Case report

Efficacy of rituximab in severe and mild abdominal vasculitis in the course of mixed cryoglobulinemia

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ABSTRACT

Abdominal vasculitis represents a rare, but life-threatening manifestation in mixed cryoglobulinemic syndrome (MCsn), despite aggressive immunosuppressive treatments. Anti-CD20 monoclonal antibody, rituximab (RTX) has already been used with good results in MC in preliminary studies. No data have been provided, however, on the efficacy of RTX in gastrointestinal involvement of MCsn. Herein, we report the favourable outcomes of the gastrointestinal manifestations in five patients treated with RTX, where the diagnosis of abdominal vasculitis was confirmed by histopathological findings in 2 out of 5 patients, while in the other three patients the diagnosis was made on the basis of positive endoscopy or by integrating clinical and laboratory data.

Introduction

Life-threatening abdominal vasculitis rarely complicates the mixed crioglobulinemic syndrome (MCsn), with rapid worsening and poor prognosis (1-5). Vague and diffuse abdominal complaints may be referred at first. Occasionally, the disorder mimics inflammatory bowel disease, both clinically and radiographically (6), and thus, this organ manifestation must be first of all suspected and investigated in its early stages. Despite prompt treatment, the mortality remains high in any case. Rituximab (RTX) has already shown efficacy and good safety in MCsn in two preliminary pilot studies (7, 8) as well as in smaller series of MC nephritis (9, 10) and in other systemic vasculitis (11). Up to now, no data have been provided on the efficacy of RTX in gastrointestinal involvement of MCsn (12-14). We report both the short and the long-term efficacy of RTX on the gastrointestinal manifestations in 5 patients with MCsn, with life-threatening intestinal vasculitis in 2 out of those 5 patients.

Case reports

We describe 5 unselected consecutive patients with gastrointestinal involvement in the course of MCsn treated with RTX. Patients' characteristics are described in Table I. Two patients presented a definite life-threatening intestinal vasculitis (patients 1 and 5), while the remaining three patients complained of a less severe gastrointestinal symptoms consistent with initial gastrointestinal involvement in MCsn. In two patients (patients 1 and 5) the diagnosis of intestinal vasculitis was confirmed on pathologic tissue sample analysis (Fig. 1); in one patient (patient 2) the diagnosis was confirmed by the endoscopy findings only, while in the remaining two cases the diagnosis was based only on the clinical and laboratory features (Table I).

All the patients underwent RTX 375 mg/m^2/weekly for 4 weeks (in patient 1 the third and the fourth infusion were administered at week +8, and week +26, respectively). Gastrointestinal bleeding due to acute intestinal vasculitis was the indication for RTX therapy in 2 out of 5 patients (patients 1 and 5), while in the other three patients RTX was administered for other MCsn manifestations (Table I). High doses of corticosteroids were also given in patients 1 and 5, while in the other three patients (patients 2, 3 and 4) with mild gastrointestinal symptoms high doses of corticosteoids were avoided (patients 2, 3 and 4 were taking low to medium doses of corticosteroids for the other active MCsn-related manifestations). All the patients clinically responded to RTX. In both life-threatening patients

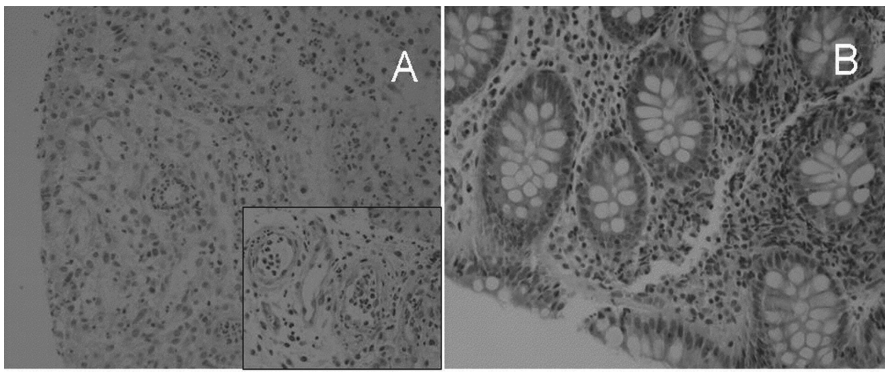

Fig. 1. Panel **A** (magnification 20x) shows intestinal vasculitis in gut biopsy obtained immediately before RTX therapy. Perivasculitis with lymphomonocytic inflammatory infiltrates and erosion of the endothelium and endovasculitis with many polymorphonuclear cells inside the vessels are shown in detail at major magnification (magnification 40x). Panel **B** (magnification 20x): gut biopsy six months after RTX first cycle shows modest lymphomonocytic infiltrates and normal intestinal glands with preserved mucus production, in the absence of vascular damage.

