Cholestatic Liver Disease Overlap Syndromes

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KEYWORDS

• Overlap • Variant • Biliary cirrhosis • Sclerosing cholangitis • Autoimmune hepatitis

KEY POINTS

- Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) may share some clinical features with autoimmune hepatitis (AIH), but when substantial features of AIH are present, prognosis can be affected and immunosuppressive treatment with corticosteroids may be warranted.
- Standard diagnostic criteria for overlap syndrome are lacking. Proposed criteria for overlapping AIH include the presence of (1) alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN), (2) IgG > 2 × ULN and/or positive anti–smooth muscle antibody, (3) liver biopsy with moderate or severe periportal or periseptal inflammation and International Autoimmune Hepatitis Group (IAIHG) simplified criteria for the diagnosis of AIH.
- AIH and PSC commonly overlap in children and this combination should be actively excluded in the pediatric population.
- The presence of severe interface hepatitis in PBC portends a worse prognosis and should prompt evaluation for possible AIH overlap and consideration of treatment with immunosuppression.
- Drug-induced liver injury and IgG4 disease may masquerade as AIH or PSC and are important to consider in the differential diagnosis of the overlap or variant syndromes.

Overlap syndrome refers to the simultaneous presence in a single patient of what is considered 2 distinct diseases. Both diseases may be present at the initial diagnosis, or they may become clinically apparent in sequential fashion. Most cases of overlap in adults are between PBC and AIH, whereas in children most are between PSC and AIH. PBC and PSC are virtually never seen together in the same patient. The term, *overlap syndrome*, is sometimes used synonymously with the term, *variant syndrome*, but overlap syndrome is more than making an observation that one disease has some features of another. The implication is that true overlap requires treatment of both diseases.

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Each of the major autoimmune hepatobiliary diseases (PBC, AIH, and PSC) has its characteristic clinical, biochemical, serologic, and histologic profiles (**Table 1**), although none of these individual features is exclusive. The clinician's responsibility lies in assimilating as much data as needed to determine where on the spectrum of autoimmune hepatobiliary diseases an individual patient is positioned and weighing that information against an individual's comorbidities and personal situation to determine the most appropriate therapy. Overlap syndromes are rare and not clearly defined, so there is a stark paucity of data to guide management. As such, overlap syndromes is a field of hepatology where the art of clinical judgment frequently presides over the science of medicine.

A firm grasp of the range of clinical presentation for each of the autoimmune hepatobiliary diseases is needed to be able to differentiate what is within the reported spectrum of each disease versus which features indicate the presence of 2 distinct diseases. The clinical spectrum of each of these diseases is described, with attention to which features are or highly specific for each condition versus which features are not discriminating. The descriptions are not meant to provide a complete clinical review of each disease (more comprehensive descriptions of these entities can be found in the articles by Czul and colleagues and Zein elsewhere in this issue) but are meant to highlight or devalue the clinical criteria often considered in the diagnosis of overlap syndromes.

CLINICAL SPECTRUM OF PBC

Epidemiology

PBC is defined as a chronic cholestatic liver disease in which the small-sized to medium-sized bile ducts are the target of inflammatory destruction. The large, extrahepatic ducts should never be affected in PBC. The median age of presentation in the United States for PBC is 52 and the disease has never been reported in a prepubertal child. More than 90% of the patients are women. Approximately 15% to 20% of patients with PBC also have limited scleroderma (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, and Telangiectasias [CREST syndrome]), a syndrome that is not associated with AIH or PSC.

Laboratory

Because the disease is cholestatic, the degree of ALP elevation should be higher than the degree of transaminase elevation. One exception is that in early PBC, the alkaline phosphatase (ALP) may be normal and only mild elevation (<2 × ULN) of transaminases seen. Once the disease is well established, the ALP rises and the transaminases may also rise to 1 to 4 times the ULN. Elevation of transaminases above 500 IU/mL is

Table 1
Classical clinical features of the autoimmune hepatobiliary diseases

	PBC	PSC	Type I AIH
Symptoms	Itch, fatigue, asymptomatic	Itch, fatigue, jaundice, recurrent cholangitis	Episodic abdominal pain, nausea, arthralgias
Serology	AMA	pANCA/pANNA	ANA
Liver enzymes	Elevated ALP	Elevated ALP	Elevated AST and ALT
Histology	Nonsuppurative granulomatous cholangitis	Fibrosing obliteration of bile ducts	Lymphoplasmactyic interface hepatitis
Therapy	Ursodeoxycholic acid	None	Corticosteroids