

Extraintestinal Manifestations of Hepatogastrointestinal Diseases

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Hepatogastrointestinal 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.¹ 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.

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.^{2,3} Historical

HEPATO-GASTROINTESTINAL DISEASES ASSOCIATED WITH POLYARTICULAR JOINT PAIN

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

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.³

SPONDYLOARTHROPATHIES

The spondyloarthropathies are a group of inter-related 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.⁴ HLA-B27 is a major histocompatibility complex antigen capable of presenting potentially arthritogenic peptides to cytotoxic T lymphocytes; HLA-B27 also appears to enhance

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Table 1. Extraintestinal Manifestations of Hepatogastrointestinal Diseases

Disease	Associated	Dermatologic	Musculoskeletal
Inflammatory bowel disease			
Crohn's disease	Fever, abdominal pain	Erythema nodosum, pyoderma gangrenosum	Axial arthritis more common
Ulcerative colitis	Bloody diarrhea	Erythema nodosum, pyoderma gangrenosum	Axial and peripheral arthritis similar in frequency
Enteric infections			
<i>Shigella</i> , <i>Salmonella</i> , <i>Yersinia</i> , <i>Campylobacter</i>	Bloody diarrhea	Keratoderma blennorrhagica	Reactive arthritis
Malabsorption syndromes			
Celiac sprue	Iron deficiency anemia	Dermatitis herpetiformis	Polyarthralgia
Whipple's disease	Fever, lymphadenopathy		Polyarthralgia
Viral hepatitis			
Hepatitis B	Polyarteritis nodosa	Jaundice (hepatitis), livedo reticularis, skin ulcers (vasculitis)	Prodrome that includes arthralgias; mononeuritis multiplex
Hepatitis C	Mixed cryoglobulinemia	Jaundice (hepatitis), palpable purpura	Can develop positive rheumatoid factor
Henoch-Schönlein purpura	IgA nephropathy, abdominal pain	Palpable purpura over buttocks and lower extremities	Arthralgias

Table 2. Features of the Spondyloarthropathies

Radiographic sacroiliitis
Variably inflammatory peripheral arthritis, enthesitis, and dactylitis
Association with gastrointestinal diseases including inflammatory bowel disease and dysentery
Association with psoriasis and other mucocutaneous lesions
Tendency for anterior ocular inflammation
Increased familial incidence
No association with rheumatoid factor
Strong association with HLA-B27

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

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-B27.⁵ The features of the spondyloarthropathies are summarized in **Table 2**.⁶

Inflammatory Bowel Disease

IBD includes ulcerative colitis and Crohn's disease. Ulcerative colitis is limited to the colon, while Crohn's disease most commonly affects the distal ileum and colon but may occur in any part of the gastrointestinal tract. The most common gastrointestinal manifestation

of ulcerative colitis is bloody diarrhea, while the most common gastrointestinal manifestation of Crohn's disease is abdominal pain. Crohn's disease may also present with fever, anorexia, and weight loss. The 2 diseases share several extraintestinal manifestations, including polyarticular joint pain, back pain, pyoderma gangrenosum, and erythema nodosum (**Table 3**). Extraintestinal manifestations are common and may predominate over gastrointestinal symptoms. Pyoderma gangrenosum is a painful noninfectious cutaneous ulcerating disease that is often misdiagnosed (**Figure 1**).⁷ Pyoderma gangrenosum is a diagnosis of exclusion, and it is important to rule out infectious and vascular etiologies.⁸ Erythema nodosum is an inflammatory disease of the skin characterized by tender red nodules, predominantly in the pretibial region (**Figure 2**).

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 colleagues⁹ 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 (polyarthritits), 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%.¹⁰ In another study, inflammatory back pain was the most common articular manifestation in patients with IBD, occurring in 30%.¹¹ *Yersinia enterocolitica* enteritis can mimic Crohn's disease

Table 3. Extraintestinal Manifestations of Inflammatory Bowel Disease

	Ulcerative Colitis, n (%) (n = 976)	Crohn's Disease, n (%) (n = 483)
Erythema nodosum	9 (0.9)	27 (5.6)
Pyoderma gangrenosum	5 (0.5)	6 (1.2)
Arthralgias	52 (5.3)	62 (14.3)
Type 1 arthropathy*	35 (3.6)	29 (6.0)
Type 2 arthropathy†	24 (2.5)	20 (4.0)
Inflammatory back pain	34 (3.5)	42 (8.7)

*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

Adapted with permission from Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998;42:388.

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 non-purulent 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



Figure 1. Pyoderma gangrenosum. (Adapted with permission from Trost LB, McDonnell JK. Important cutaneous manifestations of Inflammatory bowel disease. *Postgrad Med J* 2005;81:581, BMJ Publishing Group.)



Figure 2. Erythema nodosum.

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.

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



Figure 3. Keratoderma blennorrhagica. (Reprinted with permission from <http://www.risg.org/images/kb6mo.jpg>.)

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.^{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**).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.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 monoarticular 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



Figure 4. Dermatitis herpetiformis. (Reprinted with permission from Mackie RM. *Clinical dermatology: an illustrated textbook*. 3rd ed. New York: Oxford University Press; 1991: 254.)

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.^{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 *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.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.²²

HBV infection also can be associated with polyarteritis

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

	Women (n = 996)			Men (n = 440)		
	Age Group			Age Group		
	< 2 y (n = 250)	2–14 y (n = 225)	> 14 y (n = 521)	< 2 y (n = 124)	2–14 y (n = 143)	> 14 y (n = 173)
Prevalence of DH, n (%)	2 (0.8)	73 (32.4)	13 (2.5)	4 (3.2)	52 (36.3)	14 (8.1)

Adapted with permission from Bardella MT, Fredella C, Saladino V, et al. Gluten intolerance: gender- and age-related differences in symptoms. *Scand J Gastroenterol* 2005;40:15–19.

nodosa, a leukocytoclastic vasculitis that effects small- and medium-sized arteries.^{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.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.^{26,27} HCV is also commonly associated with joint pains when mixed cryoglobulinemia develops.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 includes glucocorticoids, plasmapheresis, and cyclophosphamide.

