Epitogastrointestinal diseases typically present with abdominal pain, nausea, diarrhea, and jaundice. However, certain hepatogastrointestinal diseases can present with extraintestinal signs and symptoms that can be misleading, such as skin rash and joint pains. Joint pains can be the initial manifestation reported by the patient with a hepatogastrointestinal disease and may precede disease onset by 1 year. Similarly, dermatologic conditions can be important clues to the diagnosis of some hepatogastrointestinal diseases, such as dermatitis herpetiformis in celiac sprue or pyoderma gangrenosum in Crohn’s disease. Conversely, some nongastrointestinal disease processes, such as the vasculitides, may present with abdominal pain, leading the examiner to focus on a gastrointestinal process.

Diseases that have hepatogastrointestinal, musculoskeletal, and dermatologic manifestations include inflammatory bowel disease (IBD), celiac sprue, Whipple’s disease, dysentery, viral hepatitis, and certain vasculitides (Table 1). Polyarteritis nodosa and Henoch-Schönlein purpura are 2 vasculitides that can have gastrointestinal involvement of the mesenteric vasculature with abdominal pain as a manifestation. In addition, polyarteritis nodosa is a known complication of hepatitis B infection, and mixed cryoglobulinemia is a complication of hepatitis C infection.

A thorough history and physical examination are needed to differentiate among the possible diagnoses in a patient presenting with diffuse joint pains, skin rashes, and gastrointestinal symptoms. This article discusses hepatogastrointestinal diseases that have associated joint pains and dermatologic manifestations.

**Hepatogastrointestinal DISEASES ASSOCIATED WITH POLYARTICULAR JOINT PAIN**

- Inflammatory bowel disease
- Reactive arthritis
- Celiac sprue
- Whipple’s disease
- Viral hepatitis (hepatitis B and C)

**Spondyloarthropathies**

The spondyloarthropathies are a group of interrelated chronic inflammatory rheumatic diseases that includes ankylosing spondylitis, the arthritis associated with IBD, and reactive arthritis. The spondyloarthropathies are characterized by inflammation of the entheses, or the points of attachment of ligaments and tendons to bone. Enthesitis most commonly occurs at sites that bear the greatest physical stress (eg, Achilles’ tendon). The spondyloarthropathies are also strongly associated with the HLA-B27 gene. HLA-B27 is a major histocompatibility complex antigen capable of presenting potentially arthritogenic peptides to cytotoxic T lymphocytes; HLA-B27 also appears to enhance points that may help differentiate among the potential underlying causes of arthritis include the number of joints involved, their location and distribution (eg, symmetric versus asymmetric), whether the pain is acute (present for < 6 wk) or chronic, and whether the arthritis is migratory.

**Joint Pains**

*Arthritis* refers to joint pain accompanied by swelling, whereas *arthralgia* refers to joint pain without objective swelling. *Polyarthritis* is defined as pain and swelling in more than 4 joints, whereas *oligoarthritis* is pain and swelling limited to less than 4 joints. Historical points that may help differentiate among the potential underlying causes of arthritis include the number of joints involved, their location and distribution (eg, symmetric versus asymmetric), whether the pain is acute (present for < 6 wk) or chronic, and whether the arthritis is migratory.

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the invasion of enteric pathogens that are known to trigger reactive arthritis. However, routine serologic testing for HLA-B27 is not clinically useful as the spondyloarthropathies can occur in its absence. One study found that only 36% of patients presenting with reactive arthritis secondary to a dysenteric infection were positive for HLA-B27. The features of the spondyloarthropathies are summarized in Table 2.

### Table 2. Features of the Spondyloarthropathies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated</th>
<th>Dermatologic</th>
<th>Musculoskeletal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiographic sacroiliitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Variable inflammatory peripheral arthritis, enthesitis, and dactylitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Association with gastrointestinal diseases including inflammatory bowel disease and dysentery</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Association with psoriasis and other mucocutaneous lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tendency for anterior ocular inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increased familial incidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No association with rheumatoid factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strong association with HLA-B27</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission from Khan MA. Update on spondyloarthropathies. Ann Intern Med 2002;136:897.

