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EDITORIAL

ARTICULAR AND OTHER IMMUNE-MEDIATED EXTRA-INTESTINAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASES

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The articular involvement in patients with inflammatory bowel diseases is included in the group of immune-mediated extra-intestinal manifestations, occurring approximately in a range from 6.2-36% of the patients. This group is also made up of the skin and eyes manifestations, that usually but not invariably are correlated with intestinal inflammatory disease activity. Rheumatic manifestations are the most frequent extra-intestinal findings of this group with a prevalence from 20-50%. They are divided into two different clinical subsets: peripheral and axial joint involvement (including sacroiliitis with or without spondylitis). Peripheral arthritis is the most frequent finding in both Crohn's disease and ulcerative colitis, occurring with a frequency ranging from 17-20%, and it is more common in Crohn's disease. Axial involvement is more common in Crohn's disease (5-22%) than in ulcerative colitis (2-6%) and generally the prevalence of sacroiliitis (asymptomatic and symptomatic) is between 12-20% and of spondylitis is between 2-16%. The IBD is also associated with other rheumatic diseases such as rheumatoid arthritis, Sjogren syndrome, Takayasu arteritis and fibromyalgia. The management of patients with EA requires an active cooperation between gastroenterologists and rheumatologists.

Rheumatic manifestations are the most frequent extra-intestinal findings of inflammatory bowel disease (IBD), occurring in a range between 20% and 50% of patients and can be diagnosed before, simultaneously, or after the diagnosis of IBD (1).

The relationship between bowel and joints was originally reported in 1922 by Smith, who described an improvement of articular symptoms in patients with rheumatoid arthritis (RA) who had undergone surgery for colectomy (2). Later, Bargen and Hench described a peripheral arthritis involvement in patients with IBD and also reported the tendency of arthritis to flare with exacerbation of the colitis and to recede with the remission of bowel symptoms (3, 4).

Key words: enteropathic arthritis, inflammatory bowel disease, spondyloarthropathies

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In the following years, some Authors described the occurrence of sacroiliitis in patients with ulcerative colitis (UC) (5) and Crohn's disease (CD) (6). Until the 1960s, the arthritis associated with IBD was considered a variant of the RA, but the tendency for rheumatoid factor to be seronegative suggested its distinction from RA. In fact, in 1964 the American Rheumatism Association (ARA) classified arthritis associated with IBD, also called enteropathic spondyloarthritis (EA) (7), as an independent clinical form (8), and, in 1976, Wright and Moll included EA definitively among Spondyloarthritis (SpA) group (9).

Articular manifestations

The articular manifestations have been characterized by many Authors since the first report by Bargen and Hench in the 'thirties and are currently considered the most common extra-intestinal manifestations of IBD (1, 3, 4). The symptoms may range from arthralgia to arthritis and occur in both axial and peripheral joints. Males and females are equally affected and the age of onset is generally between 25 and 45 years for peripheral arthritis, while, for the axial involvement the male/female ratio is 3:1 and age of onset is earlier.

The arthritic manifestations of IBD were firstly classified into three different clinical subsets by Gravallese and Kantrowitz (10). The Authors described a unique form of peripheral arthritis occurring in 15–20% of IBD patients, a spondylitis form, clinically and radiographically indistinguishable from idiopathic ankylosing spondylitis (AS), occurring in 3–6% of IBD patients and an isolated sacroiliitis (symmetric and bilateral), occurring in 4–18% of IBD patients (10). At present, the joint involvement of EA is classified into two clinical subsets: peripheral and axial (including sacroilitis with or without spondylitis) (Table I). There may be other periarticular manifestations such as enthesopathy, dactylitis, tendonitis, periostitis, clubbing, granulomatous lesions (in joints and bones), osteoporosis and osteomalacia (11).

Peripheral arthritis is the most frequent finding in both CD and UC, and may occur with a frequency ranging between 17% and 20% (7), and it is more common in CD (10). The onset of peripheral arthritis is often abrupt and reaches the peak symptoms within 48 hours. It is characterized by involvement of asymmetric joints which generally affects the large joints of the lower limbs, less frequently those of the upper limbs. The course is generally migratory and recurrent with spontaneous remission within about 6 months; a small percentage of patients tends to become chronic. Knee and ankle are the joints most usually affected, but elbow, metacarpophalangeal, shoulder and hip can be involved as well (1). The peripheral arthritis is frequently non-erosive and non-deforming, although erosive arthritis of hip and small joints have been reported by Mielants (12, 13).

