ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Immunoglobulin G4-Associated Autoimmune Cholangiopathy

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G&H What is the typical presentation of immunoglobulin G4-associated autoimmune cholangiopathy? Does this condition frequently co-occur with other autoimmune disorders?

KL Immunoglobulin (Ig)-G4–associated autoimmune cholangiopathy can range from asymptomatic cases in which the only sign of disease is an abnormal liver test to patients with jaundice and weight loss, so there is a very broad spectrum of disease. While co-occurrence with other conditions is not universal, patients with IgG4-associated autoimmune cholangiopathy may also have autoimmune pancreatitis. Most often, doctors caring for patients with pancreatic disease will note biliary strictures; clinicians who focus primarily on biliary tract disease do not see pancreatic involvement as frequently. Patients with IgG4-associated autoimmune cholangiopathy can also have involvement of the salivary glands and/or fibrosis in the retroperitoneal space, but these associations have most often been found in patients who already have pancreatic involvement.

G&H How does IgG4-associated autoimmune cholangiopathy differ from clinically similar conditions?

KL Among patients with bile duct radiographs that look like primary sclerosing cholangitis (PSC), those who have elevated serum IgG4 levels have a much more severe course of disease; these patients are more likely to die or require transplantation than patients who have normal IgG4 serum levels. Fortunately, patients with IgG4-associated disease are often very responsive to steroid therapy, which is not the case with PSC. Finally, patients with IgG4-associated disease often present with strictures at the point where the bile duct splits above the gallbladder; while strictures in this area can be associated with jaundice and can simulate bile-duct cancer, this type of obstruction is less common in patients with PSC. Overall, the clinical presentation can be more severe in patients with IgG4-associated disease, but frequently these patients are also more easily treated.

G&H What causes IgG4-associated autoimmune cholangiopathy?

KL We do not really know. Pathologically, areas of inflammation have been shown to contain B cells—which make immunoglobulins and stain positive for IgG4—but we do not know what causes B cells to be in these areas or what causes them to be activated.

G&H How is IgG4-associated autoimmune cholangiopathy related to other IgG4-associated conditions?

KL Currently, our hypothesis is that IgG4-positive cells are activated in or recruited to various tissues—including the salivary glands, pancreas, or tissues within the liver or bile ducts—but we do not know the identity of the activating factor. In other autoimmune diseases, or even infectious diseases, a single causative organism or process can cause different effects depending on the involved organ. I think that IgG4-associated disease is similar: I

think that something activates the immune system, and something else—we do not know what, yet—determines where the preponderance of the inflammation and destruction will occur.

G&H Which tissues are most affected in patients with IgG4-associated disease?

KL This issue has not been well studied. In a series that looked at extrapancreatic involvement in patients with IgG4-associated autoimmune pancreatitis, the biliary system was found to be the most common extrapancreatic site, followed by the salivary glands and the retroperitoneal space.

G&H How has understanding of this condition evolved in recent years?

KL Understanding of this condition has been evolving, but it is a slow process, both because IgG4-associated autoimmune cholangiopathy is not a common condition and because there is still no real consensus on how to define this condition. Clinicians and researchers in this field are developing their own understanding of the condition, but groups are using different diagnostic criteria, which makes it difficult to clearly understand the natural history of this condition. The lack of a common definition will also pose a challenge as we try to understand treatment responses; since clinicians are not using the same criteria to make the diagnosis, we may be seeing different groups of patients, which naturally will affect patients' responses to therapy.

G&H What is your definition for IgG4-associated autoimmune cholangiopathy?

KL My practical definition for IgG4-associated autoimmune cholangiopathy is bile duct strictures consistent with PSC in patients with elevated serum IgG4 levels. I do not necessarily require a biopsy that demonstrates IgG4 involvement, although a number of other definitions do have this requirement. I prefer to base my definition on serum IgG4 levels in part because tissue is hard to obtain in the biliary system, and even if biopsies are taken, IgG4 is not always found in these samples. My definition of IgG4-associated autoimmune cholangiopathy also does not require involvement of other tissues, such as the pancreas or the salivary glands. Only a minority of patients with IgG4-associated disease have such involvement, so requiring involvement of multiple organs as part of a definition for IgG4-associated autioimmune cholangiopathy would exclude the majority of patients with the condition. However, if patients do have other areas of involvement, this finding certainly strengthens our diagnostic certainty.

