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HCV Extrahepatic Events: Cryoglobulinemic Syndrome – A Case Report in an Over-70-Year Old Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Author AM wrote the case report. Authors AM, GR and PG wrote the first draft of the manuscript. Authors AC and Gaetano Russo managed the literature searches. Authors PG, NMM and Alfonso Ciaccio revised the manuscript and the English language. Author PG was the author for correspondence. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Mixed Cryoglobulinemia (MC) is the most severe among the extrahepatic manifestations of hepatitis C virus. It is a circulating immune disease due to a virus-induced proliferative disorder of B lymphocytes, mainly involving low and medium-sized vessels. Diagnosis of cryoglobulinemia is based upon the presence in the serum of immunoglobulins which may reversibly precipitate at temperature inferior to 37℃.

Presentation of Case: In the present paper we report an interesting case of a 72-year-old man with MC. The two main findings in MC are vasculitis and neuropathic syndrome. Cryoglobulinemic

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syndrome is characterized by purpura, which is one of the earliest and common clinical manifestations in over 80% of the cases. In this case report the neurological picture is represented by severe sensorimotor polyneuropathy, characterized by burning dysesthesia and lack of sensitivity and strength in the limbs.

Discussion and Conclusion: The therapeutic approach to the patient with cryoglobulinemic syndrome should be tailored to the clinical characteristics of the patient and the degree of disease activity. The present clinical picture occurring with severe neurological impairment may be included among the most severe forms of the disease.

Keywords: Mixed cryoglobulinemia; hepatitis C virus; purpura; neurological impairment; immunoglobulins.

1. INTRODUCTION

Mixed Cryoglobulinemia (MC) is the most severe among the extrahepatic manifestations of hepatitis C virus (HCV) [1]. It is a circulating immune disease due to a virus-induced proliferative disorder of B lymphocytes, mainly involving low and medium-sized vessels [1]. The diagnosis of cryoglobulinemia is based upon the presence in the serum of immunoglobulins (Ig) which may reversibly precipitate at temperature inferior to 37℃ [2]. Three types can be distinguished [1]:

1) Type I: Production of monoclonal Ig (usually IgM or IgG), which rarely act as rheumatoid factor (RF);
2) Type II: Polyclonal Ig (usually IgG) and monoclonal Ig (usually IgM);
3) Type III: Polyclonal Ig.

The types II and III are the so called mixed forms, or mixed cryoglobulinemia and immune-globulins act as rheumatoid factor.

Type I cryoglobulinemia can be found in myeloproliferative disorders, whereas MC can be linked to infectious or neoplastic diseases [1]. In non selected patients affected with C chronic hepatitis, prevalence of MC ranges between 19 and 54%; in two-third of the cases cryoglobulins are type III, whereas in the remaining one third cryoglobulins are type II [1].

The mechanisms of production of cryoglobulins are not definitely explained; clonal expansion of B cells in the peripheral blood and the finding of bone marrow and liver lymphoid infiltrates suggest the lymphoproliferative pathogenesis [1,2]. It might be triggered by antiapoptotic mechanisms following processes of gene rearrangement [3]. Further evidence derives from the possible lymphomatous evolution, occurring in about 10% of the cases and regarding type B non Hodgkin lymphomas [3].

The B-lymphocyte proliferation was first described by Meltzer and Franklin in 1966 [4]; it is a syndrome characterized by the triad purpura, weakness and arthralgias, involving organ damage such as nephropathy and peripheral neuropathy. However, it has been shown that the amount of circulating cryoglobulins weakly correlates with the severity of clinical manifestations and not rarely it is exclusively a laboratory concern [5]. To this purpose it is possible to distinguish a condition characterized solely by the presence of serum cryoglobulins, cryoglobulinemic syndrome, with a wide range of clinical events and eventually both mild or paucisymptomatic frameworks (purpuric lesions, occasional arthralgias) and severe forms, with rapidly progressive renal impairment [1,3].

