

Cryoglobulinemia in elderly patients with HCV-related chronic hepatitis

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Abstract

Hepatitis C virus (HCV) infection affects about 3% of the world's population and often leads to chronic liver disease. In some industrialized countries, HCV prevalence increases with age, but the optimal management of older patients has not been accurately defined. HCV infection can also lead to lymphoproliferative disorders, the most common being mixed cryoglobulinemia (MC), and also for this condition that frequently affects elderly patients, the optimal therapeutic strategy is still debated. We report the case of a 77-year-old Caucasian woman with HCV-related chronic hepatitis and cutaneous manifestations consisting of urticaria and pruritus related to MC resistant to antihistamines. The patient underwent a treatment with interferon and ribavirin. Such a treatment led to early biochemical and virological response associated with the resolution of cryoglobulinemia and cutaneous symptoms. After the end of treatment, HCV replication

relapsed, but cryoglobulinemia and cutaneous symptoms did not recur. In the absence of definite treatment guidelines in this particular context, our experience suggests that the presence of symptoms related to HCV-infection that deeply affect patient quality of life warrants antiviral therapy even beyond the age limits that currently exclude patients from treatment.

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Key words: Cryoglobulinemia; Elderly patients; Hepatitis C virus chronic hepatitis; Antiviral treatment

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INTRODUCTION

Hepatitis C virus (HCV) infection affects about 3% of the world's population and often leads to chronic liver disease. HCV infection can also lead to lymphoproliferative disorders, the most common being mixed cryoglobulinemia (MC)^[1].

In some industrialized countries, such as Japan and Italy, the prevalence of HCV infection increases with age^[2]. Unfortunately, antiviral therapy with PEG-interferon alpha and ribavirin, which represents the current treatment of choice, often fails in older patients, especially in those affected by HCV-related MC. Moreover, in this context,

neither the optimal therapy strategy nor prognostic criteria have been accurately defined^[1].

We report the case of an elderly woman with HCV-related chronic hepatitis associated with MC, presenting with severe urticaria and itching resistant to antihistamines, who underwent PEG-interferon and ribavirin treatment.

CASE REPORT

In January 2007, a 77-year-old Caucasian woman with HCV-related chronic hepatitis, diagnosed in the early 1990s, was referred to our outpatient clinic because of urticaria and itching resistant to antihistamines. The most common causes of urticaria had been previously excluded, such as allergic and haematologic diseases, other gastrointestinal infections, parasitosis, autoimmune diseases (other than MC), and taupathies. In 1998, she had undergone treatment with interferon 3 times a week with no benefit. The patient was not able to report either type or dosage of interferon or treatment duration. When we first saw the patient, she was in good physical condition and was not affected by heart, lung, renal or neurological diseases. Physical examination revealed urticaria and scrabble signs. Laboratory tests are listed in Table 1.

Liver, renal and thyroid functions were normal, as well as serum immunoglobulins, anti-DNA, anti-mitochondrial, anti-nuclear antibodies and anti-neutrophil cytoplasmic antibody, lactate dehydrogenase and β -2-microglobulin. The serological markers of HBV and HIV infections were negative. Physical examination and laboratory tests excluded renal or neurologic involvement of MC; purpura was absent. Ultrasound examination showed moderate hepatosplenomegaly, without evidence of cirrhosis and portal hypertension. No focal liver lesions were detected. A reactive lymph node of about 1 cm was present at the hepatic hilus.

After written informed consent, the patient was treated with PEG-interferon α -2a (180 μ g/wk) plus ribavirin 800 mg/d. After 3 wk, PEG-interferon α -2a was shifted to human leucocyte interferon- α at the dosage of 6 MU thrice a week, because of progressive reduction of neutrophil granulocyte count and profound weakness. Thereafter, the treatment was well tolerated and did not require further dosage adjustment. Overall treatment lasted 6 mo.

The patient's cutaneous manifestations resolved in 10 d, and HCV-RNA and cryoglobulins were negative 1 mo from the beginning of treatment. After 3 mo from the end of treatment, ALT and AST again increased and HCV-RNA became detectable. However, the relapse of viral replication was not accompanied by the recurrence of cryoglobulinemia, and serum cryoglobulins were negative after a 2 year follow-up.

DISCUSSION

Chronic HCV infection is the most common cause of MC. 70% to 80% of patients with MC are infected by HCV^[2]. Conversely, cryoglobulinemia is detected in a third of patients with HCV infection, although most are asymptomatic^[2]. The close association between HCV and

MC is witnessed by the finding of HCV-RNA in both cryoprecipitate and supernatant^[3], but the mechanism (s) through which HCV may induce MC remains unclear.

Cryoglobulinemia is defined by the presence of circulating immunoglobulins, which precipitate with cold temperature and re-solubilise when reheated. The most common symptoms are weakness, arthralgias and purpura (Meltzer and Franklin triad). Raynaud phenomenon, peripheral neuropathy, sicca syndrome, renal involvement, lung disorders, fever and thrombocytopenia can also be observed^[1]. In addition to purpura, MC-associated dermatological disorders include the presence of leukocytoclastic vasculitis, leg ulcer, pruritus and urticaria^[4]. In a retrospective study on 62 MC patients, pruritus was reported in 8% of cases and urticaria in 6%^[5]. Moreover, pruritus was the most frequent (15%) cutaneous manifestation in 2000 consecutive HCV patients, 40% of whom presented with cryoglobulinemia, even though the extent of association between pruritus and MC was not reported^[6]. Indeed, even in the absence of MC, it should not be forgotten that several other dermatological manifestations may result from disorders potentially associated with HCV infection, such as porphyria cutanea tarda, lichen planus (LP), psoriasis, polyarteritis nodosa, systemic lupus erythematosus, sarcoidosis, xerosis, pruritus and non-specific excoriation^[4].

