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Extra-Articular Manifestations in Spondyloarthritis are Common and Should be Screened

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Abstract

Spondyloarthritis should not be considered just a group of musculoskeletal inflammatory diseases, but systemic diseases that are associated with the presence of HLA-B27 gene. In these diseases there is great diversity of events that occur at sites outside of the axial skeleton and peripheral joints. Extra-articular manifestations of spondyloarthritis include uveitis, skin lesions such as psoriasis, involvement of gastrointestinal tract characterized by inflammatory colitis and also other less common manifestations. The use of anti-TNF biological agents provides clinical improvement in most of these clinical findings. On the other hand there is a lack of evidence on the effects of these drugs on cardiac and pulmonary involvement in spondyloarthritis.

Keywords: Ankylosing spondylitis; Inflammatory bowel diseases; Psoriasis, Uveitis; Extra-articular manifestations

Introduction

Spondyloarthritis (SpA), a group of disorders that includes Ankylosing Spondylitis (AS), psoriasis arthritis (SpA related to cutaneous psoriasis), enteropathic arthritis (SpA related to Inflammatory Bowel Disease, IBD) and reactive arthritis (post-infection SpA), should not be seen exclusively as a musculoskeletal inflammatory disease, but systemic diseases that are associated with HLA-B27 gene. In these diseases there are a great number of clinical features that occur at sites outside of the axial skeleton and peripheral joints. In a survey based on a Belgian epidemiological study of 847 patients, the most frequent extra-articular manifestations of SpA were uveitis, psoriasis and colitis [1]. An interesting aspect of the various extra-articular manifestations of SpA is the possibility that these features may occur with the presence of HLA-B27, even without axial skeleton or peripheral joint involvement. This reinforces the concept of a HLA-B27-related systemic disease rather than a simple musculoskeletal disorder.

The diagnosis of SpA should be done at the initial stage of the disease. In this regard, it is important to note that the new classification criterion for SpA do not require in all patients the presence of sacroiliitis on imaging test, considering that this appears late in the disease [2]. This criterion enables patients with back pain for more than 3 months and age less than 45 years are classified as having spondyloarthritis, if, in the presence of HLA B27, there are at least two clinical characteristics related with SpA. These features include peripheral arthritis and extra-articular manifestations such as enthesitis, dactylitis, uveitis, psoriasis and colitis [2].

However, who routinely investigates the presence of extra-articular manifestations in patients with SpA? A survey of 453 physicians from five European centers and one Canadian center showed that about 60% of rheumatologists who deal with spondyloarthritis usually screen the presence of extra-articular manifestations, which often are not clinically expressed [3]. If the physician does not routinely search for these extra-articular manifestations must at least be aware of them in the subgroup of patients with AS who have peripheral arthritis, considering that in these, dactylitis, enthesitis and uveitis are frequently found [4].

Bowel Involvement

It is known that 5 to 10% of patients with SpA have Inflammatory Bowel Disease (IBD), including Crohn's disease or ulcerative colitis. In addition, colonoscopies in SpA patients show silent ileitis or colitis in 30% to 40% of patients and histologic examination reveals microscopic inflammation in up to 60% of patients with SpA. The link between IBD and SpA is also evident when we observe that patients with IBD often have peripheral arthritis or sacroiliitis [5,6]. In a study that included 103 patients with IBD, with no previous diagnosis of SpA, 30% had inflammatory back pain and 18% had asymptomatic sacroiliitis [5].

A CARD15 gene polymorphism is common in patients with inflammatory bowel disease. This polymorphism is also more prevalent in SpA that has intestinal involvement subclinical, in contrast to those that have no intestinal involvement. The same is true for patients with IBD, in which the prevalence of this polymorphism is higher in patients with IBD who have sacroiliitis (even if it is asymptomatic) [6]. Thus, we could consider that IBD and SpA are part of a same group of diseases, which is reinforced by the knowledge that certain gene polymorphisms are associated with both spondyloarthritis and Crohn's disease and different expressions of the disease [7]. In this scenario, factors such as the presence of HLA-B27 would be responsible for differentiation into a specific form of disease [8].