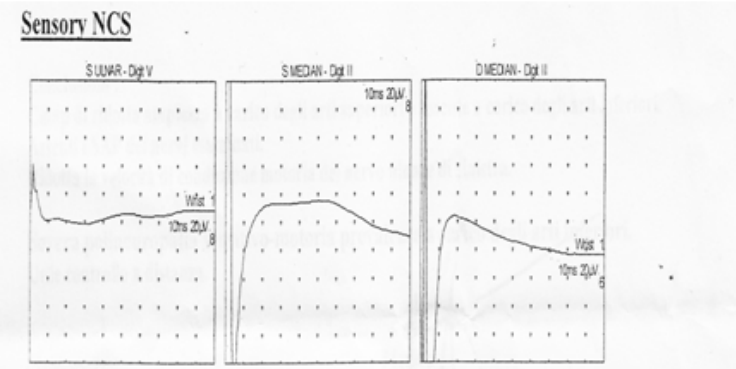
In the present paper we report an interesting case of a 72-year-old man with MC.

2. PRESENTATION OF CASE REPORT

A 72-year-old man was visited at the Emergency Room for the sudden onset of cutaneous lesions to lower limbs and inability in extending the right hand in the last 24 hours; furthermore, he has been presenting burning pains and paresthesia (tingling) and numbness in the hands (especially at the right hand) and in the feet, extending to the leg up to the knee.

The patient presented a history of hospitalizations in internal wards because he was affected with HCV mixed etiology/ genotype1/exotoxic hepatic cirrhosis complicated by cryoglobulinemia. He had already undergone two sessions of plasmapheresis. He was also affected with hypertension, moderate mitral insufficiency, hypofunctioning multinodular goiter. He was taking furosemide 25 mg on alternate days, propranolol 20 mg twice a day, levothyroxine 75 mcg/day, omeprazole 20 mg/day, losartan 50 mg/day. Physical examination showed that the patient was alert

and collaborative, heart sounds were rhythmic with a frequency of 68 beats/min; a 3-4/6 systolic murmur propagated to the armpit was present and arterial pressure was 110/60 mm Hg; body weight was 68 kg. Thorax examination showed that breath sounds were reduced on all fields; the bases of the chest were mobile and no noise added was present. Abdomen appeared globose with skin lesions due to scratching and superficial vein circles; it was treatable on palpation, mobile dullness on the variation of decubitus, probably linked to mild abdominal effusion. The lower limbs presented numerous purpuric patches with edema. Neurological findings were the inability to extend the right wrist with fingers abduction and thumb opposition deficits, even if Mingazzini was negative at the four limbs. Gait was performed through small steps and enlargement of the base plate. Blood tests pointed out macrocytic anemia (hemoglobin 8.9 g/dl, mean corpuscular volume (MCV) 100, 4 fl) and leukopenia (white blood cells (WBC) 2.500/mm^3), moderate renal impairment (urea 66 mg/dl, plasma creatinine 1.8 mg/dl, creatinine clearance assessed through Cockroft and Gault's formula 35,68 ml/min, potassium 4.92 mEq/dl) and presence of blood and proteins in the urine (30 mg/dl). High blood levels of liver enzymes (aspartate transaminase (AST) 72 U/L, alanine transaminase (ALT) 54 U/L, γ-glutamyl-transferase (γ-GT) 125 U/L), decrease in cholinesterase 1886 U/L and in C4 complement fraction (4.5 mg/dl)**,** positive direct and indirect Coombs test, rheumatoid factor (53 UI/ml), cryocrit (4.5%) and C-reactive protein (CRP) (3.44 mg/dl) were also present. Electromyography documented neurogenic injury with denervation on all the muscles examined, in particular on the right, the reduction of voluntary movements on the first dorsal interosseous muscle (Figs. 1,2). Four more cycles of



