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Amplifying the concept of psoriatic arthritis: The role of autoimmunity in systemic psoriatic disease

Maria Sole Chimenti[a,*,1], Francesco Caso[b,1], Stefano Alivernini[c], Erica De Martino[a], Luisa Costa[b], Barbara Tolusso[c], Paola Triggianese[a], Paola Conigliaro[a], Elisa Gremese[c], Raffaele Scarpa[b], Roberto Perricone[a]

[a] Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[b] Rheumatology Unit, Department of Clinical Medicine and Surgery, School of Medicine and Surgery, University Federico II, Naples, Italy
[c] Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that may be present in near 30% of patients affected by psoriasis (PsO), clinically characterized by inflammation of periarticular (e.g., enthesis) and articular structures. Recently, an autoimmune footprint of PsA pathogenesis has been demonstrated with the presence of autoantigens and related autoantibodies in PsA patients' sera. In this context, histological features of PsA synovitis supports the relevance of an autoimmune pathogenesis of the disease. Since there is no currently validated test for PsA, the analysis of PsA synovial tissue revealed pathognomonic characteristics of PsA that may support the clinician in the clinical practice. PsA synovitis is characterized by a sublining infiltrate with T and B cells, vascular proliferation and a relative thin lining layer of proliferating intimal synoviocytes. PsA synovial histopathology shows that ectopic lymphoid-neogenesis with an increase of IL-23 expression. These new pathogenetics features and the systemic nature of the disease raised the concept of a Systemic Psoriatic Disease (SysPsD), characterized by multiple extra-cutaneous and –articular manifestations, highlightening the great heterogeneity of this condition. SyPsD represents a heterogeneous chronic inflammatory condition with a wide spectrum of phenotypical manifestations. The purpose of this review is to describe the new pathogenetic mechanisms and the different clinical pictures of SysPsD, with the ultimate goal of improving the knowledge of this heterogeneous chronic inflammatory condition.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, present in near 30% of patients affected by psoriasis (PsO), clinically characterized by inflammation of periarticular (e.g., enthesis) and articular structures [1]. The pathogenesis is multi-factorial, underlying a relevant role of genetic factors, innate immunity and autoimmune mechanism. The autoimmune footprint of PsA pathogenesis has been firstly hypothesized by the presence of autoreactive T cells in synovium from PsA patients, which were activated by a homologous protein antigen, expressed in the synovium [2]. Then, during the last years, the evidence of autoantigens has been demonstrated as well as the presence of related autoantibodies in PsA patients' sera. Histologic features of PsA synovitis supports the relevance of an autoimmune pathogenesis in the disease. In 2006, in order to emphasize the wide pathogenetic and clinical heterogeneity of psoriasis and Psoriatic Arthritis (PsA), the term “psoriatic disease” (PsoD) was proposed by Scarpa and colleagues [3]. In recent years, the additional evidences on the multiple extra-cutaneous and –articular manifestations have highlighted the great heterogeneity of this condition, that today we feel of recognizing with the comprehensive term of Systemic Psoriatic Disease (SysPsD). Thus, SysPsD represents a heterogeneous chronic inflammatory condition with a wide spectrum of phenotypical manifestations, which can occur only at joint level, or in combination, with several clinical manifestations and multiple different courses. The better knowledge of the pathogenetic mechanisms, of the systemic nature of the disease and of the different treatments options that are considered for PsA patients' treatments underlined challenges in PsA management and treatment. Firstly, several clinical

* Corresponding author at: Rheumatology, Allergology and Immunology, University of Rome Tor Vergata, Via Montpellier 1, Rome, Italy.
E-mail address: maria.sole.chimenti@unroma2.it (M.S. Chimenti).
[1] Equally contributed.

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manifestations and comorbidities needs a better definition and a unique treatment approach. Then, gender differences are relevant in defining clinical phenotype and in choosing the best treatment option [4]. The purpose of this review is to describe SysPsD, focusing on its new pathogenetic approach and clinical aspects, with the ultimate goal of improving the knowledge of this heterogeneous chronic inflammatory condition.

2. Pathogenesis

2.1. Evidence of autoimmunity

In a "continuum model" of immunology, PsA has been hypothesized as a mixed autoimmune - inflammatory disease. In PsA, main inflammatory conditions are represented by activation of innate immune cells, with resultant skin and articular damage [5]. Conigliaro et al. described an abnormal distribution of peripheral blood B cells in both Rheumatoid Arthritis and PsA patients [6]. Peripheral B cells were reduced in PsA patients and their levels were restored after Tumour necrosis factor inhibitor (TNFi) treatment suggesting a role of B cells in PsA pathogenesis [6]. Actually, no reliable serological markers are available for diagnosis and follow-up of PsA patients and laboratory evaluation shows usually negative serological test for Rheumatoid Factor (RF) and anti-citrullinated peptide autoantibodies (ACPA) [7]. However, also during PsA inflammation as well as in RA, several protein modifications may occur supporting the strong link between autoimmunity and inflammation. Although rarely, proteins citrullination, as a post-traslational modification, and the positivity of ACPA, which represents a characteristic marker of RA, can also be found in PsA patients correlating with a polyarticular subset, female sex, more aggressive and erosive joint involvement and higher use of systemic therapies [8–10]. The effects of carbamylation on proteins and its effect in inflammatory arthritis has been also investigated in both RA and PsA. Carbamylation is a post transcriptional modification which occurs during inflammation, and carbamylated proteins are recognized by circulating antibodies, the anti-carbamylated protein (anti-CarP) antibodies [11]. The presence of anti-CarP antibodies in PsA patients' sera with active disease, in the absence of RF and/or other known autoantibodies specificities, was demonstrated. A further support of an autoimmune origin of PsA is the evidence of an autoimmune antigen, called the PsA antigen, recognized by IgG derived from PsA patients' sera. This peptide express several homologies with skin, joint and enthesis [12]. The detection of ectopic lymphoid structures and neogenesis in PsA synovial tissues suggests a possible role of antibodies against local autoantigens [13]. Recently, the cationic antimicrobial peptide, cathelicidin LL37, has been recognized as self-antigen for circulating and cutaneous psoriatic autoreactive T-cells [14]. LL37 binds nucleic acids and induce the synthesis of pro-inflammatory cytokines and type I interferon (IFN-I), plasmacytoid/myeloid dendritic cells via Toll-like-receptor (TLR) 7/8/9 [15]. Results from a recent study from Frasca and colleagues have suggested that anti-LL37 antibodies could represent possible pathogenetic biomarker in PsA. In particular, antibodies to carbamylated-LL37 have been correlated with articular severity and as potential disease activity biomarkers [16]. The authors suggest that innate immunity and in particular complement system (CS) fragments as C5a and GM-CSF play a role in the activation of pathogenic pathways that ultimately lead to autoimmunity via neutrophil activation. This hypothesis is supported by the fact that GM-CSF levels in the synovial compartment correlate with autoantibody reactivity. This association has been demonstrated in the presence of anti-LL37 antibodies that react to the post-translational modified versions of LL37 carbamilated [16].