In 1998, Orchard et al. distinguished two subtypes of peripheral arthritis without axial involvement: type 1, the pauci-articular form and type 2, the poly-articular form.

The type 1, pauci-articular form (involving fewer than 5 joints), is usually acute, self-limited and may precede the diagnosis of IBD, even 3 years before the onset of colitis. The joint symptoms, related to disease activity of the underlying intestinal disease are typically asymmetric and migratory, with involvement of both large and small joints, generally of the lower limbs. The patients with pauci-articular form, moreover, have a high frequency of extra-intestinal manifestation such as erythema nodosum, stomatitis, uveitis and pyoderma gangrenousum. Finally, type 1 pauci-articular form is associated with HLA DRB1*0103, B27 and B35 (14).

The type 2, poly-articular form (involving 5 or more joints), is a symmetrical arthritis, frequently involving the small joints of the hand, with symptoms lasting for months or years and with a more severe course, independent from the disease activity of IBD. The onset may occur at any time during the course of IBD or before, and in CD, it is reported more commonly in colonic disease. It is associated with uveitis but not with other extra-intestinal manifestations (11). Finally type 2 poly-articular form is associated with HLA B44 and MICA (14, 15).

Recently, Smale et al. showed another type of peripheral arthritis (type 3) that includes patients with both axial and peripheral forms (16).

The spectrum of axial involvement ranges from inflammatory lower back pain with or without sacroiliitis (often asymptomatic) to spondylitis, indistinguishable from idiopathic AS. It is more

common in patients with CD (5–22%) than in those with UC (2–6%), and generally the prevalence of sacroiliitis (asymptomatic and symptomatic) is between 12–20% and of spondylitis between 2–16% (1). The clinical presentation in spondylitis is practically similar to idiopathic AS, with inflammatory back pain, characterized by morning stiffness, improvement with exercise, insidious onset, persistence at least 3 months and young age at onset (before 40 years), and disease progression leads to increasing immobility of the spine, resulting in ankylosing. The articular symptoms usually precede the IBD and are independent from the disease activity of the bowel. The spondylitis associated to IBD can develop at any age and the male/female ratio is 1:1. The association with HLA B27 is less (50–80%) than those observed in idiopathic AS (17) and it is associated with uveitis in 25% of the patients. Isolated sacroiliitis seems not to be related to HLA B27 and is generally asymptomatic and not progressive (18).

Some studies showed that the prevalence of axial involvement was higher than those reported previously. In fact, in these studies, based on the European Spondyloarthropathy Study Group (ESSG) criteria for SpA (19) (Table II), the Authors detected a frequency ranging between 10–25% for spondylitis and 30–36% for sacroiliitis (1, 20).

A spinal complication of spondylitis in patients with IBD is the development of erosive sclerotic lesions of vertebral body adjacent to disc also defined spondylodiscitis, the diagnosis of which is sometimes delayed, particularly in patients with an insidious onset and non-specific symptoms (21). Even though in AS some Authors reported a frequency of discovertebral erosions in a range of 1.5–28% (22, 23), in EA our research group has recently found a high prevalence of this lesion (30.55%), confirming that they are an important characteristic aspect of all SpA. In particular, we found a high prevalence in patients with axial and peripheral subset (31.82%), suggesting that spondylodiscitis could be a characterizing feature of the overlap subset, type 3 axial and peripheral forms (16). Furthermore, in contrast with what was reported for AS (22) and PsA (24), the occurrence of these lesions in patients with UC and CD was earlier and often asymptomatic.

Isolated sacroiliitis is often asymptomatic, non-progressive and non-associated to HLA B27. Its occurrence, related to the radiological method used, ranges between 18–52%. This may represent a forme fruste of enteropathic ankylosing spondylitis, a stunted form of axial involvement because of therapy, or a third category of rheumatic disease associated with IBD (25).

Other clinical features of articular involvement in EA patients include enthesitis, dactylitis and tenosynovitis. Enthesitis, inflammation at the insertion site to bone of the tendon, ligament and joint capsule, generally occur at the insertion of the Achilles tendon and/or at the plantar fascia at the heel and/or the patellar tendon at the knee, their occurrence is not different from the other SpA. Dactylitis, swelling of one or more fingers or toes caused by tenosynovitis of the flexor tendons, occasionally seems to be the only articular manifestation in EA patients (1).

