CASE REPORT

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New onset of mixed cryoglobulinemia vasculitis after persistent hepatitis C virus eradication

A propósito de um caso clínico de vasculite crioglobulinémica mista após erradicação persistente do vírus da hepatite C

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ABSTRACT

Introduction: Since its identification, hepatitis C virus infection has been implicated in the pathogenesis of several B cell disorders, specifically mixed cryoglobulinemia. **Case Report:** The authors describe the case of a 41-year-old male, who developed a mixed cryoglobulinemia vasculitis with renal involvement, several years after successful eradication of HCV with interferon therapy. **Discussion:** Similar cases described in the literature are reviewed in this report. Possible explanations for the physiopathology of the disease and its implications in therapy are commented.

Key-Words: B cell; hepatitis C virus; membranoproliferative glomerulonephritis; mixed cryoglobulinemia.

RESUMO

Introdução: Desde que foi identificado, o vírus da hepatite C tem sido implicado na fisiopatologia de diversas doenças linfoproliferativas do tipo B, nomeadamente na crioglobllulinemia mista. **Caso clínico:** Descrevemos o caso de um homem de 41 anos, a quem foi identificado o desenvolvimento de uma crioglobulinemia mista com envolvimento renal, apesar de prévia erradicação do VHC. **Discussão:** Revemos casos similares descritos na literatura, assim como a fisiopatologia e tratamento desta entidade clínica.

Palavras-chave: célula B; crioglobulinémia mista; glomerulonefrite membranoproliferativa; vírus da hepatite C.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem, being one of the leading causes of end-stage liver disease and a major liver transplant indication. Additionally, it is also associated with a variety of extrahepatic manifestations, some of them life-threatening[1]. Hepatitis C virus is the most common cause (50-90%) of mixed cryoglobulinemia (MC), a systemic vasculitis that may involve skin, musculoskeletal system, kidneys and nervous system[2]. The most frequent type of cryoglobulinemia in patients with HCV is type II MC, which is characterized by polyclonal IgG immunoglobulin linked with a monoclonal antigloblulin, usually IgM class, that acts as an anti-IgG rheumatoid factor. Renal manifestations range from isolated mild proteinuria with microscopic haematuria to an acute full blown nephritic syndrome with renal insufficiency. Type 1 membranoproliferative glomerulonephritis is the most common histological pattern of kidney biopsy in these patients[3]. The B cell lymphoproliferative diseases are another frequent association with HCV infection.

Prior to the association of HCV, treatment of MC syndrome generally consisted of glucocorticoids, cytotoxic agents and plasmapheresis, typically described as transiently effective and with significant adverse effects[3-4]. Later, targeted therapy with antiviral treatment, such as interferon alpha (INF-a) or with PEGylated interferon alpha (PEG-INF-a) plus ribavirin provided a new approach to HCV related MC, proved to be much more successful at achieving remission[5-6]. Recently, with better understanding of HCV lymphotropism and related expansion of rheumatoid factor positive B cell population, therapy with rituximab (RTX), an anti-CD20 monoclonal antibody that depletes B cell population, has been successfully used in the treatment of severe, resistant or relapsing MC[7-8].

There has been a strong correlation between antiviral and vasculitic response, shown in virtually all studies. Sustained virologic responses have been connected with effective and enduring remissions. Quite the opposite, recurrence of symptoms attributable to MC is often paralleled by recurrence of detectable viral replication in those previously treated for HCV[5-8]. However, there are some cases of persistence of MC syndrome despite demonstration of effective HCV eradication. These cases suggest that HCV infection plays a role in the early activation and proliferation of autoreactive B cell population, but other biological mechanisms may be involved in the maintenance of MC disease in these patients[9].

We present a case of new onset MC vasculitis with renal involvement after persistent HCV eradication and discuss the possible underlying mechanisms with a brief literature review.

CASE REPORT

A 38-year-old Caucasian male, heroin addicted, was first diagnosed with HCV infection (genotype 1a) after evaluation due to elevated aminotransferase levels. At this time, he had no extrahepatic manifestations and his hepatic biopsy was suggestive of chronic hepatitis infection. Hepatitis C virus replication activity was detected by HCV RNA quantification (real-time PCR assay, Roche) with viral load of 2,920,000 IU/mL. He received a successful 12-month course of PEG-INF-α and sustained viral response was obtained (no detectable virus for a sensitivity of < 15 IU/mL). Additionally, he abandoned drug consumption and was enrolled in a detoxification programme with methadone.

