CASE REPORT

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Complicated diverticulitis in a *de novo* kidney transplanted patient

LILIANA ANA TUŢĂ[1)], MĂDĂLINA BOŞOTEANU[2)], EUGEN DUMITRU[3)], MARIANA DEACU[2)]

[1)]*Department of Nephrology, Faculty of Medicine, "Ovidius" University of Constanţa, Romania*

[2)]*Department of Pathology, Emergency County Hospital, Constanţa, Romania; Department of Pathology, "Ovidius" University of Constanţa, Romania*

[3)]*Department of Gastroenterology, Emergency County Hospital, Constanţa, Romania; Department of Internal Medicine, "Ovidius" University of Constanţa, Romania*

Abstract

Diverticular disease is frequent amongst the elderly and immunosuppressed patients. It mainly presents as sigmoid diverticulitis, but severe complications, like bleedings, infections and colon perforation may occur, frequently due to immunosuppressive therapy. Moreover, antibiotherapy and hemostatics may not efficiently control evolution in such cases. Early diagnose and adequate treatment of colonic diverticulosis complicated with lower gastrointestinal bleeding and diverticulitis in immunocompromised patients. We report a 55-year-old patient who underwent *de novo* renal transplantation one year ago and recently developed a severe diverticular bleeding complicated by hemorrhagic shock. Colonoscopic examination revealed diverticular disease with diverticulitis and severe, diffuse bleeding, mainly in the descending colon. Due to his immunocompromised status and unfavorable evolution under hemostatics, recombinant coagulation factor VIIa (rFVIIa) was given to avoid surgery. The bleeding stopped after two doses of rFVIIa. Unfortunately, after three weeks, lower quadrant pain, tenderness, abdominal distention, and fever occurred, in spite of immunosuppressive drug changing and adequate conservative therapy. Abdominal computed tomography (CT) scan revealed complicated diverticulitis, so patient underwent surgery, with partial colectomy, followed by total recovery. In conclusion, diverticulosis coli complicated with lower gastrointestinal bleeding and diverticulitis in immunocompromised patients was for us a challenging diagnosis, as well as a therapeutic issue. Treatment options, usually based on our local resources and expertise, considered conservatory therapy as the first choice, keeping surgical maneuvers just as a rescue solution.

Keywords: diverticular disease, diverticulitis, kidney transplant, immunosuppression.

Introduction

Diverticulosis or diverticular disease is described as the presence of diverticula without associated inflammation, whilst diverticulitis means inflammation of a diverticulum or diverticula, usually accompanied by microscopic or macroscopic perforation [1]. Diverticular disease was frequently described in patients with end-stage kidney disease (ESKD) [2]. Although the incidence of diverticulitis does not appear to be increased in immunocompromised patients, the complications and sequelae of the diverticulitis are more severe in this special group. Diverticular bleeding is a common cause of major lower gastrointestinal tract bleeding, especially in the elderly [3]. Bleeding occurs in 15% of patients with diverticulosis and in most patients, the hemorrhage stops spontaneously; however, the risk of re-bleeding is around 30% after the first episode and increases to 50% after the second bleeding [4].

Continuous massive bleeding in a patient whose hemodynamic status is unstable is an indication for an emergent operation, which may be associated with high morbidity and mortality, either due to the elderly age, or to the immunocompromised status of most patients [5, 6].

Mycophenolate mofetil (MMF) is an immunosuppressive drug that lately replaced the older anti-proliferative drug, Azathioprine. It is usually used as part of the therapy for transplant recipients, combined with a calcineurin inhibitor (Cyclosporine or Tacrolimus) and a corticosteroid (Prednisolone). MMF' administration was associated with persistent, afebrile diarrhea, the commonest gastrointestinal symptom in transplanted patients (30%) [7]. Various studies conducted in transplant recipients in the past have revealed that this drug can induce colonic inflammation with varying phenotypes and similar, but not identical pathology, mimicking ischemic colitis and angiodysplasia of the colon, with hemorrhagic complications [8].

The aim of study was to underline the importance of rapid diagnosis and appropriate therapy of severe, hemorrhagic, diverticulitis, as a complication caused by immunosuppressive drugs, in a rare group of patients, like *de novo* kidney recipients. Surgical intervention may be associated with loss of renal graft so conservatory therapy, if possible, have to be preferred. This is the first published case report of a severe diverticular bleeding successfully treated with recombinant coagulation factor VIIa (rFVIIa) in a renal transplanted patient, excepting other reported surgical conditions, like: liver transplantation, retropubic prostatectomy or post-surgical intra-abdominal bleeding.

