Neutrophilic Dermatoses and Joint Disorders

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Introduction

Inflammatory joint disorders such as rheumatoid arthritis and spondyloarthritis are chronic systemic diseases with an immune-mediated pathogenesis. They may be associated with neutrophilic dermatoses, particularly pyoderma gangrenosum, Sweet's syndrome and hidradenitis suppurativa [1–3].

Both inflammatory joint disorders and neutrophilic dermatoses share a number of pathophysiological features related to the pro-inflammatory cytokine expression profile [4, 5]. Furthermore, it is well recognized that in neutrophilic dermatoses any organ system can be potentially involved, giving rise to the concept of "neutrophilic disease" [6, 7]. Among the extracutaneous manifestations of neutrophilic dermatoses, joint involvement is regarded as the most frequent [6, 7].

In this chapter, we focus on the main rheumatic diseases associated with neutrophilic dermatoses as well as on the articular involvement of "neutrophilic disease", providing a simple approach for the recognition of these associations.

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D. Wallach et al. (eds.), *Neutrophilic Dermatoses*,
https://doi.org/10.1007/978-3-319-72649-6_19

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized not only by inflammation of the joints (synovitis), but also by a systemic inflammation that may lead, if untreated, to severe extra-articular manifestations [8]. RA may be seropositive, in the presence of rheumatoid factors (RF) and/or anti-citrullinated peptide autoantibodies (ACPA), or seronegative, in their absence. Seropositive RA seems to have a worse prognosis in terms of bone erosions and disability [9]. The diagnosis of RA is straightforward in the presence of tender and swollen joints, morning joint stiffness with duration >1 h, abnormal laboratory tests such as elevated concentrations of C reactive protein or erythrocyte sedimentation rate and if RF or ACPA positivity are present. Bone erosions of the small joints of the hands or feet are typical of the disease [8, 10]. However, radiographic signs of erosions usually are not present in the early phase of the disease and antibodies may be absent. Therefore, classification criteria for RA have been recently revised in order to help achieving a definite diagnosis also in early arthritis (Table 19.1) [11]. Both seropositive and seronegative RA may present various cutaneous manifestations, among which there are neutrophilic dermatoses [12]. A possible common pathway may be represented by the involvement of autoinflammatory mechanisms related to the overproduction of IL-1beta,

Table 19.1 The 2010 classification criteria for rheumatoid arthritis (RA) of the American College of Rheumatology/European League Against Rheumatism

	Score
A. Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR 0	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

A total score higher than 6/10 is needed for classification of a patient as having definite RA
ACPA anticitrullinated protein antibody, *CRP* C reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor

a pivotal pro-inflammatory cytokine in both RA and neutrophilic dermatoses [5, 13, 14]. Furthermore, IL-8, a pro-inflammatory chemokine, which is able to attract neutrophils and lymphocytes, is elevated in the joints and serum of patients with RA and may play a role in the development of neutrophilic dermatoses in these patients [4, 5, 15].

Although neutrophilic dermatoses are not commonly reported in RA, possibly due to misdiagnosis, their early recognition is important to avoid potentially severe complications. In RA, the most frequent neutrophilic dermatosis is pyoderma gangrenosum, followed by Sweet's syndrome and rheumatoid neutrophilic dermatosis.

Pyoderma Gangrenosum

Pyoderma gangrenosum in RA usually presents with single or multiple painful skin ulcers with undermined erythematous-violaceous borders on the lower extremities. Other rare atypical variants are recognized, mainly including the pustular, bullous and vegetative forms [16]. It is still controversial whether pyoderma gangrenosum is a true skin manifestation of RA, since pyoderma gangrenosum often occurs in other systemic disorders and has no relation with the course of RA. Furthermore, pyoderma gangrenosum associated with RA has no specific histologic presentation but early lesions demonstrate a predominant neutrophilic infiltrate in the dermis and subcutaneous tissue [17, 18].

In a classic retrospective study of 86 patients with pyoderma gangrenosum from the Mayo Clinic, RA was the second most common disease association (14%) after inflammatory bowel diseases [18]. These findings have been more recently confirmed in a larger series of patients with pyoderma gangrenosum, by Langan et al., who observed a similar prevalence of RA (12% of cases) [1].

Sweet's Syndrome

Sweet's syndrome can be associated with RA, although uncommonly. Lesions present as single or multiple erythematous papules, nodules or raised plaques, associated with fever, malaise, arthralgia and myalgia. Localisation is prominent at the face, neck and upper extremities, however, any site could be potentially targeted. The lesions are usually tender and sharply demarcated with a characteristic superficial vesiculation on their surface [19, 20]. Histopathology reveals a dense neutrophilic infiltrate in the superficial derma with massive oedema. Leukocytoclastic vasculitis is usually absent [21].