Three years later, the patient was referred to a nephrology consult due to a hypertensive crisis. He had returned to drug addiction three months earlier, and complained of macroscopic haematuria, lower limb oedema and fatigue. At clinical examination we observed a purpuric rash in his legs and feet dorsum. Laboratory results showed renal insufficiency (SCr 2,6 mg/dL) with nephrotic proteinuria (15 g/day) and red cell casts. He also presented with anaemia (Hb 8.4 g/dL), hypocomplementemia [C_3 33 mg/dL (normal range 90-180); C_4 8 mg/dL (normal range 10-40)], normal aminotransferase levels and undetectable HCV RNA or cryoglobulins.

Kidney biopsy was performed and histology was compatible with type I MPGN (Fig. 1): diffuse endocapillary proliferation which results in a lobular appearance and diffuse capillary wall thickening with subendothelial deposits at light microscopy. Mesangiocapillary deposition of IgM, IgG and C3 were present at immunofluorescence. Only at the third attempt, type II IgM/k cryoglobulins were detected, confirming

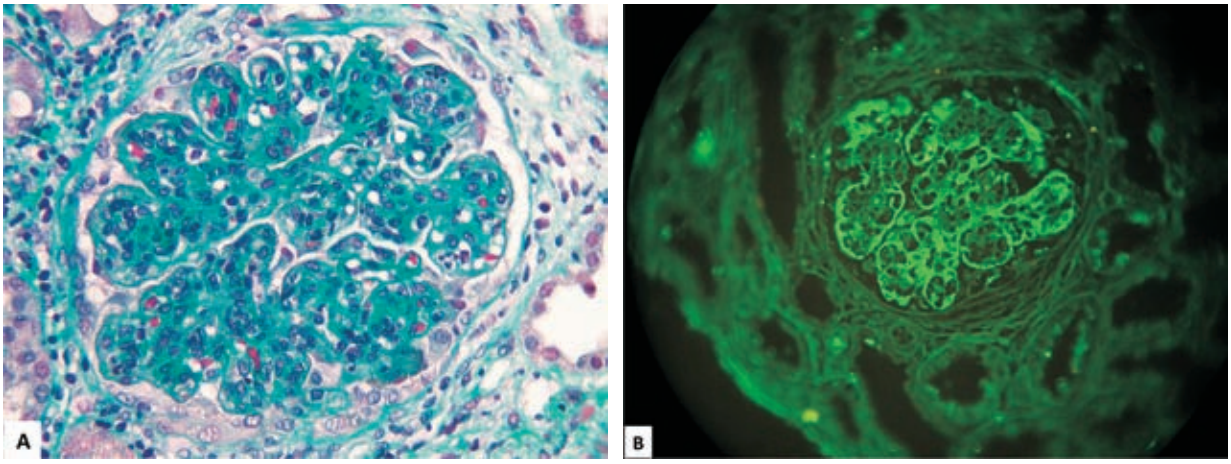

Figure 1

A: Trichrome stain showing endocapillary proliferation with lobulation and diffuse capillary wall thickening (double contours)(x400). B: C3 mesangiocapillary deposition in IFA (x400).

MC disease with renal involvement despite sustained HCV eradication.

The patient returned to drug detoxification programme and was treated with methylprednisolone pulse therapy (1 g/day for 3 consecutive days), followed by prednisone 1mg/Kg/day. After one week of treatment, a response was obtained with disappearance of cutaneous rash, severe reduction of urinary protein excretion (2 g/day) and partial recovery of renal function (SCr 1,8 mg/dL). One month later the patient had markedly improved his renal function (SCr 1.0 mg/dL). At three months, while tapering glucocorticoids, the patient maintained normal renal function, without any MC vasculitis manifestations or cryoglobulins. HCV RNA replication was still undetectable.

During that time, alternative conditions that could predispose to cryoglobulinemia after HCV eradication were excluded, namely, autoimmune diseases, other infectious diseases or a malignant lymphoproliferative disease.

