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Rheumatic Manifestations of Gastrointestinal Diseases

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Summary Points

- Impairment of the gastrointestinal barrier function may play a role in the pathogenesis of arthropathies.
- Arthritis is the most common extracolonic manifestation of chronic ulcerative colitis.
- Reactive arthritis is one of the most common arthritides affecting young adults.

Introduction

Pathologic changes in the gastrointestinal tract may be associated with clinical complaints in multiple organs including the musculoskeletal system. Impaired barrier function and immunogenetic mechanisms are implicated (1). In some instances, the association between gastrointestinal pathology and extraintestinal disease is so strong that treatment of gastrointestinal disease resolves many of the patient's extraintestinal complaints. This article will focus primarily on the rheumatic manifestations of the gastrointestinal diseases and the available treatment modalities.

Gastrointestinal Pathophysiology

The gut has multiple mechanisms to regulate the efficient absorption of nutrients while excluding bacterial and dietary antigens. Impairment of the gastrointestinal barrier function can be observed in several diseases including inflammatory bowel disease (IBD) and other spondyloarthropathies, and this defect may play a role in the pathogenesis of arthropathies.

Ileocolonoscopy and multiple biopsies were carried out in 96 patients with seronegative spondyloarthropathy, 17 patients with osteoarthritis taking nonsteroidal anti-inflammatory drugs (NSAIDs), and 19 patients with chronic abdominal discomfort. Inflammatory gut lesions were detected in two thirds of the patients with spondyloarthropathy, 12.5% of patients with osteoarthritis, and 16% of patients with abdominal discomfort. More recently, an Italian study confirmed microscopical mucosal inflammation on biopsy in 15 people with psoriatic arthritis but without bowel symptoms, 6 of whom had normal appearing mucosa by colonoscopy (2).

Altered gut permeability may also play a role in the pathogenesis of arthropathies. Permeability may be measured by oral feeding of different tracers (eg, ⁵¹Cr-labeled EDTA, lactoglobulin, lactalbumin, polyethylene glycol particles, lactulose, or mannitol) followed by urine analysis of excretion. Increased intestinal permeability was found in all subtypes of juvenile chronic arthritis with correlation between abnormalities in lactulose/mannitol test and the histopathological features of the gut mucosa (3). Another study showed an increase in the 24-hour urine excretion of ⁵¹Cr-EDTA in 34 patients with Behcet's syndrome and 10 patients with ankylosing spondylitis (AS), when compared with 15 healthy controls (4).

Because the results obtained from such studies are entirely dependent on normal gastric emptying, normal renal function, and an accurate urine collection, they should be interpreted carefully. Also, the results may be altered by possible effect of the NSAIDs on prostaglandin synthesis and gut permeability.

Most recently, Salmi et al concluded that different leukocyte populations derived from inflamed gut of patients with IBD bind avidly to synovial vessels using a distinct repertoire of adhesion molecules, suggesting that their recirculation may contribute to the development of reactive arthritis in inflammatory bowel diseases (5). This study is the first experimental support of the homing of lymphocytes from the gut mucosa to joint tissue in enteropathic arthritis.

Inflammatory Bowel Disease (IBD)

Crohn's disease and ulcerative colitis (UC) are both associated with a number of extra-intestinal chronic inflammatory diseases. Arthritis is the most common extracolonic manifestation of chronic UC (6). Patients with Crohn's disease also have an increased prevalence of inflammatory joint disease although arthritis is more common in patients with colitic disease than small bowel inflammation alone (7).

The type of arthritis associated with IBD may be either axial or peripheral (Table 1). Peripheral joint disease occurs in 10% to 20% of patients with IBD and is not usually associated with HLA-B27. The onset of arthritis either accompanies or follows the onset of the colitis and the activity of the joint disease generally parallels the activity of the IBD. Patients can present with an oligoarthritis but no bowel symptoms and yet have IBD as the cause of their arthritis. The course is usually asymmetric oligoarthritis lasting 2 to 6 weeks and radiographic changes in the joints are rare (8).