Case presentation

A 55-year-old male presented to the Department of Nephrology with one-month history of mucous diarrhea, first with few strains of blood, followed in the last 48 hours by severe rectal bleeding, and diffuse abdominal pain. His past medical history included primary idiopathic chronic

glomerular disease, secondary renal hypertension, first renal transplant for ESKD, in 1995, subsequent chronic allograft nephropathy and second kidney transplant in 2015, after six months of hemodialysis. He had symptoms pleading for irritable bowel syndrome from several years, but systematically refused to perform colonoscopy. All his medications including Bisoprolol 35 mg once-daily (od), Amlodipine 10 mg od, Allopurinol 100 mg od, Aspirin 75 mg od, Atorvastatin 20 mg od, Tacrolimus 4 mg twice per day (*bis in die* – bd), Prednisolone 5 mg od, and Mycophenolate mofetil 750 mg bd (re-started five months ago by the renal transplant team, after a break of six months, during hemodialysis), were longstanding. He was an ex-smoker, drank a glass of white wine every two days and had a family history of cardiovascular diseases and gout.

The clinical examination confirmed a bad general health condition, with intermittent fever up to 38°C and shivering. He was hypotensive (80/50 mmHg), had an increased pulse rate (118 beats/min) and tachypnea (22 breaths/min). The abdomen was distended, with normal bowel sounds and rebound tenderness, without any organomegaly. Furthermore, the clinical examination was unremarkable. Per-rectal examination revealed severe rectal bleeding. His blood tests on admission were as follows: sodium 126 mmol/L, potassium 4.1 mmol/L, urea 116.9 mg/dL, creatinine 2.96 mg/dL, hemoglobin 10.5 g/dL, white cell count 8000/µL, platelets 239 000/µL, C-reactive protein 34 mg/dL, and normal liver function tests. Other investigations included a normal stool culture, plain abdominal X-ray, and ultrasound scan of the abdomen (Figure 1).

Doppler ultrasound showed normal vascularization, absence of pathological elements in the *de novo* renal graft, with atrophy of the native kidneys. A colonoscopic examination of the large bowel was performed in order to evaluate the severe rectal bleeding, and revealed diverticular disease, complicated with severe hemorrhage (Figures 2 and 3).

On the current admission, diverticula in descending colon were identified by colonoscopy as the source of bleeding. Despite receiving six units of red blood cells and two units of fresh frozen plasma in six hours, his hemoglobin level decreased from 10.5 g/dL at the time of admission, to 6.3 g/dL. Results on coagulation tests were within normal ranges [Quick time, international normalized ratio (INR), partial thromboplastin time (PTT)]. The bleeding continued and the patient's hemodynamic status became more unstable every hour. Therefore, we decided to avoid surgical intervention and we used rFVIIa, as a last attempt to avoid surgery.

An intravenous bolus injection of 80 µg/kg rFVIIa was given, followed by a second dose of 40 µg/kg one hour later. In the next three days, no fresh blood was detected in the stool and the bleeding stopped completely without recurrence. No further blood transfusions were required. The next day fibrinogen level was light elevated and other coagulation tests [prothrombin time (PT), INR, PTT] were normal. There were no adverse events related to the use of rFVIIa. The patient was released from the hospital 12 days after the administration of rFVIIa, with the following blood tests: hemoglobin 10.8 g/dL, white blood cell count 6700/µL, platelets 210 000/µL, sodium 136 mmol/L, potassium 3.9 mmol/L, urea 46.9 mg/dL, creatinine 1.44 mg/dL, and normal liver function tests.

Unfortunately, three weeks after discharge, the patient accused brutal occurrence of lower quadrant pain, tenderness, abdominal distention, and fever, so he was hospitalized again in the Department of Nephrology. Paraclinical investigations showed leukocytosis (21 000/µL) with neutrophilia (18 400/µL), elevated C-reactive protein. Computed tomography (CT) scan image without contrast substance, because of elevated creatinine levels (>2 mg/dL) revealed sigmoid colon displaying diverticulosis with bowel wall thickening, and adjacent fat stranding, and suspicion of extra-colonic air and contrast, so patient started antibiotic therapy (Meropenem 1 g i.v. every 12 hours, and Metronidazole 500 mg/100 mL i.v. bd), with hemodynamic and hydroelectrolyte pre-operative correction. Afterwards, he underwent emergency surgery, a one-stage procedure with resection followed by primary anastomosis.