(patients 1 and 5) a clinical improvement started from the third week after the first RTX infusion and the complete clinical response (faecal occult blood test negative, disappearance of abdominal pain, diarrhoea solving) was observed at week +10 and +8 after the first RTX infusion, in patient 1 and 5, respectively. In patient 1, recovery from intestinal vasculitis was also demonstrated at the tissue level at week 26, with repeated endoscopy and biopsy. In patients 2, 3, 4 the clinical response, with focal occult blood test becoming negative and disappearance of abdominal pain, was observed at month +1 (*i.e.* at the end of the first month after the first RTX infusion). Mean follow-up was 14 months (range 6-27 months). Maintenance treatment with rituximab was employed in 2/5 patients starting at month +6 in both: patient 1 with a single infusion of RTX 375 mg/m^2 every two months in the first year and then every four months in the second year (last follow-up month 21+), and patient 5 with a single infusion of rituximab 375 mg/m^2. Then, patient 5 was treated with antiviral therapy for her hepatitis from month +7 (HCV-RNA was negative at

Table I.

Pts.	Age, sex	Diagnosis	Liver disease	Gastrointestinal symptoms	Fecal occult blood test	Instrumental tests	Histology	Other active MCsn manifestations	Previous treatments for intestinal vasculitis	Concomitant treatments for GI symptoms	Follow-up
1	74, F	HCV-related MCsn, SS	Chronic hepatitis	Severe, diffuse abdominal pain, bloody diarrhea leading to hypovolemic shock	Positive	Mucosal ulcers up to transverse colon (endoscopy)	MC-related vasculitis	Fever, serositis, peripheral neuropathy, arthralgias	CYC, AZA, high-dose steroids	MP 40 mg/day, tapered in 7 days to 12 mg/day, then suspended for 6 months	RTX maintenance therapy from month +6 (last follow-up month 21+)
2	74, F	HCV-related MCsn	Chronic hepatitis	Insidious, persistent abdominal pain	Positive	Petecchiae in the left colic flessure (endoscopy)	NA	Purpura, peripheral neuropathy, arthralgias	None	None	Relapse at month +24, then died for hepatorenal syndrome (last follow-up month +27)
3	60, M	HCV-related MCsn	Cirrhosis	Diffuse, colic abdominal pain, bloody diarrhea	Positive	ND	NA	Purpura, peripheral neuropathy	None	None	Relapse at month +15, then II RTX cycle (last follow-up month +16)
4	46, M	HCV-related MCsn	Cirrhosis	Continuous, diffuse abdominal pain, non responsive to fentanyl-transdermal	Positive	ND	NA	Purpura, skin ulcers, peripheral neuropathy	None	None	Stable remission (last follow-up month 6+)
5	31, F	HCV-related MCsn	Chronic hepatitis	Acute, colic abdominal pain, diarrhea, vomiting	Positive	Intestinal perforation (abdomen RX and CT scan)	Ischemic and vasculitic ulcers in the small bowel	Fever, purpura, GN, peripheral neuropathy	Plasma exchange, high-dose steroids	PD 1 mg/kg/day, tapered to 5 mg/day in 2 months	RTX single infusion at month +6, then antiviral therapy (last follow-up month 14+)

F: female; M: male, HCV: hepatitis C virus; MCsn: mixed cryoglobulinemic syndrome; SS: Sjögren's syndrome; ND: not done, NA: not available; GN: glomerulonephritis; CYC: cyclophosphamide; AZA: azathioprine; GI: gastrointestinal; MP: methylprednisolone; PD: prednisone; RTX: rituximab.

the last follow-up month 5+ from the beginning of the antiviral therapy with PEGylated interferon and ribavirin). Relapses with abdominal pain and focal occult blood test becoming positive again were recorded in 2 out of the 3 patients (patients 2 and 3) who did not undergo maintenance treatment with RTX. Patient 2 developed a hepatorenal syndrome and died. Patient 3 underwent a second full cycle of RTX (month +15 from the first RTX cycle). All the other clinically active manifestations (fever, purpura, peripheral neuropathy, glomerulonephritis, skin ulcers, serositis), when present, responded to RTX. Patient 1 developed a cytomegalovirus colitis after the second infusion, so the remaining two infusions were delayed.

