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EDITORIAL

Expanding the spectrum of spondyloarthritis (SpA): post-streptococcal reactive arthritis (PSRA)-related psoriatic spondyloarthritis (PSpA)

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The unifying concept of spondyloarthritis (SpA) was introduced by the group of Wright et al. in 1974 [1, 2] following a series of studies in a group of inflammatory disorders until then considered to be variants of rheumatoid arthritis (RA). It was, however, their own clinical work on psoriatic arthritis (PsA) that led them to formulate their concept of SpA [2]. The basic characteristics that bound the group were the following: (a) absence of rheumatoid factor; (b) absence of subcutaneous nodules; (c) peripheral arthritis; (d) radiologic evidence of sacroiliitis, with or without ankylosing spondylitis (AS); (e) tendency to manifest clinical interrelationships between individual members of the group, particularly psoriasiform skin or nail lesions, ocular, buccal, genitourinary inflammation, or bowel ulceration, erythema nodosum, pyoderma gangrenosum, and thrombophlebitis; and f) familial aggregation.

Initial considerations for inclusion in this group were the following: PsA, reactive arthritis (ReA) (formerly Reiter's disease), ulcerative colitis, Crohn's disease, Whipple's disease, Behcet's syndrome, and AS. At present, further advances in the field have led to removing from the group Whipple's disease and Behcet's syndrome, and studies led by the group ASAS have proposed newer classification criteria that are being used for clinical research studies [3].

Other inflammatory disorders, including gout, Still's disease, and hemochromatosis, were initially considered for inclusion but not considered further due to their lack of clinical, familial aggregation. Gouty arthritis, including axial gout, may merit further investigation [4, 5].

In this issue of *Clinical Rheumatology*, Dagan et al. described acute onset of psoriatic spondyloarthritis (PSpA) in three patients following a recent streptococcal infection and concluded that acute psoriatic SpA (PSpA) should be considered in the differential diagnosis of new-onset inflammatory back pain followed by psoriasis in young adults who had a recent throat infection [6]. All patients exhibited inflammatory back pain with evidence of acute axial SpA on MRI and psoriatic SpA occurred within 7–10 days of a confirmed streptococcal infection. One patient had guttate psoriasis, another developed pustular psoriasis, while the third had an exacerbation of pustular palmoplantar psoriasis. Due to the severity of the clinical picture and lack of clinical response to conventional anti-inflammatory therapy, two patients required treatment with TNF-α inhibitors. Authors further comment that axial involvement in post-streptococcal reactive arthritis (PSRA) is a rare event and that acute psoriatic SpA as a manifestation of PSRA has yet to be described.

Streptococcus pyogenes, the group A *Streptococcus* (GAS), is the most common cause of bacterial pharyngitis in children and adults, and a number of inflammatory manifestations are described with GAS pharyngitis, which can lead to chronic diseases in patients. Other groups including B, C, and G can also be associated with disease in humans.

Group A *Streptococci* are best known for their association with rheumatic fever, but other clinical well-established associations are guttate psoriasis, post-streptococcal glomerulonephritis, scarlet fever, cutaneous vasculitis, and post-streptococcal reactive arthritis (PSRA) [7, 8]. Of particular relevance to this discussion is the distinction between acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA). There are no gender differences between ARF and PSRA. There is a bimodal age distribution in PSRA, with a peak incidence at 8–14 years and a secondary peak at 21–37. In ARF, there is a single peak at 12 years. Genetics may also

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appear to be different, with an increased expression of HLA-DRB1*16 alleles in ARF and increased expression of HLA-B27 allele in PSRA. In ARF, inflammatory joint involvement occurs 2–3 weeks post-streptococcal infection, is migratory, is flitting, affects large joints, and is self-limiting, usually lasting 2 to 3 weeks. In PSRA, arthritis appears 7–10 days post-streptococcal infection, non-migratory, additive, and it affects small, large, and axial joints. The arthritis of ARF responds well to aspirin or NSAIDs, while in PSRA, clinical response is not as good. In addition, PSRA is associated with a low incidence of carditis with late onset in 6% of cases and the absence of the major Jones criteria. It should be noted, nevertheless, that the clinical distinction between ARF and PSRA can be difficult at times [7, 8].

According to these characteristics, the three patients described in the present report fit well the description of PSRA, having developed inflammatory back pain within 7–10 days following streptococcal pharyngitis, confirmed by a positive throat culture or ASO titer. A diagnosis of psoriasis was made by the CASPAR criteria, and bilateral sacroiliitis was confirmed by MRI, exhibiting a low-moderate clinical response to NSAIDs and glucocorticoids, and 2 patients required TNF-α inhibitors therapy.

All clinical manifestations exhibited by the three patients on this report are well-known complications of streptococcal infection and can occur in up to 50% in some reports. Axial involvement, including bilateral sacroiliitis, cervical and thoracic spine, has been described to occur between 5–51% in some series, in both ARF, especially in atypical presentation, and in PSRA [9, 10]. The diagnosis was made by conventional radiography and ultrasound imaging, and might be associated or not with the presence of HLA-B27 positivity. What is missing in this study is long-term data about its natural history, clinical response to therapy, and whether or not the current therapy including the use of biologic therapy alters its natural history. The three patients in the present series eventually had a good clinical response to therapy including the two patients who received TNF-α inhibitor therapy, but unfortunately, there were no follow-up imaging studies.

