Editorial

The Gut in Ankylosing Spondylitis and Other Spondyloarthropathies: Inflammation Beneath the Surface

Spondyloarthropathies (SpA) are a related group of disorders with common clinical and genetic characteristics, which have a global prevalence between 0.5 and 1%. Ankylosing spondylitis (AS) is the prototype disease in this concept. Other entities include reactive arthritis, psoriatic arthritis, and arthritis in patients with inflammatory bowel disease (IBD). In recent years, evidence has accumulated that the gut mucosa is an important disease related site of inflammation within the SpA complex, and that this type of gut inflammation is immunologically strongly related to Crohn's disease, the prototype IBD.

Subclinical gut inflammation documented by ileocolonoscopy (macroscopical or microscopical lesions) has been described in up to two-thirds of patients with SpA (reviewed in[1]). The histological appearance of these lesions has been referred to as the acute or chronic type of inflammation[2]. The acute type resembles acute bacterial enterocolitis (preservation of mucosal architecture; infiltration of ileal villi and crypt epithelium with polymorphonuclear cells; increased number of inflammatory cells in the lamina propria). The chronic type of inflammation resembles chronic ileocolitis often indistinguishable from Crohn's disease (distortion of crypts, atrophy of the villous surface of the colonic mucosa, blunting and fusion of villi, increased mixed lamina propria cellularity and basal lymphoid aggregates in the propria). In some cases of chronic lesions, aphthoid ulcers, branching of the crypts, the ulcer-associated cell lineage (UACL or pseudo-pyloric metaplasia) and sarcoid-like granulomas are present.

Patients with SpA frequently develop endoscopically macroscopical signs of inflammation and histological inflammatory changes. Even in the absence of such lesions, one may find molecular changes that are only detected by specific immunohistochemical stainings and that are generally reminiscent of the inflammatory process in patients with overt Crohn's disease. These molecular features include lymphocyte homing markers (αEβ7) and ligands (E-cadherin) or macrophage markers (CD163). Also, immunological features like disease-specific antibodies (anti-*Saccharomyces cerevisiae* antibodies, ASCA) may link SpA to IBD.

αEß7 integrin is expressed predominantly on lymphocytes residing in intestinal sites and is involved in the interaction with epithelial cells. Our group observed an upregulated αEß7 expression among interleukin 2 (IL-2) expanded T cell lines (CD3 as well as CD8) from mucosal biopsies from patients with AS in the absence of histological signs of gut inflammation[3]. E-cadherin mediates homotypic, homophilic intercellular adhesion in epithelial cells. It is a transmembrane glycoprotein, mainly localized to the zonula adherens junctions of all normal epithelia. E-cadherin is not only involved in epithelial cell–cell adhesion; it is also a ligand for the αEß7 integrin on intra-epithelial T cells. Upregulation of E-cadherin and its associated catenins was demonstrated in clinically overt IBD[4]. In SpA, similarly, an increased expression of the proteins of the E-cadherin/catenin complex in acute and chronic subclinical gut inflammation was described[5]. A particular subset of macrophages expresses the scavenger receptor CD163. Functional analysis of CD163 macrophages suggests that they could contribute to the inflammation process of chronic gut and joint inflammation, among others, because of their capacity to produce the proinflammatory cytokine tumor necrosis factor-α (TNF-α), but not the antiinflammatory cytokine IL-10. In SpA gut, increased representation of the CD163 subset has been observed in histologically normal gut, indicating again that even histologically normal intestine already depicts subclinical immune alterations in SpA; CD163 macrophages are also selectively increased in SpA synovium[6].

ASCA have been described in patients with Crohn's disease[7]. A recent report describes increased levels of ASCA

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(IgA isotype) in patients with AS[8]. Their precise relation with gut inflammation in these patients is still under study. Yet again, this immune feature links AS to IBD.

Lamarque, *et al* in this issue of *The Journal*[9] add an interesting piece of evidence to the concept of preclinical and premacroscopical immune alterations in the gut of patients with SpA, focussing on a group of patients with AS. In particular, they describe increased expression of inducible nitric oxide synthase (iNOS) as well as increased iNOS activity in the gut mucosa of patients with AS who did not show macroscopical lesions upon endoscopic examination. Moreover, the approach is new in that the authors extend the examination of gut mucosa (colon) in patients with AS to the upper part of the small intestine (duodenum). Also at this site of the gastrointestinal tractus, they identify inflammatory changes: increased mucosal lymphocytic infiltration and increased iNOS expression.

What has become clear from the different studies describing immune alteration in the gut in patients with AS and other types of SpA is that there is a whole immune cascade from early preclinical, premacroscopical, and even prehistological molecular immune changes to clinically overt Crohn's disease. The genetic or environmental factors that determine the progression within this cascade are largely unknown. Indeed, over time, some patients with SpA and gut inflammation may reverse to normality, while others progress to develop overt Crohn's disease. A prospective study from our group was conducted, in which 123 patients with SpA who previously underwent an ileocolonoscopy were reviewed clinically after 2 to 9 years[10,11]. At the time of review, 43% of the patients were in clinical remission. In total, 6.5% of the patients with SpA who did not present a clinical sign of gut abnormality developed IBD during their disease course. All these patients initially presented subclinical inflammatory gut lesions. In the subgroup of patients with AS, 7.7% developed IBD. Risk factors for evolution to IBD included the presence of chronic inflammatory gut lesions, persistence of raised inflammatory serum variables, and HLA-B27 negativity in the presence of sacroiliitis. Further identification of biomarkers associated with progression towards overt IBD in patients with SpA and early gut mucosal immune changes could open new avenues for early therapeutic immune intervention in these patients, maybe even during the window of disease reversibility.

The recognition of the immune link between AS and SpA with IBD has given a special impetus towards the development of new therapies in SpA. Indeed, given the immunological link between the gut in SpA and IBD on the one hand and between gut and joint inflammation in SpA on the other hand[12], it was an attractive hypothesis to test that immunomodulators interfering with gut inflammation would also be of benefit for patients with SpA. Not only was salazopyrine first evaluated and found effective in patients with SpA. More recently, TNF antagonists like infliximab have been successfully utilized in AS and SPA (reviewed in[13]). A special scientific challenge in this respect is the finding that more TNF blockers are effective in AS than in IBD. Etanercept is an example of such a drug with discordant efficacy in both diseases. The biological basis of this discrepancy is currently being studied.

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