Nervo / Posizioni	Latency ms	Ampl. mV	Dur. ms	Area mVms	Ampl.% %	Dur.%. %	Area% %	Distance cm	Lat Diff ms	Vel. m/s
S ULNAR - ADM										
1. Wrist	4,05	2,9	9,35	13,2	100	100	100		4,05	
2. B.Elbow	10,50	2,4	11,60	15,2	81,5	124	115	27	6,45	41,9
Percorso 3 - 1										
S MEDIAN - APB (Palm)										
1. Palm	6,55	2,1	8,45	10,1	79	72,8	59		6,55	
2. Elbow	11,85	2,7	11,60	17,0	100	100	100	26	5,30	49,1
Percorso 3 - 1										
D MEDIAN - APB (Palm)										
1. Palm	5,90	1,1	7,95	5,2	123	98,1	116		5,90	
2. Elbow	11,25	0,9	8,10	4,5	100	100	100	26	5,35	48,6
Percorso 3 - 1										

Fig. 1. Compound Muscle Action Potential (CMAP) amplitude is decreased at the superior limbs and absent at the lower limbs

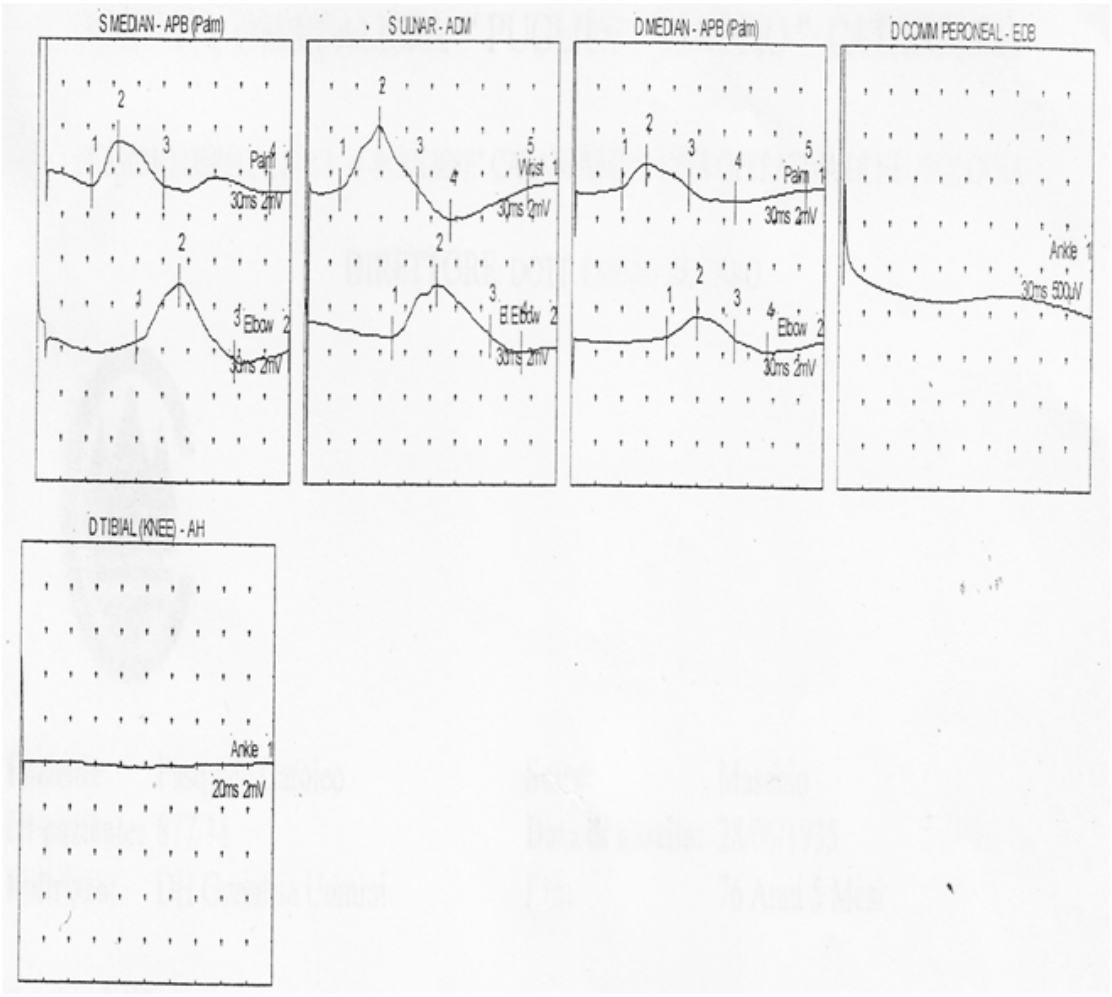


Fig. 2. Sensory Nerve Action Potential (SNAP) is absent in the nerves examined

plasmapheresis were performed and the patient started furosemide 100 mg/day, omeprazole 20 mg/day, propranolol 40 mg/day, levothyroxine 75 mg/day, losartan 50 mg/day, intravenous methyl-prednisolone 40 mg/day for three days, with gradual decrease and switching to oral prednisone 25 mg/day, intramuscular cyanocobalamin 500 mcg plus folate 50 mg every three days. Furthermore, treatment with pregabalin and the association paracetamol/oxycodone was started in order to treat the algogenic syndrome. Cutaneous vasculitis and lower limbs edema regressed; functional disturbances and mild abdominal effusion persisted. Twelve days after the hospitalization he was discharged with the following diagnosis: “Cryoglobulinemic syndrome complicated by lower limbs vasculitis and sensorymotor polyneuropathy in patient affected with HCV/ethylic cirrhosis class Child Pugh A6”.

3. DISCUSSION AND CONCLUSION

The present case reports two main findings, vasculitis and neuropathic syndrome. Furthermore, an impairment of renal funcion is present. Cryoglobulinemic syndrome is characterized by purpura, which is one of the earliest and common clinical manifestations in over 80% of the cases [5].

