Cutaneous manifestations of spondyloarthritis

Spondyloarthritis comprises a group of inflammatory rheumatic disorders with a genetic predisposition involving multiple genes that interact with environmental factors. The skin manifestations of spondyloarthritis are diverse, particularly psoriatic arthritis related to the overexpression of inflammatory cytokines such as TNF, IL-6, IL-12, IL-2 and IFN-γ; this psoriatic dermatitis is a common skin feature of spondyloarthritis. Spondyloarthritis mainly affects the spine, sacroiliac joints, ligaments and other tissues. Psoriatic lesions are erythematous plaques covered with silvery whitish scales distributed on the scalp, elbows, knees, trunk and gluteus creases, and the fingernails are frequently involved. Individuals with reactive arthritis and Crohn's disease may exhibit psoriasiform dermatitis and other manifestations including ocular inflammation, oral ulceration, erythema nodosum and/or thrombophlebitis. In the case of reactive arthritis, male patients may exhibit circinate balanitis and keratoderma blennorrhagica. In summary, dermatological manifestations of spondyloarthritis represent clinical clues and a unique scenario to explore the related pathophysiology and therapeutic approaches.

KEYWORDS: cutaneous manifestations ■ nail psoriasis ■ psoriasis ■ reactive arthritis ■ spondyloarthropathies

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Spondyloarthritis

Spondyloarthritis comprises a group of inflammatory rheumatic diseases that share a common genetic predisposition but distinctive clinical features that primarily affect the spine, sacroiliac joints and ligaments. Extra-articular manifestations in organs such as the intestines, urinary tract, heart, eyes and skin are also frequently observed.

The conditions grouped within the spondyloarthritis family include ankylosing spondylitis, psoriatic arthritis, arthritis/spondylitis associated with inflammatory bowel disease, reactive arthritis, undifferentiated spondyloarthritis, uveitis associated with the B-27 antigen, atrio-ventricular block, aortic insufficiency and juvenile chronic arthritis [1].

The onset of the disease occurs between the third and fourth decades of life but can also occur during childhood and adolescence in a form called juvenile spondyloarthritis; however, the time of onset and clinical characteristics are different from those observed in adults. The prevalence of spondyloarthritis is approximately 0.5–1.9%, and this condition may occur in both sexes but is most often diagnosed in men because women have fewer symptoms [2].

The Assessment in Ankylosing Spondylitis (ASAS) International Society has recently established criteria for the classification of spondyloarthritis as summarized in Table 1 [3]. This classification includes joint, axial and peripheral manifestations and considers systemic and joint manifestations, demographic characteristics and other clinical parameters such as the age of onset and the presence of uveitis, psoriasis or ulcerative colitis/Crohn's disease; a history of preceding infection (urethritis/cervicitis or diarrhea 1 month before the onset of arthritis/enthesitis/dactylitis); HLA-B27 positivity; sacroiliitis demonstrated by x-ray or MRI; and a family history of spondyloarthritis among first- or second-degree relatives [4].

Notably, extra-articular manifestations are observed in 20–60% of cases at some time during the disease course and are associated with axial or joint inflammation, including anterior uveitis in 51%, psoriasis in 20%, inflammatory bowel disease in 19% and combined symptoms in 10% of patients [5].

Etiology

The etiology of spondyloarthritis is unknown; however, the interaction of multiple genes and environmental factors are implicated in the pathogenesis of these diseases. Notably, over 90% of patients with ankylosing spondylitis carry the *HLA-B27* allele [6]. Psoriasis is associated with a group of susceptibility genes called *PSOR 1–7*; the *LCE3B/3C* gene, which is related to epidermal differentiation; the *IL-23* gene; and the gene encoding the transcription

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Table 1. Classification criteria for spondyloarthritis by the Assessment of Spondyloarthritis International Society.