Despite the prevalence of colitis in patients with SpA, we shouldn't perform colonoscopies in all patients with SpA but only in those who have clinical manifestations such as abdominal pain, diarrhea or blood in the stool, since only 6% of those with subclinical intestinal involvement will evolve to IBD [9,10]. Also, there is evidence that the control of peripheral arthritis may be associated with the resolution of the inflammatory bowel disease [11].

Arthritis occurs in 9 to 53% of patients with IBD and is more common in cases involving the large intestine, compared with the involvement of the small intestine [12]. There are two types of presentation of arthritis in patients with IBD, described in 1998 by Orchard et al. [13] type 1 (oligoarticular, in large joints, with more acute inflammation, and parallel evolution with intestinal crisis) and

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type 2 (polyarticular and more chronic, does not match the bowel inflammation symptoms) [13].

Finally, it is also important to be aware that bowel inflammation in patients with arthritis does not necessarily define the presence of SpA associated to IBD because other conditions such as Behcet's disease, Whipple´s disease and parasitic infections may provide similar clinical features [10].

Eye Involvement

Uveitis as a manifestation of extra-articular SpA is typically acute, anterior and recurrent. It usually leaves no sequelae, but can rarely complicate with synechiae and glaucoma. In psoriasis and IBD, uveitis may have a chronic course, can be bilateral and may involve the posterior uveal tract [14,15]. Acute anterior uveitis is found in the conjunctival limbal region (the region between the cornea and sclera), with a contracted pupil and ocular pain. If untreated, inflammation in the anterior chamber may become very important, even leading to the appearance of hypopyon [16].

In a study involving 175 patients with HLA-B27 uveitis, SpA was the disease responsible for about 50% of cases [17]. Considering the frequency of systemic diseases in patients with uveitis, these patients should be evaluated by a rheumatologist cooperating with the ophthalmologist in most occasions. In the investigation of uveitis, the detection of HLA-B27 has a strategic role because it defines a subgroup with SpA and a prognosis of well-defined recurrence [18-20].

An analysis of 347 patients with uveitis, which are part of a group of 2,012 patients in the Ibero and Latin American registry respondia, found that uveitis was more often associated with AS, compared with other SpA. It is consistent with previously published studies and strongly correlated with the presence of HLA-B27. In this study, uveitis had no association with peripheral joint involvement or with psoriatic arthritis [21].

Beyond HLA-B27 and SpA, however, when evaluating a patient with uveitis and arthritis, one should also consider infectious diseases in differential diagnosis such as tuberculosis, Lyme disease, syphilis and HIV, and other systemic inflammatory diseases such as sarcoidosis, vasculitis, juvenile idiopathic arthritis and relapsing polychondritis [22].

Enthesitis

Enthesis is the insertion of ligaments or tendons on bone surface and it has fibrocartilaginous structure. Some authors have preferred the concept of "enthesis organ" to emphasize that the enthesis is a complex mechanical structure that comprises the tendon, the adjacent bone, fibrocartilaginous structures, bursae, synovium and fat pad. All these structures are commonly affected in enthesitis [23,24]. The mechanism of osteoproliferation in enthesitis is believed to occur in the same context of bone injury reparation of spondylitis. Mechanical factors are probably involved in its origin as the plantar and calcaneal enthesitis are commonly involved [25]. Other sites commonly involved are the ligaments of the costochondral joints, the tibial tuberosity, iliac crest and greater trochanter of the femur. The clinical picture is characterized by pain and swelling on the site [4]. There is also an unbalance involving osteoimmunology, in which the expression of osteogenesis inhibitors is reduced, as DKK1 or sclerostin appear to be diminished [26].

It is known that many patients whose are HLA-B27 positive have enthesitis in the absence of sacroiliitis. In an interesting study, Muñoz-Fernandez et al. evaluated the frequency of enthesitis in five groups: one with AS, two with recurrent acute anterior uveitis, with and without HLA-B27, one group with other etiologies of uveitis and one control group of healthy people. The presence of enthesitis was more frequent in the group with AS and also in the group with acute anterior uveitis associated with HLA-B27, reinforcing the concept of a systemic disease associated with HLA B27 [20].

