Editorial

Mixed cryoglobulinaemia and hepatitis C virus: a paradigm of a virus-related autoimmune and lymphoproliferative disorder

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Thirty years ago, in the November-December 1991 issue, *Clinical and Experimental Rheumatology* published the results of a research showing the presence of hepatitis C virus (HCV) infection in the majority of Italian patients with mixed cryoglobulinaemia (MC) (1). It represented the first demonstration of the association between HCV viraemia and MC (2) based on the serum HCV RNA detection by reverse transcriptase polymerase chain reaction in 86% (36/42) of Italian MC patients' series (1); in the same period, a variably increased prevalence of circulating anti-HCV antibodies was observed by means of first- and second-generation enzyme linked immunosorbent assay (3-7). In the following years, this striking association was largely confirmed by an increasing number of clinico-epidemiological, pathological, and laboratory investigations, together with the variable prevalence of HCV-MC among patients' populations from different countries (8-10).

Just two years before, a global effort through epidemiological and virological researches had allowed the discovery of HCV that can be considered a milestone in 20th-century medicine, with the major contributions of Harvey J. Alter, Michael Houghton, and Charles M. Rice recipients of the 2020 Nobel Prize in Physiology or Medicine (11).

The discovery of HCV (11, 12) represents a decisive turning point in identifying the aetiology of some puzzling disorders of unknown origin (8-15) (Fig. 1).

Firstly, the large number of post-transfusion hepatitis, not caused by hepatitis B or hepatitis A, were long termed "non-A, non-B hepatitis"; with its identification, the HCV was found to be the main cause of "non-A, non-B hepatitis", as well as of liver cirrhosis and hepatocellular carcinoma (HCC). It led to the drastic reduction of post-transfusion hepatitis and allowed to cure and more recently to eliminate its causative agent (11).

Secondly, the MC syndrome, synonymous with cryoglobulinaemic vasculitis, represents a double-sided disorder characterised by either diffuse vasculitic alterations (leukocytoclastic vasculitis) affecting the skin and visceral organs, and 'benign' lymphoproliferative alterations, potentially complicated by frank B-cell non-Hodgkin' lymphoma (10, 13-20). MC can be associated with several well-known infectious, immunological, or neoplastic diseases (10, 13-20); in these cases, its clinical course and outcome is mainly linked to underlying conditions; in the absence of any apparent causative factor, MC was classified as "essential" (21-24).

Besides the typical clinical triad -purpura, weakness, arthralgias- and variable spectrum of organ involvement, a chronic hepatitis may be also observed during the clinical course of MC, not rarely complicated by cirrhosis and hepatocellular carcinoma (19-24). Liver involvement is observed in over half MC patients and only occasionally found in the course of other systemic vasculitides; therefore, it has long been hypothesised a possible role for hepatotropic viruses in the etiopathogenesis of the MC (25, 26). A role for HBV in MC was investigated during the 1970s, when the association of this virus with polyarteritis nodosa had been demonstrated (27, 28). However, HBV antigenemia was rarely recorded, and anti-HBV antibodies var-