Axial spondyloarthritis			Peripheral spondyloarthritis		
Age at onset <45 years Back pain, ≥3 months (with/without peripheral manifestations)			Peripheral manifestations only Arthritis or enthesitis or dactylitis		
Sacroiliitis on imaging plus ≥1 spondyloarthritis feature:	Or	HLA-B27 plus ≥2 other spondyloarthritis features:	Plus ≥1 of:	Or	Plus ≥2 of the remaining:
Inflammatory back pain Arthritis Enthesitis (heel) Uveitis Dactylitis Psoriasis Crohn's disease/ulcerative colitis Good response to NSAIDs Family history of spondyloarthritis HLA-B27 Elevated CRP			Psoriasis Inflammatory bowel disease Preceding infection for 1 month before the onset of symptoms HLA-B27 Uveitis Sacroiliitis on imaging (radiographs or MRI)		Arthritis Enthesitis Dactylitis Inflammatory back pain ever Family history of spondyloarthritis

CRP: C-reactive protein.
Data taken from [3].

factor NF-κB. These last two genes are associated with spondyloarthritis in addition to autoimmunity [7]. The HLA-Cw6 allele constitutes a risk factor for the development of psoriasis [8]. In summary, spondyloarthritis is associated with a genetic background accompanied by immunological abnormalities, which play a role in its pathogenesis [9].

Psoriasis is the gold standard of skin involvement

Psoriasis is a disease that results from a complex combination of concerted pathophysiological events, which take place mainly in the skin, ligaments and joints. The disease process is related to epidermal proliferation, hyperkeratosis, skin regeneration, skin metabolism and inflammation. The expression of the involved genes is choreographed to produce pathologic changes in the skin and related tissues; these changes result clinically in the expression of a certain phenotype, which is the basis for classification. We focus on psoriasis because, among the spondyloarthritis group of diseases, this disease presents the pathology that affects the skin most strongly.

Pathophysiology

T cells, monocytes and activated macrophages play a key role in psoriatic inflammation of the skin and joints, over-regulation of inflammatory cytokines such as TNF, IL-6, IL-12, IL-2 and IFN-γ induce different cellular interactions.

An initial trigger such as an infection (*Streptococcus*, *Klebsiella*, virus), trauma (Koebner phenomenon), stress or drugs could

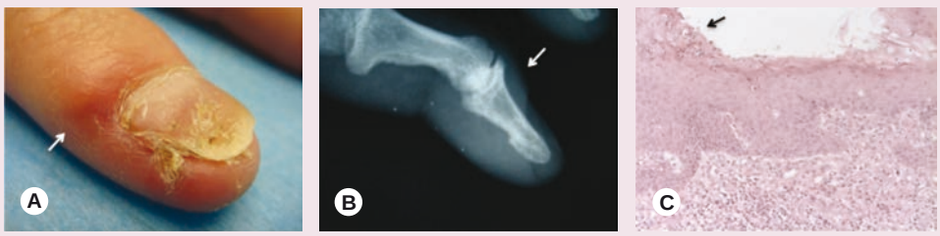

Figure 1. Nail and enthesitis. (A) Nail psoriasis; the arrow shows edema and erythema around the nail due to enthesitis. **(B)** Radiograph showing erosive changes at the distal interphalangeal joint of the forefinger with psoriasis. The arrow indicates the area of enthesitis. **(C)** The nail-bed epithelium displays moderate acanthosis, the exocytosis of neutrophils and the formation of Munro microabscesses in its superficial portion (arrow). There is perivascular infiltration of lymphocytes in the corium.