2.2. Laboratory markers

Inflammatory markers, erythrocyte sedimentation rate (ESR), C-reactive protein (C-RP) and high sensitivity C-reactive protein (hs-CRP), are found elevated in above 25–50% of the PsA cases [7–18]. Data concerning the role of CS in PsA are poor in the literature. Early studies on psoriatic patients have shown increased plasma concentrations of iC3b, C4d, and Bb fragments, in patients with PsO and PsA [19]. Synthesis of complement components occurs in chronically inflamed tissues such as RA synovium and the synovial membrane cells thought to be responsible for such synthesis are lining cells (type A-mononuclear phagocyte, type B-fibroblast like), fibroblasts, mononuclear phagocytes and endothelial cells [20]. No data have been reported concerning production of complement factors in psoriatic synovium. Partsch et al. showed that synovial fluid (SF) from patients with PsA exhibits low percentage of the C3c cleavage product, in similar amounts than in patients with osteoarthritis (OA). The same authors showed that SF from PsA patients displays the highest C3 concentration when compared with RA and OA. These evidences suggest that synovial C3 can be helpful for establishing the differential diagnosis between PsA and RA [21]. In 2012, we demonstrated that PsA patients with a moderately to severe active disease show higher baseline C3 and C4 levels compared with a group of healthy subjects. A significant improvement of disease activity and laboratory features were observed after 22 weeks of TNFi therapy and were associated with a significant decrease in all the inflammatory markers including complement C3 and C4 [22]. Pathologically elevated complement levels of C3 may reflect the presence of an underlining systemic inflammatory process [23]. The relevance of adopting complement C3 as a marker of prediction and response to TNFi is linked with the feasibility of the assessment method, which is widely available, relatively cheap, fast, and highly standardized [22].

Other studies have focalized attention on bone remodelling and cartilage damage markers. In this context, osteoprotegerin, cartilage oligomeric matrix protein (COMP), and matrix metalloproteinase 3 (MMP-3) levels have been found higher in patients with PsA versus psoriasis [2].

Researchers are also focalized on synovial biomarkers in PsA and assessment of inflammatory severity at the single joint level [24,25]. Results from these studies have shown the participation of several cytokines and chemokines, including IL-1, IL-8, and the IL-6/IL-17 cytokine axis, in PsA inflammation, and their correlation with systemic disease activity [24,25]. In particular, the association with disease activity and IL-6 and IL-1ß levels in SF have been hypothesized as potential biomarkers of the PsA knee synovitis [24,25].

2.3. Synovial tissue features of PsA

The development of minimally invasive technique enabling the collection of synovial tissue in patients with chronic inflammatory arthritis have improved our knowledge about synovial tissue features and pathological events occurring in PsA patients in different disease phases [26]. In particular, the synovial tissue analysis in patients with seronegative (RF and ACPA respectively) Undifferentiated Peripheral Inflammatory Arthritis (UPIA) revealed that patients with high chance of future disease differentiation towards definite arthritis (including PsA) show, at the time of the first clinical evaluation, higher histological scores for inflammatory (sublining CD68+ and CD3+ cells) and vascular parameters (CD31+ vessels) and a specific microRNA synovial tissue signature. In particular, UPIA patients with the highest risk rate of differentiation showed at synovial tissue level, repression of miR-346 associated with increased expression of TNF in synovial tissue lysates suggesting that the stability of TNF is epigenetically regulated in such patient category [25]. Belasco et al. conducted a

