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Autoimmune Hepatitis

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Continuing Education Activity

Autoimmune hepatitis refers to chronic and progressive inflammation of the liver from an unknown cause. The proposed mechanism for the development of autoimmune hepatitis is thought to be the interplay of genetic predisposition, an environmental trigger, and failure of the native immune system resulting in chronic inflammation of hepatocytes and subsequent fibrosis of the liver. There are two known types of autoimmune hepatitis. Type 1 is distinguished by the presence of anti-smooth muscle antibodies (ASMA) with or without anti-nuclear antibodies (ANA). Type 2 autoimmune hepatitis presents with positive anti-liver/anti-kidney microsome (anti-LMK) type 1 antibodies or anti-liver cytosol (anti-LC) type 1 antibodies. This activity reviews the pathophysiology, causes, presentation, and diagnosis of autoimmune hepatitis and highlights the role of the interprofessional team in its management.

Objectives:

- Identify the etiology of autoimmune hepatitis.
- Review the workup of a patient with autoimmune hepatitis.
- Outline the treatment and management options available for autoimmune hepatitis.
- Explain the interprofessional team strategies for improving care coordination and communication regarding the management of patients with autoimmune hepatitis.

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Introduction

Autoimmune hepatitis refers to chronic and progressive inflammation of the liver from an unknown cause. The proposed mechanism for the development of autoimmune hepatitis is thought to be the interplay of genetic predisposition, an environmental trigger, and failure of the native immune system resulting in chronic inflammation of hepatocytes and subsequent fibrosis of the liver. [1][2][3]There are two known types of autoimmune hepatitis. Type 1 is distinguished by the presence of anti-smooth muscle antibodies (ASMA) with or without anti-nuclear antibodies (ANA). Type 2 autoimmune hepatitis presents with positive anti-liver/anti-kidney microsome (anti-LMK) type 1 antibodies or anti-liver cytosol (anti-LC) type 1 antibodies.

Etiology

There is no specific evidence of the cause. Sixty percent of patients have chronic hepatitis but without serologic evidence of a viral infection. The disease is associated with anti-smooth muscle autoantibodies. [4]

Epidemiology

Epidemiological data on autoimmune hepatitis is scarce and very likely unreported and underrecognized. Of the two

types of autoimmune hepatitis, 80% of cases are diagnosed as type 1. Seventy-five percent of type 1 autoimmune hepatitis is known to manifest in young or middle-aged females. Autoimmune hepatitis is more common in females than males with a ratio of 3.6:1. [5][2] Due to the lack of exact epidemiological data, the true incidence and prevalence in the United States are unknown. However, it is reported that 100,000 to 200,000 individuals are affected each year. Based on European studies, the incidence of autoimmune hepatitis is 0.9-2/100,000 populations per year and the prevalence of 11-25/100,000 per year. Type 2 autoimmune hepatitis is most commonly diagnosed in children and young adults and usually presents with fulminant hepatic failure.

Pathophysiology

The etiology of autoimmune hepatitis is unknown. The current proposition for pathogenesis is thought to be secondary to a failure of immune tolerance in a genetically susceptible individual leading to a T-cell mediated inflammation caused by various environmental triggers. Common triggers include infections, medications, and toxins. Certain human leukocyte antigen (HLA) haplotypes are more susceptible to the development of autoimmune hepatitis. Susceptible alleles are different in different ethnic groups. Among White North Americans and Northern Europeans, susceptible alleles are located on the short arm of chromosome 6, specifically within the region of DRB-1. Nitrofurantoin and minocycline are well-documented culprits of drug-induced autoimmune hepatitis. Tumor necrosis factor-alpha drugs have been more recently linked to autoimmune hepatitis.

Histopathology

The hallmark histologic feature of autoimmune hepatitis is interface hepatitis. However, it is nondiagnostic as it is present in most cases of viral hepatitis. Various histological findings are associated with autoimmune hepatitis, but all of them are nonspecific.

The specimen of liver biopsy should include 6 portal triads for autoimmune hepatitis diagnosis. Typical autoimmune hepatitis biopsy includes mononuclear inflammatory infiltrate mostly plasma cells, located primarily in the portal tracts. This inflammation leads to piecemeal necrosis of hepatocytes leading to the destruction of limiting plate (interface hepatitis), bridging fibrosis (connecting portal and central area of hepatocytes), regenerating nodules, and finally cirrhosis. Twenty-five percent of cases show changes in bile ducts such as ductopenia, cholangitis.

