Necrotizing acute pancreatitis following therapeutic plasmapheresis in HCV-related cryoglobulinemia

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Abstract

Mixed cryoglobulinemia and hepatitis C virus infection are strongly connected and the therapeutic approach is standardized according to the severity of the symptoms.

We report the difficult management of 59 year old female HCV patient presenting cutaneous lesions and arthralgia due to mixed cryoglobulinemia. No therapy was able to achieve a complete remission and during the six years of active disease we observed several clinical recurrences. The intensive plasmapheresis regimen led to a complete remission of the symptoms but it was associated with severe complications. In this case report we describe an episode of acute necrotizing pancreatitis due to intravascular haemolysis following therapeutic plasmapheresis.

To the best of our knowledge the association between plasmapheresis and acute pancreatitis has not been previously described. (Acta gastroenterol. belg., **2011**, 74, **355-358**).

Key words : cryoglobulinemia, hepatitis C virus, haemolysis, plasmapheresis, pancreatitis.

Introduction

HCV is a RNA virus that causes hepatic disease and has also the potential to induce extrahepatic manifestations. These extrahepatic manifestations are often difficult to manage through standard antiviral treatment. In this case report we describe the extrahepatic manifestations of a 59 year old female HCV positive patient who did not only badly respond to treatment, but also developed some severe treatment related complications.

Acute pancreatitis has traditionally been defined as an acute inflammatory process of the pancreas (1) that is associated with abdominal pain and elevations in serum levels of pancreatic enzymes and disrupts normal pancreatic architecture and function until the illness resolves (2). The most important risk factors for acute pancreatitis in adults are gallstones and excessive alcohol use. Other causes include metabolic disorders (hypertriglyceridemia), duct obstruction (related to tumour or pancreas divisum), drugs, and trauma (3). The pathogenesis of acute pancreatitis is related to inappropriate activation of trypsinogen to trypsin and a lack of prompt elimination of active trypsin inside the pancreas (4). This leads to a pancreatic injury causing an inflammatory response that may progress beyond the pancreas to a systemic inflammatory syndrome, multiorgan failure or death.

Therapeutic plasmapheresis or plasma exchange is performed using a cell separator to extract unwanted plasma components. It is used in several diseases such metabolic diseases (eg. familial hypercholesterolemia), hematological diseases (eg. thrombotic thrombocytopenia purpura), autoimmune diseases (eg. cryoglobulinemia) and neurological diseases (eg. myasthenia gravis) (5).

To the best of our knowledge an association between acute pancreatitis and plasmapheresis has never been observed before and the role of plasmapheresis as a cause of acute pancreatitis will be discussed.

Case report

A 59 year old female patient was referred to the Gastrointestinal and Liver Disease Department in December 2002 for recurrent episodes of bilateral arthritis in the ankles, associated with an evident vasculitis cutaneous eruption composed of confluent erythematous maculae and dermal nodules localized above the malleolar area. Moreover, some small red spots were clearly observed on the legs, above the ankles. Her clinical history showed only a Hashimoto's thyroiditis treated with levothyroxin 150 µg/day.

At the admission, laboratory analyses showed increased liver enzymes and a positive rheumatoid factor. Serology for hepatitis C virus infection was positive (Table 1).

Liver biopsy showed mild necro-inflammatory changes and portal fibrosis (grade 7 with Knodell score (6) and grade A1F1 with Metavir score (7)).

Between January and August 2003 the patient was treated with pegylated IFN α2b (1,5 µg/kg/week) plus ribavirin 600 mg/day. However, because of the presence of a positive HCV RNA PCR at week 24, the treatment was discontinued.

Antiviral therapy was not only ineffective but also rather harmful since the patient developed a severe anaemia (decline of haemoglobin (from 12,5 g/dl to 5,4 g/dl)) that required hospitalization. The first drop of

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Table 1. — **First analyses - December 2002**

		Measured value	Reference interval
Haemoglobin	(g/dl)	14	11,7-15,7
Haematocrit	(%)	42,1	34,9-46,9
Leukocytes	(cells/µl)	7880	4000-10000
Platelet count	(cells/µl)	183000	177-393
Creatinin	(mg/dl)	1,06	0,55-0,96
Glomerular filtration rate (42)	(ml/min)	56,84	75-115
Total protein	(g/dl)	8,4	6,2-8,2
Albumin	(g/dl)	4,2	3,4-4,8
Total bilirubin	(mg/dl)	0,5	0,3-1,2
INR		1,2	0,97-1,23
AST	(U/l)	54	0-31
ALT	(U/l)	65	7-31
Gamma-GT	(U/l)	45	9-36
Alpha-fetoprotein	(ng/mL)	1,76	0-15
TSH	(µU/ml)	0,077	0,27-4,2
Rheumatoid factor (RA-test)	(UI/ml)	256	< 40
Cryoglobulins		positive	negative
HCV antibody genotype 1b		positive	negative