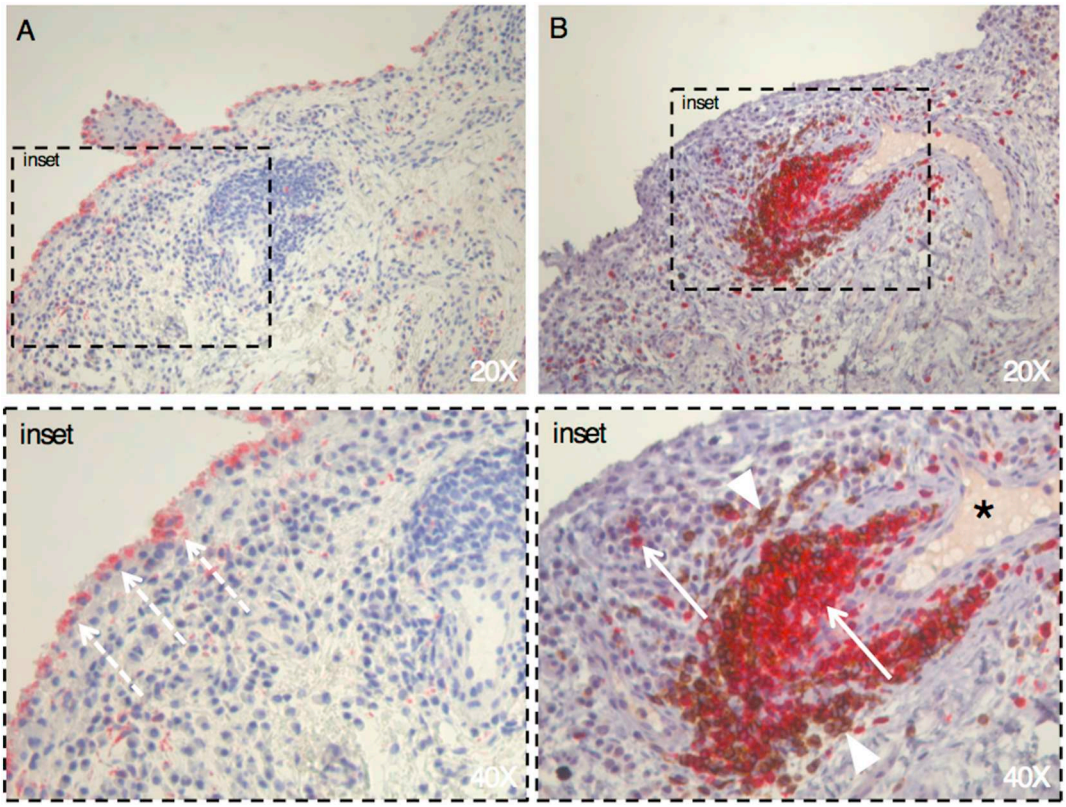

Fig. 1. Histological features of PsA synovitis. Example photos of synovial tissue from naive to treatment PsA patient, at disease onset, collected by ultrasound-guided procedure. (A) Immunohistochemistry for $CD68^+$ (RED) cells and (B) double-IHC for $CD3^+$ (RED) and $CD20^+$ (DAB) (Magnification 20×). In the insets $CD68^+$ cells are indicated by white dotted arrow, $CD3^+$ cells by white arrow and $CD20^+$ cells by white arrow head respectively. The lymphoid aggregate is located in proximity of synovial vessel (*) (Magnification 40×) (Synovial Biopsy Unit of the Division of Rheumatology – Fondazione Policlinico Universitario A. Gemelli IRCCS – Università Cattiolica del Sacro Cuore).

comprehensive analysis of cytokine and chemokine activation and genes representative of the inflammatory processes in PsA skin and synovial tissue and other forms of arthritis, finding that gene expression in PsA synovium was more closely related to gene expression in PsA skin than to gene expression in synovium in other forms of arthritis [27]. However, PsA gene expression patterns in skin and synovium arose to be clearly distinct, showing a stronger interleukin-17 (IL-17) gene signature in skin than in synovium and more equivalent TNF and INF gamma gene signatures in both tissues. Moreover, the top differentially expressed genes in synovium were not generally related to an IL-17 gene signature. Instead, many of the top genes and predicted upstream regulators were related to cartilage and bone breakdown and formation of the angiogenesis that is present in PsA [28]. At disease onset, PsA often resembles other forms of arthritis especially RA when considering the peripheral phenotype and in autoimmune seronegative clinical settings [29]. Despite the similarities between PsA and RA, their distinctive pathologies require different treatments. For example, drugs that are effective in RA may not be effective in PsA and can even cause adverse effects. Since there is no currently validated test for PsA, the diagnosis is often missed or delayed and this has functional consequences for the patient. The analysis of PsA synovial tissue revealed differentially distributed characteristics compared to RA which may support the clinician in the clinical practice. In particular, previous studies conducted using arthroscopic technique revealed that PsA synovitis is characterized by a sublining infiltrate with T and B cells, vascular proliferation and a relative thin lining layer of proliferating intimal synoviocytes (Fig. 1). Indeed, previous studies suggested that PsA synovitis may be distinguished from RA with quantitative differences in tissue features, despite there are no unique pathological hallmarks in either disease [25]. Kruithof et al. performed a comparative studies about synovial tissue features among different types of arthritis finding that PsA synovial histopathology resembles more spondyloarthritis than RA in terms of vascularity, CD163+ macrophage and neutrophil counts [30]. PsA has been widely considered to be a seronegative disease as shown by the plasma/serum negativity for RF and/or ACPA. Despite this serological feature, synovial tissue analysis of PsA shows that ectopic lymphoid-neogenesis can be detected in synovial tissue as demonstrated by the presence, at disease onset, of CD21+/CD23+ follicular dendritic cells within CD3+ and CD20+ cells aggregates [16]. Moreover, Celis et al. analyzed the cytokines and chemokines expression profile, at synovial tissue level, of PsA patients finding that, PsA patients with synovial tissue aggregates showed an increase of IL-23 expression compared to PsA patients without synovial aggregates showing a clear predominance of plasma IL-17 [31]. Lymphoid aggregates occur in association with peripheral lymph-node addressin-positive high endothelial venules and with the expression of the C-X-C Chemokine ligand 13 (CXCL13) and C-C Chemokine ligand 21 (CCL21) [32]. Prospective studies evaluating the relapse rate in PsA patients in sustained clinical remission demonstrated a high rate of disease flare in case of treatment discontinuation [25–33]. The analysis of synovial tissue obtained from PsA patients in sustained clinical and ultrasound remission gave new insights into the tissue composition of such patient category [34]. In particular, despite clinical and imaging remission, PsA