These histologic findings are nonspecific for autoimmune hepatitis. Thus, a scoring system was developed for the diagnosis of autoimmune hepatitis. In 1993, the International Autoimmune Hepatitis Group (IAIHG) initially proposed criteria that classified patients as “probable” or “definite” for autoimmune hepatitis based on multiple factors: gender, the presence of transaminitis, the presence of autoantibodies, and a history of autoimmune disease in first-degree relatives. These criteria also took into account whether or not other causes such as viral or alcohol-induced hepatitis had been excluded. In 1999, the scoring system was updated to include response to treatment. Since that time, a simplified scoring system has been introduced and is more conducive to everyday use by clinicians. Using the new scoring system, the sensitivity and specificity for probable autoimmune hepatitis are 91% and 94%, respectively; the sensitivity and specificity of definite autoimmune hepatitis are 75.5% and 100%, respectively.

History and Physical

Autoimmune hepatitis can present in a variety of ways from an asymptomatic elevation of liver enzymes noted on routine lab tests to fulminant hepatitis. Clinical manifestations of autoimmune hepatitis depend on how acute liver disease is at presentation, the stage of inflammation, or the complication of liver cirrhosis. The most common features of autoimmune hepatitis are fatigue, malaise, jaundice, abdominal pain, and sometimes, arthralgias.

Features of a failing liver such as ascites, hepatic encephalopathy, and variceal hemorrhage are a rare initial presentation of autoimmune hepatitis. Only a few patients present with acute liver failure. Autoimmune hepatitis may present concurrently with other autoimmune diseases like Graves disease, rheumatoid arthritis, celiac disease, type I diabetes, ulcerative colitis, hemolytic anemia, and immune thrombocytopenia. Specifically, autoimmune hepatitis is present in approximately 10% of individuals with autoimmune polyendocrine syndrome type 1.

About 25% of patients with autoimmune hepatitis are asymptomatic. The most common physical findings in autoimmune hepatitis are hepatomegaly (78%) and jaundice (69%) in patients with severe disease. Another common physical finding is splenomegaly with or without cirrhosis.

Evaluation

Autoimmune hepatitis should be considered in all individuals with both acute and chronic liver disease. Diagnosis of autoimmune hepatitis requires exclusion of other chronic causes of liver disease including Wilson disease, drug-induced hepatitis, nonalcoholic hepatosteatosis (NASH), chronic viral hepatitis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC).[6][7][8]

A multi-pronged approach is used to make a diagnosis. This approach includes determining symptoms, laboratory tests, and biopsies, as no single diagnostic test is pathognomonic for autoimmune hepatitis. Marked elevation of serum transaminases (AST, ALT) and gamma-globulin is common; elevation in alkaline phosphatase is less common. The serum levels of AST, ALT, and gamma globulin reflect disease severity and immediate prognosis at presentation.

The serologic markers required for the diagnosis of autoimmune hepatitis include antinuclear antibody (ANA), smooth muscle antibodies (SMA), and antibodies to liver-kidney microsome type 1 (anti-LKM1). Indirect immunofluorescence detects ANA, SMA, and anti-LKM1. The diagnostic accuracy, specificity, and sensitivity of these markers are 74%, 99%, and 43%, respectively. Anti-liver cytosol type I, anti-soluble liver antigen (SLA) antibodies, and perinuclear antineutrophil cytoplasmic antibodies (pANCA) can also be associated with autoimmune hepatitis. [9]Conversely, anti-mitochondrial antibodies are more commonly seen with primary biliary cirrhosis and are usually absent in autoimmune hepatitis; however, they can be present in those with overlapping syndromes. Atypical perinuclear antineutrophil cytoplasmic antibodies are commonly associated with type-1 autoimmune hepatitis and primary sclerosing cholangitis. Anti-LKM1 is common in type 2 AH autoimmune hepatitis and is mainly observed in children.

Anti-SLA antibodies are more useful from a prognostic standpoint as these are associated with more severe disease, treatment failure, and a higher relapse rate. Liver biopsy is required for both diagnosis and staging of autoimmune hepatitis.

Treatment / Management

The treatment guidelines for autoimmune hepatitis are continually evolving. Untreated individuals develop cirrhosis and subsequently die of liver failure two years from diagnosis. [10][11][12] Nonetheless, a handful of cases are reported to have increasing and decreasing clinical stages and may even progress into prolonged spontaneous remission. Therapy for autoimmune hepatitis should begin in patients who fit any or all of the following criteria:

- Elevated AST and ALT more than ten times the upper limit of normal, or at least five times the upper limit of normal
- Gamma globulin at least two times the upper limit of normal
- Presence of bridging necrosis and multilobular necrosis in liver biopsy.

