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Caso clinico

Case reports

Recombinant Human Erythropoietin (RHuEpo) and Granular Colony Stimulating Factor (G-CSF) in hepatitis C virus (HCV) related to mixed cryoglobulinaemia associated to membranoproliferative glomerulonephritis type I: a case report description

Eritropoietina ricombinante umana (RhuEpo) e fattore di crescita granulocitario (G-CSF) nella crioglobulinemia mista HCV correlata, associata a glomerulonefrite di tipo 1: descrizione di un caso

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INTRODUCTION

HCV infection is involved in the development of mixed cryoglobulinaemia (MC) (1). Renal involvement is reported in one third of cryoglobulinaemic patients and is associated with MC type II [1, 2]. Mazzaro et al. highlighted that HCV-related MC with renal involvement is featured by immune system impairment, progression to renal failure and poor survival (identified as Hepatitis C Virus Risk Syndrome, HCV-RS) [3]. Moreover HCV therapy, based on Pegylated Interferon (Peg-INF) with ribavirin (RBV) showed efficacy and safety in HCV-related MC with renal involvement [4]. However, the therapy Peg-INF plus RBV comes with haematological side effects whose management in patients with HCV-related MC and glomerulonephritis do not seem to have been well studied [5].

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CASE REPORT

In May 2010, a 53-year-old man (weight 51 kg, height 160 cm) was admitted to our medical division at the hospital with hypertension, bilateral lower-extremity oedema, palpable purpura (score 2), arthralgia and peripheral paraesthesia with hypoaesthesia of lower limbs. His medical history included high serum levels of transaminases. Laboratory tests result in urinary protein excretion 4.2 g/day, serum creatinine 1.5 mg/dl, alanine aminotransferases (ALT) 984 U/L, blood count was white blood cells 3220/µL (neutrophils 1600/µL), haemoglobin 11 g/dl, platelets 120000/µL. Type II (IgG-IgM-k) MC was detected with a cryocrit of 10%. The serum levels of C4 were low (2 mg/dl; normal value 20-50 mg/dl). The patient was tested for anti-HCV and the results were

positive; instead HBV and HIV tests were negative. The genotype of HCV was 2a/c and the HCV-RNA copies were 1,636,000 UI/ml. Because of the high levels of proteinuria, we performed a percutaneous kidney biopsy which showed features of membranoproliferative glomerulonephritis type I (MPGN I). Based on clinical assessment for the need of HCV therapy and to establish the severity of the liver disease we performed a biopsy which showed features of cirrhosis according to METAVIR. Electromyography of lower limbs highlighted chronic sensitive polyneuropathy. Since HCV infection could also be related to non-Hodgkin Lymphomas (NHL), we performed a immunophenotyping of peripheral white blood cells that showed a monoclonal B cell lymphocytes population CD19+/CD20+/CD5- [6]. Therefore, in order to complete haematological evaluation, total body CT scan and bone marrow biopsy were carried out. In particular, total body CT scan showed hepatosplenomegaly and in the bone marrow biopsy we found interstitial infiltration of small lymphocytes and lymphoplasmacytoid elements (30% infiltration of monoclonal B cell lymphocytes with the same immunophenotyping of peripheral B cell lymphocytes). The diagnosis of HCV-related MC to renal involvement was given (identified as HCV-RS). In June 2010, we started treatment with Peg-INF alfa-2b 50 mcg subcutaneous weekly for six months and RBV 400 mg twice daily for six months in combination with a low dose of steroids (prednisone 10 mg/die per os), ACE inhibitor (ramipirl 5 mg/die per os), diuretics (furosemide 25 mg/die per os) and poor sodium diet. At the end of the 4th week of therapy, the haemoglobin level decreased from 11 g/dl to 9.8 g/dl; therefore we reduced RBV to 400 mg once daily. However, at the end of the 8th week, haemoglobin levels showed a further decrease (8.6 g/dl) and the initial mild neutropenia worsened (from 1660/µL to 400/µL). Therefore we started RHuEpo (in particular subcutaneous epoetin alfa 40,000 UI/weekly) in combination with G-CSF 150 µg three times weekly in order to maintain neutrophils >750/µL without a further drug dose

Table 1 - Clinical and laboratory baseline data, during therapy and follow-up.