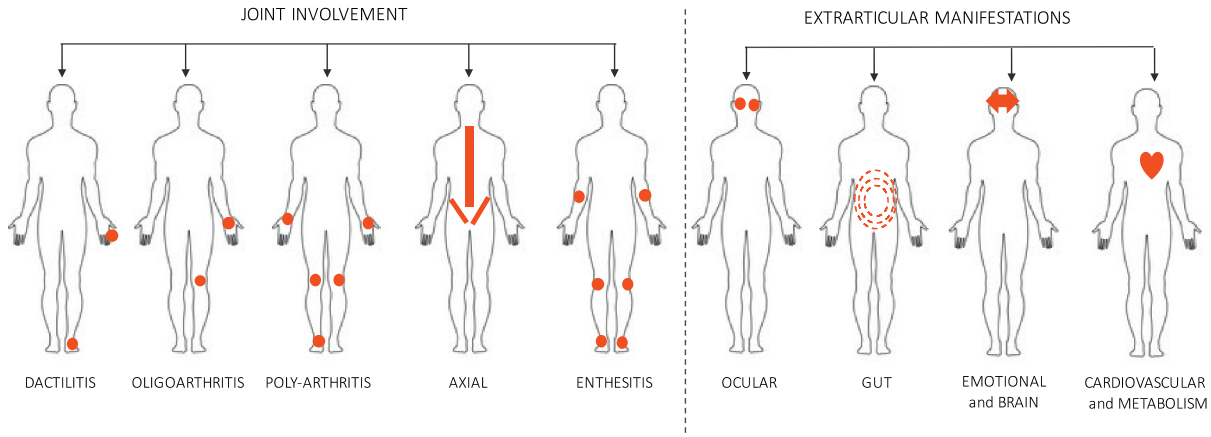

Fig. 2. Multisystemic aspects of Systemic Psoriatic Disease.

patients showed clear signs of histologically proven subclinical synovitis, in terms of CD68 + and CD3 + cells residual infiltrated as well as CD31 + synovial vessels. These data suggest that an urgent medical need in the management of PsA patients is even the identification of useful biomarkers for the selection of PsA patients eligible to treatment modification after sustained clinical and ultrasound remission achievement. (See Fig. 2.)

3. Clinical aspects

3.1. The cutaneous phenotypes of systemic psoriatic disease: psoriasis

Among the phenotipical manifestations, PsO represents the cutaneous expression of the SysPsD, and it can occur alone or in concomitance of articular and/or extrarticular manifestations [35] PsO represents a chronic inflammatory skin condition showing a high prevalence with a frequency ranging from 0.1% to 3% in different populations [36] Well-delineated, variably sized erythematous papules and plaques frequently covered with layers of silvery scales represent the characteristic lesions [37]. Pustular and erythrodermic lesions can also verify and be concomitant with constitutional systemic symptoms and febrile episodes [37].

Chronic plaque psoriasis, alternatively named as psoriasis vulgaris, represents the most frequent form, showing in about 80–90% of psoriasis cases [36,37]. Round or oval demarcated erythematous macules or papules, usually covered with poorly adherent silvery-white scales, show usually on the scalp, extensor surfaces of elbows and knees, and lumbosacral and intergluteal regions. After the onset, papules tend to progress to larger lesions with their fusion (plaques) remaining stable or enlarging [36,37]. In the context of plaque PsO, Koebner phenomenon represents the appearance of a new psoriatic lesion following direct cutaneous trauma and Auspitz phenomenon consists in several small isolated capillary bleeding on the surface of a psoriasis papule or plaque resulting after scales removal [36–38].

In addition to skin, also nails can be frequently involved in PsO and often associated with distal interphalangeal (DIP) joint arthritis [38,39]. Nail pitting represents a frequent sign of involvement of the nail matrix; it is characterized by small round lesions within the surface of the nail plate [38,39]. When nail bed is involved, a salmon area or oil spots sign are present. Other signs can be represented by onycholysis, subungual hyperkeratosis, leukonychia, vertical or transverse signs, and lunula red spots nail bed hemorrhages [38,39]. Studies examining clinical risks factors for PsA development among patients with PsO showed that there is a link among sites of PsO in PsA patients [40,41].

Psoriatic nail disease is associated with enthesitis, or inflammation at the site where the extensor tendon attaches to the nail unit [40,41]. Inflammation of the enthesis likely precedes joint involvement and it may be similarly true that nail disease precedes development of PsA (particularly DIP arthritis). Nail disease may be a marker of increased "immunoreactivity" which leads to the development of PsA or nail disease may not be a "risk factor" for disease but rather an early phase of PsA, and thus a predictor of the onset of clinically overt PsA [41].

A link has been hypothized with severity of PsO: severe PsO is more common among PsO patients with PsA than patients without PsA [41]. It is plausible that a higher burden of skin inflammation may lead to increased systemic inflammation and trigger development of PsA. Beyond PsO severity, location of PsO may be associated with development of PsA. Wilson et al. found that PsO involving the scalp and intergluteal and/or perianal region were associated with development of PsA [41]. This finding could also be a reflection of more severe PsO or more thorough examination of the skin (and likewise a more thorough examination of the joints). Finally, earlier age of onset of PsO has also been associated with the development of PsA in one study, suggesting that disease duration (and possibly inflammatory burden over time), may be important [42,43]. It may also be that patients with earlier onset of PsO have different genetic determinants of disease which may also contribute to development of PsA [43].

3.2. The articular phenotypes of systemic psoriatic disease: psoriatic arthritis

PsA is characterized by a heterogeneous arthropathy and it represents the articular phenotype of Systemic PsoD [44]. PsA can affect equally men and women with an average onset age around the fourth decade of life [35]. Involved articular sites are represented by sacroiliac joints and spine (axial pattern; spondylitis), peripheral joints (peripheral arthritis), insertion sites of tendons and ligaments into bone (enthesitis), and proximal and distal interphalangeal (PIP and DIP) joints and soft tissue of digits (dactylitis) [7–35]. Any of these phenotypical aspects can occur as isolated manifestation or in a combined manner, leading to a very wide heterogeneity of the disease. Classification Criteria for Psoriatic Arthritis (CASPAR) criteria are used to categorize research cohorts, showing high specificity (99%) and sensitivity (91%) [45]. PsA represents a significant health issue with important social-related implications [7–35],mainly correlated to disability, and impacts on patients' function and quality of life (QOL) [46]. The recognition of the clinical aspects by physical examination represents the key element for addressing PsA diagnosis but the use of imaging techniques, including conventional radiography, magnetic resonance imaging (MRI) and ultrasonography (US) can represent valid tools able to support the diagnosis, and to monitor the inflammatory joint involvement and detailing the location and severity of the inflamed joints [47].