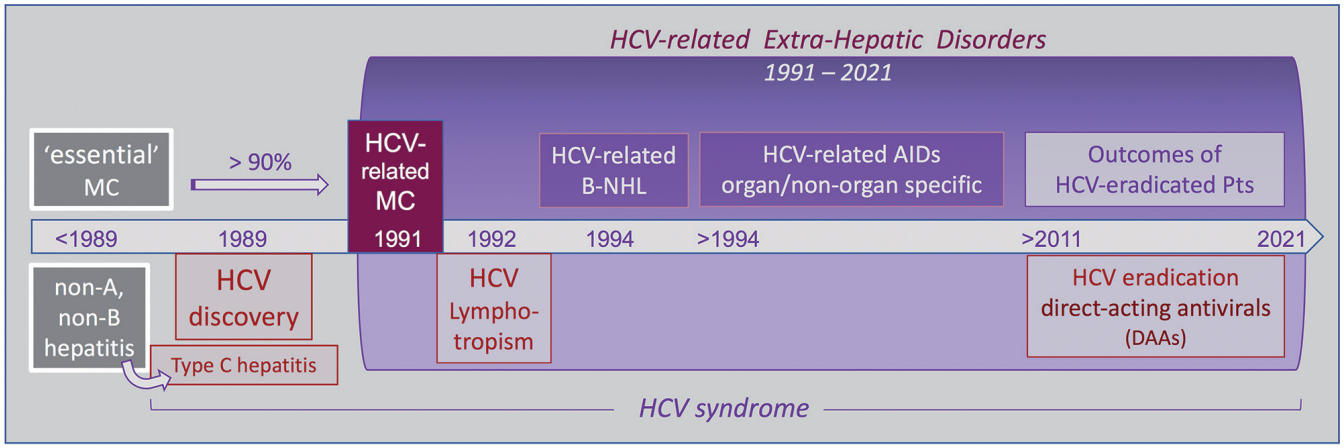

Fig. 1. Schematic representation of thirty-year history of HCV-related mixed cryoglobulinaemia and other HCV-related extra-hepatic disorders (HCV-EHDs). Following the HCV discovery (1989), the striking association between HCV and mixed cryoglobulinaemia (MC), synonymous with cryoglobulinaemic vasculitis, was demonstrated in 1991. Both dates represent a fundamental turning point in the history of two disorders previously classified of unknown aetiology: the so-called non-A, non-B hepatitis and the 'essential' MC. The association HCV-MC opened a fruitful succession of clinical-epidemiological, virological, and pathological studies that over the last three decades led to the definition of HCV-related extra-hepatic disorders (HCV-EHDs), a complex of autoimmune organ- and non-organ-specific, and lymphoproliferative disorders, mainly B-cell non-Hodgkin lymphoma (B-NHL). HCV syndrome consists of the aggregation of HCV-related hepatic manifestations (hepatitis C, cirrhosis, hepatocellular carcinoma) and extra-hepatic disorders. More recently we are experiencing another revolution following the introduction of direct-acting antivirals (DAAs), able to eradicate the HCV. However, many issues still remain open, especially as regards the persistence or relapses/flares of different HCV-EHDs, mainly the cryoglobulinaemic vasculitis and B-NHL despite HCV eradication.

ied greatly among different MC patient populations (19, 25). Actually, HBV may represent the causative factor in less than 5% of MC patients. Therefore, the association between HCV and MC (1, 8-10) definitely clarified the aetiology of the large majority of patients with formerly 'essential' MC.

A third puzzling disorder, firstly described in the early 1970s, regards the presence at post-mortem examination of liver cirrhosis in individuals deceased for malignant lymphoma (29). The absence of well-known causes, including iatrogenic damage secondary to antineoplastic treatments, posed a major question about such unexpected pathological association. Again, the discovery of the association between HCV and MC provided a possible explanation. As aforementioned, the MC may be complicated by frank B-cell NHL in at least 10% of cases (13-20); thus, the association between HCV and MC, and in turn between MC and B-cell NHL, suggested a possible causative role of HCV also in 'idiopathic' B-cell NHL. In effect, this possible association was firstly demonstrated in a significant percentage of unselected patients in 1994 (30, 31), then confirmed by several in-depth investigations showing that HCV may be included among potential triggering agents of B-cell NHL worldwide (32-33). Of note, the prevalence of HCV infection in B-cell NHL showed the same heterogenous geographical distribution already observed for the HCV-MC association (14, 17, 20, 32, 33).