In the case of UC, colectomy results in complete remission of the peripheral arthritis, whereas surgical therapy for Crohn's disease results in remission of arthritis in only 50% of cases. In contrast, spondylitis and sacroiliitis occur in 2% to 7% of patients with IBD and are generally associated with HLA-B27. Isolated subclinical sacroiliitis has been reported in 24% of patients with IBD, suggesting that axial involvement may be more common than reported previously (9). The axial disease frequently precedes the onset of GI symptoms, and follows a chronic course which is independent of the activity of the IBD. Surgery has no effect on this axial arthropathy (8).

Orchard et al (10) retrospectively assessed 976 patients with UC and 483 with Crohn's disease and found two types of enteropathic peripheral arthropathy. Type 1 is a self limited disease with presentation similar to post-dysenteric reactive arthritis, different from the polyarticular disease with a course independent of the IBD, type 2 (Table 2).

The same investigators have studied the association of peripheral arthropathies with certain HLA phenotypes (11). Fifty-seven patients with type 1 arthritis and 45 with type 2, who were identified by case note review and questionnaire, underwent genotyping by sequence-specific primer polymerase chain reaction. HLA-B27 was prevalent in 27% of type 2 patients, however, DR1 antigen was present in 33% of type 1 compared with none of type 2 and 3% of 603 controls ($P < 0.0001$). In contrast, type 2 was associated with HLA-B44 in 62% ($P = 0.01$). These data

suggest that the clinical classification into type 1 and type 2 arthropathies is consistent with immunogenetically distinct entities and establishes that in polygenic disorders, genes may determine clinical phenotype without conferring overall disease susceptibility.

Management of arthritis in IBD patients relies on good control of the underlying gastrointestinal pathology. Sulfasalazine, azathioprine, glucocorticoids, and methotrexate are widely used; experience with cyclosporine is limited. The Food and Drug Administration has approved tumor necrosis factor-alpha antibody (infliximab) for the treatment of Crohn's disease, which has resulted in a significant improvement of axial and peripheral arthritis related to this disease in early studies (12).

Low bone mineral density is a recognized complication of IBD. In a cross-sectional study by Abitbol et al (13), 34 patients with Crohn's disease and 50 with UC (49 women and 35 men) underwent a metabolic bone assessment, including serum levels of osteocalcin, phosphate, calcium, parathyroid hormone, 25-hydroxyvitamin D3, and 1,25-dihydroxyvitamin D3. Bone mineral densities were measured by dual energy X-ray absorptiometry of the lumbar spine and femoral neck. Osteopenia was present in 36 patients (43%), 27 of whom were on glucocorticoid therapy. Although no patient complained of muscular or bone pain, 6 patients (7%) had vertebral crush fractures. Risk factors for the development of osteopenia were identified as age, cumulative glucocorticoid doses, increased erythrocyte sedimentation rate, and low osteocalcin level.

Another study (14) conducted on 119 patients with Crohn's disease (ages 5 to 25 years) showed similar results with hypoalbuminemia, total glucocorticoid exposure, requirement for total parenteral nutrition, and prior use of 6-mercaptopurine being the most powerful risk factors for low bone mineral density (BMD). Patients with IBD should be advised to consume adequate vitamin D and calcium and to participate in a regular weight-bearing exercise program. Therapy with disphosphonates may be necessary as well.

Treatment with alendronate (10 mg daily) in 32 patients with Crohn's disease and a bone mass T score of -1 or more significantly increased the bone mineral density of the lumbar spine by 5%, compared with a decrease of 0.9% in patients receiving placebo ($P < 0.01$) (15). Alendronate was safe, well tolerated, and there was no difference in adverse events among treatment groups. Bone densitometry should be performed, where possible, to identify those in need of treatment, to avoid unnecessary treatment, and to monitor the effect of treatment designed to prevent bone loss. The dose of glucocorticoids should be kept to a minimum, and vitamin D deficiency should be corrected.