Extra-articular manifestations

The extra-articular manifestations are characterized by acute anterior uveitis, aortic insufficiency and cardiac conduction disturbances with a frequency of 25%, 4–10%, 3–9%, respectively (1). They seem to be related to disease duration, axial joint involvement and with HLA-B27 positivity (26). Moreover, in Literature some data clearly suggest that IBD patients, as well as those with SpA (27, 28), show an increased cardiovascular and thrombotic risk (29). A frequent occurrence of metabolic syndrome (MS) is documented in IBD, particularly in UC (30). Also the risk of hyperhomocysteinaemia is significantly higher in IBD patients than the controls (31), and an increased prevalence of hepatic steatosis, which is a recognized predictor of arterial and venous thrombosis, has been found both in the IBD population and in subjects with EA (32).

Skin lesions occur in 10–25% of the IBD patients. Erythema nodosum (EN) and pyoderma gangrenosum (PG) are described as the most common cutaneous manifestations of IBD (33). The prevalence of EN and PG in patients diagnosed with IBD is 3–8% and 1–2%, respectively (34). EN is characterized by the inflammation of the subcutaneous fat tissue and generally distributed on the lower extremities, and in IBD patients coinciding with exacerbations of the gut inflammation and thus tends to occur in

Table I. *Classification and features of articular involvement subsets in inflammatory bowel disease (IBD).*

Peripheral			Axial	
Type 1	Type 2	Type 3	Isolated sacroiliitis	Spondylitis
- Pauciarticular (less than 5 joints) - Asymmetric involvement - Acute, self-limiting attack (< 10 weeks) - Usually coincides with relapse of IBD - Strongly associated with other extra-intestinal manifestations - Lower limbs more affected - Associated with HLA DRB1, B35, B27	- Polyarticular (5 or more joints) - Symptoms persist for months or even years - May be erosive - Runs a course independent of IBD - Affects both large and small joints - Strongly associated with uveitis - Associated with HLA B44	- Both axial and peripheral involvement	- Asymptomatic - Usually non progressive disease	- Usually precede the onset of IBD - Runs a course independent of IBD - Clinical course is similar to idiopathic ankylosing spondylitis - Disease progression leads to increasing immobility and ankylosing - Associated with uveitis - Strongly associated with HLA B27

Table II. *European Spondyloarthropathy Study Group criteria* (34).

- *Inflammatory spinal pain*
- *or/and synovitis asymmetric or predominantly affecting the lower limbs (past or current)*

One or more of the following:

- *Positive family history for psoriasis, anterior uveitis, inflammatory bowel disease, reactive arthritis, ankylosing spondylitis*
- *Psoriasis (past or current diagnosed by a physician)*
- *Inflammatory bowel disease (past or current diagnosed by a physician and confirmed by endoscopy)*
- *Urethritis (non-gonococcal), cervicitis, or acute diarrhea within 1 months before the onset of arthritis*
- *Alternating buttock pain (past or current buttock pain alternating between the right and left sides)*
- *Enthesopathy*
- *Sacroiliitis*

patients with active peripheral synovitis. PG, a rare skin condition, is characterized by the necrosis and ulceration of the tissue usually from legs. It is not related to gut inflammation, which is reported in 2.2% of UC patients and 1.5% of CD patients with a female predominance (35) and is considered to be the most severe skin manifestation in IBD.

The prevalence of osteoporosis is increased in persons with IBD, though it is unclear whether this is a direct result of inflammation, or whether it results from concomitant changes in nutrition and body composition and/or the use of glucocorticoids. The risk may be greater in those persons with CD, though individuals with UC remain at risk. Patients

with IBD are also at increased risk of osteoporosis-related fractures (36).

The renal and/or urinary involvement, in IBD patients, occur in a range between 4 to 23%, and the urolithiasis is the most common urogenital manifestation in IBD (12–28%) (37). The risk of developing urolithiasis in IBD is 10 to 100 times greater than the risk for general hospital patients. Other causes for renal impairment include amyloidosis, glomerulonephritis and tubulointerstitial nephritis. There are many case reports on amyloidosis, but reviewing the literature the overall prevalence in IBD seems to be below 1% (37, 38). Glomerulonephritis has recently emerged as an extraintestinal manifestation and seems to be very rare, with about 40 reports in the literature; it appears to be linked to disease activity as renal function improves after remission of IBD (37, 38). Tubulointerstitial nephritis seems to be a common clinical feature among IBD patients, manifesting with proteinuria. As with glomerulonephritis ,here seems to be a correlation with disease activitiy (37, 38).

