presence of oligoclonal expansions of T-cells (30). While some of these expansions were shared between the joint and the peripheral blood compartments, most were restricted to the synovial fluid. Oligoclonal expansions were common in the CD8 population but expansions, though smaller and fewer were also seen in the CD4+ T-cell synovial fluid repertoire. Further data from our own department suggests that the CD4:

CD8 ratio in the synovial fluid may be lower in oligoarticular as compared to polyarticular disease (27). These observations support the concept of a "three-cell interaction" in which effector CD8+ cells are generated under the influence of cognate, regulatory CD4+ T-cells, both of which interact with antigen-presenting cells, in this case Langerhans cells (34). In additional work as yet unpublished, we have examined the TCR repertoire in inflamed synovial tissue (S. Curran, unpublished communication). To our surprise the TCR repertoire was predominantly polyclonal but following disease remission induced by methotrexate therapy, the predominantly CD8+ clonal population of T-cells was again revealed.

The proposed pathogenic mechanisms of both Ps and PsA are similar and suggests that the CD8+ T-cell is central to disease. Antigen presenting cells such as Langerhans cells and T-cells expressing CD4+ and natural killer receptors (NKR) are also clearly involved. In a series of elegant experiments using the SCID mouse model engrafted with symptomless skin, Nickoloff and his colleagues have provided support for a pathophysiologic role for the interaction between T-cells expressing NKRs and CD1d on keratinocytes, with subsequent production of Th1 cytokines (35). While the patterns of T-cell infiltration and cytokine release in Ps and PsA are similar but there are also distinct features. For instance, the cutaneous lymphocyte associated (CLA) antigen - a lymphocytes adhesion molecule preferentially expressed on cells which "home" to the skin is found in lesional Ps skin but not in the PsA synovium (36).

The key inflammatory cells produce cytokines, the balance of which skew towards Th1-type in Ps and PsA. In the skin, a high percentage of epidermal CD8+ and CD4+ T-cells were capable of producing IFN γ and IL-2, with little or no expression of IL-4 or IL-10 (37). In PsA synovium, Ritchlin *et al*. detected high levels of IFN γ , IL-2 and IL-10 but not IL-4 (38). Using quantitative PCR, we have demonstrated increased pro-inflammatory cytokine mRNA expression (IL-1a, IL-1b, IL-8, IL-15,

IFN γ and TNF α in the synovial tissue of 10 PsA patients compared to normal synovial tissue, with the dominant cytokines expressed being IL-15, IFN γ and TNF α , D. Kane, unpublished communication). Danning *et al.* have also shown a similar pattern of cytokine staining in PsA synovium with IL-1 α , IL-1 β , IL-10, IL-15 and TNF α staining localized to the lining layer and perivascular macrophages (39).

Vascular immune mechanisms

Braverman and colleagues first observed specific morphological vascular changes in the skin of Ps patients in the 1970s, when they described subtle changes in the shape and development of skin blood vessels (41). Shortly after this report changes were also noted in the tiny blood vessels of the nailfold in PsA patients using microscopic nailfold capillaroscopy (42). These findings have recently been confirmed although no difference was observed between Ps patients with and without nail disease or DIP joint arthritis (43). Studies of blood flow in Ps skin demonstrate potential abnormalities of function of these vessels, in addition to abnormal blood vessel growth, and showed this could predict the area of skin to be involved in the inflammatory process next by a psoriatic plaque (44). Initial studies of the synovial membrane in PsA described an apparent increase in the number of blood vessels identified microscopically by immunohistochemical staining of SM biopsies (26). More recently, we have examined the morphology of blood vessels in the synovial membrane macroscopically by direct visualization at arthroscopy of PsA and the related spondyloarthropathies (45). This has revealed very similar vascular morphological changes to those described in the skin and the nailfold capillaries of patients with Ps and PsA suggesting a common link. Endothelial cell (EC) activation, growth and angiogenesis are fundamental processes for cellular infiltration and chronic inflammation. Angiogenesis appears to be a prominent event in both the skin and the joint in Ps and PsA. The elongated and tortuous blood vessel pattern noted in the Ps skin and the

PsA joints suggest that angiogenesis is dysregulated resulting in new but immature vessels. Animal models of angiogenesis suggest that the initiation, propagation and stabilization of EC are sensitively controlled by growth factors (47).

Markedly increased levels of TNF- α , transforming growth factor beta (TGF- β), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are found in the skin of Ps patients, which may be responsible for increased EC function and angiogenesis (48). Work in our laboratory, recently identified high levels of VEGF and TGF- β in joint fluid from patients with early PsA (49). A highly novel family of vascular growth factors – angiopoietins are also markedly upregulated in PsA synovial tissue, which co-localise with VEGF mRNA at very high levels in the perivascular areas. Angiopoietins have now been localized to lesional Ps skin (50). These data support the hypothesis that primary vascular damage or change is central in the pathogenesis of Ps and PsA.

The similar findings of vascular morphology and growth factors responsible for regulating angiogenesis in the skin and joints of Ps and PsA, in addition to the expression of similar neuropeptides, may reflect a common neurovascular pathway.

Environmental factors

A 19th century Dermatologist from Breslau, Heinrich Koebner, described the development of lesions of psoriasis on areas of skin which had been irritated by mechanical, physical or chemical agents. It appeared that if the trauma or cutaneous injury involved the papillary layer, then lesional Ps may develop. The mechanism of the Koebner phenomenon is not clear, however the skin is highly innervated and trauma may result in release of potent pro-inflammatory neuropeptides from nerve endings (51).