Celiac Sprue

Also known as gluten enteropathy, celiac sprue is characterized by diffuse damage to the proximal small intestinal mucosa that results in villous atrophy and altered gut permeability. It is strongly associated with the HLA class II antigens: DR3 and DQw2. Arthritis is a well-known complication in children and adults. It was present in 52 of 200 adult celiac disease patients attending a routine gastroenterology follow-up clinic (16). The distribution of arthritis was peripheral in 19 patients, axial in 15, and an overlap in 18 subjects. The prevalence of joint disease was less common among patients on gluten free diet.

Recently, Usai et al found axial joint inflammation in 63% of patients with celiac disease (17); 22 patients with celiac sprue underwent bone scintigraphy using ^{99m}Tc methylene diphosphonate. Changes compatible with sacroiliitis were found in 14 cases, 11 of whom had low back pain. Five patients with low back pain had negative scintigraphy. Sacroiliac radiographs were obtained in only four patients, and all had bilateral sacroiliitis. One patient had rheumatoid arthritis but all studied individuals were HLA-B27 negative.

Arthritis and other rheumatic complaints have been the presenting symptom in patients with gluten enteropathy with improvement in the clinical abnormalities on a gluten-free diet (18,19,20). An increased level of antigliadin antibodies was seen in 9 of 74 patients with spondyloarthropathies, 1 of whom had elevated antiendomysium antibodies and biopsy proven celiac disease (21). Thus, antiendomysial antibody testing is recommended as a screening tool in patients with suspected gluten enteropathy. Another study found that 3.3% of sprue patients had Sjogren's syndrome (22).

Serial bone mineral density measurements of 55 patients with celiac disease detected osteoporosis (defined as a Z score equal or below 2) in 50% of the men and 47% of the women (23). Celiac disease was an independent risk factor for the development of osteoporosis.

Whipple's Disease

Whipple's disease is a rare multisystemic illness caused by infection with the bacillus *Tropheryma whippelii*. It can involve any organ system, but the small intestine is affected in the majority of patients. The source of infection is unknown, but no cases of human-to-human spread have been documented. It may occur at any age but most commonly affects white men in the fourth to sixth decades.

The most common complaints are diarrhea, abdominal pain, weight loss, fever, and arthritis. Axillary and cervical lymphadenopathy and generalized hyperpigmentation also are common features. Protein-losing enteropathy due to intestinal or lymphatic involvement may result in hypoalbuminemia and edema. Extraintestinal manifestations are common and often start prior to the onset of gut symptoms. Arthritis or arthralgia may be the only presenting symptoms predating other manifestations by years (24).

In a retrospective clinical study of 52 patients with Whipple's disease, 35 patients (67%) had articular manifestations as presenting features of the disease, while 8 patients (15%) presented with gastrointestinal complaints (25). At a later stage of the disease, 44 patients (85%) developed diarrhea and malabsorption while 8 (15%) did not show any intestinal symptoms throughout the course of the disease. The classic setting is long-term, unexplained, seronegative oligoarthritis or polyarthritis with a palindromic or relapsing course, although chronic destructive polyarthritis and spondyloarthropathy have been reported (26).

The diagnosis of Whipple's disease is established by duodenal or lymph node biopsy, which demonstrates infiltration of the lamina propria with PAS-positive macrophages that contain Gram-positive bacilli. A recent important diagnostic test is polymerase chain reaction of the 16S ribosomal RNA of *Tropheryma whippelii*. O'Duffy et al reported 2 patients presenting with polyarthritis and negative bowel mucosal biopsies for Whipple's disease in whom the synovial fluid of 1 and the synovial tissue of the other were positive for *Tropheryma whippelii* when examined by polymerase chain reaction (PCR) and DNA sequencing (27).

Antibiotic therapy is mandatory. The recommended regimen is trimethoprim combined with sulfamethoxazole for one year, which usually results in clinical remission and an excellent prognosis (28). Joint symptoms and fever subside in a few days, while diarrhea and malabsorption disappear within 2 to 4 weeks (29).

