Clinical Advances in Spondylitis
Chapter 1

Extra-Articular Manifestations of Spondyloarthritis

Sebastián Giraldo Quintero¹², Consuelo Romero-Sánchez³²

¹School of Medicine, Universidad Militar Nueva Granada, Bogotá, Colombia
²Rheumatology Department, Hospital Militar, Bogotá, Colombia
³Unit of Oral Basic Investigation-UIBO, School of Dentistry, Universidad El Bosque, Bogotá, Colombia

*Corresponding Author: Consuelo Romero-Sánchez, School of medicine, Universidad Militar Nueva Granada, Transversal 3 No. 49-00, Bogotá, Colombia, Tel: 57(1)6500000; E-mail: romeromaria@unbosque.edu.co

Introduction

The Spondyloarthritides (SpA) are a group of chronic inflammatory rheumatic diseases whose feature common involvement of the axial skeleton, although in different forms and evolution can affect peripheral joints, with a prevalence of approximately 1.5-2% of the general population [1,2]. Inside this entity includes ankylosing spondylitis (AS), asymmetrical synovitis with skin compromise (eg, psoriatic arthritis), arthritis accompanying inflammatory bowel disease (IBD) (eg, Crohn disease and ulcerative colitis), and reactive arthritis [3].

SpA can be dominated by spinal symptoms, however, can be the peripheral joints compromise, so it is classified as axial SpA or by peripheral arthritis [4]. The axial compromise is subdivided in two types: AS, which requires radiographic changes of the sacroiliac joints (according to the Modified New York Criteria), and the non-radiographic.

Axial SpA, which is mainly based on a combination of clinical symptoms, the presence of HLA-B27 antigen, and signs of sacroiliitis on MRI [5].

The clinical symptoms of axial SpA include inflammatory back pain during at least 3 months with onset before 45 years of age and at least one of the other SpA-features: arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn disease or ulcerative colitis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history of SpA, and elevated C-reactive protein [5].

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In SpA, extra-articular manifestations can be divided in 2 groups: those related to the SpA concept, such as involvement of the skin, eye, gut, or urogenital system, and those more reflecting chronic, longstanding inflammation, which involve the heart, lung, kidney, and nerves [1]. The related manifestations are relatively frequent (20%–60%), can occur at any moment of the disease evolution (sometimes as the first manifestation), and can sometimes be related to axial or peripheral joint inflammation [6].

Screening for extra-articular manifestations in patients diagnosed with SpA is important to ensure appropriate management as the presence of these manifestations may influence treatment decisions. Clinical signs such as a painful red eye; diarrhea; skin/nail problems; and unexplained weight loss or fever are considered classical ‘red flags’ for further investigation [3].

Some studies (eg Aquiles Spanish population study show that a substantial percentage of patients with the other diseases coexist, as well as extra-articular manifestations in the course of the disease [7].

This chapter attempts to provide a description of the clinical characteristics of extra-articular manifestations in SpA, its detection and treatment.

Uveitis

Uveitis is the most common extra-articular manifestation in patients with SpA [3]. It is a general term used to describe inflammation of the uveal tract, which is the middle layer of the eye, between the sclera, conjunctiva and the anterior chamber on the outside and the retina on the inside [3].

Acute anterior uveitis (AAU) is the most common form of uveitis, with an annual incidence rate of about 8 cases per 100 000 population [8]. In a study of 433 subjects with different types of uveitis, 44 cases (almost 10%) of SpA were detected, whereas other studies showed a percentage up to 50% of previously undiagnosed cases of SpA among subjects with uveitis [9,10].

It is a prominent manifestation of SpA with a strong link with human leukocyte antigens (HLA) B27, occurring in 30% to 40% of patients with AS. The initial episode usually has an acute onset (1 to 2 day prodrome of mild eye discomfort followed by the development of marked redness and pain—and is unilateral [3]. An attack usually lasts up to 6 to 12 weeks. In most cases, local treatment is sufficient; however, relapses are frequent. Prolonged, uncontrolled anterior uveitis can extend into the posterior part of the eye with the formation of synechiae and secondary glaucoma [11,12].
This condition usually has a good prognosis and responds to appropriate treatment with topical mydriatics, cyclopegics and corticosteroids. However, it should be managed as an emergency to avoid complications. Power and colleagues [13] found that patients who are HLA-B27 positive have a more severe clinical course with a significantly higher rate of recurrent inflammatory attacks and, hence, a higher incidence of ocular complications. Banares and colleagues [14] also described a relationship between anterior uveitis and bowel inflammation (in 60% of patients with AS-related uveitis), with a close relation between the recurrence of uveitis and the presence of chronic intestinal inflammation.

