Cryoglobulinemia—MPGN, Neuropathy, Vasculitis, Arthritis

Chronic hepatitis C virus (HCV) infection is associated with numerous and mostly autoimmune extrahepatic complications. One of the most serious is cryoglobulinaemic vasculitis (CV), which develops in 5–10% of infected patients. CV is a systemic vasculitis of small and medium-sized arteries and veins, due to the deposition of complexes of antigen, cryoglobulin and complement in the vessel walls. The main clinical features of mixed CV include the triad of palpable purpura, arthralgias, and weakness, and other pathological conditions such as glomerulonephritis, peripheral neuropathy, skin ulcers, and widespread vasculitis. The most significant accompanying kidney lesion is type I membranoproliferative glomerulonephritis (MPGN), usually occurring in the context of type II mixed cryoglobulinemia. It can sometimes have a life-threatening presentation. Baseline factors associated with a poor prognosis include the presence of severe liver fibrosis, central nervous system involvement, kidney or heart involvement. Circulating immune complexes responsible for organ damage are the result of B-cell expansion and the production of pathogenic IgMs with rheumatoid-factor activity, which is driven by the underlying chronic viral infection. The treatment of HCV-related mixed cryoglobulinemia is difficult due to the multifactorial origin and clinical polymorphism of the syndrome. It can be directed to eradicate the HCV infection, suppress the B-cell clonal expansion and cryoglobulin production, or ameliorate symptoms.

Obtaining a sustained virological response (SVR) has become the main treatment for HCV-induced CV. When this treatment is not contraindicated and sufficiently well tolerated, SVR rates are similar to that for HCV-infected patients without CV. However, in some situations, such as “severe or life-threatening manifestations- i.e., acute nephrotic or nephritic syndrome, extensive cutaneous ulcers, nervous system or gastrointestinal manifestations, and hyperviscosity syndrome”, because of the delayed and uncertain response to antiviral therapy, immunotherapy alone or in addition to antiviral treatment, either concomitantly or sequentially is necessary to treat HCV-induced CV. Some data support the short-term safety of a sequential strategy (i.e., starting with an immunosuppressive regimen alone), even in patients with advanced liver disease. In addition, in patients with CV and no virological response or contraindications to IFN and/or ribavirin, such as advanced age, uncompensated cirrhosis, uncontrolled depressive illness, or untreated thyroid disease, anti-inflammatory drugs may be warranted to avoid or control severe or debilitating complications. A major concern is the potential adverse effects that immunosuppressive therapy could have on the underlying uncontrolled chronic viral infection. A few patients may experience biological and/or clinical persistence or relapse of CV despite clearance of their HCV infection. This is probably because B-cell expansion has become, at least in part, independent of HCV stimulation. In this setting, underlying B-cell malignancy must be ruled out first. Once ruled out, the autoimmune component of the disease may be considered as autonomized and treated similarly to non-virally related CV.

During the last decade, conventional immunosuppressive treatments (i.e., cyclophosphamide and plasmapheresis) have been progressively challenged by biologics. Rituximab (RTX), a
monoclonal antibody against the CD20 antigen, which is selectively expressed on B cells is, to
date, the only biologic that has sufficient evidence to support its use for this indication, in
particular when CV is refractory to antiviral regimens. The overall response rate to RTX in
patients refractory to antivirals has been reported in recent meta-analyses to be ≥80%. The
delay in response is variable, but improvement occurs within 1–6 months. However, RTX seems
to be associated with an increased risk of severe infections in a subset of patients. In patients
refractory to antiviral regimens and who are successfully treated with RTX, more than a third will
relapse during B cell recovery, usually between 6 and 12 months. However, retreatment with
RTX after a relapse seems to be effective in most cases. Systematic maintenance of RTX
therapy has rarely been reported in CV but may be considered in severe forms, though the best
modality remains to be determined. Recent small studies with Peg-IFNα/α/Ribavirin/protease
inhibitor combination suggest that it seems highly effective in HCV-MC vasculitis, but such
therapeutic regimen should be administered cautiously considering the high rates of side
effects. As with other difficult-to-treat patients, IFN but possibly also RBV free regimes will be an
attractive alternative for these patients.

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Peg-IFNα/Ribavirin/Protease inhibitor combination is highly effective in HCV-mixed
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