Table 1
Main clinical and radiological findings of the Psoriatic Arthritis subsets.

	Main articular aspects	Possible subset overlap
Axial involvement	Bilateral or more often unilateral sacroiliitis; Spondylitis. Main radiological findings: Nonmarginal syndesmophytes distributed asymmetrically along the spine; bilateral or unilateral sacroiliitis.	Peripheral arthritis.
Symmetrical polyarthritis	Symmetrical inflammatory involvement of ≥4 peripheral joints. Main radiological findings: erosions are often associated with ankylosis and periostitis.	Axial involvement; DIP arthritis.
Asymmetrical oligoarthritis	Aymmetrical involvement of less than four joints; dactylitis can frequently occur. Main radiological findings: erosions are often associated with ankylosis and periostitis.	Axial involvement; DIP arthritis.
DIP arthritis	Symmetrical or asymmetrical DIP arthritis occurs more frequently in advanced phases and can be associated with onycopathy. Main radiological findings: Presence of marginal erosions associated with adjacent bone proliferation; resorption of the tufts of terminal phalanx both of hands and feet.	Axial involvement; peripheral involvement (symmetrical polyarthritis, asymmetrical oligoarthritis and arthritis mutilans).
Arthritis mutilans	Rare phenotype occurring in < 1% of PsA patients. It shows with osteolysis of phalanx and metacarpals with digital shortening. Main radiological findings: Osteolysis of phalangeal, metacarpal, and metatarsal bone (telescoping digits); periarticular and shaft periostitis; pencil-in-cup deformity.	Generally, Arthritis mutilans represents an isolated articular phenotype.

Legend: DIP: Distal interphalangeal; PsA: Psoriatic Arthritis.

3.3. Enthesitis and dactylitis: two common clinical features of psoriatic arthritis

Clinically, enthesitis and dactylitis represent common clinical features of PsA, being observed both in up to about 50% of PsA patients [48]. Enthesitis is a common feature of spondyloarthritis, but occurs more frequently in PsA. Indeed, it can verify in about 40–50% of PsA patients. Enthesitis represents the inflammation of entheses at sites where tendon, ligament, and capsule insert into the bone. Radiographically, it may be verifiable as spurs. It most commonly verify at level of the insertion sites of plantar fascia and Achilles' tendon, followed by insertion sites around the patella, iliac crest, epicondyles, and supraspinatus. [7–48].

Dactylitis represents the inflammation of joints, flexor tendon sheaths, and adiacent soft tissues of a whole digit. It can manifest both in acute (painful digit with clears signs of active inflammation and limitations of movements) and chronic form (swollen and not painful digit, often associated with limitations of movements) [7–49]. The inflammatory processes may involve one or more several digits and prevalently verifies at level of the third and fourth toes [50,51].

Dactylitis is frequently associated with a severe PsA pattern characterized by polyarthritis, articular erosion, and juxta-articular bony proliferations [50,51].

Psoriatic Arthritis clinical subsets.

Clinically, on the basis of the main articular site involved, PsA can be classified into five subsets: axial PsA, symmetrical polyarthritis, asymmetrical oligoarthritis, DIP arthritis, and arthritis mutilans (described in Table 1) [50–52]. These patterns can overlap and change over time. Frequent is the case of a combination between peripheral arthritis, in particular polyarthritis and DIP arthritis, with axial involvement [53]. (See Table 2.)

Axial involvement is characterized by inflammatory back pain, localized in the sacroiliac area, or the cervical, thoracic, and lumbar spine [52,53]. Pain worsening, in association with prolonged stiffness lasting > 30 min', show with inactivity, and improve with activity [53].

Isolated axial involvement is very rare occurring in up to 5% of PsA patients and it can manifest more frequently in association with peripheral arthritis [53]. Axial involvement of PsA provides a bilateral or more often unilateral sacroiliitis with erosion sclerosis and ankylosis [54].

PsA spondylitis is characterized by peculiar radiologic features, such as syndesmophytes, often asymmetrical and nonmarginal, and randomly distributed along the spine [54]. Bulky, large and asymmetrical paramarginal vertical syndesmophytes can involve more often the upper lumbar and lower thoracic spine. The ossified bridge shows separated from the external fibers of the annulus fibrosus [54,55].

Peripheral articular involvement shows often in concomitance of a more or less evident joint swelling and associated with prolonged stiffness lasting > 30 min'. Joint pain and stiffness are worse with inactivity and improve with activity [56]. Joints more frequently involved are represented by the joints of the feet and hands, followed by knees, wrists, ankles, and shoulders. Peripheral articular phenotypes can change over time and often overlap with axial involvement [56,57]. Thus, patients can present symmetrical

Table 2
Extrarticular manifestations of Systemic Psoriatic Disease.

	Prevalence	Clinical Manifestation	References
Cardiovascular	30–37.1%	Hypertension, MACE	[84,85,88,92]
Liver	28%	Steatosis, Nonalcoholic fatty liver disease	[69]
Eye	30%	Uveitis, episcleritis, scleritis, keratitis, macular oedema, glaucoma and cataract	[76–79]
Intestinal	5–7.2%	Crohn's disease, Ulcerative colitis,	[125,126]
Overweight/Obesity	72%/ 30%	high abdominal fat mass	[111–113]
MetS	10–20%	large waist circumference, increased thirst and urination, fatigue, and blurred vision	[103–105] [108,109]
Psychological symptoms	20.7%	Depression, anxiety, alexithymia	[130,131]
Lung	< 1%	Dyspnoea; Apical pulmonary fibrosis	[134]
Urogenital	< 1%	Urethritis, prostatitis, IgA nephropathy	[69]

Legend: MACE: major adverse cardiovascular events; MetS: Metabolic Syndrome.

polyarthritis, with five or more joints involved; this PsA pattern resembles that of RA [56,57]. Characterizing clinical findings which can be usually found in psoriatic polyarthritis and not in RA are mainly represented by concomitance of psoriasis, DIP involvement, enthesopathies, dactylitis, spondylitis and sacroiliitis [55–57]. Additionally, in this PsA pattern, although the great part of articular involvement is symmetric, the distribution can have a tendency to be asymmetrical [55–57]. In addition, while in RA, bone erosions represent characterizing findings and osteoporosis can represent a frequent finding both at a systemic level and at level of involved joints, in PsA, local mechanisms of bone loss are associated with new bone growth mainly represented by ankylosis, periostitis, and syndesmophytes [57].