Topically applied prednisolone acetate is well absorbed across the cornea and can be effective but is less so for posterior inflammation [13]. Dilating drops, such as scopolamine, may be used to prevent posterior synechiae and to relieve pain resulting from ciliary muscle spasms that control pupil size [13]. Periocular corticosteroid injections can also be used, as well as brief courses of oral corticosteroids, for persistent inflammation despite topical therapy. When flares of acute anterior uveitis are frequent (more than three flares per year), several studies showed that sulphasalazine could diminish the number of recurrences [5,6]. Other immunosuppressive drugs used to treat refractory uveitis, such as azathioprine and methotrexate, do not have much efficacy on the disease activity of SpA [13].

The using the TNF-inhibitors Infliximab and Adalimumab revealed that both agents significantly reduced the incidence of uveitis flares compared with placebo (placebo: 15.6/100 patient-years; infliximab: 3.4/100 patient-years; Adalimumab: 7.9/100 patient-years; p=0.01; TNF-inhibitors vs. placebo) in patients with AS [15].

Gastro-Intestinal Tract

IBD includes Crohn disease and ulcerative colitis. Approximately 10% of patients with IBD develop SpA. On the other hand, the chance of patients with SpA developing IBD is 5% to 10%. Asymptomatic IBD is find in a high percentage (60%) of patients with SpA and can be detected by endoscopy of the colon and terminal ileum [21].

A close relationship exists between joint disease and gut inflammation. For example, in predisposed individuals, bacterial infection of the gut with Shigella sp, Salmonella sp, Yersinia sp or Campylobacter sp may be followed by a peripheral arthritis (referred to as reactive arthritis within a few days to weeks after the onset of diarrhea) [16]. An immune dysfunction and increased permeability of the gut mucosa are contributing factors to local morbidity, although the mechanisms of joint involvement are unclear [16]. One theory is that memory T cells for
specific antigens circulate from the gut to the synovial membranes [16]. Additionally, an increase in bacterial growth, absorption of immune complexes, immune mediators (especially IL-6 and TNF alpha), and gut permeability may be pathogenic [16].

It is interesting to consider the relationship between SpA, infection and gut inflammation. Case reports have validated the clinical association of joint inflammation and the presence of bacteria in the gut for a long time, reactive arthritis has been considered to be a benign condition as it is a self-limiting condition in most cases. However, up to 20% of patients with reactive arthritis develop AS within 10–20 years. Crohn’s disease or ulcerative colitis has been reported to be present in 5–10% of patients with AS [3].

The association between the gut and musculoskeletal system has been known for some time. Wright, Watkinson, Bywaters and Ausell, cited in 1959 by Gravallese et al., described the clinical, radiologic and serologic characteristics of a distinctive form of arthritis associated with IBD. Some authors proposed that SpAs are not entities isolated to gastrointestinal involvement but extra-intestinal manifestations of inflammatory gastrointestinal diseases [17]. So, In case of persistent or frequently recurring diarrhea and/or blood or mucus production with the stools, it is advised to refer the patient with SpA to a gastroenterologist to perform a colonoscopy [17].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of medical therapy in AS and are recommended as first-line therapy in all AS patients. However, NSAID therapy in AS patients with concomitant inflammatory bowel disease may have deleterious effects on intestinal symptoms [3].

If a diagnosis of inflammatory bowel disease is then made, NSAIDs should probably be used intermittently in low to moderate doses and patients be monitored closely together with a gastroenterologist. The chronic use of NSAIDs can worsen the colitis manifestation; therefore it is advised to minimize the use of these drugs by patients with SpA who have IBD, except for celecoxib, which does not seem to increase the risk at exacerbation of the IBD [18].

