Viruses in IBM

Hit-and-run, hide and persist, or irrelevant?

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Inclusion body myositis (IBM) is the most common and disabling inflammatory myopathy above age 50 years, with seemingly increasing prevalence and complex pathogenesis.[1,2] Cytotoxic-perforin-secreting $CD8^+$ cells clonally expand in situ, invading healthy-appearing major histocompatibility complex class I–expressing muscle fibers; cytokines, costimulatory, and adhesion molecules are upregulated; and B cells are expanded with antibody production. Degenerative features are concurrently prominent, highlighted by autophagic vacuoles and accumulation of misfolded proteins, such as amyloid precursor protein, amyloid-β42, p62, and TDP43.[1,2] Proinflammatory cytokines enhance myocyte cell stress, which is specifically linked to amyloid-related protein misfolding.[1,3]

What triggers IBM remains elusive. Because filamentous/eosinophilic inclusions are seen in paramyxovirus-infected cultures, a viral etiology was suggested since the recognition of the disease.[4] However, attempts to amplify viruses from the muscles failed. The only convincing viral connection has been with HIV and human T-lymphotropic virus type 1, initially reported in a few patients,[5,6] but now widely seen in patients harboring retroviruses. We have hypothesized that the chronic retroviral infection triggers viral-specific $CD8^+$ cells invading muscle fibers, and have proposed that other persistent viral infections may play a similar role.[1,4,5]

In this issue of *Neurology*®, Uruha et al.[7] report an association of IBM with chronic hepatitis C virus (HCV) infection. Among 114 patients with pathologically confirmed disease, 28% harbored anti-HCV antibodies, compared to 4.5% of patients with polymyositis and 3.4% of the Japanese population in their 60s. No differences in other concurrent viral infections were observed, confirming specificity for HCV. HCV-RNA was amplified in muscles from 19/32 (59%) patients with HCV-IBM, but also in 20/21 (95%) HCV-seropositive patients without IBM; HCV peptides were present in rare perimysial macrophages, but not within muscle fibers. Half of patients with HCV/IBM had been treated prior to manifesting IBM, but some developed myopathy concurrently with anti-HCV therapy. The authors conclude that HCV may trigger and enhance IBM or contribute to its increasing incidence in Japan.

This is an unexpected finding in a large number of well-characterized patients with IBM with careful clinicopathologic correlations. The observations strengthen the view that persistent viruses may play a role in IBM, but generate several questions and renewed ideas.

HCV, in contrast to other viruses, does not cause latent infection because it does not integrate into the host genome; it can however persist undergoing low-grade replication, evading immune surveillance by means of producing variable viral proteins. Can HCV persist within muscle fibers, as suggested before,[8] and could it play a causative role in IBM? The data are insufficient to provide answers. The amplified HCV-RNA[7] is probably derived from blood within the muscle homogenates, which explains its presence also in muscles from HCV-infected patients without IBM; the HCV protein within rare perimysial macrophages[7] is etiologically irrelevant. To demonstrate muscle fiber infection would require in situ PCR, in situ hybridization, PCR in laser-microdissected fibers, tissue cultures, and animal experiments. HCV mutants, if persisting within IBM muscles, may cause smoldering inflammation, necrosis, and fibrosis, similar to HCV-induced liver cirrhosis; the vacuoles in such a scenario may be safe sanctuaries cultivating a slow-rate inflammation, or irrelevant graveyards. Work on HIV/IBM has taught us that retroviruses do not replicate within muscles, but some retroviral-infected patients as well as animals develop an acute or chronic inflammatory myopathy, like IBM[4]; HIV, like HCV, is present in endomysial macrophages but it is the retroviral-specific $CD8^+$ T cells invading muscle fibers, possibly recognizing muscle antigens, that enhance or trigger autoimmunity.[4–6]

HCV is transmitted by transfusions or transcutaneusly.[9] Since the 1990s, as transfusion-related incidents dropped, HCV infections fell in the United States to 1.6%; in the baby boomer cohort, however, born between 1945 and 1965, the infection rate

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remains high at 3.2%.[9] Most HCV-positive patients are asymptomatic or unaware of prior infection and many have normal liver enzymes. Cirrhosis, occurring in 25%, is connected to older age and persistent, >30 years, HCV infection.[9] Interestingly, the same age cohort and insidious disease course characterize IBM; further, the histopathology of HCV-related cirrhotic liver, highlighted by necrosis, inflammation, and fibrosis, has similarities with IBM muscles. Should we then screen patients with IBM for seemingly asymptomatic HCV infection, as the Centers for Disease Control and Prevention recommends for this birth cohort[9]? The Uruha et al. study suggests that we probably should, even if their HCV-treated patients had the same course as the nontreated cohort.

Viruses may hit and run and their absence does not exclude a prior attack on muscle that passed asymptomatically, but not necessarily innocently, because they could trigger autoimmunity due to cross-reactivity between viral and host autoantigens. Such autoimmunity is supported by HCV's association with autoimmune hepatitis, various autoantibodies, immune complex diseases, cryoglobulinemia, B-cell lymphoproliferative disorders, and unexplained monoclonal gammopathies.[9] It might be relevant that patients with IBM also have high incidence of monoclonal gammopathies[10] and autoantibodies; it would be informative therefore if patients with HCV-IBM are screened for both. HCV can theoretically trigger IBM when exacerbations of viral replication break tolerance, allowing sensitized T cells to recognize cross-reactive muscle antigens, as occurs when intrahepatic HLA-I-restricted cytolytic T cells trigger autoimmune hepatitis.

Since new HCV infections are falling in the western world (although increasing in young drug users), an etiologic connection with IBM would infer a declining IBM incidence in Japan and the United States, rather than a rising one as the Uruha et al. study implies, even if genotypes differ among countries. In contrast, IBM should be rising in countries with high HCV prevalence, i.e., Egypt, where 20%–50% of people born before 1960 are HCV-positive,[9] but this does not seem to occur.

So what is the message of the Uruha et al. study? Persistent, slow-replicating viruses, such as HCV or retroviruses, may be candidate agents potentially triggering autoimmunity in IBM. Viruses are unpredictable; they hit and run, hide and persist, or seem irrelevant because they can escape immune surveillance until a reactivation results in persistent inflammation and degeneration, as in HCV cirrhosis. Given the mystery of IBM, it seems reasonable to start screening older patients with IBM for HCV and explore possible pathogenetic relevance, especially since HCV is now successfully treated and viral persistence eliminated.

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