Neutrophilic dermatosis of the hands can be regarded as a localised variant of Sweet's syndrome [22]. The cutaneous picture is similar to that of Sweet's syndrome, with lesions located exclusively on the hands, especially at their dorsal aspect, and is usually not associated with systemic symptoms [22].

Rheumatoid Neutrophilic Dermatosis

Rheumatoid neutrophilic dermatosis is a rare cutaneous manifestation in patients with severe RA. It was described in 1978 by Ackerman [23]. It mainly affects patients with severe seropositive RA, predominantly women (ratio 2:1), but it has been observed also in seronegative RA [24].

Clinically, it presents with symmetric asymptomatic erythematous papulonodular lesions and/or plaques, which may persist and sometimes ulcerate. They are usually distributed on the extensor surfaces of forearms and hands as well as the neck, the shoulders and the trunk. Rheumatoid neutrophilic dermatosis lesions may resemble those of Sweet's syndrome. Histopathological examination reveals a dense neutrophilic infiltrate without vasculitis. The course of rheumatoid neutrophilic dermatosis seems to follow RA disease course [25]. Resolution may occur spontaneously or in association with improvement of RA, without scarring.

Spondyloarthritis

With the term spondyloarthritis we refer to the spectrum of diseases comprising several related but clinically distinct diseases: psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis [26]. The various clinical forms include spinal (axial) features with inflammatory back pain, peripheral arthritis predominantly of the lower limbs, dactylitis ('sausage'-like fingers or toes), enthesopathy, and extra-articular features such as uveitis, psoriasis, and inflammatory bowel diseases.

All these diseases are associated with the major histocompatibility complex HLA-B27. The presence of a common genetic basis is demonstrated by the observation of a familial clustering of different forms of spondyloarthritis [26].

The members of the Assessment of SpondyloArthritis international Society (ASAS) (Table 19.2) have recently reviewed previous criteria of the European Spondylarthropathy Study Group (ESSG) [27] and those of Amor [28].

Although spondyloarthritis has been traditionally regarded as a condition depending on an altered adaptive immunity, recently, a contributing role of autoinflammatory mechanisms has been proposed based on the observation of a genetic polymorphism in genes related to IL-1 pathway [29].

Although psoriasis is by far the most common skin manifestation in spondyloarthritis, also neutrophilic dermatoses have been reported [30]. In particular, hidradenitis suppurativa and bowel-associated dermatosis-arthritis syndrome (BADAS) are the most frequently reported in spondyloarthritis patients.

Table 19.2 Classification criteria for axial spondyloarthritis (SpA) according to the Assessment of SpondyloArthritis International Society (ASAS)

Sacroiliitis on imaging[a] *plus*	HLA-B27 *plus*
≥ 1 SpA feature[b]	≥ 2 other SpA feature[b]

The criteria encompass both patients with and without definite radiographic sacroiliitis in patients with chronic back pain (>3 months) and age at onset <45 years

[a]Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA *or* definite radiographic sacroiliitis according to modified New York criteria

[b]Inflammatory back pain; arthritis; enthesitis (heel); uveitis; dactylitis; psoriasis; Crohn's disease/ulcerative colitis; good response to non-steroidal anti-inflammatory drugs; family history for SpA; HLA-B27; elevated C reactive protein

Hidradenitis Suppurativa

Hidradenitis suppurativa, also called acne inversa, is a chronic, frequently debilitating inflammatory disease manifesting as nodules, abscesses and fistulae involving skin folds, predominantly in the axillary and inguinal regions, as well as the anogenital areas [31]. It may present in association with other neutrophilic dermatoses, also in the context of syndromic forms, or in combination with inflammatory diseases, particularly psoriasis [32]. Hidradenitis suppurativa is also often associated with extracutaneous diseases, such as inflammatory bowel diseases [33] and spondyloarthritis [3]. Strong evidence for a non-fortuitous association of spondyloarthritis and hidradenitis suppurativa is supported by the study by Richette et al., demonstrating that spondyloarthritis had a prevalence of 3.7% in their large cohort, a much higher value than the prevalence of spondyloarthritis in the general population [3].

A dysregulation of the innate immune system has been demonstrated in both hidradenitis suppurativa [34] and spondyloarthritis [26, 35]. The enhanced presence or expression in tissue lesions of neutrophils and macrophages as well as cytokines, such as IL-1beta, TNF-alpha, and IL-6 further supports this view [34, 36]. Interestingly, all these pro-inflammatory cytokines are upregulated and play a pivotal role also in the pathogenesis of spondyloarthritis [26, 37].