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

	Sensitivity, %	Specificity, %
Antigliadin IgG	57–100	47–94
Antigliadin IgA	52–100	71–100
Endomysium IgA	86–100	90–100
Transglutaminase IgA	77–100	91–100

Data from Hill ID. What are the sensitivity and specificity of serological tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* 2005;128(4 Suppl 1):S25–32.

phamide. Treatment of underlying HCV infection with interferon and ribavirin is also essential.

HENOCH-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.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.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.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



Figure 5. Palpable purpura of Henoch-Schönlein purpura. The diagnosis can be confirmed by a skin biopsy with immunofluorescence looking for IgA deposition within blood vessel walls. (Reprinted with permission from <http://vasculitis.med.jhu.edu/whatis/symptoms.html>. Courtesy of the Johns Hopkins Vasculitis Center.)

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

HP

REFERENCES

- Hunder G. Vasculitis: diagnosis and therapy. *Am J Med* 1996;100:37S–45S.
- Mies Richie A, Francis ML. Diagnostic approach to polyarticular joint pain [published erratum appears in *Am Fam Physician* 2006;73:776 and 2006;73:1153]. *Am Fam Physician* 2003;68:1151–60.
- Barth WF. Office evaluation of the patient with musculoskeletal complaints. *Am J Med* 1997;102:3S–10S.
- Sheehan NJ. The ramifications of HLA-B27. *J R Soc Med* 2004;97:10–4.
- Hannu T, Mattila L, Siitonen A, Leirisalo-Repo M. Reactive arthritis attributable to *Shigella* infection: a clinical and epidemiological nationwide study. *Ann Rheum Dis* 2005;64:594–8.
- Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896–907.
- Weenig RH, Davis MD, Dahl PR, Su WP. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med* 2002;347:1412–8.
- Trost LB, McDonnell JK. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005;81:580–5.
- Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998;42:387–91.
- Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). *J Rheumatol* 2002;29:511–5.
- de Vlam K, Mielants H, Cuvelier C, et al. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. *J Rheumatol* 2000;27:2860–5.
- Mackie SL, Keat A. An unusual complication of appendicitis [letter]. *Ann Rheum Dis* 2004;63:1526.
- Generini S, Fiori G, Matucci-Cerinic M. Therapy of spondyloarthropathy in inflammatory bowel disease. *Clin Exp Rheumatol* 2002;20 (6 Suppl 28):S88–S94.
- Thomson GT, DeRubeis DA, Hodge MA, et al. Post-*Salmonella* reactive arthritis: late clinical sequelae in a point source cohort. *Am J Med* 1995;98:13–21.
- Farrel RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180–8.
- Hepburn AL, Kaye SA. Oligoarthritis in an elderly woman with diarrhoea and weight loss. *Postgrad Med J* 2001;77:475–7.
- Bardella MT, Fredella C, Saladino V, et al. Gluten intolerance: gender- and age-related differences in symptoms. *Scand J Gastroenterol.* 2005;40:15–9.
- Zone JJ. Skin manifestations of celiac disease. *Gastroenterology* 2005;128(4 Suppl 1):S87–91.
- Ratnaike RN. Whipple's disease. *Postgrad Med J* 2000;76:760–6.
- Misbah SA, Aslam A, Costello C. Whipple's disease. *Lancet* 2004;363:654–6.
- Tschopp S, Brucker R. Aching joints and jaundice. *Lancet* 2003;361:750.
- Han SH. Extrahepatic manifestations of chronic hepatitis B. *Clin Liver Dis* 2004;8:403–418.
- Nakamura H, Shimizu T, Ohshiro S, et al. An adult patient with acute hepatitis type B which was protracted and complicated by polyarteritis nodosa: a case report. *Hepatol Res* 2002;24:439–444.
- Stone JH. Polyarteritis nodosa. *JAMA* 2002;288:1632–9.
- Deeren DH, De Backer AI, Malbrain ML, et al. Treatment of hepatitis B virus-related polyarteritis nodosa: two case reports and a review of the literature. *Clin Rheumatol* 2004;23:172–6.
- Rosner I, Rozenbaum M, Toubi E, et al. The case for hepatitis C arthritis. *Semin Arthritis Rheum* 2004;33:375–87.
- Bombardieri M, Alessandri C, Labbadia G, et al. Role of anti-cyclic citrullinated peptide antibodies in discriminating patients with rheumatoid arthritis from patients with chronic hepatitis C infection-associated polyarticular involvement. *Arthritis Res Ther* 2004;6:R137–41.
- Casato M, Lilli D, Donato G, et al. Occult hepatitis C virus infection in type II mixed cryoglobulinaemia. *J Viral Hepat* 2003;10:455–9.
- Passam FH, Diamantis ID, Perisinaki G, et al. Intestinal ischemia as the first manifestation of vasculitis. *Semin Arthritis Rheum* 2004;34:431–41.
- Mukhopadhyay S, Mousa S, George BR, Perl A. Palpable purpura, polyarthritis and abdominal pain. *Med J Aust* 2004;180:121–2.
- Gonzalez-Gay MA, Calvino MC, Vazquez-Lopez ME, et al. Implications of upper respiratory tract infections and drugs in the clinical spectrum of Henoch-Schonlein purpura in children. *Clin Exp Rheumatol* 2004;22:781–4.