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The Changing Pattern of Autoimmune Liver Disorders

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Q. What are the typical features of autoimmune hepatitis?

Autoimmune hepatitis was originally described as a chronic inflammatory liver disease affecting mostly young white women. Typical histologic findings are plasma cell infiltration, emperipolesis, interface hepatitis, and advanced liver fibrosis. While these changes are characteristic, they are not specific, therefore liver biopsy alone is not diagnostic. The typical laboratory profile includes hypergamma-globulinemia and autoantibodies (antibodies to antinuclear antigen – ANA; antibodies to smooth muscle; anti SMA, to soluble liver antigen; anti-SLA, antibodies to liver cytosol type 1; anti-LC1, and liver kidney microsome type 1; anti-LKM-1). Certain autoantibodies have high diagnostic specificity for autoimmune hepatitis and possible prognostic value, but again are not specific. Thus, the “classic” form of autoimmune hepatitis is diagnosed by the Scoring System of the International Autoimmune Hepatitis Group which combines laboratory, histologic and clinical data[1] or by the more recently published “simplified criteria”[2] for the diagnosis of autoimmune hepatitis.

Q. How has the spectrum of this condition evolved over the years?

Now, decades later, the spectrum of autoimmune hepatitis has become more complex. Autoimmune hepatitis has a variable occurrence, clinical phenotype, genetic background and outcome, and the factors contributing to this variability are uncertain. The worldwide incidence of autoimmune hepatitis ranges from 0.7 to 2 per 100,000 population, while the prevalence ranges from 4 to 25 per 100,000.

The increasing incidence of autoimmune hepatitis in several European countries including Spain, Italy, Denmark, and the Netherlands suggests that a new etiological trigger has been introduced or that the susceptible population has changed. One explanation of the increased incidence is the improved awareness for AIH. Changes in the clinical phenotype of autoimmune hepatitis have evolved as awareness of the disease has increased, and the diagnosis is now considered in all patients with acute or chronic hepatitis of unknown cause lead to increased case detection.

Modern lifestyle, dietary habits and environmental factors including exposure to herbicides, pesticides and other toxic compounds found in the nutrition or in drinking water may lead to hepatic changes mimicking autoimmune hepatitis. Consequently, the incidence of autoimmune and inflammatory diseases has been increasing worldwide. Perturbed microbial composition and function, termed ‘dysbiosis’, has been associated with autoimmune diseases including autoimmune liver disease (for extensive review of the link of changes in the microbiome and autoimmunity see[3]. From an immunological point of view, the liver is exposed to large numbers of foreign molecules coming from the gastrointestinal tract via the portal vein. These non-self-antigens are either food derived (including

peptides derived from gluten and related cereals), or originate from gut microbiota (i.e. bacterial components and products). Among nutritional factors exposure to gluten is of particular interest. The prevalence of celiac disease in patients with autoimmune hepatitis is significantly higher than that found in the general population, and may be as high as 6.4%. Both diseases share a common immunological basis. Several sequencing studies have reported an altered gut microbial community in PSC and PBC.

Drug-induced liver injury (DILI) and hepatic injury due to herbal and dietary supplements (HDS) can adapt clinical characteristics of autoimmune hepatitis, such as the appearance of autoantibodies and infiltration of the liver by immune competent cells. To describe these cases of DILI/HDS, the poorly-defined term “autoimmune-like” DILI/HDS (or “Drug induced AIH”) was coined. Due to the overlap of clinical characteristics of “immune-mediated” drug-induced (DILI)/HDS and AIH, both entities are not easy to differentiate.

Data from the DILIN network (http://www.dilin.org/) showed that most cases of DILI attributed to nitrofurantoin or minocycline and about half of cases that were due to methyldopa and hydralazine have a phenotype of autoimmunity similar to AIH. These features decrease with recovery of the injury and are not associated with the typical HLA alleles found in patients with idiopathic AIH. Immune checkpoint inhibitors block CTLA-4, PD-1 and PD-L1, or other molecules that control anti-tumor activities of lymphocytes. These products are associated with a broad array of immune-related toxicities affecting a variety of organs, including the liver. Immune checkpoint inhibitor-associated immune-mediated hepatitis ranges in severity between mild and life-threatening and is marked by findings that bear both similarities as well as differences with idiopathic autoimmune hepatitis.

Q. What allows differential diagnosis between DILI and autoimmune hepatitis?

Only through exact diagnostic evaluation, exclusion of differential diagnoses and prolonged follow-up can the correct diagnosis reliably be made. Features supporting the diagnosis of autoimmune hepatitis are a relapse of transaminases and IgG/gammaglobulins after steroid withdrawal and a chronic, fluctuating course. Diagnosis of DILI/HDS requires taking an extensive drug/toxin exposure history which should also include dietary supplements and off label products (herbal compounds marketed as alternative treatments for a variety of diseases). The diagnosis of DILI is made by establishing a temporal relationship between drug exposure and development of signs and symptoms of liver disease. Detailed information can be obtained from the LiverTox website (www.livertox.nih.gov).

Q. What are the major challenges of treatment of autoimmune hepatitis?

The demarcation of autoimmune hepatitis from DILI is important with regard to treatment: AIH requires long-term, mostly lifelong immunosuppression, whereas DILI/HDS does not. Patients with autoimmune hepatitis may have features of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Similarly, patients with classic features of PBC or PSC may have features of autoimmune hepatitis. The diagnostic boundaries between these diseases are not well defined, and clinical, laboratory, and histological features can be shared. The overlap syndromes occur in 3% to 17% of patients with autoimmune liver disease.

Some AIH cases fulfill the criteria of IgG4-related disease. The histologic pattern is highly characteristic. The major histologic features associated with IgG4-related disease include (1) a dense lymphoplasmacytic inflammatory infiltrate with increased numbers of IgG4+ plasma cells and often increased eosinophils; (2) a storiform pattern of fibrosis; and (3) obliterative vasculitis[4].

References

1. Alvarez F, Berg PA, Bianchi FB, et al. J Hepatol 1999;31:929-938
2. Hennes EM et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-76.
3. Bo Li et al. The microbiome and autoimmunity: a paradigm from the gut–liver axis. Cellular & Molecular Immunology 2018;15:595–609
4. Weindorf SC Frederiksen JK. IgG4-Related Disease: A Reminder for Practicing Pathologists. Archives of Pathology & Laboratory Medicine 2017;141:1476-1483