The current report is unique in presenting the concomitant presence of streptococcal infection followed by the development or exacerbation of psoriasis with axial involvement, which so far has not been reported in the literature. Psoriasis vulgaris and guttate psoriasis are known complications of streptococcal infection, but pustular psoriasis is not as common. HLA-B27 antigen was not seen on any of the patients, which leads to curiosity as to what other genetic components might be at play.

The pathogenesis of both ARF and PSRA is complex, multifactorial, and not completely elucidated. But, the presence of throat infection by GAS occurs in the majority of cases, as well as the presence of antibodies to *Streptococcus pyogenes*. Streptococcal proteins M, T, and R are the most important antigenic structures, localized in the outer portion of the cell wall, and, due to their strong anti-phagocytic activity, are recognized rheumatogenic markers of the bacteria [11]. Protein M, abundant component of GAS, decreases the activation of the alternate pathway of the complement system leading to a reduction of PMN-related phagocytosis. Antigenic differences exhibited by protein M allow the classification of *Streptococcus* in more than 80 serotypes, and the expression of these serotypes vary in the distinct geographic areas, within the same populations, and the microorganism serotype profile may vary from year to year. Streptococcal antigens mediate the activation of antibodies against streptococcal components, which cross-react with host proteins (molecular mimicry) and result in immune-mediated tissue inflammation and injury [12].

Molecular mimicry has been implicated as a leading hypothesis in the auto-immune mediated pathogenesis of ARF, particularly valvular disease [13]. In addition, immunization with recombinant streptococcal protein M antigens induces the autoantibody formation and valvular inflammatory changes in the Lewis rats [14]. Kim et al. recently described the immune response to group A *Streptococcus* in PBMNC from an aboriginal ARF cohort and found a dysregulated IL-1B-granulocyte-macrophage colony-stimulating factor (GM-CSF) cytokine axis. Persistent IL-1B production was coupled to the overproduction of GM-CSF and selective expansion of CXCR3+CCR4-CCR6-CD4 T cells, which are a major source of GM-CSF. CXCL10, a potent T helper 1 chemoattractant, was elevated in the sera of ARF patients [15].

On the other hand, there has accumulated for many years evidence suggesting that the Gram-positive bacteria play an important role in the pathogenesis of both psoriasis (Ps) and PsA. In 1952, Norholm-Pederson studied 133 psoriasis patients and found that 44% had an intermittent streptococcal infection, usually tonsillitis, and 21% had a positive throat culture. He noted the association with guttate Ps and also the overlap with plaque Ps, but no mention of PsA was made [16]. Tervaert et al. divided 200 Ps patients into three groups: acute guttate, chronic plaque, and acute plaque. Throat cultures for group A *Streptococci* were positive in 82, 71, and 34%, respectively [17]. Group B *Streptococci* were found in 0, 19, and 33%, respectively. No notation on the presence of PsA was made. Authors wondered if the dermal vascular changes could be a direct or indirect effect of the bacterium. Quimby determined serum titers of antibodies to deoxyribonuclease-B (streptococcal exotoxin) in 71 Ps patients and found 41% of those with psoriasis were positive, and also positivity was found in 10/17 (51%) with PsA [18]. Vasey et al. were able to reproduce those findings [19]. In addition, it has been shown that in genetically susceptible rat strains, injection of fragments of peptidoglycan-polysaccharides from group A *Streptococci* can induce chronic erosive arthritis. Two independent groups have identified by PCR groups A and B *Streptococci* in patients with PsA and not in RA [20, 21].

Elevated serum levels of IgA in PsA heralded the relevance of the recent finding in the gut microbiota in patients with PsA and ReA [22, 23]. The latter findings are of great relevance in view of the microscopic gut inflammation observed in most patients with spondyloarthritis, including PsA.

The presence of staphylococcal superantigens in psoriasis patients also provides support to the notion that the Gram-positive bacteria play a cardinal role in the pathogenesis of PsA patients.

The above discussion does not preclude the role of other infectious agents including the human immunodeficiency virus (HIV), forms of chlamydia, or Gram-negative organisms in certain patients [24, 25].

The report of Dagan et al. [6] is of great significance and relevance, and puts forward the interplay of environmental, genetic, and immune factors, and clinical expression of spondyloarthritis and post-streptococcal reactive arthritis (PSRA). Although a large group of investigators consider PSRA independent of ARF, there is another segment that deems PSRA as a heterogeneous clinical entity, with a subset that appears more like rheumatic fever, and a second subset more like HLA-B27-related spondyloarthritis [8, 26].

Wright's work and legacy remain relevant today as the present report attests, and the clinical spectrum of *Streptococci*- induced reactive arthritis continues to expand.

Compliance with ethical standards

Disclosures None.

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