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Systemic Causes of Cholestasis

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KEYWORDS

• Amyloidosis • Cholestasis of sepsis • Congestive hepatopathy
• Granulomatous hepatitis • Lymphoma • Sarcoidosis • Sickle cell disease
• Total parenteral nutrition

KEY POINTS

- A profound systemic inflammatory response such as sepsis can disrupt the elimination of bile salts at the level of the hepatocyte and provoke cholestasis.
- A detailed clinical history, including travel, exposures, and underlying immunosuppression, is crucial when evaluating a patient with cholestasis.
- Systemic autoimmune disease in association with cholestasis should trigger an evaluation for primary autoimmune cholestatic liver disease.
- The hallmark of hepatic amyloidosis and lymphoma is a prominently increased serum alkaline phosphatase level.
- Extrahepatic biliary obstruction with subsequent cholestasis can result from a variety of systemic diseases, such as posttransplant lymphoproliferative disorder, sickle cell disease, Henoch-Schönlein purpura, and infection with cryptococcus, cytomegalovirus, or tuberculosis.

Systemic causes of cholestasis constitute a diverse group of diseases across organ systems. The pathophysiology of cholestasis in systemic disease can be a consequence of direct involvement of a disease process within the liver or extrahepatic biliary system or secondary to immune-mediated changes in bile flow (**Table 1**). Evaluating a patient with cholestasis for a systemic cause requires an understanding of the patient's risk factors, clinical setting (eg, hospitalized or immunosuppressed patient), clinical features, and pattern of laboratory abnormalities.

BACTERIAL INFECTIONS

Nearly any significant extrahepatic bacterial infection can cause cholestasis. Osler described jaundice occurring with curious irregularity in patients with pneumonia in the first edition of *The Principles and Practice of Medicine*.[1]

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Table 1
Mechanisms of cholestasis in systemic disease

Mechanism	Examples
Cytokine-mediated	Graft-versus-host disease Hodgkin disease (vanishing bile duct syndrome) Sepsis and severe bacterial infections Stauffer syndrome (renal cell carcinoma)
Granulomatous hepatitis	Bacterial infections: *Yersinia enterocolitica, Brucella abortus, Mycobacterium tuberculosis* infections Crohn disease Fungal infections*: Candida* species infection, coccidioidomycosis, cryptococcus, histoplasmosis Sarcoidosis
Obstructive jaundice	Henoch-Schönlein purpura Infections: cytomegalovirus, cryptococcus Porta hepatis lymphadenopathy: posttransplant lymphoproliferative disease, *Mycobacterium tuberculosis* infection Sickle cell disease (pigment bile duct stones)
Hepatic infiltration	Amyloidosis Hemophagocytic syndrome Hepatic congestion (heart failure) Hodgkin or non-Hodgkin lymphoma Infections: miliary tuberculosis*, Mycobacterium avium* complex infection, actinomycosis Sickle cell intrahepatic cholestasis

Bacterial infections that do not necessarily involve the liver or bile ducts may lead to jaundice. Sepsis is most frequently linked to cholestasis, particularly in the intensive care unit setting (**Table 2**).[2] Both gram-positive and gram-negative organisms are potentially culpable, with *Escherichia coli* being the most common isolate in 1 retrospective analysis.[3] Jaundice develops in up to one-third of neonates and infants

Table 2
Systemic cholestasis in the intensive care unit[a]

Diagnosis	Diagnostic Tests	Treatment
Sepsis or severe bacterial infection	Blood cultures, imaging for source of infection	Antibiotics
Hepatic congestion (heart failure)	Cardiopulmonary testing (eg, echocardiography)	Measures to increase cardiac output based on cause (eg, thrombolysis for pulmonary embolism)
Progressive sclerosing cholangitis after burns or trauma	Exclusion of other causes	Aggressive volume resuscitation and treatment of underlying cause
Total parenteral nutrition	Exclusion of other causes	Initiation of enteral nutrition, cycling of parenteral nutrition, ursodeoxycholic acid

[a] Acalculous cholecystitis and drug-related cholestasis should always be excluded.

with sepsis,[4] and the incidence in adult patients is estimated to range from 6% to 54%.[5,6] Cholestasis from infections and sepsis is the second most common cause of jaundice in hospitalized patients (after malignant biliary obstruction).[7] In adults, conjugated hyperbilirubinemia, typically less than 10 mg/dL, predominates; the bilirubin level can be higher in neonates as a consequence of their underdeveloped efflux capacity. Serum alkaline phosphatase levels 2 to 3 times the upper limit of normal are typical, whereas aminotransferase levels are either normal or only modestly increased. Apart from jaundice, symptoms such as pruritus and clinical signs such as hepatomegaly are uncommon. Treatment is supportive with fluid resuscitation and antibiotics. One prospective analysis[6] did not find an association between the presence of jaundice and increased mortality.