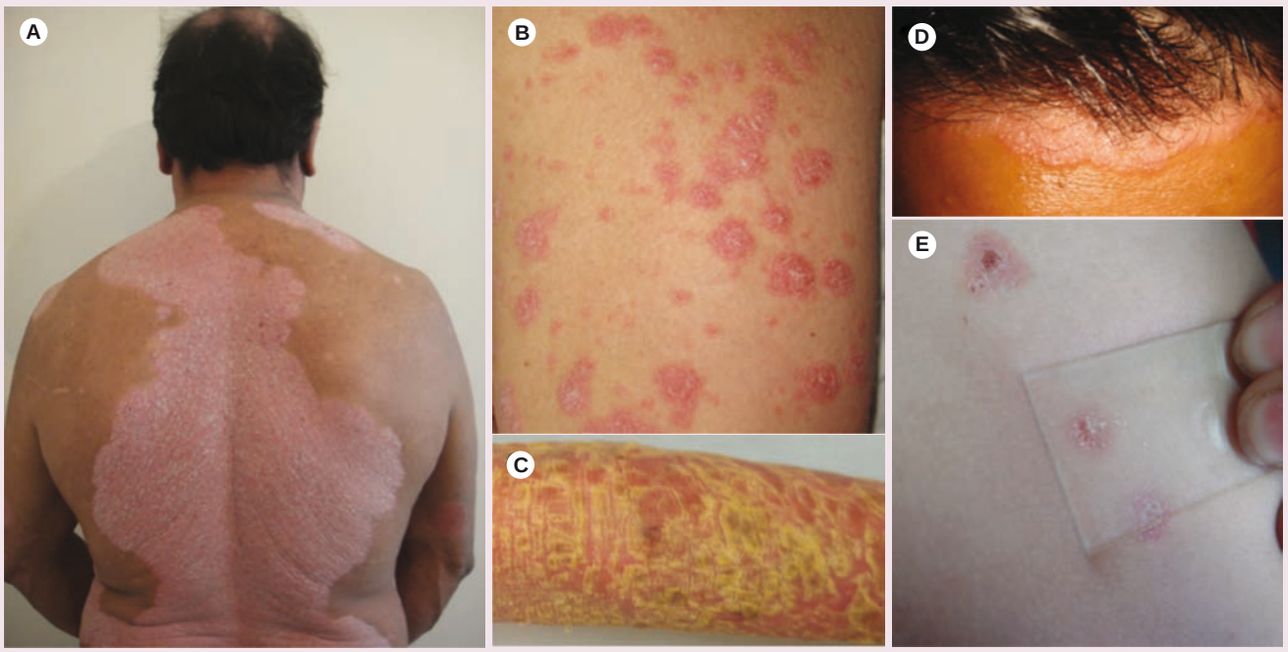

Figure 2. Psoriasis: clinical phenotypes. (A) Plaque psoriasis. **(B)** Guttate. **(C)** Generalized. **(D)** Lesions on the scalp. **(E)** The Auspitz sign or bloody-mist sign was observed in early lesions.

set off the disease; then, a sum of different transcription factors, receptors and cytokines may induce and maintain keratinocyte hyperproliferation and inflammatory infiltrates along plaques. These infiltrates become recurrent and, in addition to the presence of cytokines such as IL-8, enhance neutrophil accumulation in psoriatic plaques [10,11].

Psoriasis is a papulo-squamous and desquamative disorder characterized clinically by sharply demarcated erythematous plaques covered with silvery whitish scales. Psoriatic lesions are chiefly distributed on the scalp, elbows, knees, trunk and gluteus creases. The fingernails are frequently involved and show the following features in 50–80% of patients: nail matrix psoriasis: pitting, leukonychia, nail plate crumbling, red spots in the lunula and nail-bed psoriasis: onycholysis, oil-spots, hyperkeratosis, erythronychia and/or splinter hemorrhage (Figure 1) [12,13].

The clinical phenotypes of psoriasis are as follows: guttate, plaque, pustular, erythrodermic and inverse (Figure 2). Psoriatic arthritis is an extracutaneous manifestation observed in 5–20% of patients with any of the skin features of psoriasis, the nails are invariably affected in these patients. In most cases, the clinical evolution exhibits clinical improvement in the summer and worsens in the winter [14]. Chronic plaque and guttate psoriasis exhibit differences in terms of the levels of protein expression of SCCA2, cytokeratin 14, cytokeratin 17, enolase, superoxide dismutase and galectin, suggesting that although guttate and plaque psoriatic lesions are manifestations of the same disease, these phenotypes represent the differential expression of some skin proteins [15–18].

Other dermatologic manifestations of spondyloarthritis diseases

Reactive arthritis and Crohn's disease are probably the spondyloarthritic diseases with different cutaneous manifestations. These pathologies share some clinical features, such as the

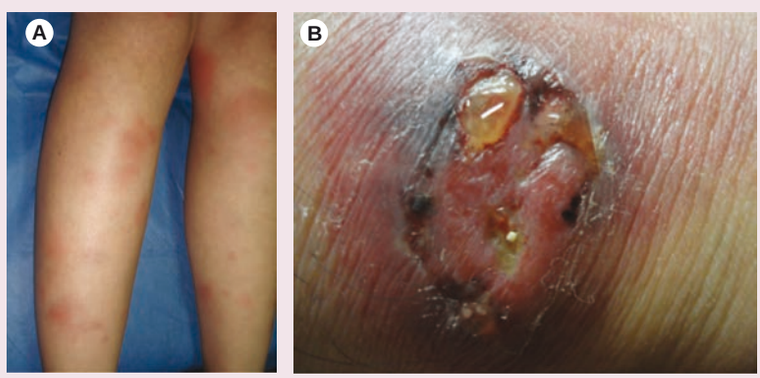

Figure 3. Other skin manifestations of spondyloarthritis. (A) Erythema nodosum. **(B)** Pyoderma gangrenosum.

seronegative polyarthritis affecting the lower limbs. Spondylitis is seen in most of these patients, as are other signs or symptoms related to epithelial and endothelial effects such as ocular inflammation (conjunctivitis with or without uveitis), oral ulceration, erythema nodosum, pyoderma gangrenosum and thrombophlebitis (Figure 3). These clinical features are not specific and can also be observed in individuals with Behçet disease [19].