There are several case reports of trauma initiating PsA, providing substantial evidence that it may be an important aetiological factor, more than in other forms of arthritis. A number of reports demonstrate a contiguous tem-

poral association between traumatic injury and the onset of PsA at the site of injury (52, 53). In a controlled study by Punzi *et al.* 1998, PsA occurs following trauma more frequently than in RA or ankylosing spondylitis (54). The authors also describe higher levels of the cytokine IL-6 in the SF of the PsA patients, as a discriminating factor at the onset of disease. The response of joint inflammation in PsA, arising at the site of trauma, resembles a 'Koebner phenomenon' in Ps. The possible role of the nervous system is also strengthened by the observation that Substance P release from the synovial membrane into joint fluid is blocked when the nerve supply is interrupted (55). In addition, a case described above of digital denervation prevented the development of arthritis in the affected digital interphalangeal joints (5). These observations support a hypothesis of direct neural activation in the translation of a traumatic stimulus into an immunological response (56). The role of trauma in the development of Ps and PsA may represent a common pathogenic pathway, a Koebner phenomenon.

Stress has been implicated as a factor in the onset of Ps, although the disease itself may cause significant stress (57). A number of psychological factors have long been identified as important in Ps (58). Stress may represent a psychological or non-physical trauma, which results in the somatic manifestation of Ps or PsA. Stress-induced manifestations of disease similar to physical trauma, are not clearly understood, however a neuroendocrine link has been suggested (59). CD4 $^{+}$ T-lymphocytes have also been implicated in a model of stress-induced arthritis in animals (60). The primary event is as yet unclear stimulation of neuropeptide release from peripheral nerve endings or activation of T-cells in the target tissue may both represent such an event.

A number of positive clinical and temporal associations suggest infection may represent a causative agent in PsA. Guttate Ps is one clinically distinct form of Ps precipitated by Streptococcal throat infections. In addition, bacteria are closely associated with Reactive

arthritis, which shares oligoarthritis, dactylitis, enthesitis as well as axial skeletal involvement and skin lesions as common clinical manifestations with PsA. Specific organisms including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter* and *Chlamydia* (sexually transmitted) are most well described as triggering a Reactive arthritis. PCR analysis for bacterial DNA, which is highly sensitive, is increasingly positive in inflamed synovial tissue. Such highly sensitive analysis however is demonstrating bacterial antigens in other tissues including uninvolved synovium, so the pathogenic significance of these findings is in some doubt. Finally, as discussed above there are close clinical associations between Ps and PsA with the human immunodeficiency virus (HIV).

One study by Vasey *et al.* in PsA provides some evidence of a link between streptococcal infection and articular inflammation (61). In this controlled study, there were higher levels of antibodies to streptococcal exotoxin in the sera of PsA patients compared to those with Ps alone or RA. These results suggest previous infection while it does not prove a pathogenic role for such antigens. In another study Ishihara *et al.*, demonstrated antibody titers against heat shock proteins of *E. coli*, GroEL and *A. actinomycetemcomitans* DnaJ, which were higher in the sera of patients with another distinct subtype of psoriasis, pustulosis palmaris et plantaris, compared to controls (62). It is not uncommon for secondary infection of psoriasis skin plaques to occur. Bacterial antigens in tissues remains controversial as such antigens have been demonstrated in joint tissue from spondyloarthropathies and from RA (63). In a similar approach, we have recently demonstrated mycobacterial antigens in RA (64). These data suggest that while bacterial or mycobacterial antigens may be present in the skin and the joint, this does not prove a cause or effect role.

Viral infections, as mentioned above, in particular HIV may provide a common basis for Ps and PsA (31). Espinoza *et al.* also noted an increased prevalence of Ps and PsA in patients with HIV in-

fection (65). In a recent study of an AIDS epidemic in Zambia (66) there was a massive increase in reported cases of both Ps and PsA in HIV positive individuals, especially in the earlier stages of infection. The arthritis appeared to be polyarticular, progressive and predominantly with lower limb joint involvement. The observations of a link between Ps, PsA and HIV further support the hypothesis of a specific CD8⁺ T cell response in the pathogenesis. Other viruses may have possible pathogenic links to PsA. Associations between hepatitis C virus (HCV) and PsA have been reported with significantly higher levels of HCV antibodies found in PsA sera (67). The authors compared healthy and Ps controls to PsA, supporting a role for HCV in the pathogenesis of PsA over and above Ps alone. Further studies of DNA showed cytomegalovirus or human Herpes simplex viruses 6 and 7 occurred more frequently in chronic psoriatic plaques, however no specific role has been identified for these viruses in the pathogenesis of Ps (68).

Conclusion

The mechanisms of chronic inflammation in Ps skin and PsA joints appear to share many common features. Although there are a few shared genetic factors, it appears likely that distinct genes may be responsible for skin and joint involvement. Environmental factors provide useful clues to the pathogenic mechanisms. Infection which has been directly implicated in Ps, may also be implicated in PsA, the HIV most strongly associated in this respect. Trauma may be an important factor in the pathogenesis, both physical and psychological (stress) trauma is linked through a number of case reports and epidemiological studies. The clearest evidence in the pathogenesis of PsA points to immune and vascular mechanisms, which suggest CD8⁺ T cells may provide the dominant drive, while angiogenesis another prominent feature, may represent a primary event. In the absence of a single unifying hypothesis, it is likely that a number of factors including genetic, environmental and immunological act in combination

to create the distinctive clinical manifestations of such a complex disease as PsA.

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