Bowel-Associated Dermatosis-Arthritis Syndrome (BADAS)

BADAS is characterised by fever, flu-like symptoms, arthritis and inflammatory skin involvement. The latter is characterised by lesions recalling different neutrophilic dermatoses such as papules and plaques (Sweet's syndrome), pustules and ulcers (pyoderma gangrenosum) or nodules, abscesses or fistulae (hidradenitis suppurativa) [38]. In addition, acne and neutrophilic panniculitis can be associated [38, 39]. Patients usually experience a symmetrical, non-erosive polyarthritis that predominantly involves small joints [40].

This syndrome has been initially described in patients undergoing jejunoileal bypass for bariatric surgery and named "bowel-bypass syndrome" [41, 42]. Later, the term BADAS was introduced, based on the observation that a similar presentation could occur also in patients undergoing surgery such as Billroth II for peptic ulcer disease, biliopancreatic diversion [43] and in patients with chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis [44]. More recently, it has been described also in patients with diverticulosis and appendicitis [45].

The pathogenesis of BADAS is still poorly understood. Evidence suggests that gut microbiota could play a pivotal role in its pathogenesis [46]. In particular, BADAS could be caused by small intestine bacterial overgrowth [39]. This condition may predispose to the release of pro-inflammatory cytokines and chemokines and effector molecules eventually leading to neutrophil-mediated inflammation.

Joint Involvement in the "Neutrophilic Disease" and Syndromic Forms

Since the first reports of neutrophilic disorders, the observation of a possible multisystem involvement has led researchers to coin the term "neutrophilic disease" [6, 7]. During the course of neutrophilic dermatoses almost any organ can be involved, particularly lungs, with parenchymal infiltrates, or kidneys, usually with a nephrotic syndrome. However, joints are the most frequent extracutaneous site with arthralgia in more than in 50% or overt arthritis in 10–37% of patients [6]. Joint manifestations may precede by years the onset of dermatosis [47].

It is not always easy to distinguish chronic inflammatory arthritis such as RA or spondyloarthritis and neutrophilic dermatosis-related arthritis. Nevertheless, the clinical presentation, the distribution and the localisation together with laboratory findings may help in the differential diagnosis.

For example, RA and spondyloarthritis are chronic, characterised by recurrent flares and may progress with erosions and deformity if untreated [48]. By contrast, arthritis associated with neutrophilic dermatoses seems to follow the course of skin involvement with remission after treatment and usually no flare-up [6]. When a flare-up of arthritis occurs, a chronic inflammatory rheumatic disorder should be suspected. Nolla et al. reported in patients with Sweet's syndrome an asymmetric non-erosive arthritis with predominant neutrophilic and mildly inflammatory infiltrate usually involving large joints [49]. These characteristics can be found also in RA and therefore are not useful in differential diagnosis. Radiographs are often normal in arthritis related to neutrophilic dermatoses [49]. However, in the early phase of the disease also RA and spondyloarthritis may not show erosions or other signs. In this case, ultrasound with power-Doppler assessment or magnetic resonance imaging are more sensitive than plain radiographs [50]. It is possible that the pattern of arthritis mainly described by Holt et al., namely a chronic, progressive, symmetric, seronegative destructive polyarthritis with axial and peripheral involvement or both, could actually be a seronegative arthritis or a spondyloarthritis [47]. Furthermore, this kind of arthritis could also be associated with hidradenitis

suppurativa or acne conglobata and in some patients, "the arthritis of ulcerative colitis" was hypothesised [47]. Finally, undifferentiated spondyloarthritis in association with pyoderma gangrenosum has been reported [51].

No data regarding the prevalence of ACPA is available in patients with neutrophilic dermatoses. Although not very sensitive, ACPA are very specific for RA and may help in the differential diagnosis. The specificity of RF depends on its titre: low titres are not specific, whereas high titres are more specific for RA, particularly when associated with ACPA [52].

Therefore, it is advisable that patients with articular symptoms are referred as soon as possible to a rheumatologist in order to make a correct diagnosis, to decide the optimal treatment and to perform regular follow-up of the patients.

Joint involvement also typically occurs in the context of several syndromic forms of neutrophilic dermatoses, namely SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis), PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis) syndromes.

SAPHO Syndrome

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome was initially described in 1987 [53]. SAPHO syndrome is a rare condition, also possibly due to misdiagnosis [54].