Mucosa associated lymphoid tissue (MALT) lymphoma was excluded by normal upper and lower gastrointestinal endoscopies and accessory salivary gland biopsy. Unfortunately, four months after initial diagnosis, the patient resumed his drug addiction and was lost for follow-up by abandonment. Further investigation of underlying malignant lymphoproliferative disorder was, therefore, impossible.

DISCUSSION

We describe a very unusual case of *de novo* mixed cryoglobulinemia syndrome with renal involvement after long-term successful HCV eradication, without any evidence of underlying lymphoproliferative malignant disease.

Despite the knowledge about the risk of vasculitic symptoms exacerbation with INF treatment[10], the first report of onset cryoglobulinemic vasculitis after initiation of INF therapy was done by Beuthien *et al.*[11]. In this case, the MC was diagnosed ten months after the beginning of PEG-INF treatment for HCV; at that time, HCV RNA was undetectable, however, the patient was still undergoing INF therapy, which could be implicated in a vasculitic response, which did not occur in our case.

Levine *et al.*[12] described four patients developing symptomatic cryoglobulinemia regardless of sustained HCV eradication after antiviral therapy. Those patients experienced a relapse of MC during the first year after therapy withdrawal, with rising cryoglobulin levels despite HCV RNA negativity. In all but one,

exhaustive search for lymphoproliferative malignant disorders and also HCV RNA PCR analysis on cyoprecipitates was performed, but the results were negative. This report was complemented by an interesting study from Landau *et al.*[13] about eight patients who experienced relapse of HCV associated MC, despite sustained viral response to antiviral treatment. In all patients, HCV RNA replication was undetectable both in sera and cryoprecipitates. In this study, relapse occurred early after the end of treatment and was usually mild and brief, with only one case of nephropathy. In two of the three patients who had persistent symptoms of vasculitis and high levels of cryoglobulins, B cell lymphoma was diagnosed and only after chemotherapy vasculitis remission was achieved. Both studies highlighted the possibility of cryoglobulinemia syndrome relapsing after successful HCV eradication and contributed to the belief that, as in other autoimmune diseases[14], in HCV associated MC, the pathogenic events involving the immune system downstream by the triggering infection, may become independent from the initial stimulus.

Another proposed explanation to these phenomena could be the possibility that despite sustained viral response there may exist viral replication, supported by the demonstration of persistent small quantities of HCV RNA in peripheral blood mononuclear cells (PBMCs), as well as in the liver of patients with a sustained viral response[15,16]. In fact, Landau *et al.* used the most sensitive method available to