G&H How do you image the biliary tree when assessing a patient for IgG4-associated autoimmune cholangiopathy?

KL We need to look for strictures in the biliary tree to make a diagnosis of PSC or IgG4-associated autoimmune cholangiopathy. For PSC, imaging is increasingly being performed noninvasively via magnetic resonance cholangiography—rather than via endoscopic retrograde cholangiopancreatography (ERCP)—and magnetic resonance cholangiography can also be used to demonstrate biliary strictures in patients with IgG4-associated autoimmune cholangiopathy. If a clinician's definition of IgG4-associated autoimmune cholangiopathy requires tissue involvement, then a biopsy sample would also need to be collected via ERCP or another means.

G&H What other conditions do you have to rule out when making the diagnosis?

KL The main differential diagnosis that clinicians worry about is bile-duct cancer. When patients with PSC develop bile-duct cancers outside of the liver itself, two thirds of these cancers are in the area where the bile duct splits, which is the same area commonly involved in IgG4-associated disease. Cancer is a concern for patients at any age, but it is even more likely to occur in older patients. Ruling out cholangiocarcinoma sometimes requires that clinicians do an ERCP with brushings and biopsies, but cancer can be missed even when these samples are taken. The main thing that helps to differentiate IgG4-associated autoimmune cholangiopathy from cancer is the response to steroid therapy. IgG4-associated disease usually responds very quickly and very well to steroids, whereas a patient with cancer would not respond to this treatment. If a patient responds to steroids within 6 weeks to 3 months, then clinicians can be fairly confident that the patient has IgG4-associated disease.

G&H What is the standard treatment for patients with IgG4-associated autoimmune cholangiopathy?

KL I treat these patients in much the same way that I treat patients with autoimmune hepatitis. The main point is that patients with IgG4-associated disease usually seem to need a longer course of therapy—approximately 18 months, on average—and they are best treated using a combination of prednisone and azathioprine. Because IgG4-associated disease is not particularly common, clinicians do not have good data from randomized controlled trials to prove that this treatment approach is beneficial, so this approach is based primarily on clinical experience.

When I have treated patients with higher doses of steroids in shorter bursts, patients often experienced significant steroid side effects and rebound recurrence of strictures after treatment was discontinued. Based on this experience, I now use a longer course of steroids. Because side effects can accumulate when steroids are used for a long period of time, however, I also add azathioprine to the regimen, which allows me to reduce the steroid dose.

G&H Are there any other treatments that you might consider for these patients?

KL IgG4 is produced by B lymphocytes, so patients with IgG4-associated autoimmune cholangiopathy might benefit from rituximab (Rituxan, Genentech/Biogen Idec), which is a monoclonal antibody directed against B cells. A few case reports have shown that rituximab can be beneficial in patients who have not responded to steroids; however, this drug is very expensive and it has not been well studied in patients with IgG4-associated autoimmune cholangiopathy. Nonetheless, rituximab makes sense as a treatment for IgG4-associated disease, given our understanding of the potential mechanisms of the disease and the mechanism of action of the agent, and limited clinical experience suggests that this drug might provide a treatment option for refractory cases.

G&H What further research is needed regarding IgG4-associated autoimmune cholangiopathy?

KL First, clinicians need to have a consensus about the definition of this disease so that we can be sure we are looking at a consistent group of patients when we evaluate treatment responses. Also, it is always helpful if we understand what causes a condition, so I would like to see more research regarding the etiology of IgG4-associated autoimmune cholangiopathy. Information about the natural history of IgG4-associated disease and differences in the way the condition presents would also be helpful. A few questions that should be explored include: Is IgG4-associated disease in patients with pancreatic involvement the same as disease in patients with isolated biliary strictures? Does the presence of other associated conditions affect the prognosis or treatment response? Finally, could the presence of other associated conditions give us some insights into the cause of the disease?

G&H Have clinicians attempted to come up with a standardized definition of IgG4-associated autoimmune cholangiopathy?

KL There has been much discussion about how to define this condition. In situations like this one, however, people often have their own definitions that they work hard to defend. Also, we do not yet have comparative data that could help us better understand how well a definition defines a population, so we currently lack the foundation on which to form a solid consensus.

Suggested Reading

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