Pulmonary involvement is relatively rare in IBD, but occasionally potentially harmful. It represents a confounding diagnostic problem and must be distinguished from the complications of intestinal inflammation and from the side effects of drugs used in its treatment.

Recently, our research group investigated the occurrence of chronic autoimmune thyroiditis or Hashimoto's thyroiditis (HT) in EA patients (39). HT is known to be an extraintestinal complication of IBD and the increased prevalence of thyroid antibodies in UC patients has been reported to range from 0.82% to 3.7% (40). Our results show that HT occurs more frequently in EA patients. In detail, TPOAbs positivity occurs more frequently in patients with a long disease duration and active rheumatic disease than in the other patients, suggesting a possible relationship between the maintenance of the inflammatory process in EA patients and the positivity of TPOAbs. Furthermore, EA patients affected by thyroiditis show a peripheral involvement, with a significantly high prevalence of poly-articular subset or type 2 (39).

Interestingly, some extra-intestinal manifestations, such as erythema nodosum or pyoderma gangrenosum, in association with active bowel disease, family history of IBD, appendectomy, cigarette smoking, are potential risk factors for arthritis in IBD patients (41, 42).

Diagnosis and classification criteria

Diagnosis is generally established on medical history and physical examination, because at present no "gold standard" criteria are available for the diagnosis of EA. Thus, the SpA are a group of distinct diseases with similar clinical features and a common genetic predisposition, that is why the diagnosis of EA was generally made according to the ESSG criteria (19). In fact, IBD is a criterion of SpA, thus, patients with IBD presenting with inflammatory back pain and/or synovitis (predominantly of the lower limbs) are diagnosed as having spondyloarthropathy. These criteria, although not defined for diagnostic purposes, may be a useful guide for the clinician in the identification of patients with EA. Moreover, the ESSG criteria, designed to be applicable without radiological examination and laboratory testing, have good sensitivity (86%) and specificity (87%), at least in established disease.

Therefore, the diagnosis of peripheral arthritis is made clinically. The radiographic findings do not show erosions or deformities in the early stage of articular disease, but only an increased volume of the soft tissue. Patients with a chronic articular disease, instead, may develop joint erosion and loss of joint space, in particular in the hand and/or hip (12, 13). Synovial fluid analysis and histology of synovial tissue show a non-specific inflammation. Similarly, the diagnosis of axial arthritis is possible in the presence of clinical signs of axial involvement: inflammatory back pain and/or alternate buttock pain with morning stiffness and improvement with exercise (43). The radiographic findings of the axial involvement may range from sacroiliitis alone, in the case of isolated sacroiliitis, to the typical changes of AS (squaring, syndesmophytes, bamboo spine).

Magnetic resonance imaging (MRI), an imaging technique usually accepted to evaluate the peripheral (44, 45) and axial involvement of SpA (46), may be useful for the early diagnosis of EA or when there are no findings with conventional X-ray examination. In fact, recently some studies established a link between inflammatory sacroiliitis on MRI at baseline and sacroiliitis on x-ray many years later (47). In 2009, the ASAS (Assessment of SpondyloArthritis international Society) group

published new criteria for the classification of axial spondylarthropathy, based on sacroiliitis on MRI in patients without structural damage (48). In detail, the ASAS criteria for classifying axial involvement in SpA require the imaging presence of sacroiliitis for a diagnosis of AS, and MRI can identify sacroiliitis at all stages of progression (49). Osteitis/bone marrow edema, enthesitis, capsulitis, and synovitis are typical MRI findings in patients with active sacroiliitis associated with axial involvement, but bone marrow edema is the only indispensable criterion for a diagnosis of active sacroiliitis; structural damage due to previous inflammation of the sacroiliac joints, such as subchondral sclerosis, subchondral/periarticular erosions, periarticular fat deposition, or bony bridges/ankylosis, is not sufficient for the diagnosis but is very helpful during the follow-up (48). Moreover, the ASAS recently developed the Ankylosing Spondylitis Disease Activity Score (ASDAS) based on both clinical and laboratory variables. The ASDAS is a simple, reproducible, and discriminating tool for rapidly separating different disease activity levels, although it is not yet used in everyday practice or official recommendations (50). The ASAS has not yet published data on the ASDAS cutoffs indicating a remission or a need for a change in treatment. Many studies have established the good discriminating power, validity, and reliability of the ASDAS (51).