haemoglobin drop (from 12,5 g/dl to 9,8 g/dl) was observed after one month of therapy. During this combined treatment the liver function tests normalized (ALT 23 U/l) and the arthritis and the cutaneous lesions gradually came under control. However after the treatment was discontinued, the lesions recurred and a therapy based on IFN α2a (180 µg/week) and methylprednisolone (24 mg/day) was initiated. A clinical response was seen because the lesions regressed with a reduction in the dimensions and disappearance of the dermal nodules. After two months of treatment the patient reported great excitement, fatigue, sleepiness, anxiety and hyperphagia. These symptoms were interpreted as side effects of steroid therapy and disappeared with the reduction of glucocorticoids. The combination therapy based on IFN α2a (180 µg/week) and methylprednisolone (24 mg/day with dose reduction) was given for 3 months (November-January 2005) and the IFN α2α (180 µg/week) was never interrupted.

In August 2006, after a long period of clinical remission, the patient was again referred because she was suffering from a new flare-up of the vasculitis. IFN α2a (180 µg/week) associated to a session of plasmapheresis every 20 day was started. This scheme was not sufficient for the remission of the symptoms and the plasmapheresis was increased to two times per week. Complete remission was obtained but the plasmapheresis course was abruptly interrupted by two critical events that required hospitalization. The patient was hospitalized in the Nephrology Department in March 2007 for a syncopal episode with bradycardia, palpitations and mild shortness of breath (NYHA 2) and in the Gastroenterology Department in August 2007 for a necrotizing acute pancreatitis. The diagnosis of the acute pancreatitis was based on a sudden severe epigastric pain radiating to the back, vomiting and nausea, with increased serum amylase up to 850 U/l (normal value 0-100) and lipase up to 1400 U/l (normal value 0-60) and on more specific diagnostic techniques such as ultrasound and CT (Fig. 1).

In addition, laboratory analyses showed also : haemoglobin 7,8 g/dl, haptoglobin 0,17 g/l (normal value 0,3-2), indirect bilirubin 0,95 mg/dl (nv 0,2-0,8) and lactate dehydrogenase 1100 U/l (nv 231-462). Moreover, the analysis of the peripheral blood smear showed the presence of schistocytes probably due to red blood cells membrane damage.

To note, the analysis before the first plasmapheresis session showed normal values for haemoglobin, haptoglobin, indirect bilirubin and lactate dehydrogenase.

These results permitted us to suspect the likely connection between pancreatitis and haemolytic anaemia. To substantiate this alcohol abuse, choledocholithiasis and viral causes were excluded.

Moreover, we included in the differential diagnosis also autoimmune pancreatitis, a rare type of pancreatitis characterized by an autoimmune inflammatory process (8). Immunological abnormalities including hypergammaglobulinemia and elevated serum IgG4 levels are important markers of the disease (9). However, the negative IgG4 pattern of the patient led us to exclude it as a concrete possibility.

The plasmapheresis was discontinued and a progressive recovery of physiological levels of haemoglobin was clearly observed with a normalization in the haemolytic pattern and with a reduction in the pancreatic enzymes. It was decided to administer off-label treatment with rituximab. No clinical nor biochemical side effects were

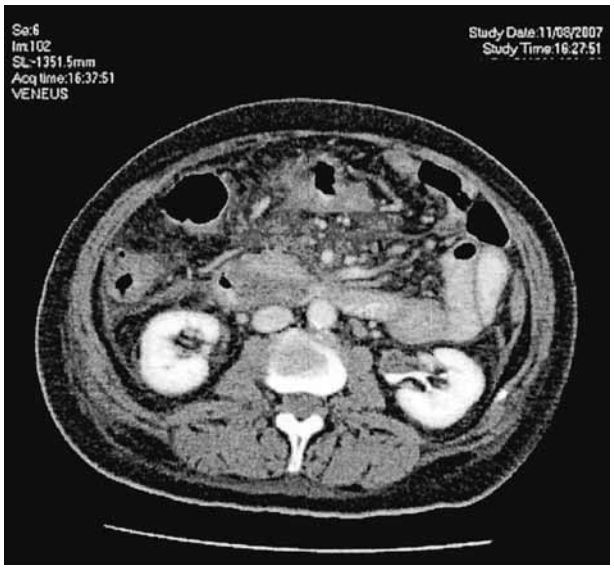

Fig. 1. — A necrotic area of about 3 centimeters in the pancreas parenchyma is visible involving its head and part of the body. No calcifications are visible in the pancreas parenchyma. Clear peri-pancreatic fluids that do not appear encapsulated.

observed during and after rituximab treatment and after 15 months the patients is still asymptomatic except for some very mild swelling of the joints.