The arthritis of IBD can involve the axial joints or peripheral large joints. Axial arthritis is more commonly associated with Crohn’s disease. Orchard and colleagues have classified the arthropathy associated with IBD as type 1 (pauciarticular), which has fewer than 5 joints involved, is characterized by acute self-limiting episodes, and is associated with relapses of IBD; and type 2 (polyarthritis), which is often persistent and is not always associated with disease flares. In a study involving 654 persons with IBD, the overall prevalence of spondyloarthropathy was 22%. In another study, inflammatory back pain was the most common articular manifestation in patients with IBD, occurring in 30%. Yersinia enterocolitica enteritis can mimic Crohn’s disease.
and even appendicitis and can have a reactive arthritis as a manifestation.12

Aminosalicylates are first-line agents in medical therapy for IBD, and corticosteroids are second-line agents. Oral 5-aminosalicylates available for the treatment of IBD include sulfasalazine, mesalamine, balsalazide, and olsalazine. Corticosteroids are rapid-acting anti-inflammatory agents and are indicated for acute flares of disease only. Control of the bowel disease generally will also control the arthritis in IBD, although the arthritis can occur independently of active bowel disease. The 5-aminosalicylates are considered the first choice of treatment for the arthritis associated with IBD.13

Reactive Arthritis

Reactive arthritis refers to an episode of acute nonpurulent arthritis that occurs 1 to 2 months after a primary infection. The infections are mainly enteric (Salmonella, Shigella, Yersinia, Campylobacter) or urogenital (Chlamydia). Reiter’s syndrome is the clinical triad of arthritis, urethritis, and conjunctivitis, but this term has been used synonymously with reactive arthritis. As with other spondyloarthropathies, there is a strong association between reactive arthritis and HLA-B27 tissue antigen. Symptoms of reactive arthritis generally appear 1 to 2 weeks from the onset of the urogenital or enteric infection. Symptoms include fever, malaise, and joint pains that worsen with rest, along with the symptoms associated with the primary infection. The arthritis can present as inflammatory low back pain, enthesitis, or oligoarthritis affecting the lower extremities. Two separate studies that looked at the prevalence of reactive arthritis among patients with Salmonella and Shigella enteritis found a 6% prevalence in patients with Salmonella infection and a 7% prevalence in patients with Shigella infection.5,14

Other nonarticular manifestations of reactive arthritis are worthy of mention. Keratoderma blennorrhagica is a skin rash that can appear on the palms of the hands and soles of the feet of patients with reactive arthritis; it consists of hyperkeratotic skin that begins as clear vesicles on erythematous bases and progress to macules, papules, and nodules (Figure 3). Conjunctivitis is an associated sign of Reiter’s syndrome.15

MALABSORPTION SYNDROMES

Many diseases can cause malabsorption, but this discussion will focus on 2 diseases that have polyarticular joint pain as a manifestation: celiac sprue and Whipple’s disease. Patients with symptoms of malabsorption

Table 3. Extraintestinal Manifestations of Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative Colitis, n (%) (n = 976)</th>
<th>Crohn’s Disease, n (%) (n = 483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema nodosum</td>
<td>9 (0.9)</td>
<td>27 (5.6)</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>5 (0.5)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>52 (5.3)</td>
<td>62 (14.3)</td>
</tr>
<tr>
<td>Type 1 arthropathya</td>
<td>35 (3.6)</td>
<td>29 (6.0)</td>
</tr>
<tr>
<td>Type 2 arthropathyb</td>
<td>24 (2.5)</td>
<td>20 (4.0)</td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>34 (3.5)</td>
<td>42 (8.7)</td>
</tr>
</tbody>
</table>

* Fewer than 5 joints involved, characterized by acute self-limiting episodes, associated with disease flares.

† 5 or more joints involved, often persistent, not always associated with disease flares

generally present with diarrhea, weight loss, abdominal distention, weakness, and cachexia. The stools are loose, floating, oily, and foul smelling.

