Diagnosis and Management of Overlap Syndromes

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KEYWORDS

• Overlap syndrome • Autoimmune liver disease • Autoimmune hepatitis
• Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis
• Management

KEY POINTS

- Overlapping features between autoimmune hepatitis and cholestatic disorders (primary biliary cirrhosis, primary sclerosing cholangitis, or indeterminate cholestasis), so-called overlap syndromes, are not uncommon and usually show a progressive course toward cirrhosis and liver failure without adequate treatment.
- Overlap syndromes should be considered in the differential diagnosis when a patient with autoimmune liver disease deviates from the normal clinical course, classical biochemical and serologic findings, and expected response to therapy. Autoimmune hepatitis–primary sclerosing cholangitis overlap is increasingly common in patients with young age and inflammatory bowel disease.
- The diagnosis of overlap syndrome requires the prominent features of classical autoimmune hepatitis (positive antinuclear antibody or antismooth muscle antibody findings, elevated immunoglobulin G levels, and interface hepatitis) and secondary objective findings of primary biliary cirrhosis (positive antinuclear antibody findings, elevated immunoglobulin M, and florid duct lesion) or primary sclerosing cholangitis (abnormal cholangiography). The possibility for immunoglobulin G4–associated cholangitis and drug-induced liver injury should also be excluded in patients with possible autoimmune hepatitis–primary sclerosing cholangitis and autoimmune hepatitis–primary biliary cirrhosis overlap, respectively.

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- Empiric treatment for patients with autoimmune hepatitis–primary biliary cirrhosis overlap is immunosuppressive therapy plus ursodeoxycholic acid, and the response is nearly similar to that of classic autoimmune hepatitis.
- Empiric treatment for patients with autoimmune hepatitis–primary sclerosing cholangitis and autoimmune hepatitis–cholestatic overlap is immunosuppressive therapy with or without ursodeoxycholic acid. However, the clinical responses are highly variable, and disease in most patients eventually progresses to cirrhosis.
- Liver transplantation is indicated for patients with overlap syndrome who have end-stage liver disease. After liver transplantation, such patients tend to have a higher rate and aggressive disease recurrence when compared with patients with single autoimmune liver disorders, but the overall survival seems comparable.

INTRODUCTION

Autoimmune liver diseases encompass a spectrum of immune-mediated disorders targeting the hepatocytes and bile ducts, which are generally defined by a combination of clinical, biochemical, serologic, histologic, radiologic, and liver histology findings. They comprise 2 broad categories: those with a predominance of hepatocellular injury, such as, autoimmune hepatitis (AIH), and those with a predominance of cholestatic features including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Although the exact mechanism is unclear, broadly similar pathogenic themes of injury have been postulated for AIH, PBC, and PSC, and these comprise environmental triggers, genetic predisposition, and failure of immune tolerance mechanisms, which, in turn, collaborate to induce an antibody- and T cell–mediated immune attack against liver-specific targets, leading to a progressive necroinflammatory and fibrotic process in the liver (**Fig. 1**).[1–4] In AIH, immune-mediated liver injury is most pronounced in the portal/periportal areas, although a few patients can have antimitochondrial antibodies (AMA) and coincidental bile duct injury or loss (2%–13%), focal biliary strictures and dilations based on cholangiography (2%–11%), or histologic changes of bile duct injury or loss in the absence of other features (5%–11%).[5] In PBC and PSC, the pattern of liver injury is predominantly directed toward biliary epithelial cells, although a degree of parenchymal damage can be observed.

Conditions exhibiting features of 2 different autoimmune liver diseases occur in a small subgroup of patients and are commonly designated as overlap syndromes. With regard to the pathogenesis of overlapping features between hepatocyte-predominant and bile duct–predominant immune-mediated liver injuries, there remains debate as to whether this syndrome forms a distinct entity or is a variant of AIH. Several clinical presentations and pathophysiologic mechanisms of the overlap syndromes have been suggested: (1) a pure coincidence of 2 independent autoimmune diseases; (2) a different genetic background that determines the clinical, biochemical, and histologic appearance of one autoimmune disease entity; and (3) a representation of the middle of a continuous spectrum of 2 autoimmune diseases.[6,7] The prevalence of overlap features is difficult to ascertain because of publication bias, challenges in definitions, and limitations in test interpretation, particularly those that are qualitative or subjective.[8] Because of the heterogeneous presentations and absence of well-validated diagnostic criteria, the diagnosis of overlap syndrome requires prompt pattern recognition, careful interpretation of serologic and radiologic findings, exclusions of other causes, and histologic evaluation by an experienced