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Review

Impact of a multidisciplinary approach in enteropathic spondyloarthritis patients

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ABSTRACT

Spondyloarthritis (SpA) and inflammatory bowel disease (IBD) are chronic autoinflammatory diseases that partially share the genetic predisposition and the unchecked inflammatory response linking the gut to the joints. The coexistence of both conditions in patients and the increased cross-risk ratios between SpA and IBD strongly suggest a shared pathophysiology. The prevalence of Enteropathic-related Spondyloarthritis (ESpA) in IBD patients shows a wide variation and may be underestimated. It is well accepted that the management of joint pain requires rheumatological expertise in conjunction with gastroenterologist assessment. In this view, we aimed at assessing, in a prospective study performed in a combined Gastro-Intestinal and Rheumatologic "GI–Rhe" clinic: (1) the prevalence of ESpA and other rheumatologic diseases in IBD patients with joint pain; (2) the features of the ESpA population; and (3) the diagnostic delay and the potential impact of the combined assessment. From November 2012 to December 2014, IBD patients with joint pain referring to a dedicated rheumatologist by the IBD-dedicated gastroenterologist were enrolled. Clinical and biochemical evaluations, joint involvement and disease activity assessment, diagnostic delay, and treatment were recorded. IBD patients (n = 269) with joint pain were jointly assessed in the "GI–Rhe" Unit. A diagnosis of ESpA was made in 50.5% of IBD patients with joint pain. ESpA patients showed a peripheral involvement in 53% of cases, axial in 20.6% and peripheral and axial in 26.4% of cases. ESpA patients had a higher prevalence of other autoimmune extra-intestinal manifestations and received more anti-TNF treatment compared with IBD patients. A mean diagnostic delay of 5.2 years was revealed in ESpA patients. Patients with joint disease onset in the 2002–2012 decade had reduced diagnostic delay compared with those with onset in the 1980–1990 and 1991–2001 decades. Diagnostic delay was further reduced for patients with joint onset in the last two years in conjunction with the establishment of the GI–Rhe clinic. Multidisciplinary approach improved management of rheumatic disorders in IBD patients allowing a more comprehensive care.