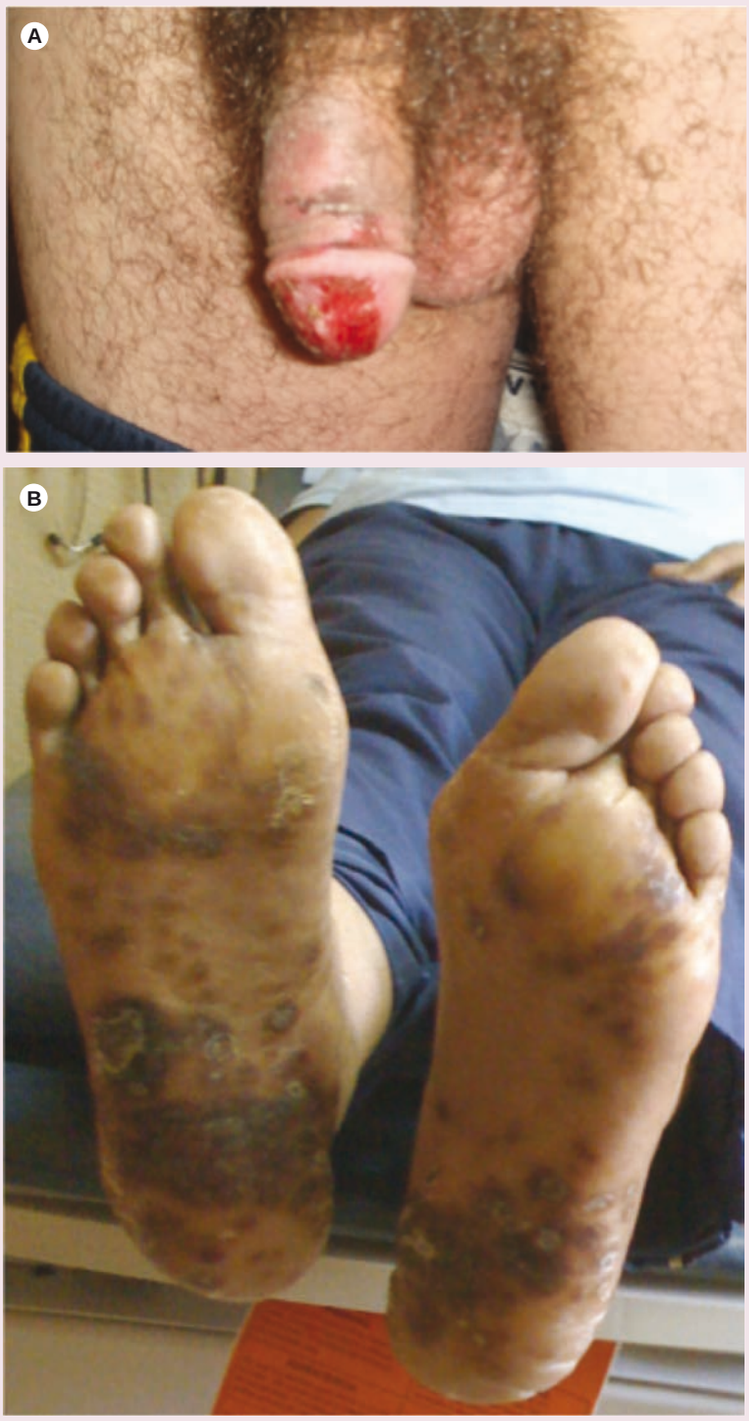

Figure 4. Reactive arthritis. (A) Circinate balanitis and **(B)** keratoderma in reactive arthritis.