However, it is important to remember that enthesitis does not occur exclusively in SpA, but also in arthritis caused by calcium pyrophosphate deposition and in rheumatoid arthritis. In these diseases the presence of joint synovitis eventually obscures the picture of enthesitis.

Skin Involvement

Cutaneous manifestations in SpA include oral ulcers, erythema nodosum, pyoderma gangrenosum, keratoderma blennorrhagica and psoriasis. The first three suggest the presence of an inflammatory bowel disease. In fact, about 15% of patients with IBD develop Erythema Nodosum, which usually appears concurrent with the intestinal inflammation and peripheral arthritis [11].

Psoriasis is a common cutaneous manifestation in SpA. Fortunately, the skin lesions predate joint condition in three quarters of the cases, which facilitates the diagnosis. In a smaller portion of cases, the musculoskeletal picture may precede the skin lesions. Patients with psoriasis and SpA often have more peripheral arthritis. Although psoriatic arthritis occurs in 20 to 30% of patients with cutaneous psoriasis, the involvement of the sacroiliac joints and spine occurs only in about 5% of patients with psoriasis [27]. A point that needs further clarification is whether the different subtypes of psoriatic arthritis are genetically similar and have the same response to treatment.

Interestingly, SpA treatment with anti-TNF agents can induce the appearance of psoriasiform skin lesions. A recently published review compiled 127 cases, and found that lesions were more common with the use of infliximab, although there were cases reported with all TNF alpha blockers. The presentation of palmoplantar psoriasis was the most frequent (41% of cases), followed by psoriasis vulgaris with plaque-type lesions (33%), contrary to psoriasis unrelated to anti-TNF [28]. It is questionable if these cases would actually be psoriasis. It has been already detected the presence of Chlamydia trachomatis in the skin of some patients. *In vitro* studies demonstrate increased replication of Chlamydia, inversely proportional to the levels of TNF. Thus, it has been discussed whether these psoriasis-like lesions are actually a form of keratoderma blennorrhagica [29].

Osteoporosis

Osteoporosis is a well-established complication of spondylitis, which can lead to the occurrence of vertebral fractures. Its etiology is related to increased chronic inflammatory cytokines and restriction of mobility secondary to pain and loss of range of motion. Much has been discussed about the relationship between the increase of chronic inflammatory cytokines, loss of bone mass and bone formation in spondylitis. It is known that chronic increase in proinflammatory cytokines such TNF in AS inhibit the proliferation and maturation of osteocytes and stimulates osteoclastogenesis but does not prevent the formation of syndesmophytes. Moreover, the use of anti-TNF alpha is extremely effective in controlling the inflammatory activity in spondylitis but does not result in inhibition of progression of syndesmophytes. When it blocks TNF, also blocks DKK1, an inhibitor of the wingless signaling, inducing the maturation of osteocytes and

allowing osteoproliferation [30]. Sclerostin is also a natural inhibitor of the wingless signaling pathway, and studies show a reduction of its expression by osteocytes in patients with spondylitis [31].

Cardiovascular Involvement

Life expectancy is reduced in patients with severe AS, and cardiovascular events are responsible for that. However, most of the available data on this correlation come from a time when tools for early diagnosis and intensive treatment were not available. Aortic regurgitation, atrioventricular block and other less common cardiovascular manifestations can occur in AS as in other SpA. In AS patients, a study with transesophageal echocardiograms showed some degree of change in aortic valve or the aortic root in 82% of patients. Subclinical conditions prevailed, with little importance [32]. Anyway, it is worth remembering that AS and other inflammatory diseases, which include Takayasu's arteritis, giant cell arteritis, Cogan's syndrome and relapsing polychondritis, can cause aortitis [33]. Aortic involvement in SpA is usually restricted to the ascending aorta and aortic arch, and tends to occurs late in the disease.

Besides AS has been recognized as a cause of cardiac conduction defect, some authors speculate that there may be a direct association between presence of HLA-B27 and cardiac conduction disturbances [34,35].

The prevalence of cardiovascular clinical events related to atherosclerosis is higher in patients with systemic lupus erythematosus and rheumatoid arthritis compared to general population. In the same way, nowadays it is also established that ischemic heart disease, subclinical atherosclerosis and peripheral vascular disease are more prevalent in patients with AS and psoriatic arthritis. Chronic inflammation, physical inactivity and unfavorable lipid profile may contribute to these findings [36].

