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CASE REPORTS

SCLEROTHERAPY OF ESOPHAGEAL VARICES IN SEVERE HEMOPHILIA A PATIENT AND HIGH TITER INHIBITOR – CASE REPORT

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In cirrhotic hemophilia patients bleeding from esophageal varices is a serious clinical condition due to congenital deficiency of clotting factors VIII or IX, decreased prothrombin synthesis and hypersplenic thrombocytopenia. In hemophiliac with high-titer inhibitor bypassing therapy is required with activated prothrombin complex concentrates (aPCC) or recombinant activated coagulation factor VII (rFVIIa). Doses and duration treatment with these agents following endoscopic treatment of esophageal varices have not been yet established.

Authors report the first case of a severe hemophilia A patient with high titer inhibitor (40 BU) treated with repeated injection sclerotherapy. The patient was admitted with symptoms of massive esophageal variceal hemorrhage ceased with emergency sclerotherapy. Bypassing therapy was administered with aPCC at initial dose of 72.5 U/kg and then with average daily dose of 162 U/kg through 5 days. To achieved a total eradication of esophageal varices the patient was then subjected to four elective sclerotherapy procedures. Two were covered by aPCC with daily dose of 120 U/kg and 145 U/kg for 4 and 3 days respectively and the following two procedures were covered by rFVIIa with the initial dose of 116 μg/kg and the next doses of 87 μg/kg administered every 3 hours in procedure day and every 4 hours on the next two days. During all procedures excellent hemostasis was achieved and no hemorrhagic or thromboembolic complications were observed. Bypassing regimen therapy with aPCC and rFVIIa we applied have been shown to be safe and effective in this patient subjected to sclerotherapy procedures.

Key words: hemophilia, inhibitor, esophageal varices, injection sclerotherapy, aPCC, rFVIIa

Esophageal variceal bleeding is the most severe complication of portal hypertension, still burdened with high mortality. In hemophilia patients portal hypertension develops in the course of liver cirrhosis most often caused by chronic viral hepatitis B. Most patients with hemophilia were infected by hepatitis B or hepatitis C virus from intravenous infusions of contaminated plasma-derived clotting factors concentrates before 1987. As result of chronic infection with hepatotropic viruses approximately 10 to 20% patients progressed to cirrhosis during 20-year time span and are at risk for complications including end-stage liver diseases manifested by esophageal varices, ascites and encephalopathy (1). In cirrhotic hemophilia patients bleeding from esophageal varices is a serious clinical condition due to congenital deficiency of clotting factors VIII or IX, decreased prothrombin synthesis and hypersplenic thrombocytopenia.

Up to date only few cases of management for esophageal varices in hemophilia patients have been reported in literature. These include spleno-renal shunt (2), transjugular intrahepatic portal systemic shunt (3), esophageal variceal sclerotherapy (4-7) and ligation (8). These methods however have never been applied in severe hemophilia patients with high titer inhibitor.

Standards of by-passing therapy covering hemostasis in surgical procedures in hemophilia patients with high titer inhibitor include only two agents: plasma-derivated activated prothrombin complex concentrates (aPCC) – FEIBA® (Factor Eight Bypassing Activity, Baxter AG, Vienna, Austria) and recombinant activated coagulation factor VII (rFVIIa) – NovoSeven® (Novo Nordisk A/S, Bagsvaerd, Denmark). FEIBA® is applied in doses of 50-100 units/ kg b.w. every 8 or 12 hours up to maximum daily dose of 200 U/kg. NovoSeven® is applied in a single dose of 120-180 mcgr/kg b.w. before procedure and 90 mcgr/kg b.w. every two hours on day one and 2 after procedure, every 3 hours on 3-4 day, every 4 hours on day 4-6 and every 6 hours on days 7-10. For endoscopic sclerotherapy of esophageal varices the doses and treatment duration with these agents have not yet been established.

The aim of the paper was to present the first case of severe hemophilia A patient with high-titer inhibitor treated with repeated esophageal injection variceal sclerotherapy covered by consecutively applied aPCC and rFVIIa.

CASE REPORT

A 38-year-old man with severe hemophilia A and high-titer inhibitor (40 Bethesda Units, BU) was referred to our Department in November 2010 by a district hospital with symptoms of massive upper gastrointestinal bleeding. For this patient with diagnosed liver cirrhosis (Child-Pugh A) due to chronic HCV infection it has been the first episode of bleeding in life. Before transport he received 5000 units (U) of FEIBA® and two units of packed red cells. After admission, on physical examination, a heart rate was 120 /min, a blood pressure was measured as 115/80 mm Hg and a body weight of 69 kg. The other vital signs were of normal. Laboratory findings showed: Hb 7.9 g/dL, RBC 2.73x 10^{12}/L, Ht 24, platelet count 96x10^{9}/L, bilirubin 43 μmol/L. Coagulation parameters were as follows: aPTT 94 s, prothrombin time 12 s, prothrombin index 82%, INR 1.2, fibrinogen 2.4 g/l. The other laboratory findings were of normal.