Overall, the aetiopathogenetic link between HCV and MC revealed the other side of chronic HCV infection. It expanded the boundaries of the so-called HCV syndrome (13-17), namely the complex of both hepatic (hepatitis C, cirrhosis, HCC) and HCV-related extra-hepatic disorders (HCV-EHDs) (Fig. 1). The latter include a broad spectrum of organ-and non-organ specific autoimmune diseases and malignancies, mainly some lymphoproliferative B-cell disorders (15-20). These conditions may mirror both pathological and clinical alterations of MC, a condition that can be regarded as a crossroad between autoimmune and lymphoproliferative disorders (13-20).

Most pathogenetic alterations affecting the immune system, responsible for the manifestations of HCV syndrome, can be ascribed to the key biological characteristic of this virus, namely lymphotropism. This distinctive feature has been widely demonstrated since 1992 with some pioneering studies focusing on patients' series with either hepatitis C or HCV-MC (37, 38). The finding of peripheral mononuclear blood cell infection by HCV was a decisive step in understanding both autoimmune and lymphoproliferative/neoplastic manifestations of HCV syndrome, which is the result of multistep and multifactorial etiopathogenetic process, including host genetic and environmental co-factors (13-20, 39). Besides liver manifestations, HCV-EHDs may encompass porphyria cutanea tarda, thyroiditis, type 2 diabetes mellitus, male gonadal dysfunction, glomerulonephritis, peripheral neuropathies, sicca syndrome, polyarthritis, and interstitial lung involvement (13-20, 40-44).

Each of the putative HCV-EHDs, *per se*, can be regarded as a clinical syndrome, characterised by a spectrum of clinical phenotypes; the latter may be the result of multifactorial and multistep process secondary to a variable combination of genetic, environmental, and infectious factors. In this scenario, HCV can be considered as one of possible causative agents responsible for a percentage of distinct autoimmune/neoplastic disease subsets (17).

Over the last thirty years, following the identification of HCV-MC association, a long succession of researches tried to better define the actual role of the virus in single disorders and the boundaries of HCV-EHDs, as well as to standard-

ise the therapeutic strategies (13-20, 45). The latter were developed on three different levels, namely symptomatic/pathogenetic (corticosteroids, low antigen-content diet, plasma-exchange, etc.), pathogenetic (rituximab, other immunomodifiers), and aetiological treatments (antivirals) (45-52). Since the years preceding the discovery of HCV, several discouraging therapeutic attempts with alpha-interferon as immunomodulating therapy (48) were carried out, also in combination with ribavirin (45, 49). On the contrary, the more recent introduction of direct-acting antivirals (DAAs), able to eradicate the virus, greatly changed the natural history of HCV infection and its overall prognosis, especially with regards to the hepatic manifestations, while the long-term outcomes of HCV-EHDs, mainly the MC, were less predictable (53-54). On the whole, they remained the residual challenge for the clinicians in this field. On the one hand, many patients with sustained virological response show a stable remission of either MC syndrome or other HCV-EHDs such as some B-cell neoplasias. On the other hand, we can observe the persistence of MC syndrome or its relapse/flare even after HCV eradication as well after transitory MC clinical remission (53-54). A possible explanation of such unpredictable outcomes might be the stage of underlying immune system alterations that, in individual patients, may have reached the point of no return, regardless the presence/absence of the remote causative agent (47, 52-56). In this respect, the identification of reliable markers predictive of clinical response after HCV eradication represents a prime concern to clarify. A recently published study dealing with this specific topic suggested that neuropathy, weakness, and sicca syndrome, together with standardised disease severity indexes might predict the long-term clinical response of HCV-MC patients before initiating antiviral treatment (57).

Despite the remarkable results achieved in the last thirty years, some aspects of the complex HCV-related hepatic and extra-hepatic disorders still remain to be addressed.

To complete the whole scenario, the aetiology of 'essential' MC, a condition quite superimposable to HCV-MC as regards its pathological, serological, and clinical features, still remains unknown (58). Thus, future investigations on the actual prevalence and causative factors of 'essential' MC represent the last frontier in the field.

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