The pathophysiology of cholestasis in sepsis is the topic of several excellent reviews.[8–10] Kupffer cells, and to a lesser extent hepatocytes and sinusoidal endothelial cells, react to bacterial endotoxins such as lipopolysaccharide by elaborating proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-2, IL-6, and IL-12. Endotoxemia in rats has been shown to cause downregulation of bile uptake (Na^+-taurocholate cotransporting polypeptide and organic anion-transporting polypeptide) and export (bile salt export pump and multidrug resistance protein 2) transporters for cholestasis,[11] but a posttranscriptional mechanism is favored in studies involving human liver tissues.[12] Nitric oxide and free radicals in the hepatic microvasculature can contribute to endothelial damage and the formation of fibrin microthrombi. Histologically, hepatocellular and canalicular bilirubinostasis predominates, often with nonspecific portal-based inflammation and Kupffer cell hyperplasia.[13]

A distinct cholestatic picture termed progressive sclerosing cholangitis can emerge in the setting of severe septic shock.[14] This entity may evolve as a result of biliary ischemia from systemic hypotension and has also been described after extensive trauma or burns.[15,16] The pathophysiology is poorly understood but likely involves a similar diminution in the expression of bile transporters as a result of cytokine induction as well as stasis of toxic bile salts within the ducts. Cirrhosis can result.[17]

Certain systemic bacterial organisms capable of infecting the liver directly have a predilection for cholestasis. An increase of serum alkaline phosphatase levels and jaundice frequently accompany pyogenic liver abscess. Recent case series indicate that up to 60% of liver abscesses are cryptogenic and therefore can be considered systemic.[18–21] *Actinomycosis*, caused by *Actinomyces israelii*, a filamentous gram-positive rod, can present with liver involvement in rare instances. Whereas hepatic abscess is the most common presentation of actinomycosis,[22] affected patients may also follow a more indolent course of fever, abdominal pain, and anorexia associated nearly universally with increases of the serum alkaline phosphatase level.[23] Biopsies of infected tissue show characteristic sulfur granules, and treatment with penicillin or tetracycline is usually curative. Severe shigellosis can cause a cholestatic hepatitis with portal and periportal polymorphonuclear inflammatory infiltrates,[24] whereas yersiniosis can produce a granulomatous hepatitis in patients with diabetes mellitus and those predisposed to iron loading.[25]

Certain zoonotic infections, particularly brucellosis, also may lead to cholestasis, in which the development of jaundice may correlate with the severity of the illness. Necrotizing hepatic granulomas can occur in the hepatic lobules or portal tracts in association with focal mononuclear infiltrates.[26,27] Weil syndrome develops in 5% to 10% of patients with leptospirosis, a spirochetal infection acquired in warm climates from water contaminated with the urine of wild or domestic animals. Jaundice over a few weeks may denote the first phase of the illness and is followed by fever and subsequently

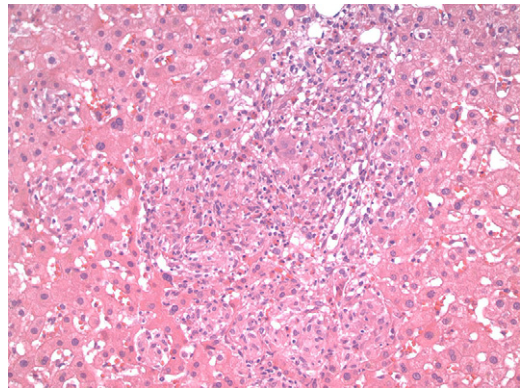

Fig. 1. Histopathology of hepatic syphilis, showing portal and lobular granulomas associated with mixed inflammation (hematoxylin-eosin, original magnification, ×10). (*Courtesy of* Joseph Misdraji, MD, Department of Pathology, Massachusetts General Hospital, Boston, MA.)

hepatic and renal injury.[28] Conjugated hyperbilirubinemia reflects intrahepatic cholestasis, which along with hypertrophy of Kupffer cells is apparent on liver biopsy specimens. Another spirochetal infection associated with cholestasis is syphilis, which can cause a lymphocytic portal triaditis with pericholangiolar inflammation and a markedly increased serum alkaline phosphatase level (**Fig. 1**). Syphilitic hepatitis in persons infected with human immunodeficiency virus (HIV) is well described, and in 1 case series of 7 patients, the average serum bilirubin level at diagnosis was 4.1 mg/dL.[29] Tick-borne illnesses such as Q fever, Rocky Mountain spotted fever, and ehrlichiosis can infect the liver and cause cholestasis in rare instances, but a component of hemolysis undoubtedly contributes to the jaundice.