The treatment options offered to patients with active AS associated with inflammatory bowel disease include conventional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, azathioprine or sulphasalazine and anti-TNF agents [19]. In most cases, the efficacy of other immunosuppressive drugs used in IBD has no proven efficacy in SpA [20]. Among the TNF-blocking agents, only infliximab and Adalimumab are effective in SpA and IBD. Golimumab is effective in SpA, but not yet registered for IBD [21,22]. Etanercept works well for spinal symptoms in SpA but not on IBD and, even
worse, new manifestations of IBD might occur during Etanercept treatment [21,22]. So, Infliximab and Adalimumab are licensed for the treatment of Crohn’s disease in Europe and the USA, whereas Infliximab is additionally licensed for the treatment of ulcerative colitis and pediatric Crohn’s disease in Europe and the USA [22].

**Skin**

Psoriasis is an immune-mediated skin disease which affects 2-4% of the worldwide population. Approximately 20-30% of patients with psoriasis develop psoriatic arthritis (PsA), a frequently destructive and disabling condition and specific form of inflammatory arthritis termed psoriatic arthritis (PsA), which is characterized by chronic inflammation of the joints, entheses, and spine [23]. In Europe, it is estimated to affect 5.1 million people. The most common form of psoriasis is plaque psoriasis, which occurs in approximately 80% of all patients with psoriasis. Some patients with psoriasis develop [23].

The prevalence vary depending on the population studied and the method of assessment, but the true estimate is likely around 30%, however in the Aquiles Study consider the relation between SpA and skin compromise can be around 27.8 % of the subjects evaluated (N:601) [15].

The skin and nail lesions in SpA are largely identical to isolated skin disease (mostly plaque psoriasis); but the lesions are sometimes localized on more atypical localizations, such as the palms of hands and feet (Hallopeau’s acrodermatitis continua) [24].

Traditional systemic treatment of psoriasis with methotrexate, retinoids, and cyclosporine has been in use for more than 20 years and still represents the first-line systemic treatment in Europe for patients with psoriasis who cannot be controlled with topical agents or phototherapy [10].

NSAIDs do not play a role in the treatment of skin or nail psoriasis. Drugs, such as indomethacin and ibuprofen, have occasionally been reported to exacerbate psoriasis [25].

Evidence for the efficacy of sulfasalazine on skin psoriasis is scarce, as it was only evaluated in a small prospective, randomized, double-blind, placebo-controlled study. In this study twenty-three patients received active treatment (ranging from 1.5–4.0 g of daily sulfasalazine), and six patients discontinued because of the side effects. In the remaining 17 patients, seven had marked (60%–89%) change and another seven had moderate (30%–59%) improvement. The placebo arm (n: 27) had only one subject who showed moderate improvement, whereas the rest of the group had only minimal improvement or worsening.
of psoriasis [26].

Dermatologists were among the first to embrace methotrexate as antiinflammatory/immune-modulating agent, with Edmunson and Guy [25] reporting its efficacy in the treatment of psoriasis in 1958. One of the earliest studies with methotrexate in 50 patients, reported more than 50% improvement in psoriasis [27]. It has since been claimed that in 30% to 50% of patients treated aggressively with methotrexate could improve their clinical status [28].

Cyclosporine is a highly effective and rapidly acting systemic agent belonging to the family of immunosuppressant drugs known as calcineurin inhibitors. The original observation that cyclosporine is an effective therapy for psoriasis was the consequence of an investigation for the treatment of arthritis. Four patients in the study group had PsA; in these patients, the high doses of cyclosporine in use at that time cleared the patients of psoriasis within 2 weeks of therapy initiation [6].

The only placebo-controlled analysis of cyclosporine enrolled 85 adult patients with moderate to severe psoriasis into 3 dosing arms (3.0, 5.0, and 7.5 mg/kg daily); a fourth group received placebo. Efficacy was measured after 8 weeks and quantified the patients becoming “clear or almost clear” [29]. In this study concludes that cyclosporine given at a dosage of 3 mg/kg daily for 12 to 16 weeks leads to rapid and dramatic improvement in psoriasis with a PASI (Psoriasis Area Severity Index) (75 response in 50% to 70% of patients and even a PASI 90 response in 30% to 50% of cases) [30,31]. Because of concerns of organ (renal) toxicity, cyclosporine is used mainly in short-term (12 weeks) intermittent course [31].