	Baseline	*1st month of therapy*	*2nd month of therapy*	*6th month (end therapy)*	*+6 months follow-up*	*+48 months follow-up*
White Blood Cells/µL	3220	1620	800	1820	3000	3500
Neutrophils/µL	1600	800	400*	900	1300	1400
Haemoglobin g/dl	11	9.8	8.6**	10	10.5	10.8
Platelets/µL	120000	100000	90000	100000	120000	140000
ALT U/L	84	28	36	24	30	36
Creatinine mg/dl	1.5	1.5	1.5	1.5	1.3	1.4
Proteinuria g/24 h	4.2	2.8	2.6	0.9	0.8	0.8
RF UI/ml	400	160	160	110	115	120
Complement C4 mg/dl	2	2	2	2	2	2
HCV-RNA copies UI/ml	1.636.000	N.A.	N.D.	N.D.	N.D.	N.D.
Cryocrit %	10	6	2	0	0	0
Purpura score	2	0	0	0	0	0
Arthralgia	+	-	-	-	-	-
Neuropathy	+	-	-	-	-	-
Oedema to inferior limbs	+	-	-	-	-	-

Legend: ALT (Alanine aminotransferases), RF (Rheumatoid Factor), NA (not available), ND (not detectable), *Start G-CSF, **start epoetin alfa.

reduction. At the 12th week of treatment, proteinuria, creatinine, aminotransferases and cryocrit decreased while HCV-RNA was undetectable. After the 24th week, a complete virological response was achieved and the patient was asked to follow up every three months. Currently the patient is asymptomatic; there are no signs of bilateral lower-extremities oedema or palpable purpura, and HCV-RNA levels are still undetectable. Laboratory data at baseline, during treatment and follow-up, are summarized in Table 1.

DISCUSSION

HCV infection is not only related to hepatic disease but also to lymphoproliferative disorders such as MC, mainly type II and III and non-Hodgkin lymphomas (NHL) [6]. The most common histological types of HCV-associated NHL are lymphoplasmacytic, primary nodal marginal zone, splenic marginal zone; mucosa-associated lymphoma tissue (MALT) and diffuse B large cell-lymphoma [6]. MC type II is rare, involving 5-10% of all HCV infected patients [7]. Clinically, MC features are weakness, purpura, arthralgia and peripheral neuropathy. Cryoglobulinemic vasculitis, involving small and medium-sized vessels, is due to deposition of circulating cryoglobulins activating complement with organ damage. In particular, renal involvement is reported in one third of cryoglobulinaemic patients and is associated with MC type II [12]. The most significant accompanying kidney lesion is type I membranoproliferative glomerulonephritis (MPGN I), usually in the context of MC type II [8]. The combination of HCV-related MC with renal involvement has been associated with immune system impairment, progression to renal failure and poor survival and identified as Hepatitis C Virus Risk Syndrome (HCV-RS) [3]. HCV infection therapy is based on Peg-INF and RBV in combination with bocepevir or telapevir (triple therapy) for genotype 1, and Peg-INF plus RBV alone for other genotypes [9, 10]. The involvement of HCV in pathogenesis of MC (HCV-related MC) provided the opportunity to use antiviral therapy especially in mild-moderate disease [4]. First, Mazzaro and co-workers highlighted that interferon was effective in treatment of HCV-related MC [11]. Later, in other reports, Peg-INF plus RBV combination seemed be the treatment of choice for HCV-associated cryoglobulinemic MPGN [4]. In spite of more recent therapies, HCV-related MC is characterized by a lower virological response rate and by several relapses compared to HCV without MC [13]. Moreover, RBV induces haemolytic anaemia and Peg-INF causes anaemia, neutropenia and thrombocytopenia by bone marrow suppression [5]. RBV dose reduction alone could not be enough to avoid decreases in haemoglobin. Moreover, higher sustained virological response rates in patients receiving adequate doses of both drugs have been shown [14]. Therefore in HCV-infected patients, RBV dose reduction associated to RHuEpo use is considered an effective strategy to maintain haemoglobin and treat the disease at the same time [5]. The use of G-CSF for neutropenia is not routinely recommended. However, in some European countries as soon as the neutrophil count falls below 750-500/μL, G-CSF is introduced in the therapy [5]. Moreover, scheduled injections of RHuEpo and G-CSF are not well established especially in HCV-related MC cases [5]. In 2011, in a multicentre open label study, Mazzaro and his coworkers reported efficacy and safety of Peg-INF plus RBV in HCV-related MC [13]. In the latter study 86 consecutive patients were enrolled, ten cases (12%) had clinical and laboratory alterations of renal function and one of these cases required RHuEpo for therapy-related anaemia [13].

