

Chapter 2

Viral Hepatitis Related Vasculitis

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Abstract

The relation between viral hepatitis and certain types of vasculitis is well known. This relation seems to be strong in polyarteritis nodosa-like medium sized vessel vasculitis with hepatitis B virus and to a lesser extent hepatitis C virus (HCV). Small sized vessel vasculitis with mixed cryoglobulinemia seems to form another strong association with HCV. Research is ongoing to clarify all aspects of viral hepatitis associated vasculitis.

Introduction

Since Australia antigenemia, latter known as hepatitis B virus (HBV) surface antigen, was found in patients with polyarteritis nodosa (PAN) in 1970 [1], the interest grows in the field of vasculitis related to hepatitis virus infections. For around twenty years the association between PAN and HBV infection became clearer and stronger. In 1990, Hepatitis C virus (HCV) was found in patients with cryoglobulinemia type II [2], and another area of this growing knowledge had been lightened.

Hepatitis A Virus

Hepatitis A virus (HAV) is an atypical Picornaviridae that causes acute hepatitis in humans [3], and was identified in 1973 [4]. It is usually a self-limited illness that does not become chronic. Unlike HBV and HCV, HAV has rarely been described to be associated with other ex-

tra-hepatic manifestations. They occur most commonly in patients who have protracted illness such as relapsing or cholestatic hepatitis [5] Cutaneous vasculitis and arthritis were reported with cryoglobulinemia. The cryoglobulin consists of polyclonal IgM and IgG, with high molecular weight rheumatoid factors of both isotypes [6].

The diagnosis is established by detection of serum immunoglobulin IgM anti-HAV antibodies. While Serum IgG antibodies appear early in the convalescent phase of the disease, remain detectable for decades, and are associated with lifelong protective immunity [7].

Hepatitis B Virus

Hepatitis B virus is a double stranded DNA virus and a member of Hepadnaviridae family of viruses [8]. Three types of syndromes were described in association with HBV; first, a prodroma consisting of skin eruption, polyarthralgia or arthritis and urticaria which may appear from the first to the sixth weeks in up to 20 percent of patients, and disappears by the appearance of jaundice, The pathogenesis of this syndrome is thought to be due to circulating immune complexes composed of hepatitis B surface antigen (HBsAg) with subsequent consumption of complement [9]. Second, the typical PAN, and third, an immune complex type of glomerulonephritis. Its incidence ranges from 0.1 to 25 percent [10].

The HBV-PAN represents the most typical form of classic PAN, which is a medium-sized vessel systemic necrotizing vasculitis not associated with Anti-neutrophil cytoplasmic antibody (ANCA) [11].

Before the vaccination against HBV was manufactured on 1986 [12] HBV infection was reported in more than one third of PAN patients. The Presence of hepatitis B surface antigen or antibody in serum was one of the 10 disease features of PAN selected by the American College of Rheumatology (ACR), 1990, to establish criteria for research purposes in order to differentiate PAN from other forms of vasculitis [13]. On 2000, Guillevin et al, claimed that only 5% of patients with PAN had HBV infection [14]. Using the 2012 Chapel Hill Consensus Conference (CHCC) nomenclature, Hepatitis B virus-associated vasculitis comes under the heading ‘vasculitis associated with probable etiology’, as their specific etiology is known [11].

Clinically, HBV-PAN usually presents with constitutional manifestations, myalgia, arthralgia, mononeuritis multiplex, malignant hypertension, renal infarction, orchitis and skin manifestations in the form of palpable purpura nodules and erythematous rashes (figure 1). Inflammatory markers are elevated, and the diagnosis relies on the histological changes found in the affected organs, or angiographic findings, including small saccular or fusiform aneurysms and stenoses [15].



Figure 1: Erythematous rashes in HBV-cutaneous polyarteritis nodosa.

The presence of viral antigens in the vessels of PAN patients was rarely reported and the pathogenesis of HBV-related necrotizing vasculitis was thought to be caused by the deposition of immune complexes [16]. This is different from the pathogenesis of the classic PAN that probably involves both the innate and adaptive immune systems [17,18]. The deposition of immune complexes was the idea behind treating PAN associated with HBV by corticosteroids and plasma exchange to clear up those immune complexes [16]. Cyclophosphamide is used if the disease is life- or organ-threatening. In addition to the

antiviral treatment, vidarabine, that works by interfering with the synthesis of viral DNA [19]. Lamivudine that is phosphorylated to active metabolites that compete for incorporation into viral DNA is effective for the treatment of chronic HBV infection [20] and for acute HBV infection [21,22].