FUNGAL HEPATITIS

The systemic mycoses are considered opportunistic pathogens with only infrequent hepatic involvement. A high index of suspicion in the appropriate setting is crucial to expedite treatment. In the appropriate clinical context, fungal pathogens can disseminate to the liver and lead to varying degrees of cholestasis. Immunocompromised patients with hepatic candidiasis can present with suppurative granulomas, neutrophilic inflammation, and edema surrounding bile ducts.[30] High fever and an increased serum alkaline phosphatase level are typical features. Infection with the yeast *Cryptococcus neoformans* can present with several hepatic manifestations, including jaundice caused by cholangitis. Bucuvalas and colleagues[31] described a 15-year-old girl with right upper quadrant pain and jaundice in whom cryptococci were cultured from the bile duct. Tissue staining with India ink highlights the capsule, but detection of serum cryptococcal antigen is now the diagnostic test of choice. A hepatitislike picture may develop in 40% to 60% of cases of disseminated coccidioidomycosis, which is endemic in the southwest United States and can affect immunocompetent hosts. Pulmonary infiltrates with a granulomatous hepatitis, in conjunction with a markedly increased serum alkaline phosphatase level, are a classic presentation.[32] Histoplasmosis can spread from the lungs to the liver as well, generally in immunocompromised hosts. Cholestasis resulting from histoplasmosis typically occurs secondarily from development of hemophagocytic syndrome[33] (see later discussion).

MYCOBACTERIAL INFECTIONS

Hepatobiliary tuberculosis is rare, although well documented. A 10-year experience of close to 2000 patients with tuberculosis identified only 14 cases of hepatobiliary tuberculosis, of which 9 had multiorgan involvement.[34] Jaundice is classically caused by extrahepatic biliary obstruction from bulky lymphadenopathy around the porta hepatis or postinflammatory biliary strictures.[35] A characteristic granulomatous hepatitis, marked by fever, anorexia, weight loss, and night sweats with an infiltrative cholestasis, is present in 90% of patients with miliary tuberculosis. Disseminated *Mycobacterium avium* complex (MAC) infection can also present with dramatic cholestasis with only minimal increase of the serum aminotransferase levels.[36] MAC infections have become infrequent in patients with HIV infection since the availability of effective antiretroviral therapy.

SYSTEMIC VIRAL INFECTIONS

Viral diseases can occur as latent infections that reactivate in immunocompromised hosts or de novo infections in otherwise healthy persons. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are DNA viruses in the herpesvirus family that can involve the liver in either scenario. Jaundice in acute mononucleosis occurs in up to 10% of cases.[37] By contrast, EBV reactivation with subsequent development of posttransplant lymphoproliferative disorder (PTLD) is often characterized by jaundice in liver transplant recipients (see later discussion). A similar mononucleosislike illness can occur in healthy patients with acute CMV infection, which is characterized pathologically by focal hepatocyte and bile duct damage.[38] CMV infection has specific cholestatic features in certain immunocompromised settings, as in neonates, in whom obstructive biliary disease and neonatal giant cell hepatitis with cholestasis can occur.[39] Jaundice was found in 9 of 9 infants infected perinatally with CMV in a case series from Saudi Arabia.[40] CMV infection in patients with AIDS has been a cause of HIV cholangiopathy, an infectious form of sclerosing cholangitis that is rarely seen. CMV infection usually occurs 1 to 4 months after solid organ transplantation and is typically characterized by acute hepatitis with pathologic features in the liver of CMV inclusions and foci of microabscesses. Agarwal and colleagues[41] reported a case of fibrosing cholestatic hepatitis caused by CMV infection in a renal transplant recipient. After solid organ transplantation, CMV-positive recipients or recipients of CMV-positive donor organs should receive prophylaxis with valganciclovir.

Severe viral infections such as influenza and severe acute respiratory syndrome are believed to be associated with immune-mediated liver damage as a result of cytokine activation; neither infection generally leads to cholestasis. By contrast, measles (rubeola) may result in 1 of 2 patterns of hepatic dysfunction: most commonly, asymptomatic increase of the serum aminotransferase levels and rarely, prolonged jaundice and cholestasis, which develop as the usual symptoms of measles resolve.[42]

HEPATIC SARCOIDOSIS

Typically, sarcoidosis presents with noncaseating granulomas in the lungs and lymph nodes. The liver is an occasional extrapulmonary site of disease. In 1 retrospective series,[43] liver biochemical test abnormalities were found in 204 of 837 (24.4%) patients with sarcoidosis, of whom 15.2% were believed to have hepatic sarcoidosis. Prevalence rates are highest among African American and Scandinavian persons between the ages of 20 and 40 years. Liver involvement in sarcoidosis is usually clinically silent.

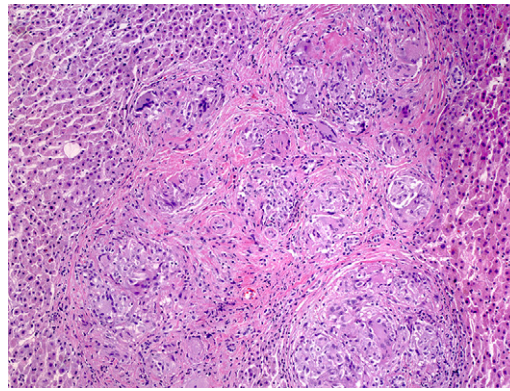

Fig. 2. Histopathology of hepatic sarcoidosis, showing portal tract with multiple noncaseating epithelioid granulomas encased in fibrosis characteristic of hepatic sarcoid (hematoxylin-eosin, original magnification, ×10). (*Courtesy of* Joseph Misdraji, MD, Department of Pathology, Massachusetts General Hospital, Boston, MA.)