Here we report a rare case of HCV-related MC with MPGN type I (comparable to HCV-RS) complicated by bone marrow infiltration of lymphoplasmacytic monoclonal cells. At onset, in the blood count, mild anaemia and neutropenia were already detectable because of multi-factorial bone marrow failure (not only because of HCV infection but also lymphoid infiltration). In the first month of therapy, because of worsening anaemia, we reduced the RBV dose from 800 mg/die to 400 mg/die. However, in the second month of therapy, haemoglobin levels continued to decrease and severe neutropenia appeared.

In line with literature, we considered another dose reduction as non-optimal. Indeed, RBV standard doses increase sustained the virological response rate by reducing relapse rates [14]. On the other hand, emerging data suggest that suitable doses of Peg-INF and RBV play a key role in achieving sustained virological response [14]. Therefore, from the second month until the end of treatment, we introduced RhuEpo

(epoetin alfa 40.000 UI weekly) in combination with G-CSF 150 µg thrice weekly by maintaining neutrophils >750/µL without a further dose reduction of Peg-INF/RBV.
During the 12th week of treatment, proteinuria and cryocrit decreased, and HCV-RNA was undetectable. By the end of the therapy with Peg-INF/RBV, complete virological response had been achieved. In July 2013 the patient was in sustained virological response.
To our knowledge, this is the first case of HCV-related MC with MPGN type I (known as HCV-RS) associated to lymphoid bone marrow infiltration with anaemia and neutropenia treated by RHuEpo in combination with G-CSF [3].
In conclusion Peg-INF/RBV is the treatment of choice in HCV-related MC MPGN I (as HCV-RS), showing efficacy and safety, especially in mild-moderate cases. However, it should be taken into consideration that anaemia and neutropenia are not rare side effects. In particular, dose reduction of drugs might not be enough to manage anaemia or neutropenia, and the efficacy of treatment could be reduced. On the other hand, the RHuEpo/G-CSF combination could be a highly useful option in treating anaemia/neutropenia without a further dose reduction in such patients.

Keywords: hepatitis C virus (HCV), cryoglobulinemia, membrane proliferative glomerulonephritis, interferon, ribavirin.

SUMMARY

HCV infection is related to hepatic disease and mixed cryoglobulinaemia (MC). Renal involvement is reported in one third of cryoglobulinaemic patients. The combination of HCV-related MC with renal involvement has been associated with poor survival and identified as "Hepatitis C Virus Risk Syndrome (HCV-RS)". Here we describe antiviral treatment and management of side effects (anaemia and neutropenia) with RHuEpo and G-CSF in a rare case of HCV-RS.

RIASSUNTO

L'infezione da HCV è correlata a malattia epatica e crioglobulinemia mista (MC).
Il coinvolgimento renale è riportato in un terzo dei pazienti crioglobulinemici. La combinazione HCV/MC con coinvolgimento renale è stata associata a ridotta sopravvivenza e identificata come "Hepatitis C Virus Risk Syndrome (HCV-RS)".
Si descrive il trattamento degli effetti collaterali (anemia e neutropenia) con RhuEpo e G-CSF in un raro caso di HCV-RS.

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