Pathological assessment of the surgical specimen, represented by a segmental colectomy measuring 30 cm in length, showed characteristic aspects of colonic diverticulosis. Gross examination revealed multiple sessile outpouchings along colonic serosa surface of 0.5–1 cm diameter, with a brown-grayish color and elastic consistency (Figure 4).

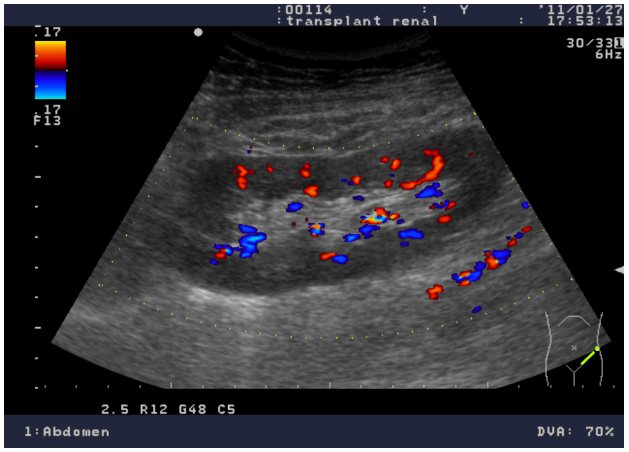

Figure 1 – ***Ultrasound exam: functional de novo kidney allograft.***

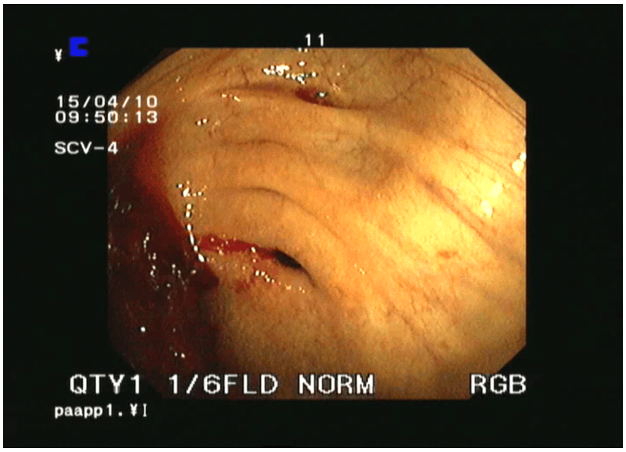

Figure 2 – ***Colonoscopy: diverticular hemorrhage.***

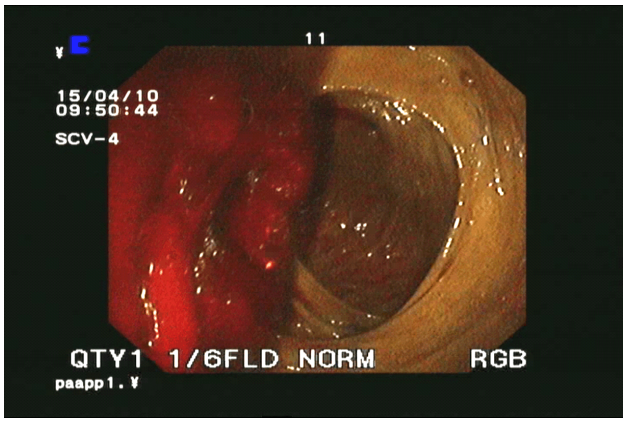

Figure 3 – ***Massive colonic diverticular hemorrhage.***

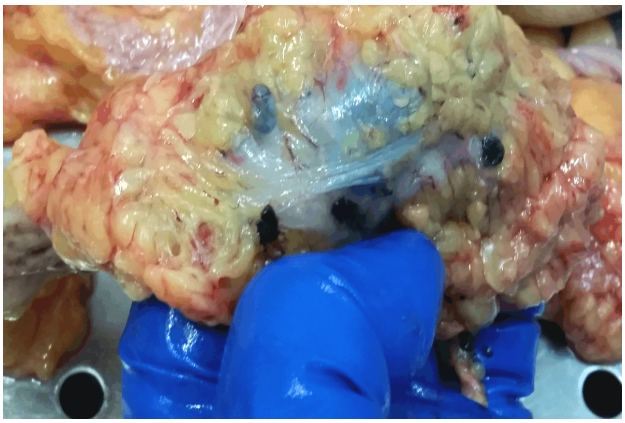

Figure 4 – ***Gross aspect of a diverticula on a serosal surface of the surgical specimen.***

Round to oval openings of 0.4–0.5 cm were identified on the mucosal surface, corresponding to serosal outpouching (diverticulum), filled by stools (Figure 5).

