Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/gi-insights/primary-biliary-cholangitis-pathophysiology-from-genetic-risk-to-immune-dysregulation/29159/

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Primary Biliary Cholangitis Pathophysiology: From Genetic Risk to Immune Dysregulation

Announcer:
Welcome to *GI Insights* on ReachMD. On this episode, we'll hear from Dr. Aliya Gulamhusein, who holds a Professorship in PSC Research and serves as an Assistant Professor in the Division of Gastroenterology and Hepatology at the University of Toronto. She'll be discussing the pathophysiology and diagnosis of primary biliary cholangitis. Here's Dr. Gulamhusein now.

Dr. Gulamhusein:
The immunologic mechanisms involved in the pathogenesis of primary biliary cholangitis are complex and include an interplay between the innate and the adaptive immune system. So in the context of genetic risk and as yet undefined environmental trigger, the immune system is triggered to generate a response against the host or the individual's intrahepatic bile ducts. So the innate system starts off, and that triggers the adaptive immune system, which includes both the T-cell lineages and the B-cell lineages, and that results in the development of antibodies, specifically the antimitochondrial antibodies that are a very specific marker of PBC. That inflammatory process, which is a dysregulated process—normally, the immune system is not supposed to attack its own host cells—that dysregulated process leads to a specific attack on the intrahepatic bile ducts in the liver, leading to what's called lymphocytic cholangitis or a lymphocytic infiltration against a small bile ducts in the liver that can be seen pathologically.

So the genetic and environmental triggers involved in the pathogenesis of PBC have been extensively studied. Genetics have been studied in several types of studies, including twin studies, small series of gene-finding studies, and most recently what's called genome-wide association studies, which genotype the entire genome and look for associations with disease. And the most common genetic signals in PBC are at loci within the HLA, so immune regulatory genes that are also seen in other autoimmune conditions, including rheumatoid arthritis, celiac disease, type 1 diabetes, et cetera. So there are genetic predispositions that have been associated with PBC, but that's not enough to cause the disease on its own. So essentially, disease manifestation is a result of what's usually referred to as a Swiss cheese model. There has to be several things that line up for the disease to become overt or manifest. Genetics are one of them, but the environmental triggers are also an important component as well, and these have also been extensively studied and are variably reported in the literature but have included things like infections, specifically things like urinary tract infections in women; smoking has been associated with PBC as an environmental risk; exposure to certain toxic chemicals, so there is a higher prevalence of disease in patients or people who live in certain areas, sometimes associated with waste sites, and also xenobiotics. So xenobiotics are chemicals that are present in the environment have been potentially associated with toxicity, and some xenobiotics that have been associated with PBC include things that are prevalent in cosmetics, like lipsticks, nail polishes, and things like that. So genetics on its own and then the environmental risk on its own is not sufficient to cause disease, but together, they can result in disease becoming manifest.

So the immunology of PBC is fundamental to the diagnosis, and as mentioned, the immune system is key. The dysregulated immune system is key in generating the pathologic response against the bile duct. That starts with the innate system and transitions to the adaptive immune system. And the adaptive immune system is really what's responsible, particularly the B-cells, in generating antibodies, and the antimitochondrial antibody is a very disease-specific autoantibody and is characteristic and pathognomonic really for PBC. So that adaptive immune response generates the antimitochondrial antibody, which is an antibody that's against a mitochondrial antigen. That's the diagnostic test, really, in patients with PBC.

So a patient that presents with abnormal liver tests—most commonly a middle-aged woman with abnormal liver tests—if an antimitochondrial antibody is positive, that is sufficient for the diagnosis of PBC, and that antibody has been generated because of the

triggers within the patient, both the genetic and the environmental triggers that have resulted in an antigen being presented within the mitochondria that's triggered the antibody to be developed. So the antimitochondrial antibody is by far and away the most effective diagnostic test in patients with PBC and is sufficient in the setting of elevated liver tests to confirm diagnosis.

Announcer:
That was Dr. Aliya Gulamhusein talking about the pathophysiology and diagnosis of primary biliary cholangitis. To access this and other episodes in our series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!