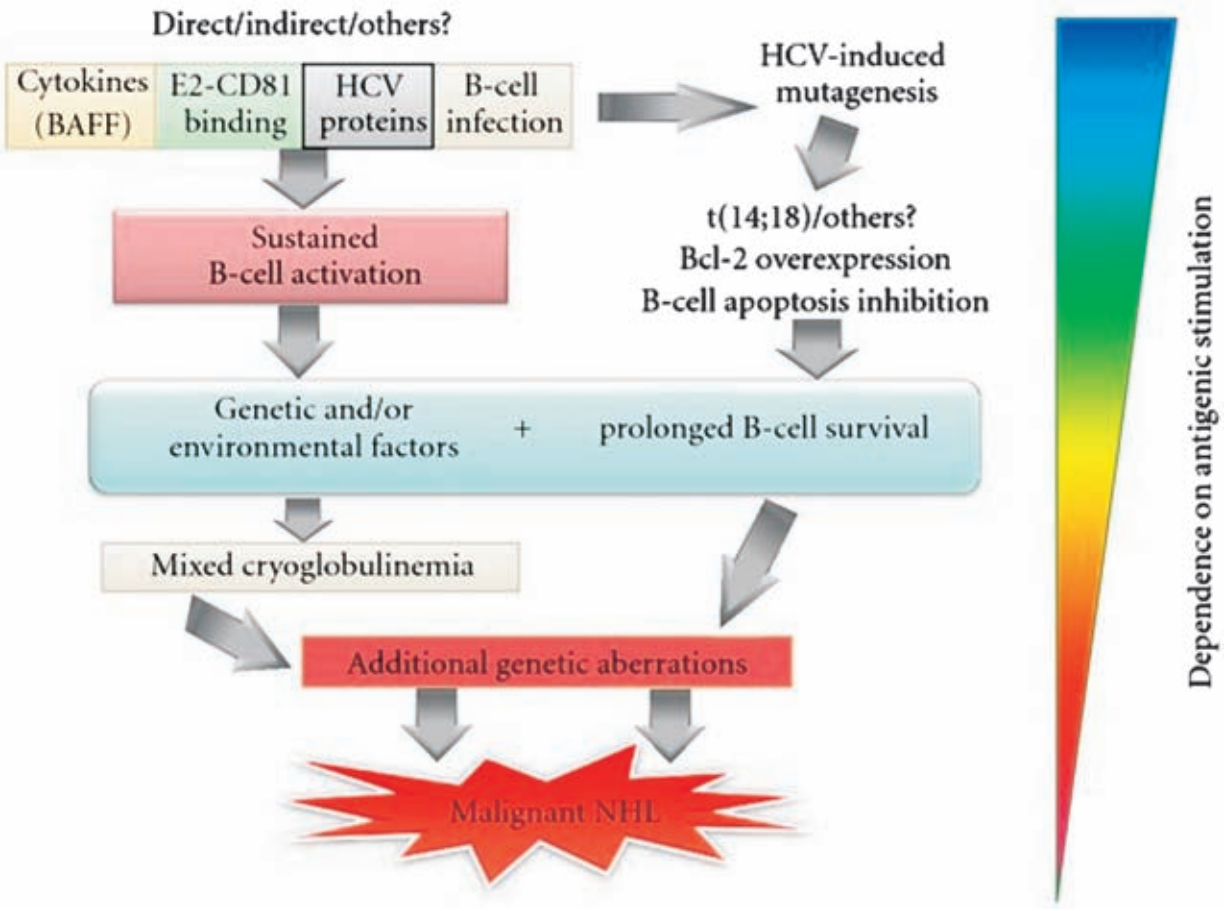

Figure 2

Multistep process of HCV related B cell disorders (reprinted with permission from (22) – Zignego AL, Giannini C, Gragnani L. HCV and lymphoproliferation. Clin Dev Immunol. 2012; 2012:980942).

date for the detection of HCV RNA in their report, and still it was negative, which significantly reduced the likelihood that active viral replication had been the cause of MC vasculitis relapse.

Finally, Quartuccio *et al.*[17] reported a case quite similar to ours, of new onset of MC four years after persistent HCV eradication. Yet, the unique feature of our case was the severe renal involvement manifested by an acute nephritic/nephrotic syndrome with membranoproliferative histology.

All these cases suggest a relationship between HCV and B cells. In fact, soon after its discovery, it was shown that HCV was a lymphotropic virus[18] and consequently with a connection between HCV infection and lymphoproliferative disorders, mainly MC and B cell non-Hodgkin's lymphomas (NHL). This was supported by strong evidence on epidemiological studies that have shown higher risk of NHL development in HCV patients[19,20] and demonstrated that effective antiviral therapy can induce haematological remissions in patients with HCV-related NHL[21].

The exact mechanism linking HCV and the B cell is not perfectly understood. Several hypotheses, usually interconnected with each other, have been proposed (Fig. 2)[22]. Main key factors seem to be the sustained HCV antigenic stimulation of the B cell compartment, chromosomal aberrations and immune mediators, such as cytokines and chemokines[23-28]. The explanation for the seemingly autonomy of the B cell disease development from antigenic HCV stimulus, may be related with the prolonged survival and accumulation of potentially auto-reactive B cells, even after withdrawal of the inciting stimulus, as demonstrated by Visentini *et al.*[29]. These considerations are the rationale for the use of a B cell depletor, like rituximab, in the treatment of severe or relapsing MC disease. This approach seems effective and could be preferential when significant renal involvement coexists limiting the use of conventional antiviral therapy. In our case, although considered, the good response to glucocorticoids and the immediate unavailability of RTX precluded its use. However, it would be a reasonable choice in similar cases.

In conclusion, with this report, we emphasize the possibility of HCV related MC occurrence and its renal manifestations, in patients with sustained virus eradication. Our discussion highlights the latest advances in the physiopathology understanding of HCV related B cell disorders and its implications on the therapeutic regimen choices.

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