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1. Introduction

Spondyloarthritis (SpA) is a variety of inflammatory disorders that primarily affect entheses, small and large joints, and the axial skeleton joints [1]. This disease is characterized by the presence of inflammatory back pain — lumbar or buttock/hip pain lasting longer than 3 months associated with improvement with activity, worsening with rest, relief with non-steroidal anti-inflammatory drugs (NSAIDs), and morning stiffness lasting longer than 30 min [2]. The hallmark of SpA is inflammatory back pain while enthesitis, inflammation of tendonous or ligamentous insertions onto bone, is one of the most characteristic findings. SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, SpA associated with inflammatory bowel disease (IBD), non-radiographic axial (nr-ax) SpA and forms which do not meet criteria for the definite categories of SpA that are designated as undifferentiated SpA [3]. SpA pathogenesis is incompletely understood and the pathophysiological role of the synovium is just beginning to be elucidated. SpA is considered an enthesal disease and this hypothesis links mechanical stress (entheses) to immunologically active tissue (synovium) [4]. The Assessment in Spondyloarthritis International Society (ASAS) defined classification criteria considering SpA a distinct group of diseases with similar clinical features and a common genetic predisposition. As above mentioned, SpA frequently occurs in combination with other autoimmune conditions such as psoriasis, anterior acute uveitis, and IBD (Enteropathic SpA, ESpA) [5]. The ASAS-endorsed recommendations for early referral of patients suspected for having axial SpA by primary care physicians or non-rheumatologists include the extra-articular manifestations (psoriasis, IBD and/or uveitis) among the parameters for a diagnosis of SpA in patients with chronic low back pain (duration ≥ 3 months) with onset before 45 years of age [6,7]. In 1998 the Oxford Criteria were proposed to classify the joint involvement in SpA patients with IBD including a type 1 peripheral arthritis that is the pauciarticular form involving fewer than 5 joints, a type 2 peripheral arthritis that is the polyarticular form involving 5 or more joints and a type 3 involvement with both axial and peripheral involvement [8,9]. Later, the joint involvement observed in IBD was usually classified mainly into two subsets: axial (including sacroileitis with or without spondylitis) and peripheral [10,11]. Evidence shows that the frequency of the joint involvement in IBD is affected by the criteria applied to define the clinical findings [12]. In particular, axial involvement is present in 2–16% of IBD patients and the prevalence of sacroileitis (asymptomatic and symptomatic) is 12–20%, ranging from 3.9% to 18.9% when HLA-B27 is associated [13,14]. However, studies adopting the former European Spondyloarthropathy Study Group (ESSG) criteria for SpA detected a frequency ranging between 10–25% for spondylitis and 30–36% for sacroileitis [11,15]. Overall the prevalence of ESpA in IBD shows marked variations (18–45%) and may be underestimated by gastroenterologists [16]. Joint pain is a frequent and relevant clinical manifestation in IBD patients and its management requires rheumatologic expertise in conjunction with gastroenterologist. Flares of peripheral type 1 arthritis associated with IBD tend to occur with aggravation of the bowel disease, whereas the axial disease and peripheral type 2 arthritis tend to occur (and flare) independent of activity of intestinal inflammation [17]. Prompt diagnosis of rheumatologic diseases as SpA and PsA is necessary for the optimal patient management since the prevalence of undiagnosed disease remains high. Delay in diagnosis in turn delays introduction of appropriate disease-modifying treatment and may contribute to poor patient outcome [18]. Magnetic resonance imaging (MRI) is the gold standard for detecting sacroileitis in SpA patients [16]. Ultrasonography is a non-invasive and easily reproducible method of detecting early pathological changes in SpA patients [16]. It can identify characteristic features of SpA such as enthesitis, bone erosions, synovitis, bursitis, and tenosynovitis and is therefore helpful for diagnostic purposes. Laboratory abnormalities in SpA are nonspecific and not as useful as the clinical presentation for diagnosis of a specific disease. Patients often show nonspecific markers of inflammation including elevated C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and normochromic normocytic anemia. However, elevated CRP is one of the criteria of ASAS classification for axial SpA [19]. Interestingly, elevated CRP is also a risk factor for radiographic progression together with tobacco smoking and the presence of syndesmophytes [20]. Nevertheless, specific and reliable biomarkers are needed [2]. HLA testing represents the most useful laboratory evaluation in appropriately selected patients. The recommendations for the treatment of active SpA included use of NSAIDs, use of TNF-inhibitors (TNF-i) when activity persists despite NSAID treatment, avoid systemic glucocorticoids, use of physical therapy and hip arthroplasty for patients with advanced hip arthritis [21]. No particular TNFi was suggested except in patients with concomitant IBD or recurrent iritis, in whom TNFi monoclonal antibodies should be preferred [21]. In patients with active nr-ax SpA despite treatment with NSAIDs, it is conditionally recommended treatment with TNFi [21]. There is little evidence of the efficacy of disease-modifying antirheumatic drugs (DMARDs) in SpA [22,23]. In controlled studies, sulfasalazine, methotrexate, and leflunomide have shown modest efficacy on the peripheral manifestations of AS, but the utility of these drugs in axial disease is unclear; therefore, DMARDs are not included as an alternative treatment in patients with ax-SpA refractory to NSAIDs [23].

2. Enteropathic SpA: insights on the pathogenesis

The association between SpA and IBD is largely established. The coexistence of both conditions in patients and the increased cross-risk ratios between SpA and IBD strongly suggest a shared pathophysiology [24]. Both the innate and adaptive immune responses are likely to contribute to the establishment of chronic inflammation [25]. An intricate cytokine milieu with a distinct contribution to systemic and joint inflammation has been described in SpA [26]. Evidence from genetics (the strong genetic association with the interleukin (IL)-23 receptor gene) and experimental models (e.g. the increased IL-17 production in HLA-B27 transgenic rats) strongly supports the involvement of the IL-23/IL-17 axis in the pathogenesis of SpA [27]. Likewise, T helper (Th)17-related cytokines are produced in excess in Crohn's disease (CD) and ulcerative colitis (UC) tissue and it becomes evident that some Th17 cytokines have both proinflammatory and tissue-protective properties in IBD [28]. Although IL-23 was originally identified as a factor necessary for expanding/maintaining Th17 cells, recent studies have shown that IL-23 can also facilitate the deviation from a Th17 to a Th1 phenotype [29,30]. Moreover, IBD gene-wide association studies showed that polymorphisms of Th17-related genes, such as *Stat3* or *IL-23R*, associate with IBD, supporting the involvement of the Th17 pathway into IBD pathogenesis [31]. HLA-B27 is involved in antigen presentation in the immune system and is thought to have a key role in the pathogenesis of the SpA. HLA-B27 recognizes an elevated prevalence in patients with AS, PsA, reactive arthritis, and ESpA but