We have studied a relatively small sample (42 AS patients compared with 42 controls) and found no difference in the presence of plaques or the thickness of the inner medial layer. However, a considerable portion of AS patients was using statins due to the presence of dyslipidemia. Thus, patients did not escape the reality of an unfavorable lipid profile and intensive dyslipidemia treatment could be protective against early atherosclerosis [37].

Pulmonary Involvement

Regarding pulmonary involvement, apical pulmonary fibrosis has been described in AS, which can cause pneumothorax. Usually, lung fibrosis found in AS is subclinical and has been rare [38]. In a series of 52 patients with AS evaluated by computed tomography, it was found that 40% of patients had pulmonary abnormalities, such as nonspecific parenchymal opacities, lymphadenopathy, emphysema, bronchiectasis and pleural abnormalities [39].

Renal and Urogenital Involvement

Regarding to renal involvement, secondary amyloidosis is the most common manifestation. Nowadays it is less frequently found, probably due to earlier diagnosis and effective treatment. The second most common form of kidney involvement is IgA nephropathy [40].

Urogenital manifestations rarely occur in patients with spondyloarthropathies, and include infectious urethritis, especially those caused by Chlamydia trachomatis, which trigger cases of reactive arthritis [41]. Other events to be remembered that connect the urogenital system with spondyloarthropathies are cases of reactive arthritis induced by intravesical instillation of BCG in patients with bladder cancer [42]. Although the incidence of chronic prostatitis has been described, including as a cause of persistent antigenemia, nowadays their presence is rarely found [43].

Treatment of Extra-Articular Manifestations

There are plenty of recent data regarding anti-TNF therapy in extra-articular manifestations of SpA. A meta-analysis showed that the incidence of uveitis was reduced when using an anti-TNF agent, compared with placebo [44].

A retrospective study compared infliximab, adalimumab and etanercept in AS patients and the percentage of uveitis episodes was much lower in those who were using an anti-TNF agent [45]. In another study, which evaluated the use of adalimumab in various subgroups of uveitis (background, exacerbations in the last 12 months, symptomatic or chronic), clinical response was achieved more frequently with the use of anti-TNF agents compared with placebo [46].

The expression of TNF is higher in aqueous humor of patients with Uveitis [47].It is therefore easy to understand the efficacy reported with anti-TNF agents in patients with different causes of uveitis, such as those secondary to Behcet disease and sarcoidosis [48,49]. On the other side, there are few data on the efficacy of traditional antirheumatic drugs in the treatment of uveitis associated with SpA. In a study sulfasalazine proved effective in a manner similar to etanercept [50].

In IBD, the occurrence of flares of ileitis or colitis was much lower with the use of infliximab compared to etanercept or placebo [51]. It is unclear why the monoclonal antibodies have higher efficacy in the treatment of DII than etanercept. Maybe this fact could be related to differences in the mechanism of action of TNF blockers [52]. A review has proposed an algorithm for treatment of SpA in patients with symptoms of IBD. If the patient has clinical manifestations, we should perform ileocolonoscopy. If there is an obvious intestinal inflammatory disease, it should be treated as an IBD. If there is no evident disease and only subclinical inflammation, it is suggested to avoid using anti-inflammatory non-hormonal drugs for a long period of time and, if there is no improvement with anti-inflammatory drugs including glucocorticoids, we can try other therapies which include the use of anti-TNF monoclonal antibody [10].

One protocol indicates that anti-TNF agents can be used in the treatment of extra-articular manifestations of psoriatic arthritis [53]. Also, in a sub analysis of the ASSERT study, it was noted that the use of infliximab in the treatment of SpA induced an increase of bone mass in densitometry testing [54].

In conclusion, there is a great diversity of extra-articular manifestations in SpA that should be screened. The use of anti-TNF biological agents provides clinical improvement in most of these clinical findings. It has lead rheumatologists to treat SpA patients with anti-TNF agents more frequently, because there is lack of evidence on efficacy of drugs such as non-steroidal anti-inflammatory drugs, sulfasalazine and methotrexate on the extra-articular manifestations of SpA.

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