Also, gross examination of a diverticulum, after the removal of the stool deposits, showed hyperemia and superficial ulcerations covered by fibrin. At the same time, colonic mucosa between outpouching openings had prominent folds, pearly-pink color and firm consistency (Figure 6).

Microscopic examination of the samples taken from outpouching areas showed complete herniation of a mucosa and submucosa through colonic muscle layer, reaching serosal surface. Herniated layers were surrounded by a thin coat of smooth muscle cells, composing muscularis mucosae (Figure 7).

Lamina propria had enlarged lymphoid follicles and increased inflammatory infiltrates composed predominantly by lymphocytes. Glands showed moderate architectural distortion and mild cryptitis. We noticed also superficial ulcerations of the mucosa covered by deposits composed by fibrin, red blood cells and neutrophils (Figure 8).

On a corresponding serosal layer, we observed fibrosis and hyaline deposits, expanding into the surrounding adipose tissue, as well as thickened wall vessels (Figure 9).

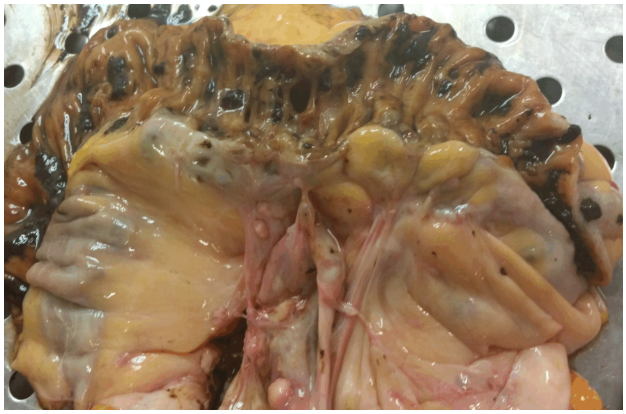

Figure 5 – ***Mucosal openings corresponding to diverticula.***

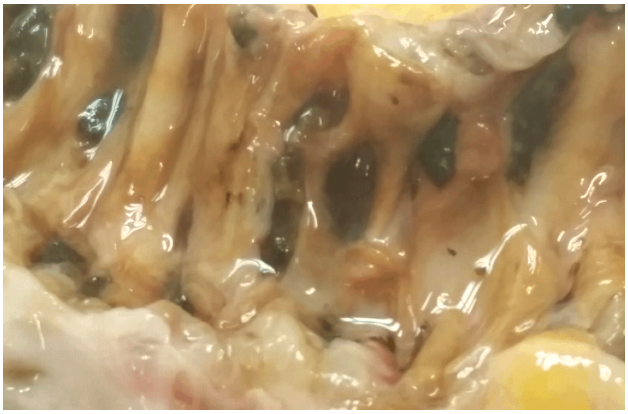

Figure 6 – ***Prominent folds of a mucosa between diverticular openings.***

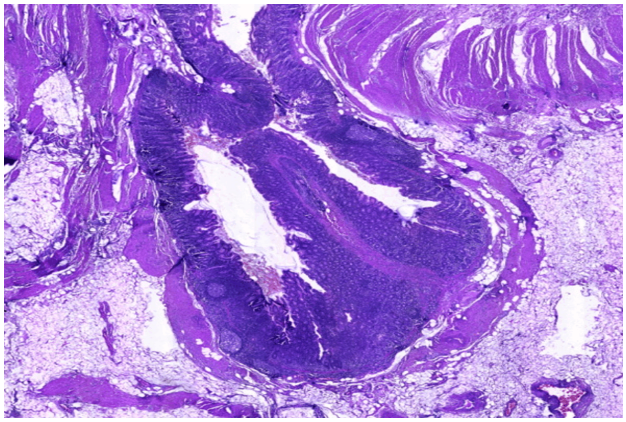

Figure 7 – ***Complete herniation of the mucosa and submucosa, through colonic muscle layer (HE staining, ×40).***