Discussion

Gastrointestinal manifestations of systemic vasculitides are a challenge for the clinician due to the variety and possible severity of the individual vasculitis, ranging from isolated involvement (15), to life-threatening disease related to massive intestinal disease (*e.g.* acute mesenteric ischemia or infarction) (16). Generally, acute intestinal vasculitis presents as rapidly evolving disease with intensive abdominal pain, followed by signs of peritonitis and ileus, and may progress into a life threatening shock syndrome with high mortality (16). On the other hand, chronic intestinal vasculitides may account for the 10% of chronic vascular diseases not related to arteriosclerosis. However, chronic vascular diseases can mimic all types of gastrointestinal disorders. Chronic intestinal vasculitides are associated with important morbidity and mortality (16).

MC syndrome may rarely complicate with life-threatening abdominal vasculitis (1-5, 16). Vague and diffuse abdominal complaints may be referred at first. Thus, this organ manifestation must be primarily suspected and specifically investigated in its early stages. In a panarteris-like subset of MC syndrome necrotizing vasculitis may lead to the small aneurysm findings (mesenteric, celiac, hepatic, as well as renal) by abdomen arteriography (17, 18), as seen in classical panarteritis nodosa, while colic mucosa biopsy may show non-specific pathologic findings. A picture of acute abdomen and bowel infarctual lesions may then follow, though it may also develop *ab initio*. Finally, colitis pseudomembranosa may superimpose if the patient has been treated with large-spectrum antibiotics in our experience, and this further complicates the diagnostic and treatment approach. Such rare, though severe intestinal vasculitic complications of MCsn must be diagnosed and treated promptly, and mortality is high in any case. Therapy includes high-dose steroids and cyclophosphamide. Plasmapheresis is another treatment option as an induction therapy (19)**.** Gastrointestinal bleeding due to peptic ulcer, MC-unrelated, or due to oesophageal varices associated with portal hypertension in HCV-related cirrhosis (20) should be always considered in the differential diagnosis. The association of protein-losing enteropathy and cryoglobulinemia was recently reported in one patient (21). Another patient with MC syndrome and chronic diarrhoea, possibly due to intestinal vasculitis, has been reported (6). Of note, intestinal vasculitis also developed during interferon plus ribavirin therapy (22).

RTX has been used with benefits in a severe case of MCsn presenting also with inflammatory colonic stenosis (12), while Koukoulaki *et al*. (13) described a case of MCsn where an intestinal vasculitis occurred soon after RTX infusion, and responded to a single dose of infliximab 5 mg/kg. It is therefore unclear whether RTX alone, infliximab alone, or the combination proved effective in this case (13). Finally, in a recently published work by Visentini *et al*. (14) on the efficacy of low doses of RTX in MCsn were uneffective in one patient with intestinal vasculitis.

In our 5 cases, two patients experienced a severe, life-threatening intestinal vasculitis, while the remaining three patients complained symptoms and signs of 6 month duration related to less severe intestinal vasculitis. Of note, the diagnosis of intestinal vasculitis was confirmed by histopathological findings in the two acute life-threatening cases, while in the other three milder cases the diagnosis of intestinal vasculitis was supported by clinical and laboratory data, and "ex adiuvantibus" by the efficacy of RTX even on the gastrointestinal symptoms and signs. In both the cases of life-threatening intestinal vasculitis high doses of steroids in combination with immunosuppressors or plasmapheresis failed due to inefficacy or side effects. Even if RTX may have a long latency for its clinical efficacy, usually more than one month (9, 10), in our experience RTX provided an early clinical improvement in all patients, within the first month. Cytomegalovirus colitis was a serious adverse event recorded during RTX therapy in one case. Subsequent RTX maintenance infusions were administered in 2/5 patients, those with the life-threatening intestinal vasculitis, with no disease relapse in 2/2. By contrast, an intestinal disease relapse occurred in 2 out of the 3 patients who did not undergo maintenance RTX infusions, despite a milder gastrointestinal disease at onset. Thus, given that intestinal vasculitis in the course of MCsn has a very bad prognosis and may be difficult to treat or non responsive to aggressive treatments (plasma exchange, cyclophosphamide, pulse steroids) (1-5), RTX could be consider as an alternative treatment option for its efficacy and safety profile after the failure of the standard of care. Furthermore, the severity of the gastrointestinal involvement in MCsn and the high rate of relapses may justify a maintenance treatment regimen with RTX, in the absence of further experience.

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