Treatment

The management of patients with EA needs an active cooperation between gastroenterologists and rheumatologists. The use of corticosteroids and/or DMARDs and/or of anti-TNFα, helpful to contain bowel inflammation, usually leads to the reduction of peripheral type I arthritis symptoms, which also respond well to rest, to physiokinesitherapy and to intra-articular injections of steroids. On the contrary, the management of type II and III is more complex and they may persist despite the relapse of IBD. Sulfasalazine and 5-aminosalicylic acid are often used for the treatment of IBD, their effectiveness also being confirmed for the management of mild peripheral arthritis, particularly in patients with UC. Their effectiveness on CD has not yet been completely proved. These drugs have no effect on the evolution of joint damage to severe forms of arthritis and their usefulness in the axial subset is marginal; they do not seem to prevent the possible onset of colitis in patients with SpA (52).

Methotrexate, azathioprine, cyclosporine, and leflunomide show their efficacy in some patients with peripheral arthritis and other extra-intestinal manifestations (1, 7, 52). Recently, our team has been studying the efficacy and the tolerability of methotrexate at a dose of 20 mg/week, in patients with peripheral arthritis under UC, and we have shown a rapid and effective reduction of joint symptoms with significant improvement in laboratory parameters and in rates of disease activity (53).

Patients with IBD and articular involvement who have an inadequate response to conventional treatment are candidates for the therapy with anti-TNFα. Infliximab, adalimumab, etanercept and golimumab can be used on IBD patients with articular involvement, although golimumab has not been approved for CD. The anti-TNFα, infliximab and adalimumab, are efficacient in the control not only of the intestinal involvement but also of the articular ones (both axial and peripheral subset), especially in patients with CD. Etanercept, instead, seems to be effective only in controlling articular symptoms but not intestinal ones (54).

Recently, an Italian Expert Panel compiled the guidelines on the management of patients with coexisting SpA and IBD (55). The Authors recommend the treatment with anti-TNFα therapy in the case of active not complicated luminal CD associated with axial SpA, with the exception of etanercept. Induction and maintenance doses should be those that are effective for both diseases: 5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks for infliximab; 160 mg at week 0, 80 mg at week 2 and then 40 mg every 2 weeks for adalimumab. In cases of prolonged and stable remission for patients with both axial and intestinal manifestations, given the high probability of axial SpA relapse, anti-TNFα agents should be continued (55).

In CD disease complicated by obstructive symptoms, intestinal perforation or intra-abdominal abscesses, the surgical treatments must precede any medical therapy for both intestinal and musculoskeletal symptoms. After surgery and complete resolution of the complication, anti-TNFα agents should be started for treatment of SpA and

the remaining active luminal disease; biological therapy may also be useful for the prevention of post-operative recurrence of CD. In UC patients the anti-TNFα therapy is a preferred choice in cases of lack of efficacy of azathioprine and 6-mercaptopurine on axial SpA. Moreover, anti-TNFα agents should be started when NSAIDs are insufficient to control axial symptoms, in patients with active axial SpA and quiescent IBD (55).

In addition, anti-TNFα agents should be considered the first line therapeutic approach when moderate-to-severe luminal CD is associated with polyarthritis. They are also useful for musculoskeletal manifestations refractory to the conventional therapy. In cases of prolonged and stable remission for both musculoskeletal and IBD manifestations, an exit strategy that allows the discontinuation of anti-TNFα should be considered. In patients with polyarthritis and active UC, anti-TNFα agents should be started in addition to sulfasalazine (55).

Finally, in patients with active musculoskeletal disease and IBD remission, specific anti-TNFα agents should be started at rheumatologic doses. Nevertheless, the choice of a specific anti-TNFα should be influenced by the possible effect on underlying IBD: etanercept should be avoided considering that it was reported as a possible triggering factor for new onset of CD (55).

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