It is now well established that the use of corticosteroids leads to complete remission and in most cases improves mortality. The American Association for the Study of Liver Diseases recommends monotherapy with prednisone or combination therapy with prednisone and azathioprine. However, due to multiple adverse effects of long-term use of prednisone, combination therapy is preferred over monotherapy with prednisone. Monotherapy with prednisone is preferred in cases of pregnancy, intolerance to azathioprine, an absence of thiopurine methyltransferase (TPMT) activity, or severe cytopenia. Immunosuppressive therapy should not be started in patients with preexisting comorbid conditions such as vertebral compression, brittle diabetes, uncontrolled hypertension, psychosis.

For monotherapy, a typical induction dose of prednisone is 60 mg daily for 1 week followed by 40 mg in the second week, and 30 mg daily in the third and fourth week. The maintenance dose of prednisone is 20 mg daily until the endpoint or deep clinical remission. The prednisone should be tapered over time and eventually discontinued.
The American Association for the Study of Liver Diseases recommends at least 3 years of treatment. Upon completion of prednisone, patients are classified as in remission, relapsed, or treatment failure based on their histological and laboratory response to steroids, and the presence or absence of clinical symptoms. Histologic regression lags by 3 to 6 months, so treatment must be continued despite normalization of liver enzymes. For combination therapy, the induction dose of prednisone is 30 mg daily for 1 week, followed by 20 mg daily for 1 week, followed by 15 mg daily for 2 weeks. The maintenance dose is 10 mg daily until the endpoint. The dose of azathioprine in combination therapy for

both induction and maintenance is 30 mg oral daily.

Budesonide may be used instead of prednisone to reduce the adverse effects associated with steroid treatment. The combination of budesonide and azathioprine is emerging as an alternative first-line therapy. In cases of inadequate or incomplete response, or azathioprine intolerance, mycophenolate mofetil, cyclosporine A, and tacrolimus can be used.

Remission occurs when the patient becomes asymptomatic with normalization of inflammatory markers, transaminases, gamma globulin, and histological improvement in liver biopsy.

Relapse can occur after a patient in remission stops therapy. About 50% of patients have disease relapse within 6 months of discontinuing therapy. Relapse is defined by the elevation of AST (three times the upper limit of normal), the reappearance of histological findings after discontinuing therapy.

Liver cirrhosis can develop in about 7% to 40% of treated patients. The development of cirrhosis is associated with incomplete response, treatment failure, and multiple relapses. Once cirrhosis develops, upper endoscopy should be performed for esophageal varices surveillance. Regular screening for hepatocellular carcinoma should be done with biannual liver ultrasound and alpha-fetoprotein. Overall, management of liver cirrhosis in autoimmune hepatitis is similar regardless of etiology. Finally, liver transplantation is considered the standard of care in patients presenting with fulminant hepatic failure or those with the progression of disease despite multiple lines of therapy. Patients are also encouraged to avoid alcohol, unregulated herbal supplements, and high amounts of dietary fats.

Differential Diagnosis

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E

Pearls and Other Issues

Prognosis can vary widely but appears to be most dependent on treatment. Several randomized, controlled trials have shown that untreated autoimmune hepatitis patients have a 5-year and 10-year survival rate of 50% and 10%, respectively. Sixty percent to 80% of patients will enter remission after the proposed duration of treatment. Approximately 50% of these patients will relapse requiring therapy resumption. Some patients require life-long immunosuppression. Treatment failure occurs in 10% of patients that undergo treatment with prednisone. For those who undergo liver transplantation, approximately a third of patients have a recurrence of autoimmune hepatitis.

Enhancing Healthcare Team Outcomes

The diagnosis and management of autoimmune hepatitis are complex and best done by an interprofessional team that includes a gastroenterologist, pharmacist, internist, and hepatologist. Specialized gastrointestinal nurses assist in the care, education of the patient and family, and coordination of the treatment and follow-up. It is now well established that the use of corticosteroids leads to complete remission and in most cases improves mortality. The American Association for the Study of Liver Diseases recommends monotherapy with prednisone or combination therapy with prednisone and azathioprine. The pharmacist should educate the patients on all the potential complications of steroids and when to seek medical help. At the same time, the primary care provider and nurse practitioner should thoroughly examine the patient for worsening of the liver condition.

The prognosis for most patients with autoimmune hepatitis is guarded. While survival has improved over the past 2 decades, it still is low. Relapse of the condition is common and some patients may benefit from a liver transplant.[13]

[14] [Level 5]

Review Questions

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