PsA oligoarthritis represents another peripheral articular pattern of the disease. It is characterized by asymmetrical involvement of less than four joints (asymmetrical oligoarthritis) [55]. It can verify in about 40% of the PsA patients and more frequently in early phases [51,55]. Dactylitis may represent a typical clinical feature [55]. Distal interphalangeal arthritis (DIP arthritis) can occurr symmetrically or asymmetrically and frequently associated with psoriatic onycopathy, likely because of the contiguity between nail, extensor tendon attachment site, and DIP joint [57]. Erosive changes start at level of the margins of DIP joint, and later progress centrally. DIP arthritis occurs less frequently as a single manifestation of PsA and more often combined with other articular phenotypes [58]. This verifies in concomitance of about 15% of all axial cases [57,58].

In several PsA cases, especially when involvement of DIP joints occurs isolated, it needs differential diagnosis with erosive Osteoarthritis (OA) of the hands and in doubtful cases, MRI can be useful to detect inflamed entheses with bone edema, addressing the PsA diagnosis [59].

Arthritis mutilans represents a rare (in < 1% of patients), rapidly destructive and severe PsA peripheral phenotype. It generally can show more often as an isolated articular subset or associated with nail dystrophy and axial involvement. It occurs more frequently at a younger age and with poorer function when compared with other PsA pattern [52,60]. The prominent findings are represented by the osteolysis of phalanx and metacarpals (opera glass) [60].

Psoriatic arthritis sine psoriasis is characterized by HLA-Cw*6 positivity, dactylitis and DIP arthritis in the absence of an overt PsO and in presence of a familial history of PsO in first- and/or second-grade relatives. Enthesitis, tenosynovitis and axial involvement can occur but show less frequently than in PsA with clinical evidence of PsO [61].

3.4. Gender related differences in clinical phenotypes

Finding potential factors that may improve management of PsA patients is raising significant importance in the context of a personalized medicine. Gender related differences have a crucial role in response to treatment and rates of remission in PsA patients. Although it is established that both genders are affected equally in PsA [62,63], it has been shown that men and women present different clinical patterns of joint involvement. Female sex has been associated with a prevalent polyarticular phenotype, along with higher swollen joint counts and greater functional impairment [64], while an oligoarticular-form, as well as a major rate of extrarticular manifestations and higher Psoriasis Area Severity Index (PASI) scores, are more frequent in male sex [65]. Compared to women, males suffer from more severe axial spine damage, while females are more likely to have peripheral erosive joint involvement and a reduced quality of life [66]. Overall, higher scores in disease activity, pain and lower Health assessment questionnaire (HAQ) scores have been demonstrated in women than men. It has been hypotizesed by Lubrano and colleagues that this difference might be due to the presence of fibromyalgia (FM), which could often overlap in SpA women and be a confounding factor [4].

Distinct patterns of the disease can probably depend on different factors, such as hormonal changes, differences in occupational physical activity and also overexpression of certain MHC genes between the two genders, as postulated by Queiro et al. [67], but data in literature are still controversial. According to Kemal et al., gender specific differences in a turkish population of PsA patients revealed that males affected tend to have higher PASI scores and longer duration to develop arthritis after the onset of PsO, while women are more likely to have higher BMI and disease activity [68]. The contemporary presence of male gender and axial subset showed an increased risk of developing extra articular manifestations, as stated by Peluso et al. Bowel, ocular and urogenital involvement were significantly increased in men, while cardiovascular diseases were present at a higher percentage in women [69]. Concerning PsA treatment, female gender is associated with poor rates of response to TNFi and lower probability of achieving remission compared to men. Gremese et al. showed that female sex is an independent predictor of failure to obtain a clinical response after 12 months of TNFi therapy in patients with axSpA treated with TNFi [70,71]. Studies in large cohorts of PsA patients confirmed that female sex and the presence of comorbidities as metabolic syndrome (MetS) are associated with a lower probability of remission and should be considered in the evaluation of target treatments in PsA patients [70,71].

3.5. Women as a special population: pregnancy and breastfeeding

Pregnant and breastfeeding women with rheumatic diseases always need special management and careful attention for the safety of both mother and fetus. Pre-conceptional counseling and risk assessment before attempting pregnancy should be performed to increase the probability of success of delivery. Evaluation of disease activity might be influenced by physiological modifications of laboratory parameters during pregnancy and adapted indexes have not been assessed [72]. The course of the disease can be extremely variable: Polachek et al. reported a favorable course of joint and skin activity respectively of 58.5% of patients over pregnancy and in 52.5% in the first year after delivery [72]. High level of oestrogens during pregnancy could be responsible for the improvement of PsO according to Murase et al., while worsening of the skin disease in postpartum period due to drop of oestrogen levels has been showed by several further studies [73–75].

3.6. Extrarticular manifestations of systemic psoriatic disease

SysPsD can show a wide spectrum of extra-cutaneous and -articular phenotipical manifestations, represented by uveitis, metabolic syndrome (MetS), atherosclerosis, colitis, emotional and psychological symptoms. These can occur with different frequencies in course of PsO and PsA and alone or in combination [46].

3.7. Ocular manifestations

Ocular manifestations represent frequent extra-articular findings, occurring in 10% of PsO patients and 30% of PsA patients [76–78]. Recurrent acute anterior uveitis represents the most frequent manifestation of ocular involvement and it shows frequently bilateral [79]. Uveitis can show severe yet in initial phases and became chronic in the course of the disease. Patients with articular involvement can show more severe ocular course than those with only cutaneous manifestations. Uveitis can precede the onset of the articular and cutaneous manifestations [80].