A few patients (4%–7%) experience symptoms such as nausea, vomiting, and abdominal pain or signs such as hepatomegaly, jaundice, and portal hypertension. Abnormal liver biochemical test levels were identified in 58 of 100 patients who underwent a liver biopsy in 1 case series.[44] The serum alkaline phosphatase level is disproportionately high. In addition, 75% of untreated patients with sarcoidosis have an increase in the serum angiotensin-converting enzyme level. The pathognomonic lesion is the noncaseating granuloma, which results from a helper T cell type 1 response to an as-yet-unidentified antigen. Pathologically, hepatic sarcoidosis can be indistinguishable from primary biliary cirrhosis or primary sclerosing cholangitis. Although granulomas can be seen within the hepatic lobule, the principal findings are in the portal tracts and include a variety of bile duct lesions, such as acute or chronic cholangitis,[45] periductal fibrosis, and bile duct loss (**Fig. 2**).[46] Presinusoidal portal hypertension can develop from scarring of portal venules. In general, treatment is not recommended in patients with asymptomatic hepatic disease but is advised when symptoms of portal hypertension or severe cholestasis are apparent. Although patients may improve symptomatically with glucocorticoids and ursodeoxycholic acid,[47] structural changes to the bile ducts can progress to biliary cirrhosis, resulting in some cases in the need for liver transplantation.[48]

HEPATIC AMYLOIDOSIS

Systemic amyloidosis may be primary (AL) or secondary (AA). The precipitation of immunoglobulin light chains characterizes AL amyloid and develops in the context of plasma cell dyscrasias such as Waldenstrom macroglobulinemia or multiple myeloma. Although the heart, kidney, and peripheral nerves are the most commonly affected organs, 1 autopsy series of primary amyloidosis reported liver involvement in 70% of cases. A Mayo Clinic study reported on the natural history of 98 patients with liver biopsy-proven AL amyloid over a 20-year period.[49] Unintentional weight loss, with hepatomegaly on examination, was the most frequent presenting symptom. Serum alkaline phosphatase levels were strikingly increased, with a median value of 657 U/L (normal level <250 U/L), and were more than normal in 86% of patients. The median survival was 5.4 months in patients with an alkaline phosphatase level

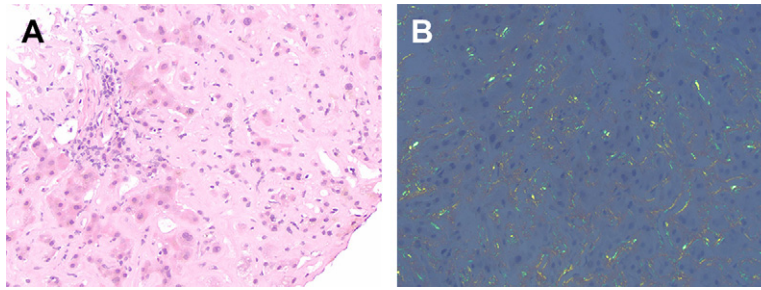

Fig. 3. Histopathology of hepatic amyloidosis. (*A*) Liver biopsy specimen showing massive sinusoidal infiltration by waxy pink amyloid deposits (hematoxylin-eosin, original magnification, ×20). (*B*) Congo Red stain of the same biopsy specimen viewed under polarized light shows apple-green birefringence, confirming amyloid (original magnification, ×20). (*Courtesy of* Joseph Misdraji, MD, Department of Pathology, Massachusetts General Hospital, Boston, MA.)

greater than 500 U/L and 1 month in those with a total bilirubin level greater than 34 μmol/L (2 mg/dL). Most patients (82%) had amyloid deposits detected in biopsy specimens from extrahepatic tissue as well. The treatment of choice for primary amyloidosis is chemotherapy and, when possible, hematopoietic stem-cell transplantation.

Secondary, or AA, amyloidosis develops in the setting of systemic inflammatory disorders such as rheumatoid arthritis or chronic infections such as osteomyelitis or tuberculosis. The pathologic protein involved is serum amyloid A, which is an acute-phase reactant produced perpetually in the liver in response to inflammatory cytokines, such as TNF-α, IL-1, and IL-6. Amyloidogenic proteins deposit in the extracellular matrices of various organs, as in AL disease. Preventing this process from occurring by identifying and treating the underlying inflammatory condition is paramount in the management of affected patients. AA amyloidosis is less common than AL amyloidosis, but the histopathologic findings are similar, with protein deposition in the space of Disse, portal tracts, and vessel walls causing architectural distortion and cholestasis (**Fig. 3**). Congo Red staining continues to be the mainstay of identifying tissue-based amyloid.