Enteric Reactive Arthritis

Reactive arthritis (ReA), formerly known as Reiter's syndrome, is one of the most common arthritides affecting young adults. In most cases ReA follows urogenital or intestinal bacterial infection, in cases of enteric infection, the longer the duration of diarrhea, the greater likelihood of developing ReA. There is a third important group of patients, those who develop clinical features of ReA with no evidence of precipitating infection. These patients should have further

investigation for the presence of covert infection, possibly in the respiratory tract or eyes, in addition to work-up for possible other features of ReA.

The actual incidence of ReA after enteritis varies according to the causative organism: approximately 2% to 3% percent of all patients with shigella, salmonella, and campylobacter infections but a much higher proportion of those with yersiniosis (30). In enteric ReA the sudden onset of an asymmetric oligoarticular or polyarticular inflammatory arthritis that usually involves the knees, ankles, or small joints of the feet may occur (31). A much smaller group presents with monoarthritis. Arthritis occurs typically 2 to 4 weeks after the onset of diarrhea and may follow an acute or chronic course. Low back pain is noted in 30% to 90% of patients with typical ReA (30). In a 4-year follow-up study of 31 patients with post yersinia arthritis, 4 patients (13%) gave a history of low back pain during the enteritis; 6 (19%) had definite sacroiliitis at follow-up, 3 (10%) of these having classic AS (32).

Over two thirds of Caucasian patients with enteric ReA are HLA-B27 positive, compared with less than 10 percent of healthy Caucasian controls (33). The mechanism by which HLA-B27 mediates susceptibility to post-enteric ReA remains unclear. Scofield et al found peptides from enteric organisms share a sequence with the binding site of the B27 molecule, which may suggest a mechanism for autoimmunity that may operate in the B27 associated spondyloarthropathies involving peptides bound to and derived from histocompatibility alleles (34).

Symptomatic treatment with analgesics and NSAIDs is the mainstay of therapy. There have been reports of the presence of *Chlamydia* particles, salmonella DNA, and yersinia antigens in the synovial fluid of patients with ReA which raised the question of whether long-term antimicrobial therapy could modify the course of the disease (35).

In a randomized, double-blind, placebo-controlled trial, Anneli et al looked at the use of lymecycline, a form of tetracycline, in the management of ReA (36). A 3-month course of treatment shortened the disease duration by approximately 24 weeks in 50% of patients with *Chlamydia*-triggered ReA than in those treated with placebo, but a similar difference was not observed in other patients with ReA. Despite evidence for persisting antigen presence, antimicrobial therapy seems of no proven value in enteropathic ReA. Patients with persistent symptoms may respond to high dose sulfasalazine (37).

Summary

The term "enteropathic arthritis" describes joint manifestations that occur in conjunction with gastrointestinal disease. The clinical picture of this entity is still evolving and has gained importance from advances in knowledge regarding gut pathophysiology and cell trafficking. It is very important to keep enteropathic arthritis in the differential diagnosis of patients with unexplained arthritis and to obtain detailed history, complete physical examination, and appropriate testing. These arthritic syndromes can be treated symptomatically, but long-term therapy should be directed at the underlying cause.

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Table 1. Joint Involvement in IBD (2)

	Peripheral joint involvement	Axial involvement
Prevalence	10% to 20%	2% to 7%
HLA-B27 association	Uncommon	50% to 70%
Association with IBD activity	Coinciding	Independent
Clinical course	Asymmetric, relapsing oligoarthritis	Persistent
Response to colectomy	Remission in UC	No response

Table 2. Classification of Enteropathic Peripheral Arthropathy (29)

	Type 1	Type 2
Number of joints	Less than 5	5 or more
Clinical course	Acute, self-limiting (<10 weeks)	Persistent (months/years)
Association with IBD activity	Coinciding	Independent
Extraintestinal manifestations	Common	Only uveitis
HLA association	B27, DR1	B44