In patients with PsO, it has been suggested that uveitis could represent a feature of systemic inflammation and an early indicator of inflammation preceding the development of articular signs [81]. PsA anterior uveitis has been reported frequently associated with HLA-B27 positivity [82]. Other ocular manifestations have been reported in

course of SysPsD and among those conjunctivitis, followed by episcleritis, scleritis, keratitis, macular oedema, glaucoma and cataract [83]. Recently, we have evaluated eye involvement in a cohort of PsA patient's sine-PsO for dry eye and retinal abnormalities (unpublished data). PsA patients presented high prevalence of dry, abnormalities in eye function and in morphology, with a strong association with systemic inflammation.

3.8. Cardiovascular and metabolic-related manifestations

In comparison with the general population, patients with PsO and PsA show an increased risk of cardiovascular (CV) risk factors and CV events. Further, the PsA phenotype shows a higher CV risk than those with PsO alone, suggesting a more severe inflammatory involvement [84]. Despite the considerable contribution to CV morbidity of traditional risk factors, CV risk appears to be also independent of traditional cardiovascular risk factors [85]. Severe PsO and PsA have been reported as independent risk factors for major adverse cardiovascular events (MACE), including myocardial infarction, and stroke [84–86]. In PsA, the number of dactylitic digits and ESR have been reported independent and significant predictors of MACE [87]. However, until today, it is not clarified how predict CV risk in patients with psoriasis and PsA. In a recent study, five original and adapted CV risk algorithms according to EULAR recommendations, SCORE, CUORE, Framingham Risk Score (FRS), QRISK2, and Reynold's Risk Score (RRS) have been reported not sufficiently accurate in predicting cardiovascular events when applied on PsA [88]. Evaluation of atherosclerotic processes by imaging can represent a valid diagnostic strategy. Indeed, in comparison with healthy controls, patients with PsO and PsA seem to have higher prevalence of subclinical atherosclerotic process, even in the absence of CV risk factors [88–90]. Subclinical echocardiographic findings of left ventricle diastolic function have been observed in up to 30% and 60% of patients with psoriasis and PsA, respectively [91–93]. Other echocardiographic findings may include alterations in aortic elasticity, pulmonary hypertension, mitral and aortal valves insufficiency, and left ventricle hypertrophy with concomitant hypertension [94–96]. It has been also described a high prevalence of subclinical atherosclerosis as measured by means of carotid ultrasonography and the average values of carotid artery intima-media thickness (IMT), both in patients with and without CV risk factors or cardiovascular disease [97,98]. A significant positive correlation has been found between the average IMT and traditional cardiovascular risk factors (Body Mass Index (BMI), systolic blood pressure, and levels of glucose) and characteristics of SysPsD, such as duration of psoriasis and axial involvement [97]. The presence of carotid plaque has been found associated with age, triglyceride levels and the severity of articular manifestations [99] and greater carotid IMT values have been found in patients with articular involvement than in patients with psoriasis alone [100]. Further, Gonzalez- Juanatey, C., et al. have found a higher prevalence of endothelial dysfunction in patients with PsA without CV risk factors or CV disease than matched controls [101]. Various studies have shown that, in comparison with healthy controls, PsA patients without CV risk factors display increased aortic stiffness, a marker of atherosclerotic disease, [102] and hypertension has been found in about 30% of PsA and psoriasis patients, with a significant higher prevalence when compared with controls [103]. The increased rate of CV events in PsoD patients has been found correlate also with the presence of traditional CV risk factors such as obesity, MetS and its components [104]. If prolonged inflammatory background may be an important cause of accelerated atherosclerosis and CV risk in patients with SysPsD, also MetS and its components particularly body mass index (BMI), dyslipidemia and diabetes Mellitus (DM) could play a key role [105,106]. In course of SysPsD, altered BMI and obesity have been proposed factors sustaining a systemic low-grade inflammation that can amplify articular, cutaneous and CV manifestations [107–109]. Not coincidentally, different studies have shown that PsA incidence rate was increased with increasing BMI. In particular, a history of increased BMI in early adulthood has been reported as a key predictor of PsA presence in adult patients; for each unit increase in BMI at 18 years of age, it has been found a 5% increase in the risk of PsA. Patients with cutaneous PsO with a history of obesity at age 18 years have been found three times more likely to develop articular manifestations than normal-weight subjects [110,111]. Further, a number of studies have reported an increased prevalence of dyslipidemia, such as a shifted and atherogenic lipid profile with decreased HDL-C and increased LDL-C levels, especially in patients with active disease, suggesting a potential relationship between the lipid profile and inflammatory state [112–114]. Both in Psoriasis and in PsA, an increased prevalence of Type II DM has been observed (in 10 to 20% of patients with articular involvement). This finding may be partially explained by increased obesity and unhealthy lifestyles, and could be related to insulin resistance associated with PsoD inflammation. However, the connections between psoriatic disease and the risk of DM remains unknown [115,116].