Purpura is linked to extravasation and is palpable and non-pruritic; it also interests legs and evolves with pousses at 7 days intervals. When the purpura disappears in the affected areas, residual brown ocher skin pigmentation due to deposits of hemosiderin can be found [6]. Histology shows a leukocytoclastic vasculitis involving capillaries and post-capillary venules of the superficial dermis [7], with immune-

fluorescence pointing out deposits of immune-globulins (IgG, IgM) and/or complement (C4) [8].

Since the nature of the microvascular damage is both on inflammatory and occlusive basis, due to the immune complexes that block small vessels circulation, purpura is followed by skin sores in a minority of patients (13-16%) [6]. Here the neurological picture is represented by severe sensorimotor polyneuropathy, with burning dysesthesia and lack of sensitivity and strength in the limbs. In some cases, impotence can develop into functional tetraparesis [9].

The neurological damage is ischemic, almost always peripheral axonal, secondary to inflammation of the nerve arterioles and/or to obstruction of the vasa nervorum by macromolecular complexes deposits. Immune-mediated processes may be associated to the loss of axonal nerve fibers and areas of demyelination [10]. Rarely the nerve damage is central and its onset occurs by transient ischemic attacks (TIA). In patients affected with type 2 MC, the finding of HCV RNA in periarteriolar mononuclear cells after sural nerve biopsies, is a clear sign of the pathogenic role of HCV [5].

The presence of proteinuria and the decrease in creatinine clearance (CrCl) suggest renal function impairment. Histological manifestations of renal disease associated with cryo-globulinemic syndrome overlap with signs of idiopathic membrane proliferative glomerulone-phritis. It is characterized by mesangial and subendothelial immunocomplexes accumulation [1], with capillar thrombi found on optical microscopy [11]. In more than one third out of patients undergoing renal biopsy, vasculitic lesions with fibrinoid necrosis and monocyte infiltrations are placed in low and medium-sized arteries [12]. In the natural history of cryoglobulinemic syndrome, renal dysfunction is one of the negative prognostic indices [1], because it significantly influences therapeutic options.