HEMOPHAGOCYTIC SYNDROME

Hemophagocytic syndrome, or hemophagocytic lymphohistiocytosis (HLH), is a rare condition involving the proliferation of macrophages responsible for phagocytosis of blood cells in hematopoietic organs. Hematologic malignancies, infections (histoplasmosis, tuberculosis, CMV infection, HIV infection), or autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Still disease) provoke a sustained immune activation of histiocytes, natural killer (NK) cells, and cytotoxic lymphocytes. Germline mutations in perforin have been found in familial cases of HLH.[50] Perforin is a cytolytic protein expressed by NK cells and cytotoxic T cells that is critical for inducing apoptosis of infected cells. Clinically, the features of HLH include fever, hepatosplenomegaly, cytopenias in at least 2 cell lines, hypertriglyceridemia or hypofibrinogenemia (or both), and a high serum ferritin level. In a case series from France of 30 patients with hepatic HLH,[51] 22 had a previous diagnosis of lymphoma or leukemia. Nineteen of the 30 patients were admitted to the hospital because of hepatic manifestations of the disease, including 50% with jaundice. Liver biopsies were performed in

25 patients and in all cases showed hemophagocytosis, Kupffer cell hyperplasia, and sinusoidal dilatation. Of the original cohort, there were 12 deaths caused by multiorgan failure or sepsis. Fifteen of 21 patients who could be treated achieved a complete remission. A high serum bilirubin or alkaline phosphatase level was associated with a poorer prognosis. HLH is a glucocorticoid-responsive disease, and current therapy combines dexamethasone with etoposide followed by an allogeneic hematopoietic stem-cell transplant in cases of genetic HLH or in the context of hematologic malignancy.

SICKLE CELL DISEASE

Cholestasis caused by sickle cell disease results from 1 of 2 processes (or both): extrahepatic or intrahepatic.[52] Extrahepatic cholestasis can be caused by choledocholithiasis. Pigment gallstones develop in roughly one-half of patients with sickle cell disease. In 1 series of 65 patients with sickle cell disease who underwent cholecystectomy, bile duct stones were found in 18%.[53] In 7% to 10% of patients hospitalized for sickle cell crisis, hepatic complications caused by sickling are found. Hepatic crisis can mimic acute cholecystitis or cholangitis, with right upper quadrant pain, jaundice, hepatomegaly, and fever. As much as 50% of the hyperbilirubinemia is attributable to conjugated bilirubin, and the total bilirubin level is relatively more increased than the aminotransferase levels. Sickle cell intrahepatic cholestasis (SCIC) is a term used in the literature to describe acute hepatic failure from sickle cell disease.[54] Bilirubinostasis identified pathologically in the liver is a consequence of sinusoidal distension from erythrocyte sickling. Erythrophagocytosis and hemosiderosis are also characteristic histologic findings. SCIC is associated with profound hyperbilirubinemia and has been treated successfully in occasional cases with exchange transfusion[55] and by liver transplantation.[56]

LYMPHOMAS

Important oncologic causes of cholestasis include Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Liver involvement is less frequent in HL than in NHL and typically occurs with disease above and below the diaphragm (stage III) or disseminated extranodal disease (stage IV). Five percent of patients with HL have liver involvement at the time of diagnosis, and Reed-Sternberg cells are pathognomonic. Forty percent of patients have an increased serum alkaline phosphatase level. Intrahepatic tumor infiltration has been seen in 45% of jaundiced patients with HL at autopsy.[57,58] Several investigators have reported intrahepatic cholestasis caused by a vanishing bile duct syndrome in HL in the absence of tumor infiltration.[59] Ballonoff and colleagues[60] reviewed 37 cases described in the literature and found an association between an improvement in cholestasis and complete response to chemotherapy or radiation therapy (or both). Acute liver failure is a potential complication of HL, either directly caused by hepatic infiltration or secondarily caused by a paraneoplastic process.

Liver involvement in NHL has pathologic characteristics similar to those in HL, including a nodular tumor infiltrate in portal tracts and epithelioid granulomas. However, primary hepatic lymphoma (PHL) is rare, accounting for less than 1% of cases of NHL.[61] PHL is defined by an absence of lymphoma involvement in the spleen, lymph nodes, and bone marrow at the time of diagnosis. B symptoms of fever and weight loss occur in one-third of patients. The most common presentation is with abdominal pain caused by hepatomegaly. Serum alkaline phosphatase and bilirubin levels are increased in 70% of cases. A solitary lesion is the most frequent finding

radiographically and is encountered in 50% to 60% of cases. Estimating the prognosis of PHL is difficult because the condition is rare. Nodular as opposed to diffusely infiltrative disease may have a more favorable outcome with chemotherapy, with 3-year survival rates of 57% and 18%, respectively. Although there are some case reports of hepatitis C–associated PHL, an increased risk of NHL (diffuse large B-cell lymphoma, marginal zone lymphoma, and lymphoplasmocytic lymphoma) in patients with chronic hepatitis C is not specifically associated with an increased risk of PHL.