Celiac Sprue

Also known as gluten enteropathy, celiac sprue is an inherited autoimmune disease in which the lining of the small intestine is damaged in response to ingestion of gluten and other proteins found in wheat, barley, and rye.\textsuperscript{15,16} Symptoms of malabsorption develop as a result of small bowel damage. Extraintestinal manifestations of celiac sprue include skin rash and skeletal manifestations. The skin rash, known as dermatitis herpetiformis, consists of pruritic papulovesicles that occur symmetrically over the extensor surfaces of the extremities (Figure 4). In one study, dermatitis herpetiformis was observed in approximately one third of children (aged 2–14 years) with celiac disease but had a lower prevalence in those younger than 2 years and those older than 14 years (Table 4).\textsuperscript{17} It is estimated that 60\% of patients with dermatitis herpetiformis have “silent” celiac disease in which patients are asymptomatic but have positive serologic and histologic evidence of disease.\textsuperscript{18}

Patients with celiac disease may have significant bone pain due to osteomalacia from malnutrition. Generalized arthralgia is a common feature and may be present for several years before the diagnosis is made. There is also an associated nondestructive arthritis, which ranges from monarticular to polyarticular. Most common is a polyarticular, symmetric, large joint pattern that often affects the hips, knees and shoulders, although axial or sacroiliac involvement may be seen as well.

Serological testing for celiac disease includes measurement of IgG or IgA antigliadin antibodies, IgA anti-endomysial antibody, and IgA tissue transglutaminase antibody (Table 5). Endoscopic mucosal biopsy of the duodenum or proximal jejunum is used for confirmation of the diagnosis in patients with a positive serologic test. Mucosal biopsy reveals villous atrophy of the small intestine. Treatment of celiac disease and dermatitis herpetiformis is a gluten-free diet; the arthritis typically responds to this treatment as well.

Whipple’s Disease

Whipple’s disease is a multisystemic disease that presents with fever, lymphadenopathy, diarrhea, and malabsorption.\textsuperscript{19,20} Arthralgias and arthritis are common extraintestinal manifestations and are often the presenting features. The arthritis may appear years before the onset of the intestinal symptoms. The disease most commonly affects white men in the fourth to sixth decades and is caused by the gram-positive actinomycete \textit{Tropheryma whippelii}. The diagnosis is established by histological evaluation of the involved tissues and detection of the organism by polymerase chain reaction. Duodenal biopsy reveals periodic acid–Schiff-positive rod-shaped deposits in macrophages. Treatment includes trimethoprim-sulfamethoxazole (1 double-strength tablet twice daily) for 1 year.

VIRAL HEPATITIS

Hepatitis B

Hepatitis B virus (HBV) is a partially double-stranded DNA virus that is transmitted hematogenously and sexually. Acute viral hepatitis can present with a prodrome of anorexia, nausea, vomiting, malaise, low grade fever, and joint pains.\textsuperscript{21} The signs and symptoms of clinical hepatitis include jaundice and right upper quadrant pain. The incubation period is 6 weeks to 6 months. In the prodromal phase 1 to 6 weeks before clinical hepatitis, a serum sickness–like syndrome can occur with arthralgias, rash, angioedema, and rarely proteinuria and hematuria.\textsuperscript{22}

HBV infection also can be associated with polyarteritis
nodosa, a leukocytoclastic vasculitis that affects small- and medium-sized arteries.\textsuperscript{23,24} The clinical onset of polyarteritis nodosa is usually insidious, with fever, malaise, weight loss, and other symptoms developing over weeks to months. Arthralgias, myalgias, and neuropathy may also develop. Mononeuritis multiplex (eg, foot-drop) is a result of vasculitic involvement of the vasa vasorum. Abdominal pain is attributed to mesenteric vasculitis. Typical skin findings include livedo reticularis (a bluish mottling of the skin), palpable purpura, and skin ulcers.