Skin involvement in Crohn's disease is present in 0.5–20% of patients as an extension of intestinal disease activity. The clinical features include perianal and perineal fissures, fistulas and abscesses. Ulceration of the scrotum or vulva is a serious complication of this disease; other skin segments can be involved, with itchy psoriasiform plaques distributed on the legs and trunk. Orofacial disease occurs at the same time as intestinal flare-up symptoms, frequently as inflammation of the gums, mucosal tags, deep linear ulcers between the cheek and gums, lip swelling and (rarely) granulomatous cheilitis [20].

Reactive arthritis presents the symptomatic triad of arthritis, urethritis and conjunctivitis. This pathology was previously known as Reiter syndrome and is one manifestation of reactive arthritis. Sometimes, this disease involves dermatological manifestations such as keratoderma, circinate balanitis and/or psoriasiform dermatitis (Figure 4). The disease is frequently triggered by infections that are sexually transmitted or can be postenteric; the primary trigger occurs 2–4 weeks before the appearance of the symptomatic triad. The genitourinary syndrome is frequently associated with urethral infection transmitted by sexual intercourse, and the microorganism most commonly involved is *Chlamydia*. The postenteric syndrome that develops after acute diarrheic syndrome is caused by *Salmonella*, *Shigella* or *Campylobacter*. A few weeks after infection, some patients develop keratoderma blenorrhagicum on the soles and/or palms. Additionally, some patients may develop psoriasiform lesions, recurrent oral ulcers or a rash on the penile head referred to as circinate balanitis, which is frequently recurrent and can sometimes become difficult to manage [21].

Conclusion

Dermatological manifestations may be an initial clue or accompanying feature of spondyloarthritis. Therefore, the skin offers a way to detect associated comorbidities. Because of its accessibility, the skin represents an important source of information about the molecular mechanisms underlying the pathophysiology of spondyloarthritis and can be used as a reliable model in the design of advanced therapeutic measures.

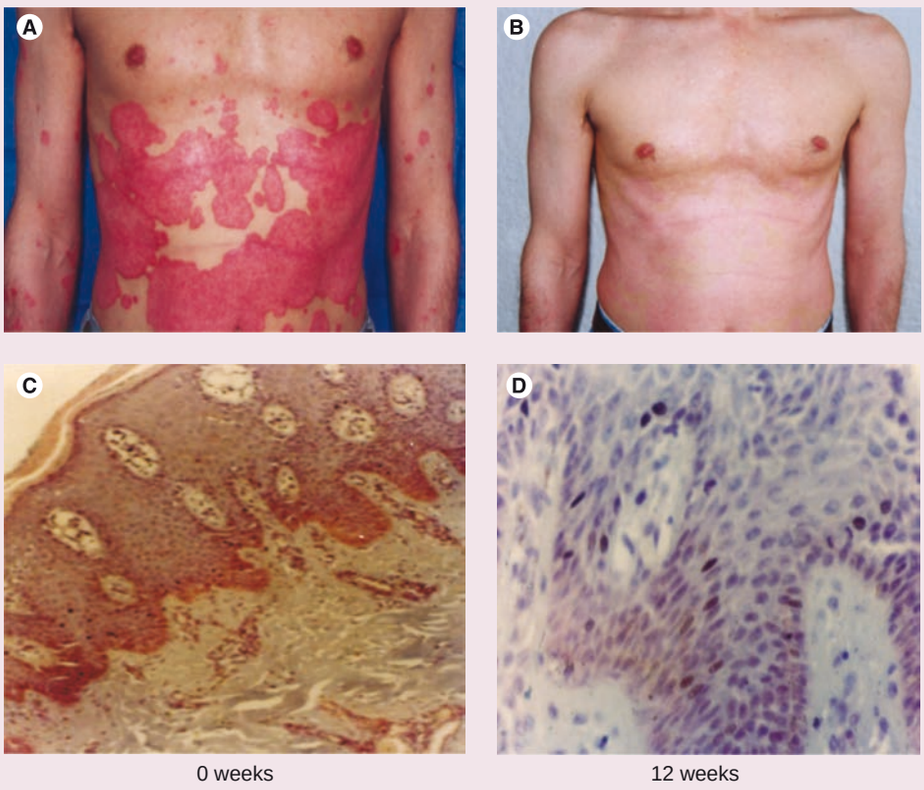

Figure 5. A patient with psoriasis before and after treatment with anti-TNF-α. (A) Before treatment and **(B)** after treatment with anti-TNF-α. Immunohistochemistry of skin biopsies shows **(C)** TNF deposition and **(D)** decreased TNF deposition after treatment.

