A Retrovirus Implicated in Primary Biliary Cirrhosis (PBC)

By David Rhodes

When my son was diagnosed with primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) in the summer of 2003, I set about reading everything I could find about this (and related) liver and inflammatory bowel diseases. Of the thousands of research abstracts I have read over the last 6 months, I was particularly impressed by several authored by Dr. Andrew Mason (currently located at the University of Alberta; formerly of Tulane University, New Orleans) on the possible involvement of a retrovirus in primary biliary cirrhosis (PBC). It seemed to me that Dr. Mason's studies represent a significant breakthrough in the understanding of the "trigger" mechanism of a cholestatic disease; advances that may eventually help in understanding the cause(s) of PSC. In this article I briefly summarize these new developments.

PBC has long been thought to be an autoimmune disease (1). However, several lines of evidence indicate that an infectious agent might be involved in triggering the disease in genetically susceptible individuals (1). PBC has been documented in unrelated care providers and in non-related family members, and in one study it was associated with a particular water supply (reviewed in 1). Several unusual geographical clusters of the disease have recently been documented (7). PBC frequently recurs after liver transplantation (1). A hallmark of PBC is the occurrence of antimitochondrial antibodies primarily directed against the pyruvate dehydrogenase complex. These antibodies begin to reappear on the biliary epithelial cells of the transplanted allograft following transplantation (1). A variety of organisms have been considered as possible causes of PBC, including viruses, bacteria and fungi, but a retrovirus has recently taken center stage (1). Retroviruses are infectious particles built on RNA rather than DNA. The most infamous retrovirus is HIV, the virus that causes AIDS. Other diseases thought to be caused by retroviruses include breast cancer and Sjogren's syndrome.

Mason and colleagues first showed that serum of PBC patients had reactivity to certain proteins characteristic of retroviruses (2). Mason and colleagues then obtained evidence that a transmissible factor can promote the appearance of antimitochondrial antibodies in normal biliary epithelial cells. Biliary epithelial cells extracted from normal liver were co-cultivated with homogenized lymph nodes from PBC patients. Normal biliary epithelial cells developed pyruvate dehydrogenase antibodies 5 to 7 days after incubation with homogenized lymph nodes from PBC patients (5). This effect could be halted by either ultra-centrifugation or by gamma irradiation of the supernatants prior to incubation, suggesting that the lymph nodes of patients with PBC harbor a transmissible, particulate agent with a radiation-sensitive nucleic acid genome (5). The agent appears to be capable of replicating and producing the characteristic antibodies of PBC in biliary epithelial cells (1).

What are PBC and PSC, and how do they differ?

Both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases. Both are presumed to have an autoimmune basis. Both conditions involve progressive destruction of bile ducts leading to chronic cholestasis and liver cirrhosis. This is often accompanied by complications, such as portal hypertension and liver failure. Both conditions may eventually require liver transplantation. Both diseases may recur following liver transplantation. Both diseases are currently treated in their early stages with ursodeoxycholic acid (UDCA).

PBC involves progressive destruction of the small, interlobular bile ducts. It affects mainly women (female to male ratio of 9:1), with a peak incidence between the ages of 40 and 60 years. PBC patients typically exhibit antimitochondrial antibodies directed against 2-oxoacid dehydrogenase complexes in the inner mitochondrial membrane, the most important being the pyruvate dehydrogenase complex.

PSC involves inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic biliary tract, with associated ductopenia. About two thirds of the patients are men, with an average age of about 40 years at presentation. Approximately 75% of patients with PSC also have inflammatory bowel disease (IBD), mostly chronic ulcerative colitis (UC), but sometimes Crohn's disease. PSC patients typically exhibit perinuclear antineutrophil cytoplasmic antibodies and/or other auto-antibodies.

Although there are clear differences between PBC and PSC, it is likely that advances in understanding the causes of one may assist in understanding the causes of the other.

Electron microscopy studies also revealed virus-like particles in the extracellular space of biliary epithelial cells of PBC patients (5). Each particle was approximately 110 to 120 nm in diameter and had an oval, eccentric nuclear dense core, compatible with viral particles (5).

More recently, a betaretrovirus has been cloned and sequenced from the lymphoid tissue of PBC patients (4). The retrovirus has striking nucleotide homology with mouse mammary tumor virus (MMTV) and with retrovirus sequences derived from human breast cancer samples (4). The human betaretrovirus nucleic acid sequences cloned from PBC patients contain five sequences encoding proteins characteristic of retroviruses, including the superantigen (Sag) protein (4). The retroviral superantigen may be responsible, in part, for triggering an inflammatory cascade leading to autoantibody production, and cholangiocyte destruction (6). Because MMTV viral replication is regulated by the female hormone progesterone (5), this may provide an explanation for the predominantly female incidence of PBC.

These findings add further impetus to ongoing trials of anti-retroviral therapies in PBC (1). Mason and colleagues have initiated small pilot trials of treatment of PBC patients with lamivudine or Combivir (a combination of lamivudine and zidovudine) (1). Significant improvements in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (Alk Phos) levels were observed in patients after 6 months of Combivir treatment (1). A reduction in serum liver biochemistry was seen in most patients taking Combivir, but not lamivudine alone (1). A reduction of serum antimitochondrial antibody levels in the majority of patients following treatment also raises the possibility that antiretroviral therapy has an effect on the pathogenesis of the disease (1).

Poupon and Poupon (6) have recently called attention to the need for a clinical trial to further test the effectiveness of anti-retroviral therapy in PBC. They urge that patients enrolled in such a trial will need to have a high concentration of viral sequences in blood or peripheral blood cells, and should be in an early stage of the disease (6).

How are these studies relevant to PSC? In 1998, Mason and colleagues also detected retroviral antibodies in patients with primary sclerosing cholangitis (2). As far as I am aware, these findings have not been pursued as tenaciously as they have been in PBC. I eagerly await follow-up investigations of the possible involvement of a retrovirus (or other infectious agents) in the pathogenesis of PSC.

David Rhodes is a member of the U.S.-based “Primary Sclerosing Cholangitis Support Group”:
http://health.groups.yahoo.com/group/psc-support/

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References