Treatment of HBV infection with antivirals (lamivudine) is helpful in reducing viral replication. Corticosteroids are helpful in reducing inflammation if polyarteritis nodosa is present but may actually delay the seroconversion from surface antigen positive to surface antibody positive.\textsuperscript{25}

**Hepatitis C**

The hepatitis C virus (HCV) is a single-stranded RNA virus. It is the major cause of chronic hepatitis in the United States. Acute HCV infection is asymptomatic in many cases and is usually not recognized clinically. Patients may have nonspecific symptoms such as fatigue or malaise. Patients with HCV infection often develop an arthritis that can be clinically similar to rheumatoid arthritis as well as a positive rheumatoid factor. The antibody anticyclic citrullinated peptide is highly specific for rheumatoid arthritis and has been shown to be helpful in distinguishing HCV-related arthritis from rheumatoid arthritis.\textsuperscript{26,27} HCV is also commonly associated with joint pains when mixed cryoglobulinemia develops.\textsuperscript{28} Cryoglobulins are immunoglobulins that undergo reversible precipitation at low temperatures. Essential mixed cryoglobulinemia can cause a systemic vasculitis characterized by palpable purpura of the lower extremities, arthralgias, weakness, peripheral neuropathy, and glomerulonephritis. Palpable purpura, as their name implies, are a result of bleeding into the skin. The palpable purpura do not blanch with pressure. These purpura are the result of a leukocytoclastic vasculitis.

Treatment options for mixed cryoglobulinemia include glucocorticoids, plasmapheresis, and cyclophosphamide. Treatment of underlying HCV infection with interferon and ribavirin is also essential.

**HENOCHE-SCHÖNLEIN PURPURA**

In addition to the mixed cryoglobulinemia associated with HCV infection and polyarteritis nodosa associated with HBV infection, the vasculitide Henoch-Schönlein purpura merits attention due to its gastrointestinal involvement and association with joint pains.\textsuperscript{29} Henoch-Schönlein purpura (Figure 5) is a small vessel vasculitis characterized by palpable purpura (commonly distributed over the buttocks and lower extremities), arthralgias, abdominal pain, and glomerulonephritis.\textsuperscript{30} It is the most common vasculitis in children. Skin biopsy is helpful in confirming a leukocytoclastic vasculitis with IgA and C3 deposition by immunofluorescence. One study reported a preceding upper respiratory tract infection in 41% of cases.\textsuperscript{31} Henoch-Schönlein purpura is a self-limited disease, and treatment with corticosteroids is generally limited to those with renal and/or gastrointestinal involvement.

**CONCLUSION**

Joint pain and skin rashes can be an important diagnostic clue to an underlying systemic disorder, including hepatogastrointestinal disorders. The clinician must consider diseases outside of the musculoskeletal system when evaluating a patient with polyarticular joint pain. A thorough history and physical examination with a

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**Table 4.** Prevalence of Dermatitis Herpetiformis (DH) in Patients with Celiac Disease

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Women (n = 996)</th>
<th>Men (n = 440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 y (n = 250)</td>
<td>2 (0.8)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>2–14 y (n = 225)</td>
<td>73 (32.4)</td>
<td>52 (36.3)</td>
</tr>
<tr>
<td>&gt; 14 y (n = 521)</td>
<td>13 (2.5)</td>
<td>14 (8.1)</td>
</tr>
</tbody>
</table>


**Table 5.** Sensitivity and Specificity of Serologic Tests for Celiac Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigliadin IgG</td>
<td>57–100</td>
<td>47–94</td>
</tr>
<tr>
<td>Antigliadin IgA</td>
<td>52–100</td>
<td>71–100</td>
</tr>
<tr>
<td>Endomysium IgA</td>
<td>86–100</td>
<td>90–100</td>
</tr>
<tr>
<td>Transglutaminase IgA</td>
<td>77–100</td>
<td>91–100</td>
</tr>
</tbody>
</table>

detailed review of systems is needed to differentiate among the entities that can cause joint pain, skin rash, and abdominal symptoms.

REFERENCES


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