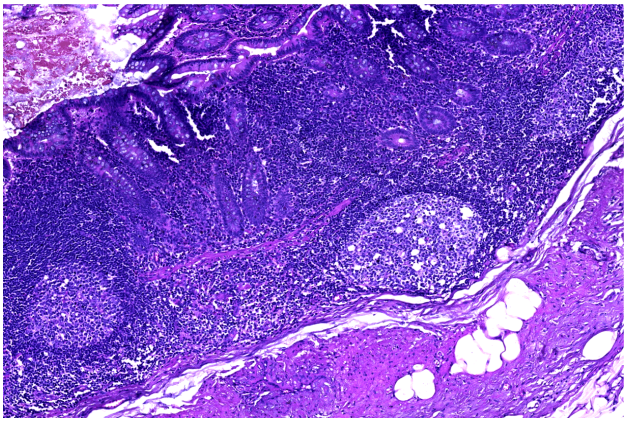

Figure 8 – ***Superficial ulcerations of the mucosal surface covered by fibrin and neutrophils, accompanied by moderate architectural distortion of the glandular structures (HE staining, ×40).***

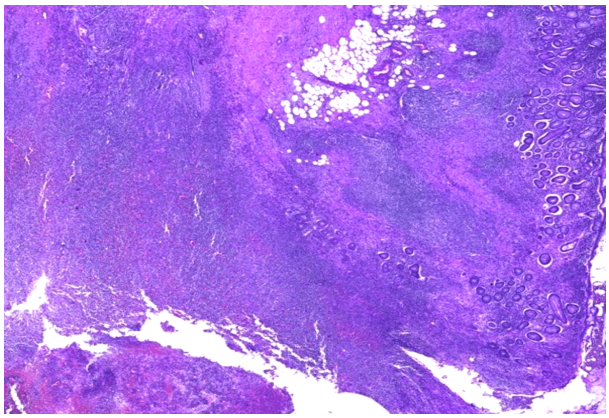

Figure 9 – *Lamina propria with enlarged lymphoid follicles and serosal surface showing fibrosis and hyaline deposits expanding into the adipose tissue (HE staining, ×200).*

The final histopathological diagnosis was complete colonic diverticulosis accompanied by chronic unspecific inflammation.

Discussion

Diverticular disease has been reported in up to 42% of patients with ESKD [8]. Complicated diverticulitis defined as diverticulitis involving free perforation, abscess, phlegmon, or fistula in transplanted patients was reported in 1.1% of the cases [9]. This group of patients may lack a normal inflammatory response and usually present with minimal signs and symptoms, which may delay an early diagnosis and adequate treatment. There is an increased rate of free perforation (43% *vs.* 14% in immunocompetent patients), increased need for surgery (58% *vs.* 33%), and increased postoperative mortality (39% *vs.* 2%) [10].

Severe diverticular bleeding in the high-risk patients (elderly, immunocompromised) can be sometimes difficult to manage. When diagnosing a patient with lower gastrointestinal bleedings, the endoscopist may use variable hemostatic methods [11]. The use of epinephrine injection, hemoclips and electrocoagulation in localized diverticular bleeding can obtain rapid hemorrhagic control in 25% of patients with active bleeding. Reviews of the literature reveals 14–25% incidence of early recurrent bleeding following endoscopic treatment of diverticular bleeding utilizing various techniques [12]. Surgical intervention may be associated with high morbidity and mortality rates due to the underlying conditions of these patients. Therefore, hemostatic treatment that can avoid surgical intervention would be beneficial.

Recombinant coagulation factor VIIa has been successfully used to control severe bleeding or reduce the need of blood transfusions in several surgical conditions, including liver transplantation, retropubic prostatectomy, and post-surgical intra-abdominal bleeding [13]. To the best of our knowledge, our patient is the first case of severe diverticular bleeding successfully treated with rFVIIa in a renal-transplanted patient. In the normal population, about 1% of circulating FVII is in the form of FVIIa; but, in the absence of tissue factor, activated FVIIa does not initiate coagulation. At the pharmacological doses of FVIIa given for bleeding episodes, all tissue factor sites are saturated, leaving excess FVIIa to bind loosely to activated platelets, and this binding can then lead to direct activation of factor X, too. Factor Xa in the presence of factor Va can then convert prothrombin to thrombin on the surface of these platelets [14, 15].

Due to the patient hemodynamic instability, we initially used rFVIIa as a last resource to stop the bleeding, in order to avoid operation and its potential complications. We consider it might be impossible that spontaneous cessation of bleeding would have been accomplished without factor VII substitution, but exactly after injection of rFVII the bleeding stopped completely, and so we may postulate that rFVII successfully treated the bleeding. Many case reports describing clinical efficacy and safety of rFVIIa in different acquired bleeding situations can be found in literature. Despite these positive experiences, randomized and controlled trials are rare. There are known factors negatively influencing the efficacy of rFVIIa (*e.g.*, hypothermia, acidosis, prolonged preadministration PT or hyperfibrinolysis), so it is obvious that these factors, especially acidosis, should be corrected prior to the administration of rFVIIa [16, 17].