The therapeutic approach to the patient with cryoglobulinemic syndrome should be tailored to the clinical characteristics of the patient and the degree of disease progression. The present clinical picture occurring with severe neurological impairment may be included among the severe forms of the disease.

The complete clinical response is marked by virus eradication. Indeed, viremia negativity is followed by the reduction in cryocrit and disappearance of lymphocyte proliferation [7]. Combination therapy with Pegylated Interferon (PEG-IFN) – Ribavirin can suppress HCV replication in about 50% of patients [13]. Treatment must be prolonged for 24 weeks for genotypes 2 and 3 and for 48 hours for genotypes 1 and 4 [14]. Virus load needs to be measured under basal conditions, after 12 and 24 weeks. The failure to reduce viremia of at least two logarithmic units on the 12th week, or the presence of viremia on the 24th week, exclude treatment continuation [15]. The efficacy of eradicating treatment is conditioned by a number of both virus- and host- related factors. Among the former, virus load at baseline, speed of reducing viremia and the characteristics of some proteins encoded by the virus (5A, E2) could influence the resistance to interferon treatment. On the contrary, among the host-related factors there are: age, gender, race, comorbidities, insulin resistance, overweight and the characteristics of immune response [16].

In this case report, since ribavirin clearance is reduced in patients affected with renal failure and hemodialysis cannot remove the drug, the occurrence of renal impairment contraindicated the combination therapy [1]. As a matter of the fact, the use of this drug is not recommended in those with CrCl inferior to 50 ml/min [17], unless dosage of plasma levels is available. Therapeutic range is 10-15 µmol/L, but the dosage must be halved if hemoglobin is inferior to 10 g/dL (such as in our case report); indeed, ribavirin can cause reversible anemia due to extravascular hemolysis and bone marrow suppression [6]. Furthermore, full dose PEG-IFN can be only used in patients with glomerular filtration > 60ml/min [13]. However, under this threshold it can be used at reduced doses, with lower efficacy. As regards the new direct acting antivirals (DAAs), the use of which was approved in Italy on December 2014, in the present case report the best treatment would be Sofosbuvir + Simprevir + Ribavirine for 12 weeks [18]. This would depend on the genotype 1 and Child Class A; however, this treatment was not used because we have no evidences in the literature about the use of DAAs in patients affected with renal failure. Besides the over reported matters, antiviral etiological therapy does not allow to rapidly counteract the immune-mediated inflammatory process secondary to cryoglobulins' precipitate in the vascular bed [19]. Furthermore, interferon could even increase the neurological damage [13]. Pathogenic treatment with

corticosteroids and cyclophosphamide (in our case report it was not used for the concomitant leukopenia) for a time not superior to 8-12 weeks is appropriate [7,8]. This treatment should be associated to apheresis (at least 6 sessions close within 2 weeks); it is aimed to remove cryoglobulins and inflammatory mediators [6]. Once clinical remission has been achieved, then we can assess whether or not the causative antiviral treatment should be started.

Additional therapeutic perspectives are the use of the monoclonal antibody Rituximab (RTX), that could replace cyclophosphamide, with respect to which has lower toxicity and greater selectivity of action [20]. It is a chimeric monoclonal antibody, directed against CD20, the specific antigen of secretory B limphocytes, which depletes selectively. The drug is currently used for treatment of non- Hodgkin lymphoma (NHL) and is usually well tolerated [21]; however, it has been shown to increase viremia, probably due to the decrease in anti-HCV antibodies rate. Therefore, in order to avoid exacerbations of hepatitis, it has been proposed to use RXT only associated to PEG-IFN and Ribavirin [22].

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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