Both solid organ and hematopoietic stem-cell transplant recipients are at risk for PTLD, a type of NHL driven in most cases by EBV infection (see earlier discussion). PTLD complicates approximately 4% of liver transplantations. Liver and spleen involvement in PTLD is not unusual, occurring in 16% of patients in a 20-year experience at the University of Pittsburgh.[62] If present in the liver, PTLD can cause intrahepatic cholestasis or extrahepatic cholestasis from bulky lymphadenopathy around the porta hepatis.

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive lymphoma that infiltrates the hepatic sinusoids. Male patients younger than 35 years with inflammatory bowel disease (IBD) and at least a 2-year history of exposure to combined thiopurine and biologic therapy may be at increased risk for developing HSTCL.[63]

SOLID ORGAN MALIGNANCIES

Stauffer syndrome, originally termed nephrogenic hepatic dysfunction, refers to a rare paraneoplastic complication of renal cell carcinoma.[64] Overexpression of IL-6 by the tumor is believed to play a role in the pathophysiology. Cholestasis typically resolves within 1 to 2 months after surgical resection of the primary tumor. Hepatic dysfunction after resection may portend tumor recurrence. The presentation is with cholestasis, sometimes with jaundice, and usually with right upper quadrant pain caused by hepatomegaly. Liver biopsy specimens show nonspecific changes, including steatosis, portal lymphocytic inflammation, and Kupffer cell hyperplasia. Renal cell carcinoma can also metastasize to the pancreas and cause obstructive jaundice. Biliary obstruction caused by primary or metastatic cancer in the head of the pancreas, ampulla, or bile duct are more common causes of obstructive jaundice.

HEPATIC GRAFT-VERSUS-HOST DISEASE

The gastrointestinal tract and liver are often affected by acute graft-versus-host disease (GVHD).[65] Acute hepatic GVHD occurs in the first 100 days after allogeneic stem-cell transplantation. GVHD arises from expansion of the population of donor T cells in the transplant recipient. Risk factors for developing GVHD include an HLA mismatch, gender mismatch, and high number of T cells transfused from the donor. Liver involvement typically follows skin and gastrointestinal involvement. When profound cholestasis develops, the prognosis is poor. A serum bilirubin level greater than 6.1 mg/dL establishes a diagnosis of severe GVHD.[66] The pathophysiology is complex and likely involves a constellation of immune-mediated features, including cytokine activation, endothelial damage from conditioning regimens, and many antigen-presenting cells in target organs. Histologically, lymphocytes are seen infiltrating small bile ducts, and epithelial cells undergo apoptosis. Ursodeoxycholic acid is effective in preventing hepatic GVHD and is administered as prophylaxis for the first 80 days after hematopoietic stem-cell transplantation.[67] Immunosuppression is the foundation of therapy for GVHD. When chronic liver GVHD occurs, destructive

bile duct damage is also characteristic, but progressive fibrosis is unusual except in cases of concomitant chronic liver disease such as hepatitis C.

ENDOCRINE DYSFUNCTION

Thyroid disease may affect hepatic dysfunction in a few distinct circumstances. Primary biliary cirrhosis and hypothyroidism may occur together because of their shared autoimmune pathogenesis. Jaundice in patients with myxedema coma is typically caused by acute hepatic congestion from heart failure.[68] Several reports in the adult and pediatric literature describe cholestatic hepatitis occurring in patients with Graves disease.[69,70] A mild increase in the serum alkaline phosphatase level occurs in 65% of patients with hyperthyroidism, although the increase can also arise from bone. Simultaneous heart failure may complicate the recognition of hepatic dysfunction caused by thyrotoxic crisis, which can eventuate in acute liver failure.

The liver can be affected in patients with diabetes mellitus, most commonly by nonalcoholic fatty liver disease. Harrison and colleagues[71] coined the term diabetic hepatosclerosis (DHS) in 2006, after reviewing liver biopsy specimens from patients with long-standing diabetes mellitus. Salient features included an absence of steatosis and dense perisinusoidal fibrosis. The original description included 14 patients with diabetes mellitus, most of whom had a normal body mass index (calculated as weight in kilograms divided by the square of height in meters), evidence of microvascular complications, and increased serum alkaline phosphatase level. A larger follow-up autopsy series from the same investigators did not find an association with cholestasis.[72] Nevertheless, DHS is believed to represent a hepatic form of microvascular disease in patients with diabetes mellitus.

