

De novo mixed cryoglobulinemia in Egyptian patients with Hepatitis C after successful treatment with direct acting antiviral drugs

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Abstract

The side effects profile of the new direct antiviral agents for the treatment of hepatitis C virus is not fully elucidated. A few reports have described adverse renal effects of sofosbuvir based regimens. In this case series, we describe 50 cases of de novo renal cryoglobulinemic glomerulonephritis after successful treatment with DAA. Methodology: Patients with HCV who did not receive antiviral therapy with peg interferon before were referred to the Nephrology Department after successful treatment with DAA for an opinion for assessment of deranged renal functions or proteinuria; the clinical manifestations ranged from lower limb edema to development of purpuric skin lesions. Cryoglobulins were tested in the serum using the PCR detection. Results: All patients had a detectable de novo cryoglobulins in the serum. The most common glomerulonephritis in renal biopsies was membranoproliferative 52% and CKD developed in 46% of cases. Conclusion: The use of the DAA for the treatment of HCV infected patients may result in unfavorable renal outcome. The observed adverse effects included de novo cryoglobulinemic glomerulonephritis and the development of CKD.

Introduction:

The kidney is an important component of the HCV clinical syndrome, besides the liver, the musculoskeletal, immune and hematopoietic systems and the skin. This notorious viral infection imposes itself as a cause of kidney disease, a major risk in dialysis wards, and a significant threat in renal transplantation. Fortunately, we are close to bringing it down to its knees, thanks to the discovery of directly acting drugs, which will soon send this review, and many on the same topic, to the archives of medical history. HCV is a world-wide diffused linear, single-stranded RNA virus which displays both hepatotropism and lymphotropism and may cause hepatic and extrahepatic manifestations. HCV-EHMs include many diseases with B-lymphoproliferative and/or autoimmune the most documented and frequent. The recent availability of mortality rates in large cohorts of subjects confirmed the association of HCV infection with many extrahepatic pathological conditions including cardiovascular, neurologic, metabolic or renal diseases and extra-hepatic tumors. The comparison between patients with persisting HCV infection and those who cleared the virus, showed that viral eradication significantly reduced the rate of extra-hepatic deaths.

HCV-EHMs can be classified according to the number and strength of supporting scientific data, as well as the underlying etio-pathogenic process.

The correct approach to patients with HCV-EHMs requires a multidisciplinary management. Specialists of different medical areas challenging with specific HCV-EHMs should take into account the pathogenetic role of HCV in different underlying pathological processes. This arises the need to define the best criteria to use antivirals and/or other therapeutic approaches previously standardized for virus-unrelated disease variants with comparable pathogenetic process. International, multidisciplinary recommendations for the therapeutic management of HCV-EHMs in the era of Interferon free anti-HCV treatment are needed. Therefore, this paper will mainly focus on the effects of new and

old anti-HCV treatments as well as non-viral therapies on the different HCV-EHMs. Different manifestations, being caused by the same etiologic agent, often coexist in the same subject. Most of available information is derived from studies carried out in patients suffering from cryoglobulinemic vasculitis, CV, the prototype of systemic HCV-EHMs that will be considered for first. Then, the main organ-specific disorders (detectable or not in patients with CV) for which enough data are available will be better detailed, in order to give, for each condition, a picture based on different and complementary focuses and the most appropriate therapeutic approach. The introduction of the first, IFN-based, antiviral therapy, led to positive effects on several HCV EHMs, improving survival rates. However, this treatment, even in its most effective combination (Pegylated-IFN plus ribavirin), had limited efficacy. AVT options have been recently expanded with the introduction of direct-acting antiviral agents, that directly target non-structural proteins with a key role in HCV replication.

Methods:

We analyzed a case series of five patients with genotype one chronic HCV complicated by MCN who had persistence of cryoglobulins despite completion of triple therapy with oral antiviral agents. A total of 12,985 Hepatitis C Patients (genotype IV) received the new DAA. After successful treatment, patients with deranged renal functions or proteinuria were referred to the nephrology department for assessment. The clinical manifestations ranged from lower limb edema to the development of purpura skin lesions. Cryoglobulins were tested in the serum using the PCR detection.

Results:

Patients with cirrhosis appear to have a decreased ability to clear immune complexes. We observed that early viral response by week 8 of therapy and longer periods of undetectable virus on treatment correlated with eventual clearance of serum cryoglobulins in patients without cirrhosis. Two patients were treated with anti-

B-cell agent rituximab prior to starting therapy for HCV; this did not lead to a more effective clearance of cryoglobulins. Fifty patients had detectable de novo cryoglobulins in the serum. The most common type in renal biopsies was membranoproliferative glomerulonephritis 52% and chronic kidney disease developed in 46% of cases.

Conclusion:

HCV is far from being an innocent by-stander in patients with kidney disease. As explained in this review, it constitutes a major risk to patients' lives at all stages of their illness. Since the damage is irreversible without treatment, every patient must be seen as a candidate for treatment. For logistic reasons, though, the lack of resources may impose treatment prioritization to those with highest expectation from treatment. Fortunately, with the recent discovery of safe and highly effective directly acting antiviral drugs, there are multiple therapeutic options that can suit different patients, taking many confounding factors into consideration. These include the CKD stage, extent of liver

disease, viral strain, co-infections, previous treatment experience, current comorbidity and concomitant medical treatment. With adequate choice of a suitable protocol, cure rates over 90% are expected in most patients, with highly positive impact on survival and quality of life. We suggest that a longer treatment course than the standard 24 weeks with triple therapy could aid in the clearance of these immune complexes and cryoglobulins in cirrhotics. More studies to determine the ideal duration of treatment for chronic HCV and coincident MCN are needed, especially in light of the new all oral direct-acting antiviral regimens that are now recommended for HCV treatment. De novo cryoglobulinemic glomerulonephritis and progression to CKD may rarely complicate successful treatment of HCV using direct-acting antivirals.