Chronic Hepatitis C Infection and Peripheral Neuropathy; Is Mixed Cryoglobulinemia Really Important?

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Mixed cryoglobulinemia (MC) has long been regarded as the causative agent of peripheral neuropathy in patients with chronic hepatitis C virus (HCV) infection. Ijichi and colleagues report in this issue of the journal that the frequency of MC, a low complement level, and a high level of Clq were not significantly different between chronic HCV infection patients with neuropathy and without neuropathy. This suggested that not only MC and its related proteins but other immunomodulatory factors may relate to the development of neuropathy in HCV-infected patients (1).

Although peripheral neuropathy may be associated with all types of cryoglobulinemias, it is a frequent complication in patients suffering from type II MC. MC is strongly associated with HCV infection and characterized by high concentrations of anti-HCV antibodies and HCV RNA in the cryoprecipitates (2). HCV infection of peripheral mononuclear cells may be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC (3). However, the role of cryoglobulins and/or HCV infection in the development of peripheral neuropathy has yet to be elucidated (4).

The most widely accepted hypothesis is as follows: the formation of immune complexes is followed by their deposition in the vessel wall and by inflammation leading to the development of small vessel vasculitis via activation of complement. The high frequency of peripheral neuropathy in MC patients strongly supports this hypothesis (5). On the other hand, a close association of HCV infection and polyarteritis nodosa (PAN)-type systemic vasculitis has also been reported (6, 7). Differentiation of MC-associated vasculitis and PAN-type vasculitis can be difficult, because they may share the same clinical conditions including peripheral neuropathy, purpuric skin lesions, myalgia and arthralgia, and renal involvement. Vascular pathology may contribute to the differential diagnosis. MC involves small sized vessels (arterioles, venules, capillaries) with an inflammatory infiltrate composed of only monocytes and lymphocytes [no polymorphonuclear neutrophils (PMN)] without necrotizing angiitis (8). In contrast, classic PAN-type systemic vasculitis affects medium and small size vessels with a mixed inflammatory infiltrate of monocytes, lymphocytes, and PMN and it is associated with a necrotizing angiitis.

PAN-type vasculitis should be distinguished from MC-type vasculitis because of differences in the clinical picture and therapeutic strategy. Patients with PAN-type vasculitis usually show very severe acute clinical manifestations with polyvisceral failure that is often life threatening; unlike those with MC-type vasculitis patients who show subacute moderate skin and neurological symptoms. The neurological involvement in the former is a severe, acute sensorimotor multifocal mononeuropathy involving all limbs, whereas a moderate subacute sensory distal polyneuropathy of the lower limbs was characteristic in the latter (7). Patients with PAN-type vasculitis related to HCV infection should be treated aggressively with a combination of prednisolone (1 mg/kg/day), plasma exchange, and interferon-α. On the other hand, considering that the increase of MC in the serum may be closely related to the vasculitis in MC-type vasculitis patients, efforts to decrease HCV replication should be the first choice of treatment; however, the efficacy of interferon-α in MC-associated vasculitic neuropathy is still controversial (4, 7).

Tropism of HCV towards blood mononuclear cells and hepatocytes and the persistence of this virus in these cells is well known, but neurotropism of HCV has never been described. However, it may be possible that HCV virus directly invades the peripheral nervous system.

Bonetti et al (9) detected HCV RNA in homogenates of nerve biopsies from peripheral neuropathy patients with MC-HCV infection and demonstrated the localization of HCV RNA in epineurial cells. The HCV infection in the epineurial cells might be related to the epineurial vasculopathy in MC-HCV patients, but the importance of MC is obscure in this study because they did not use specimens from MC-negative, HCV-infected neuropathy patients. In one patient of chronic sensory neuropathy with chronic HCV infection, intrathecal HCV-RNA and anti-HCV antibody was reported (10). Future studies concerning the presence of HCV RNA in the central and peripheral nervous system are awaited.

Other than MC-related neuropathy and PAN-type vasculitic neuropathy, chronic HCV infection-related neuropathies include immune-mediated neuropathies such as Guillain-Barré syndrome. HCV virus is lymphotropic (3) and may cause B-lymphocyte proliferation responsible for autoantibodies and immune complex formation; hence, chronic
HCV infection can also be involved in the pathogenesis of lymphoproliferative disorders (B-cell lymphoma, monoclonal gammopathy) as well as in various autoimmune diseases (thyroiditis, glomerulonephritis, autoimmune hepatitis, and various immune-mediated neurological disorders).

In conclusion, HCV infection causes at least three types of neuropathy other than neuropathy with MC-type vasculitis. Namely, in chronic HCV infected patients, peripheral neuropathy can be due to MC-type vasculitis, PAN-type vasculitis, immunological derangement closely related to HCV infection, or possibly HCV itself. Differential diagnosis of these four conditions is crucial to determine the treatment regimen in each patient. Cryoglobulinemic neuropathy in HCV patients may be overdiagnosed; since there is a close relation between the presence of anti-HCV antibody and that of MC in patient's sera, neuropathy not caused by MC-type vasculitis might be misdiagnosed as cryoglobulinemic neuropathy simply because of the presence of serum MC.

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References