CARDIAC DISEASE

Heart failure can cause a variety of hepatic manifestations, from asymptomatic increases of liver biochemical test levels to cirrhosis and acute hepatic failure.[73] Acute and chronic hepatic congestion are associated with a modest hyperbilirubinemia in 1.2% to 20% of patients, respectively. In a retrospective cohort study of 661 patients from the Royal Cornwall Hospital in England who were referred over a 4-year to 5-year period to a jaundice hotline, 8 of the 661 (1.2%) were found to have a primary cardiac cause of cholestasis.[74] The hyperbilirubinemia of heart failure is typically unconjugated, with a serum bilirubin level of less than 3 mg/dL, but it can be conjugated and associated with higher bilirubin levels. Jaundice may become worse with repeated episodes of heart failure, often in association with a cardiac index less than 1.5 L/min/m^2. Pathologically, the low-flow state of heart failure and resulting reduced oxygen tension cause zone 3 hepatic necrosis and ischemic biliary changes with cholestasis from bile thrombi formation. Bilirubinostasis is also postulated to occur as a result of extrinsic compression from sinusoidal and hepatic venule dilatation. Ischemic hepatitis (shock liver), which can result from myocardial infarction, massive pulmonary embolus, arrhythmia, or cardiac tamponade, is a distinct entity characterized by increased serum aminotransferase levels of at least 20 times the upper limit of normal and a rapid return to normal. Similarly high serum lactate dehydrogenase levels are characteristic. Seeto and colleagues[75] compared 31 patients with ischemic hepatitis with 31 patients with hypovolemic shock secondary to trauma and found an average total bilirubin level of 2.8 mg/dL in the ischemic hepatitis cohort compared with 0.8 mg/dL in the traumatic shock group. Classically, the peak in serum bilirubin occurs as the aminotransferase levels are declining.

SYSTEMIC AUTOIMMUNE DISEASES

Cholestasis may occur during the course of several autoimmune diseases. Autoimmune sclerosing cholangitis and IgG4-related disease are discussed elsewhere in this issue by Dr Marina Silveira. Several systemic autoimmune conditions may be associated with primary autoimmune liver disease; in particular, Sjögren syndrome and systemic sclerosis may coexist with primary biliary cirrhosis. The serum alkaline phosphatase level may be increased in systemic lupus erythematosus and rheumatoid arthritis, but cholestasis is uncommon. Concomitant pharmacologic therapy and joint and bone involvement in both diseases may have led to misinterpretation of increased alkaline phosphatase levels as cholestasis in older case series.

Henoch-Schönlein purpura (HSP) is clearly associated with cholestasis. HSP is a common systemic vasculitis of childhood characterized by palpable purpura and at least 1 of the following: abdominal pain, IgA deposits in biopsy specimens, arthritis, or renal involvement. The disease typically evolves in the setting of a viral infection (parvovirus B19, upper respiratory infection) or bacterial infection (group A *Streptococcus*, *Salmonella*, *Shigella*, *Campylobacter* spp). A predisposing malignancy, such as nonsmall cell lung cancer or lymphoma, is often noted in adults. The leukocytoclastic vasculitis can involve the gallbladder and cause acute acalculous cholecystitis.[76] The peribiliary vessels may be affected, thereby resulting in biliary ischemia, stenosis of the bile ducts, and obstructive jaundice.[77]

IBD may be associated with a primary autoimmune cholestatic liver disease (primary sclerosing cholangitis or IgG4-related disease). In addition, granulomatous hepatitis, characterized by an increased serum alkaline phosphatase level, is well described in patients with Crohn disease.[78] Bile salt malabsorption after ileal resection for Crohn disease increases the risk of cholelithiasis, which can cause biliary obstruction because of bile duct stones. Celiac disease has been associated with increased aminotransferase levels in many cases and occasionally with advanced liver disease.[79] Increase of the alkaline phosphatase level is less common and may be caused by bone involvement from secondary hyperparathyroidism.

TOTAL PARENTERAL NUTRITION

The consequences of parenteral nutrition on the development of cholestatic liver disease are reviewed in detail elsewhere. Cholestasis in neonates is especially problematic and can progress to life-threatening liver dysfunction. The incidence of parenteral nutrition-associated liver complications has decreased in neonates over time.[80] The duration of parenteral nutrition in infants correlates with the risk of developing more progressive cholestatic jaundice. After 10 days of parenteral nutrition, canalicular cholestasis was present in 84.2% of infants, and after 3 weeks, bile duct proliferation was found in 63.6% of infants.[81] The pathogenesis of parenteral nutrition-associated cholestasis is multifactorial. The neonatal liver is immature and unable to excrete bile salts at a normal rate, thereby leading to bile acid toxicity, particularly from the secondary bile acid lithocholate. Bacterial translocation across an underdeveloped or unused segment of intestine causes systemic endotoxemia and contributes to cholestasis in the context of altered postsurgical anatomy (eg, bypass, short bowel, absent ileocecal valve). Enteral intake stimulates bile flow as a result of cholecystokinin (CCK) release, and in the absence of CCK, gallbladder dysmotility occurs and can result in biliary sludge, gallstones, and even acalculous cholecystitis. Hepatic steatosis is a more common manifestation in adult patients on parenteral nutrition, but cholestasis from biliary sludge and gallstones is also encountered. Early resumption of oral intake is critical to preventing the development of parenteral nutrition-associated cholestasis, as