Future perspective

With the notion that spondyloarthritis is an inflammatory disease, current therapeutic approaches are focused on biological agents to ameliorate inflammation, the use of chimeric or human anti-TNF monoclonal antibodies and recombinant anticytokine receptors (Figure 5). Recently, IL-12 and IL-23 blockage has been proposed as a new strategy to prevent the production of TNF, IFN-γ and IL-2 cytokines, and represents an effective way to arrest the polarization of the Th17 phenotype, which drives inflammation in psoriasis and probably in other types of spondyloarthritis. This strategy is currently in use, and new biological agents with this effect are under evaluation. Another promising area for spondyloarthritis therapy is the manipulation of the Toll-like receptors to ameliorate inflammation [22,23].

Future efforts may strive to manipulate gene expression because cytokines are largely regulated at the transcriptional level. It therefore seems reasonable to believe that emergent therapies based on the use of miRNAs will help in spondyloarthritis treatment. Such therapy is based on mRNA decay induced by AU-rich elements in miRNA. This approach may be able to regulate the expression of cytokines involved in inflammation. The principal candidate cytokines are TNF, IL-23 and IL-20. Notably, the applicability of cytokine-encoding mRNA has been successfully used in experimental models and may be applicable for use in human beings. These novel treatments may open a new avenue to control disease at the transcriptional level in the context of psoriasis and other spondyloarthritic conditions [11].

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Executive summary

Background

- Spondyloarthritis is a group of inflammatory rheumatic diseases that share a common genetic predisposition.
- The spondyloarthritis family include ankylosing spondylitis, psoriatic arthritis, arthritis/spondylitis associated with inflammatory bowel disease, reactive arthritis, undifferentiated spondyloarthritis, uveitis associated with the B-27 antigen, atrio-ventricular block, aortic insufficiency and juvenile chronic arthritis.
- Spondyloarthritis mainly affects the spine, sacroiliac joints and ligaments.
- Extra-articular manifestations in organs such as the intestines, urinary tract, heart, eyes and skin are frequently observed.
- The onset of the disease occurs between the third and fourth decades of life, and also in a form called juvenile spondyloarthritis.

Etiology

- The etiology of spondyloarthritis is unknown; however, the interaction of multiple genes, environmental factors and immunological abnormalities are implicated in the pathogenesis of these diseases.
- The spondyloarthritis has a history of preceding infection 1 month before the onset of arthritis/enthesitis/dactylitis.
- Over 90% of patients with ankylosing spondylitis carry the *HLA-B27* allele.
- Psoriasis is associated with a group of susceptibility genes called *PSOR 1–7*.

Psoriasis is the gold standard of skin involvement

- Psoriasis is a T-cell mediated inflammatory disease, which occurs mainly in the skin, ligaments and joints.
- An initial trigger such as an infection (*Streptococcus*, *Klebsiella*, virus), trauma (Koebner phenomenon), stress or drugs could set off the psoriasis.
- Psoriasis is a papulo-squamous and desquamative disorder related to epidermal proliferation, hyperkeratosis, skin regeneration, skin metabolism and inflammation.
- The fingernails are frequently involved, showing nail matrix psoriasis with pitting, leukonychia and nail-bed psoriasis with hyperkeratosis, onycholysis, erythorniquia, oil spots and splinter hemorrhages.

Other dermatologic manifestations of spondyloarthritis disease

- Crohn's disease and reactive arthritis are probably the spondyloarthritic diseases with different cutaneous manifestations, as oral ulceration, erythema nodosum, pyoderma gangrenosum and thrombophlebitis.
- Reactive arthritis presents the symptomatic triad of arthritis, urethritis and conjunctivitis, and also involves dermatological manifestations such as keratoderma, circinate balanitis and/or psoriasiform dermatitis.

Conclusion

- Dermatological manifestations may be an initial clue or accompanying feature of spondyloarthritis.
- The skin offers a way to detect associated comorbidities.

Future perspective

- With the notion that spondyloarthritis is an inflammatory disease, current therapeutic approaches are focused on biological agents as anti-TNF monoclonal antibodies and recombinant anticytokine receptors, to ameliorate inflammation.
- Future efforts may strive to manipulate gene expression because cytokines are largely regulated at the transcriptional level.

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