Autoimmune Hepatitis: A Part of the Antiphospholipid Syndrome?

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Autoimmune hepatitis is a chronic inflammatory disorder of the liver of unknown cause, characterized by the presence of liver-associated autoantibodies and hypergammaglobulinemia. Two types of AIH have been described, both being more common in young women. It is one of the major autoimmune liver diseases, and in 20–40% of the cases is associated with other autoimmune disorders. The most common of these are thyroiditis, rheumatoid arthritis, ulcerative colitis, Sjögren syndrome, type 1 diabetes mellitus and vitiligo. Moreover, proliferative glomerulonephritis, celiac disease, autoimmune hemolytic anemia and thrombocytopenia, polyendocrinopathy and alopecia occur with increased prevalence in patients with AIH or their families [1]. However, the co-occurrence of antiphospholipid syndrome with AIH is quite rare, and only a few such cases have been described, one of them from Israel [2–7]. In this issue of *IMAJ*, Becker-Merok and Nossent [2] report another patient with AIH associated with APS [8].

Antiphospholipid syndrome is a multisystem autoimmune disease, characterized by arterial and venous thrombosis, recurrent fetal loss, thrombocytopenia, various other clinical manifestations and persistent circulating antiphospholipid antibodies, such as lupus anticoagulant and anticardiolipin antibodies [9]. This syndrome with protean clinical manifestations [9] can be either primary or secondary to other autoimmune disease, mainly systemic lupus erythematosus [10]. APS has received tremendous attention in recent years and is currently regarded as the most common acquired thrombophilia [10]. The incidence of liver disease in APS is low, and in most cases is caused by vascular occlusion of intra- and extrahepatic vessels. Hepatic vein occlusion with the development of Budd-Chiari syndrome is the most frequently recognized complication, and APS is now considered one of the most frequent causes of Budd-Chiari syndrome [11].

Autoimmune diseases have a multifactorial etiology involving viral and bacterial infections [12]. An association was found between antiphospholipid antibodies and infectious agents including bacteria and viruses, which in some cases involve overt APS manifestations [13]. APS models proved the molecular mimicry between β_2 glycoprotein-I related synthetic peptides and structures within bacteria and viruses, and confirmed their causative role in experimental APS [12,14].

Infection with hepatitis viruses and raised antiphospholipid antibody levels. Increased prevalence (27–44%) of elevated ACL antibodies without clinical manifestations of APS was observed in patients with chronic hepatitis C virus infection [15,16]. In another study the prevalence of HCV infection in patients with APS was low and similar to that in healthy controls, leading the authors to conclude that HCV infection is not involved in the pathogenesis of APS [17]. A recently published literature analysis of patients who developed APS associated with chronic viral infections identified 45 subjects with HCV infection. In comparison with other APS patients, the HCV-infected patients had a higher mean age, higher rate of myocardial infarction and intraabdominal thrombosis, and lower frequency of the more typical features of APS, such as peripheral thrombosis and neurologic involvement [18]. In a study to test whether ACL can cause APS in patients with non-autoimmune liver disease – which included 372 patients, most with hepatitis B or C virus [19] – ACL were more prevalent in patients than in healthy controls, and were not associated with thrombotic events. The investigators concluded that in patients with non-autoimmune liver disease, antiphospholipid antibody production is an epiphenomenon of the liver damage and is not associated with thrombotic complications and APS [19].

Although liver involvement in patients with systemic autoimmune diseases has been well documented, it is uncommon. Nonetheless, it raises the question whether it is a primary liver disease associated with other systemic autoimmune disease, or is the liver involvement a part of the systemic disease? In their article in this issue of *IMAJ*, Becker-Merok and Nossent [8] suggest a possible role of antiphospholipid antibody in the pathogenesis of AIH. Due to the rarity of such an association and the complexity of the pathogenesis of AIH, we suggest that this hypothesis is premature.

Should this interesting observation of the co-existence of AIH and APS change our approach to patients? We agree with the authors that APS patients with elevated liver enzymes should be

AIH = autoimmune hepatitis
APS = antiphospholipid syndrome

ACL = anticardiolipin antibodies
HCV = hepatitis C virus

screened for AIH. Would the finding of antiphospholipid antibody in a patient with AIH change the course of his or her treatment? Should we give a prophylaxis for such patients? We do not have enough data to answer these questions right now.

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