Mycophenolate mofetil, an immunosuppressive drug, has been reported to be associated with persistent, afebrile diarrhea, which is the commonest gastrointestinal symptom in 30% of the transplanted patients [2]. Reports of upper gastrointestinal tract hemorrhage (due to gastric or duodenal ulceration), large bowel perforation and pancreatitis have been reported in the past. Various studies conducted in post-transplant recipients have revealed that this drug can induce colonic inflammation and a particular pathology mimicking ischemic colitis, inflammatory bowel disease or colonic angiodysplasia [2, 18]. Histological features may vary from mucosal and submucosal edema and hemorrhage, with or without partial or complete necrosis and ulceration of the mucosa. The lamina propria has a dense eosinophilic quality. Iron laden macrophages, if present, is an additional pointer to the diagnosis [18].

From the histopathological point of view, intestinal diverticulosis consists in herniation of layers composing intestinal wall with outpouchings formation [19]. Colonic diverticulosis is named also pseudodiverticulosis, because only mucosa and submucosa are affected by herniation. This type of mucosal and submucosal prolapsing occurs on a weak point of the intestinal wall, represented by sites of entering of the blood vessels into the colonic wall. It develops along the connective tissue surrounding *vasa recta*, and it is favored by the discontinuance of the colonic longitudinal muscle [20, 21].

In 90% of cases, the main colonic locations of diverticular disease are represented by sigmoid segment followed by descending part, transversal and finally ascending segment. This preferred location of the diverticulosis on the sigmoid segment is explained by the increased number and dense distribution of *vasa recta* in this part of the colon [19]. Several studies described two types of pseudodiverticulosis: complete and incomplete. From histopathological point of view, in case of complete pseudodiverticulosis muscle layer is entirely penetrated by mucosal and submucosal prolapsing that reach serosal surface. Incomplete pseudodiverticulosis is defined as a mucosal and submucosal prolapsing arrested within muscle layer [22].

In our case, the patient presented initially with afebrile,

non-infectious mucous diarrhea after five months from starting again the use of MMF. Colonoscopy confirmed the diagnosis of drug-induced severe hemorrhagic diverticulitis, and its symptoms resolved after 15 days of withdrawal of the drug and IV administration of rFVIIa. MMF was stopped after consultation with the renal transplant team and patient was switched to Azathioprine. Currently, the cost of rFVIIa is relatively high, especially in the current socio-economic situation in Romania, but obvious is less expensive than surgery and its potential complications.

Despite important advances in interventional endoscopy, 10 to 25% of cases of lower gastrointestinal bleedings will require surgical intervention. In patients like our case, with successful preoperative endoscopic localization, a segmental colon resection is usually performed. This procedure has a reported mortality of 10%, and a 14–25% risk of rebleeding, even not only for patients with pan-colonic diverticular disease [23].

Conclusions

Our case report showed that the use of a global anti-hemorrhagic factor, such as rFVIIa, can temporary control a massive colonic bleeding, even in complicated, immuno-compromised patients with diverticulosis, in conditions of failure of traditional hemostatic therapy. The off-label use of rFVIIa implies high costs, which nowadays is generally a major issue in clinical medicine. Treatment of severely complicated diverticulitis needed broad-spectrum intravenous antibiotics, which was ineffective in our immunosuppressed patient, and the decision to proceed with elective surgery was taken on an individual basis.

Conflict of interests

The authors declare no conflict of interests.

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Corresponding author

Eugen Dumitru, Associate Professor, MD, PhD, Department of Internal Medicine, Faculty of Medicine, "Ovidius" University of Constanţa, Emergency County Hospital, 145 Tomis Avenue, 900591 Constanţa, Constanţa County, Romania; Phone +40744–761 454, e-mail: eugen.dumitru@yahoo.com

Liliana Ana Tuţă, Associate Professor, MD, PhD, Department of Nephrology, Faculty of Medicine, "Ovidius" University of Constanţa, Emergency County Hospital, 145 Tomis Avenue, 900591 Constanţa, Constanţa County, Romania; Phone +40722–300 505, e-mail: tutaliliana@yahoo.com

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