Hepatitis C Virus

Hepatitis C virus is a positive-sense (i.e. its sequence can be directly translated by the host cell) single-stranded RNA virus of the family Flaviviridae [23]. A strong association was reported between chronic HCV infection and mixed cryoglobulinemia [24,25,26], which is a small-vessel vasculitis involving mainly skin, joints, peripheral nervous system, and kidneys. Mixed cryoglobulinemia consists of polyclonal immunoglobulin IgG with or without monoclonal IgM with rheumatoid factor activity [27].

Approximately 40% of patients with HCV infection develop detectable serum cryoglobulins or cryoprecipitate (CP), and most of those patients do not have clinical or physical signs of cryoglobulinemia syndrome, which progress to cause cryoglobulinemic vasculitis. A meta-analysis of 19 studies published between 1994 and 2001 showed a highly significant association between cirrhosis and cryoglobulinemia [28]. With regard to liver cirrhosis, it was reported to be less advanced in HCV patients with vasculitis [29]. This indicates that CP in case of liver cirrhosis may be the product of its output, and may not be associ-

ated with vasculitis. While in the case of cryoglobulinemic vasculitis, which occurs often after a short period of HCV infection and with less incidence of liver cirrhosis, CP is involved in causing a large portion of cases of vasculitis.

The clinical picture of HCV-associated vasculitis vary from mild forms of arthralgia, purpura and weakness (Meltzers triad) [30] to serious visceral involvement. The manifestations of vasculitis may take one of two forms; either the manifestations of the small sized vessel vasculitis, or those of the medium sized vessel vasculitis, and this may be affected by the host genetic factors. The HCV related small sized vessel vasculitis was reported to be more associated with HLADRB1*701 of the 1st allele-suballele, and the medium sized vessel vasculitis is more associated with HLADRB1*3 of the 1st allele and HLADRB1*1301 of the 2nd allele-suballele [31].

Small size vessel involvement manifestations include purpura, small cutaneous ulceration, distal sensory polyneuropathy, presenting with painful, asymmetric paresthesia and acute or chronic membrano-proliferative glomerulo-nephritis with sub-endothelial deposits, presenting with proteinuria with microscopic hematuria [32]. While medium sized vessel involvement manifestations include larger cutaneous ulceration, levido reticularis (figure 2), digital gangrene (figure 3), cutaneous nodules and mono-neuritis multiplex. Rarely may it cause progressive renal failure due to renal vessels involvement. Sicca mani-

festations with abnormal findings on magnetic resonance sialography are common in patients with chronic HCV infection and are associated more with cryoglobulinemia [33].



Figure 2: Levido reticularis in HCV-medium sized vessel vasculitis.



Figure 3: Forefoot gangrene in HCV-medium sized vessel vasculitis.

Vasculitis may occur in the absence of detectable cryoglobulin. The immune complexes are deposited in the tissues rather than circulating in the blood [34].

Low dose of steroids and azathioprine are of help in patients with mild manifestations, while patients having more severe forms with mononeuritis multiplex with motor deficits, extensive skin disease or digital gangrene, pul-

monary involvement, digestive tract involvement or rapidly progressive renal disease should be treated by steroids, cyclophosphamides, and plasma exchange [35,36]. Rituximab is more effective and gives earlier treatment response [37]. Eradication of the HCV by Direct- Acting Antivirals results in a better clinical response of the vasculitis at the end of treatment with a low rate of serious advents compared to the combination therapy of pegylated-INF alpha and ribavirin [38,39,40].

Conclusions

The evidence for relation between viral hepatitis and certain types of vasculitis is increasing. The relation seems to be strong in PAN-like medium sized vessel vasculitis with HBV and to a lesser extent HCV. Mixed cryoglobulinemia specially with small sized vessel vasculitis seems to form another strong association with HCV. Research is ongoing to clarify all aspects of viral hepatitis associated vasculitis.

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