Although a wide spectrum of dermatological disorders have been described in association with HCV infection, their pathophysiological relationship with HCV is still a matter of debate^[4,5]. In any case, HCV particles have been localized within skin lesions in MC, LP, pruritus and psoriasis. Moreover, parallel improvement in HCV viremia and some dermatological symptoms under antiviral treatment suggests a close correlation.

In our case, the absence of other common causes of urticaria claims a relationship between HCV virus and this dermatological manifestation. Skin biopsy has an essential role in the diagnosis of urticaria vasculitis, and the lack of this information does not allow us to know for certain the exact mechanism of urticaria in our case, but the presence of MC suggests an immune mediated pathogenesis.

The treatments that can be offered to patients with MC include corticosteroids, cyclophosphamide, plasmapheresis, cryoapheresis, low-antigen continent diets and anti-CD20 antibodies. However, antiviral treatments are first line therapy in HCV-related MC^[1,3], even though the lack of standardized protocols, the high rate of relapses, and general or MC-specific contraindications to antiviral treatments (i.e. old age, severe liver disease, acute nephritis, and widespread vasculitis) render such treatments rather difficult^[1].

A main problem with our patient was associated with her age. Whether to treat patients older than 65 years with interferon and ribavirin is highly debated, especially in terms of cost/benefit ratio. In addition, the natural history of chronic hepatitis C in elderly patients is scarcely known, as the presence of comorbidities can affect illness progression and life expectancy.

Data favoring treatment are represented by the reduction in liver-related mortality and risk of developing hepatocellular carcinoma achieved by treatment in HCV-

Table 1 Laboratory tests of the patient

WBC (nr 4-10 × 1000/mmc)	7.18	Gamma glutamyl transpeptidase (nr 6-35 U/L)	25
Hb (nr 12-15 g/dL)	11.4	Anti-cyclic citrullinated peptide	Negative
PLT (nr 140-400 × 1000/mmc)	135	Rheumatoid factor	Positive
ESR (nr < 36 mm/h)	24	HCV RNA U/mL	754823
AST (nr 4-40 U/L)	53	HCV genotype	2a
ALT (nr 4-37 U/L)	58	C3 (nr 0.9-1.8 g/L)	1.24
Total bilirubin (nr 0.1-1.2 mg/dL)	1.2	C4 (nr 0.1-0.4 g/L)	0.06
Alkaline phosphatase (nr 80-280 U/L)	191	Cryoglobulin	Type 3 (IgG-IgM) 10% cryocrit

related chronic hepatitis^[7], while resistance to treatment, due to either advanced liver fibrosis or reduced interferon immunomodulatory activity, and frequent comorbidities, which limit indications and reduce tolerance, militate against treatment. In any case, it should be pointed out that the prevalence of HCV infection in elderly patients is increasing in industrialized countries^[2], and, therefore, physicians will more often face this condition.

Our 77-year-old patient did not have remarkable liver damage, and laboratory and ultrasound evidence of cirrhosis was lacking. Therefore, the risk to develop frank cirrhosis or hepatocellular carcinoma in the short run was theoretically low. However, she suffered from severe cutaneous symptoms due to HCV-related MC, which were not responsive to symptomatic therapy and deeply affected her quality of life. This was the reason that prompted us to undertake antiviral therapy. In the lack of precise guidelines for the treatment of elderly patients and, in particular, elderly patients with cutaneous manifestation of HCV-related MC, we decided to start with PEG-interferon and ribavirin as indicated for adult patients with a favourable genotype^[8,9].

Treatment led to a rapid resolution of the cutaneous symptoms. However, intolerance to treatment induced us to shift PEG-interferon α -2a to leukocyte interferon- α after 3 wk. The decision to continue with treatment was supported by fast improvement of the cutaneous symptoms, strong patient motivation, and the available and convincing data on the tolerability of this type of interferon^[10,11].

The main reason for the rapid resolution of the cutaneous symptoms we achieved in the present case is likely the concomitant virological response. Available data about treatment efficacy on MC-related cutaneous manifestations are conflicting^[4], even though the resolution of itching with antiviral treatment has already been reported^[3,4]. It is of interest to note that MC and cutaneous symptoms did not reappear for 2 years despite the relapse of viral replication. We do not have a definite explanation for this, but it may be somewhat related to the antiproliferative and immunomodulatory properties of interferon^[12] along with low immunoreactivity that characteristic elderly subjects.

In conclusion, we think that undertaking antiviral treatment with interferon and ribavirin in elderly patients in the attempt to resolve particular conditions, such as MC-induced pruritus and urticaria, can be taken into account.

Treatment should be offered after full disclosure of risks and benefits, and close patient monitoring is warranted to avoid complications. In this context, leukocyte interferon- α seems to be better tolerated than PEG-interferon.

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