Discussion

The therapeutic strategy for extrahepatic manifestations of HCV infection should be selected individually for each patient according to severity and symptoms. The treatment based on IFN and ribavirin (which tries to get rid of the HCV virus) is generally the first choice (10,11). However, in 44-46% of the patients the treatment is either ineffective or contraindicated. With this scenario the availability and the possibility of alternative therapies is of fundamental importance (12). The patient might be managed with corticosteroids, immunosuppressors or plasmapheresis, depending on the severity and presentation of HCV-associated cryoglobulinemia.

Plasmapheresis or therapeutic plasma exchange for HCV related cryoglobuliemia is indicated as second-line therapy in patients unresponsive to traditional therapies with antivirals and corticosteroids and as first-line in the patients presenting conditions at high risk of life (rapidly progressive nephritis, central nervous system, digestive and/or pulmonary involvement) (13).

The field of "therapeutic apheresis" encompasses a variety of blood processing techniques that improve the outcomes of susceptible clinical disorders.

The membrane plasma separation (MPS-Plasmaflo), performed in our patient, can be used with most dialysis machines and should be operated with a very modest transmembrane pressure (TMP < 75 mmHg) and blood flow (50 to 150 mL/min) in order to minimize the tendency to haemolysis and filter clotting.

Haemolysis associated with MPS related haemodialysis procedures follow the law "the higher the blood flow, the higher the haemolysis" (14).

To our opinion this patient developed severe haemolysis which was complicated by an acute necrotizing pancreatitis.

To our knowledge acute pancreatitis has never been associated with plasmapheresis. Tracked by a literature review, frequent complications are numbness, muscle cramps and urticaria. Less common could be hypotension, dyspnoea, coagulation abnormalities, infection, anaphylactic reactions and hypokalemia (15).

Studies in mice revealed that massive haemolysis may induce acute pancreatitis in approximately 80% of cases (16).

The precise mechanisms underlying the pathogenesis of acute pancreatitis remain unclear. The data reported in the literature are consistent with the view that heme has the potential to act as a signalling molecule involved in the triggering of the inflammatory processes associated with massive haemolysis (17). Heme released from heme proteins has been shown experimentally to promote a systemic inflammatory response and organ failure facilitating the formation of oxygen radicals, playing a role as a catalyst in the oxidation of lipids, proteins and DNA (18). Normally, heme-binding plasma proteins, such as hemopexin, can efficiently remove most of the heme produced intravascularly, and this prevent heme-induced damage. Massive haemolysis as in malaria, sickle cell disease, HELLP (haemolysis elevated liver levels and low platelet count) syndrome, can lead to very high levels of free heme, which can exceed the binding capacity of hemopexin and promote neutrophil migration, suggesting a direct proinflammatory effect of this blood component (17).

Concerning with the correlation between malaria and acute pancreatitis, only few cases have been reported. However, there has been no correlation between the infestation index and the occurrence of pancreatitis in these patients (18). The proposed pathophysiological mechanisms that result in pancreatitis are capillary blockage by parasitized red blood cells and acute haemolysis (19).

Haemolysis itself may induce acute pancreatitis neutrophil activation and chemo-attraction, such as oxidative burst, direct proinflammatory effect, microcirculatory disturbances, and increased expression of proinflammatory and immunregulatory cytokines (20,21).

In acute pancreatitis, reduction in blood flow and alterations of the microvascular integrity resulting in impaired tissue oxygenation play an important part in the initiation and progression of the disease. Several studies proposed that ischemia may be an initiating factor of pancreatic microcirculatory injury in acute pancreatitis (22,23).

Conclusions

We described the case of a patient with vasculitis lesions associated with HCV related cryoglobulinemia.

One of the main aspect discussed in this case was the adverse effects to therapies approved in the management of cryoglobulinemia. The main side effect observed was an acute necrotizing pancreatitis associated with plasmapheresis.

To the best of our knowledge such a complication has never been observed before and we believe that despite its absence among the most common complications of plasmapheresis, acute pancreatitis induced by haemolysis should be suspected in a patient undergoing therapeutic plasma exchange.

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