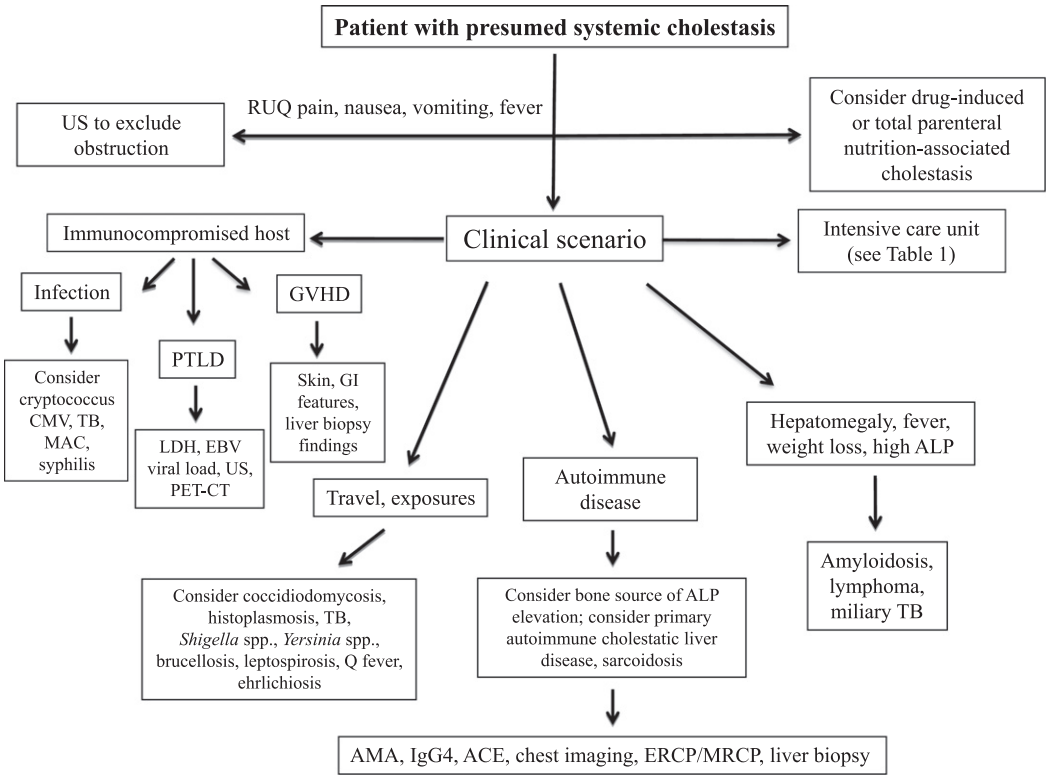

Fig. 4. Algorithm for the evaluation of the patient with systemic cholestasis. ACE, angiotensin-converting enzyme level; ALP, alkaline phosphatase level; AMA, antimitochondrial antibodies; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; GVHD, graft-versus-host disease; LDH, lactate dehydrogenase level; MAC, *Mycobacterium avium* complex; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography with computed tomography; PTLD, posttransplant lymphoproliferative disorder; TB, tuberculosis; US, ultrasonography.

is cycling of the parenteral nutrition infusion to allow for normalization of insulin and counterregulatory hormone levels. Ursodeoxycholic acid is effective for the prevention of cholestasis in patients with short bowel syndrome on long-term parenteral nutrition.[82]

SUMMARY

The evaluation of a patient with systemic cholestasis requires careful attention to the clinical circumstances (**Fig. 4**). In general, exclusion of drug-induced cholestasis, parenteral nutrition-induced cholestasis, and biliary obstruction is a useful first step in both inpatients and outpatients. Cholestasis in the intensive care unit should raise suspicion for sepsis syndrome, particularly in the pediatric patient population. Severe hypovolemic shock can cause ischemic cholangiopathy characterized by pronounced cholestasis. In adult inpatients with mild hyperbilirubinemia, a detailed cardiopulmonary physical examination and transthoracic echocardiography are useful to exclude heart failure; marked increase in serum aminotransferase levels accompanying jaundice suggests ischemic hepatitis. Cholestasis in immunocompromised patients should prompt a detailed clinical history for evidence of an infectious exposure. A comprehensive workup for infectious organisms should follow. Transplant recipients should be evaluated for PTLD; evaluation should include a serum lactate dehydrogenase level and an EBV viral load. Often, cross-sectional imaging with positron emission tomography and evaluation for obstructive lymphadenopathy with ultrasonography are warranted. Hepatic sarcoidosis is typically a histologic diagnosis, but chest imaging and a serum angiotensin-converting enzyme level are usually helpful. Striking cholestasis in the setting of weight loss and hepatosplenomegaly are highly suggestive of systemic malignancy with hepatic involvement, especially lymphoma, as well as amyloidosis. In either case, pursuing a tissue diagnosis is necessary, although liver tissue specifically is not essential. Cholestasis in the setting of a systemic autoimmune disease should prompt evaluation for a primary autoimmune cholestatic liver disease such as primary biliary cirrhosis or primary sclerosing cholangitis. An extrahepatic source of alkaline phosphatase should be excluded if the only evidence of cholestasis is an increased alkaline phosphatase level. Liver biopsy is usually definitive and the procedure of choice when the diagnosis remains uncertain after a comprehensive noninvasive evaluation. The evaluation of a patient with systemic cholestasis requires a meticulous approach, with treatment directed toward the underlying cause.

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