Although its pathogenesis is still elusive, there is increasing understanding that SAPHO shares similarities with other autoinflammatory diseases [55]. The proline-serine-threonine phosphatase interacting protein 2 (PSTPIP2), which is involved in macrophage activation, neutrophil motility and osteoclast differentiation, has recently been supposed to play a role in innate immunity and development of autoinflammatory bone disorders, including SAPHO syndrome [56]. Proinflammatory cytokines, such as IL-1beta and TNF-alpha, as well as the chemokine IL-8, seem to be important in the pathogenesis of SAPHO [57, 58]. It has been suggested that *Propionibacterium acnes*, the main pathogenic responsible for acne, may trigger autoinflammation via inflammasome activation [59, 60]. Furthermore, Th17 cells were recently found to be increased in the peripheral blood of patients with SAPHO [61].

The diagnosis of SAPHO syndrome is based upon typical clinical findings. A set of criteria has been proposed for SAPHO in 1994: (i) multifocal osteitis with or without skin symptoms; (ii) sterile acute/chronic joint inflammation with either pustules or psoriasis of the palms/soles, or acne or hidradenitis suppurativa; and (iii) sterile osteitis and any one of the above skin manifestations, with any one of the criteria being sufficient for the diagnosis [62].

Actually, the term SAPHO refers to a group of diseases in which pustular skin involvement—manifesting as acne fulminans or acne conglobata, psoriasis and palmoplantar pustulosis,—is associated with bone and joint involvement presenting as hyperostosis and osteitis—chronic inflammatory reactions involving the cortical and medullary bone—and arthritis (synovitis) [63]. Other cutaneous manifestations

of SAPHO syndrome include pyoderma gangrenosum, Sweet's syndrome and Sneddon–Wilkinson disease [55]. The sternoclavicular joints are often involved, followed by the spine and sacroiliac joints [64]. Total body bone scintigraphic imaging may show the "bullhead sign", a pattern of bone inflammation localised at the sternum and sternocostoclavicular joints, which is regarded as characteristic of this syndrome [65]. Although arthritis (synovitis) in SAPHO presents with a pattern that resembles spondyloarthritis, HLA-B27 is not characteristic of this syndrome [54]. Arthritis is erosive and usually involves axial joints, less frequently peripheral joints, with a reported association with inflammatory bowel diseases [66]. SAPHO syndrome is usually self-limiting, but may also have a chronic course, particularly if inflammatory indices, anterior chest wall involvement, peripheral synovitis and skin involvement are present at the onset and are associated with female sex [67]. It is important to consider that skin and joint/bone involvement may not be present at the same time [63].

PAPA and PAPASH Syndromes

PAPA and PAPASH belong to a group of autoinflammatory syndromes characterised by the association of pyoderma gangrenosum and sterile pyogenic arthritis. Also in these forms an over-activation of the innate immune system may lead to increased production of IL-1beta. From a genetic point of view, a number of mutations affecting the proteins of the inflammasome complex or the proteins that regulate its function have been described in these disorders [68–70]. In particular, mutations of the PSTPIP1 gene are the genetic hallmark of PAPA, which is nowadays regarded as a monogenic autoinflammatory syndrome [55, 69].

Pyogenic arthritis in these cases presents as a painful, recurrent, monoarticular arthritis mainly involving large joints such as elbows, knees and ankles. Synovial fluid appears as a seropurulent or purulent, cloudy, yellow and sterile liquid due to the prominent neutrophilic infiltrate [68]. The first episodes usually occur in childhood and may be the presenting sign of the disease. The episodes may occur spontaneously, but traumatic events may precipitate episodes of arthritis, similarly to what is observed in a "Koebner's phenomenon" in the skin [71]. Erosions and joint destruction are reported in persistent (untreated) disease, even though in young adults joint symptoms tend to decrease, whereas cutaneous symptoms become more prominent [72].

Drug-Induced Neutrophilic Dermatoses in Rheumatic Diseases

The treatment of neutrophilic dermatoses is mainly based on corticosteroids, which in most cases are effective in controlling the disease. Targeted therapies including TNF blocking agents seem to be another effective option [73]. However, treatment with anti-TNF alpha may also be responsible for a number of cutaneous adverse reactions, the most frequent of which are pustular eruptions [74]. Indeed,

neutrophilic dermatoses have been reported during the course of anti-TNF therapy with infliximab [75] adalimumab [76, 77] or etanercept [78]. The causal mechanism is still a matter of debate, but may implicate an imbalance of cytokines toward interferons, chemokines and probably IL-17 [79]. Cases of pyoderma gangrenosum have been reported also during treatment with abatacept [80, 81]. CTLA-4-Ig therapy diminishes the frequency but enhances the function of Treg cells in patients with RA and a possible explanation could be a paradoxical inhibition of T-cell function in response to CTLA-4 blockade [82, 83].

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