Leflunomide has demonstrated some usefulness in treating cutaneous psoriasis. One published prospective, multicenter, randomized, double-blind, placebo-controlled study showed mild efficacy for the treatment of psoriasis in 182 adult patients with psoriasis and PsA were randomized to either placebo or leflunomide given as 20 mg daily for 6 consecutive months [32], however will be necessary more studies which can help us about affectivity of this medicine.

In recent years, biologic therapies have offered new, exciting treatment options with improved safety and efficacy for the treatment of psoriasis. The biologic therapies used in psoriasis are defined by their mode of action and can be classified into 3 categories: T-cell modulating agents (alefacept, efalizumab), agents that block TNF-alpha, and inhibitors of interleukin (IL)12/23 (ustekinumab) [10]. The unique difference is relacionated with the doses in the first weeks of therapy, increasing the frequency of application and therefore the cost [10].

The individual treatment of patients with SpA is extremely challenging because of the heterogeneous character of the diseases that are part of this family of interrelated conditions. Not only is there a different therapeutic
approach depending on whether the main presenting rheumatologic manifestation is back pain, arthritis, enthesitis, or dactylitis but also the presence and the extent of extra-articular manifestations significantly influences the therapeutic decisions in an individual patient [10].

It is explicitly stated that the treatment should be tailored according to the current manifestations of the disease (axial, peripheral, enthesseal, and extra articular symptoms and signs) as well as the level of current symptoms, clinical findings, and prognostic indicators [10].

The optimal management requires a combination of non-pharmacologic treatment modalities, such as patient education and regular exercise, and pharmacologic therapy. Nonsteroidal antiinflammatory drugs (NSAIDs) are recommended as the first-line drug treatment for patients with pain and stiffness [29].

Corticosteroid injections can be directed to the local site of musculoskeletal inflammation, but the use of systemic glucocorticoids for axial disease is not supported by evidence. Likewise, there is no evidence for the efficacy of disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine and methotrexate, for the treatment of axial disease, but sulfasalazine may be considered in patients with peripheral arthritis [10]. The sulfasalazine doesn’t have indication in the treatment of skin compromise, of the other hand the methotrexate allows partial or total evolution in some patients with psoriasis, so it is the first systemic therapy in patients without adequate response to topical agents, not for the gastrointestinal or commitment for uveitis [27].

Anti–tumor necrosis factor (TNF) therapy should be given to patients with persistently high disease activity despite conventional treatments. With regard to axial and articular/entheseal disease manifestations, there is no evidence for a significant difference in efficacy of the various available TNF inhibitors (Infliximab, Etanercept, Adalimumab, Certolizumab, Golimumab) [28].

Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on the course of uveitis probably inferior to the monoclonal antibodies infliximab and Adalimumab [3].

**Conclusions**

This chapter allows the clinician to understand how patients with SpA should have a comprehensive management, including questioning the patient on events that may indicate the presence of extra-articular disease level, a situation that may make the treatment and follow-up. The management of patients with extra-articular manifestations of SpA may require coordination with other specialists.

The SpA is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist, with the pri-
mary goal of maximization of long-term health-related quality of life through the control of symptoms and inflammation, prevention of progressive structural damage, and the preservation/normalization of function and social participation.

Besides the well-established beneficial effects on rheumatological manifestations, biologics targeting TNF-alpha also have an impact on the extra-articular manifestations with a potential more profound efficacy of monoclonal antibodies versus soluble receptor constructs.

In the skin compromise, methotrexate is effective and well tolerated in appropriately selected patients who are adequately monitored for potential toxicities. Cyclosporine suffers from dose-related nephrotoxicity and hypertension that impede its use as a long-term agent for most patients. Given this restriction, cyclosporine is an effective drug for rapid clearing in most patients, serving as an excellent bridging agent that can be used safely for periods of 2 to 12 months. Sulfasalazine and leflunomide have poor evidence substantiating their use as monotherapy.

In most cases, attacks of anterior uveitis respond very well to (local) treatment by the ophthalmologist. In cases with refractory uveitis or a high uveitis recurrence rate, treatment with TNF-blocking agents can be successful, especially if the treatment is indicated for high disease activity of SpA. Adalimumab and infliximab seem to be more effective in lowering the recurrence rate of uveitis compared with Etanercept.

References


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