Generally, MetS is closely associated with chronic “inflammation” characterized by abnormal cytokine production, increased acute-phase reactants and other mediators, and activation of a network of inflammatory signaling pathways [114]. Hence, a complex integrative pathogenesis could interconnect PsA inflammation with metabolic and cardiovascular disorders [100,114]. Adipose tissue secretes several adipokines that produce inflammation and cardiometabolic dysfunction. Adipokines, MetS, and inflammatory severity seem to be reciprocally correlated in PsA patients [100]. Both pro- and anti-inflammatory adipokines produced by adipocytes and immune cells residing within the adipose tissue could regulate metabolism, insulin sensitivity and inflammation [114,115]. If in PsO several evidences have suggested that adiponectin, which is an anti-inflammatory molecule, could play a preventive role in the development of cutaneous manifestations [114], in PsA, its levels have been found unexpectedly increased [115]. However, for this last finding, it has been suggested that adiponectin local synthesis, effect and regulation could differ between the joint, the skin and the blood serum [115]. High serum levels of the pro-angiogenic leptin have been found higher in women with PsA compared to PsO patients [115]. Other adipokines involved in the pathogenesis of inflammatory articular and cutaneous manifestations of SysPsD including TNF and interleukin (IL)-6 have been hypothesized as possible factors underlining MetS and CV aspects of the disease [116–118]. TNF alters expression of other adipokines such as leptin, which can impact metabolism and insulin sensitivity [119]. This, in SysPsD, TNF could represent not only responsible for promoting inflammation and bone destruction in PsA patients, but can also key in promoting insulin resistance [119,120]. However, despite evidences suggest a possible involvement of proinflammatory cytokines in the pathogenesis of MetS and CV risk, the effect of different therapies on these aspects remains still unclarified [120,121]. The identification of high CV risk patients with PsO and PsA could represent a key step in order to implement preventive strategies, like lifestyle changes and pharmacological interventions.

3.9. Gut and liver inflammation

In a 2000 study, microscopic changes, increase in lamina propria cellularity, consisting of plasma cells and lymphocytes, and lymphoid aggregates were found by bowel mucosa biopsies conducted in patients with both active PsO and PsA without bowel symptoms [122]. More recently, subclinical gut inflammation has been confirmed and reported as characterized by a specific histologic and

immunologic signature represented by pronounced Paneth cell hyperplasia and Th17 and Th9 responses [123,124]. Th9 responses have been reported to be a specific PsA signature when compared with AS and Crohn's disease [125]. A possible link has also been hypothesized between intestinal and synovial inflammation through IL-9 overexpression and Th9 polarization that occur in synovitis and in the peripheral blood of patients with PsA. This could suggest a potential existence of a bowel-joint migratory axis [125]. It remains still to clarify the possible role of the specific bacterial changes in the composition of fecal microbiota and its interaction with immune system and host genetic background in modulating gut mucosa responses and systemic symptoms in SysPsD [126]. With regard the possible liver involvement in course of SysPsD, few data are available on non-alcoholic fatty disease. This has been reported be more frequent in PsA compared with the general population. Patients with PsA with more disease activity show higher-grade steatosis. Better control of the inflammatory process of patients with PsA is correlated to less US worsening of hepatic steatosis. The extent to which the observed effect is mediated by bDMARDs remains unclear [127].

Emotional and psychological symptoms.

Emotional and psychological symptoms are frequent and important in PsA. Patients with psoriasis and PsA have a high prevalence of anxiety and depression symptoms, up to 36% [128].

Depression and anxiety are associated with various disease related factors (actively inflamed joints, disability, pain and fatigue). When compared to RA patients, the prevalence of moderate to severe levels of anxiety and depression symptoms is higher in PsA patients, especially in those with severe disease (36.7%) [128,129]. Assessment of depression and anxiety in PsA is a key aspect in the management of patients with psoriasis and PsA since these correlate with a poor quality of life and with a poor adherence to therapies and reduced likelihood of joint and cutaneous remission [129]. In this context, alexithymia is conceptualized as a disorder of emotion regulation mechanisms, which involves a dissociation of emotional and physical responses to life events and bodily sensations [130]. Sifneos coined the term alexithymia to describe people who lack the ability to communicate their feelings or have limited imagination. We observed a high prevalence of alexithymia in PsA patient with an active disease. A hypothesis takes in consideration the role of TNF in the inflammatory process. This cytokine, strongly associated with the pathogenesis of RA and PsA, is able to interact with receptors expressed on the surface of the astrocytes, inducing them in a pro-inflammatory condition. TNF is also involved in some central nervous system pathologies such as Alzheimer [131]. At the same time, TNF has a role in influencing the circadian clock, mediated by the clock genes (Cry1 and Tef), with a direct action on these genes [132]. In particular, the abnormal expression of these genes, altered in cells stimulated by TNF is associated with depression.

3.10. Lung and urogenital involvement

Peluso et al. described higher rates of extra-articular manifestations in smoker male PsA patients with a prevalent axial component and prolonged disease duration. The concept of PsA as a SysPsD reveals as different sites may be involved at the same time or in differential sequential stages [69]. Urogenital tract involvement is gaining increasing attention, as it has been postulated to be early site of infection by microorganisms involved in pathogenesis of PsA. Urogenital tract clinical manifestations are more common in established PsA patients and in patients with axial subset, and they are associated with mean disease duration significantly lower than population study [65].

Pulmonary complications in SpA patients are uncommon and can be caused by rigidity of the chest wall and apical pulmonary fibrosis [133]. In PsA patients, the data on pulmonary involvement are lacking; the only studies available are clinical cases [133; 134], describing apical pulmonary fibrosis rates appear to be higher in smoker PsA patients with established form and axial subset.

4. Conclusions

In this review, we developed the concept of a heterogeneous aspects of SysPsD. Recently, this inflammatory status has been associated to an autoimmune footprint of PsA pathogenesis. This new interesting concept of the disease raised from the evidence of pathogenetic autoantigens in PsA patients and from the presence of autoantibodies linked to synovitis and disease activity. Patients affected by PsA have a high prevalence of comorbidities that are related to an inflammatory status. In Psoriatic disease, great interest has been developed concerning the concept of a Precision Medicine for PsA patients in order to put the basis for a real tailored and patient-centered therapy.

5. Take-home messages

- The Pathogenesis of PsA now includes an autoimmune process and the presence of autoantibodies has recently been demonstrated in patients with a close link with disease activity.
- PsA synovitis may be difficult to distinguish from other forms of arthritis at disease onset displaying histological features of chronic inflammation and lympho-neogenesis. Moreover, at the time of sustained clinical and ultrasound remission, PsA patients showed histological proven residual synovitis.
- Systemic PsD can show a wide spectrum of extra-cutaneous and -articular manifestations, that can occur with different frequencies in course of PsO and PsA and alone or in combination. They are relevant for the clinical and therapeutical management of patients.

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