Emergency endoscopy revealed active bleeding from esophageal varices of the III grade (fig. 1a). No other bleeding source was found. Injection sclerotherapy was performed using 15 ml of 5% ethanolamine oleate (EO) which resulted in immediate cessation of bleeding. The patient was given somatostatin in bolus injection (0.25 mg) followed by continuous infusion of 6 mg per 24 h, intravenous antibiotic, and additionally 3 units of packed red cells and 5000 U of FEIBA®. During consecutive four days the patient was administered 4000 U of FEIBA® every 8 hours and 3000 U of FEIBA® every 8 hours on the fifth day. Over a period of 5 days a total dose of 67,000 U of FEIBA® in 17 infusions was administered. On day 4 following admission the patient underwent left elbow joint puncture due to hematoma. On day 6 after admission he was subjected to the second, elective procedure of esophageal varices sclerotherapy with 10 ml of 5% EO. Before procedure, the patient received 3000 U of FEIBA® and another two doses of 3000 units every 8 hours on the same day. On the first and second post sclerotherapy day he was administered 3000 U of FEIBA® every 8 hours and on day 3 he was given 2000 U every 12 hours. No complications were observed and the patient was discharged on day 5 after admission. Over a period of 4 days a total dose of 33,000 U of FEIBA® in12 infusions was administered.

Fifteen days later, after an episode of gastrointestinal bleeding which required transfusion of 2 units of packed red cells, the patient was readmitted to our Department. No active bleeding was found during endoscopy and the patient was subjected to a third procedure of injection sclerotherapy with 10 ml of 5% EO. He received 5000 U of FEIBA® before and 12 hours after the procedure. Therapy with FEIBA® was continued for the next two days in two equal daily doses of 10000 U. Over 3 days a total dose of 30,000 U of FEIBA® was administered in 6 infusions. No complications were observed during and after the third procedure.

After three weeks the patient was admitted electively with the aim of continuing endo-

scopic treatment of esophageal varices. The fourth procedure of esophageal varices injection with 10 ml of 5% EO was performed. Before the procedure the patient received 8 mg of NovoSeven®. After sclerotherapy the patient was given two 6 mg doses of rFVIIa every two hours and then 6 doses every three hours approximating a total daily dose of 56 mg. Therapy with NovoSeven® was continued on the first and second post sclerotherapy days. On each of these days 6 mg doses were administered every 6 hours approximating a daily dose of 24 mg. Total peri-fourth sclerotherapy procedure dose were of 104 mg of rFVIIa. During sclerotherapy and in the post procedure period no complications were observed. The fifth sclerotherapy procedure was performed after 8 weeks. Protocol treatment with rFVIIa was the same as during the fourth sclerotherapy session (tab. 1).

The total costs of by-passing treatment include costs of three sclerotherapy procedures covered together by 130,000 units of FEIBA® and two procedures covered by 208 mg of NovoSeven®. The costs of treatment with FEIBA® were 98,000 Euro and with NovoSeven® 158,000 Euro.

After 6 months the patient was followed-up in the outpatient department. During this period no gastrointestinal bleeding was noted. Control endoscopy revealed total eradication of esophageal varices; esophagus, stomach and duodenum were of normal. The patient is periodically followed-up in the outpatient department. No recurrent esophageal varices were endoscopically diagnosed after three years (fig. 1b).

DISCUSSION

Sclerotherapy of esophageal varices is an effective method in the management of variceal bleeding; hemostasis is achieved in over 90% of patients (9, 10). If performed electively, as repeated obliteration procedures after variceal bleeding, it results in total eradication of varices in the majority of patients (11). There are only few literature reports on endoscopic treatment of esophageal varices in hemophilia patients. Yamada et al. (8) and Kayashima et al. (5) presented two hemophiliacs treated respectively with ligation and sclerotherapy for primary prophylaxis of variceal bleeding. Fukumoto et al. (4) reported a hemophilia A patient with high-risk varices treated with prophylactic sclerotherapy but the first cohort of hemophilia patients treated with esophageal varices sclerotherapy for emergency and secondary hemorrhage prevention was reported by Szczepanik et al. in 2000 (7). However, up to date there has been no case report of a hemophilia patient with high responding inhibitor endoscopic treated for esophageal varices.

In the presented case, successful emergency sclerotherapy for massive esophageal variceal bleeding was performed and thereafter the patient was subjected to four procedures of elective sclerotherapy to achieve variceal eradication. The emergency procedure and the next two sclerotherapy procedures were covered by FEIBA®, the two latter ones were covered by NovoSeven®. In the literature there is no data on doses or duration of bypassing therapy covering sclerotherapy procedures in hemophilia patients with high-titer inhibitor. Thereafter dosing of FEIBA® and NovoSeven® and duration of therapy were based on our own experience from treatment of hemophilia patients with no

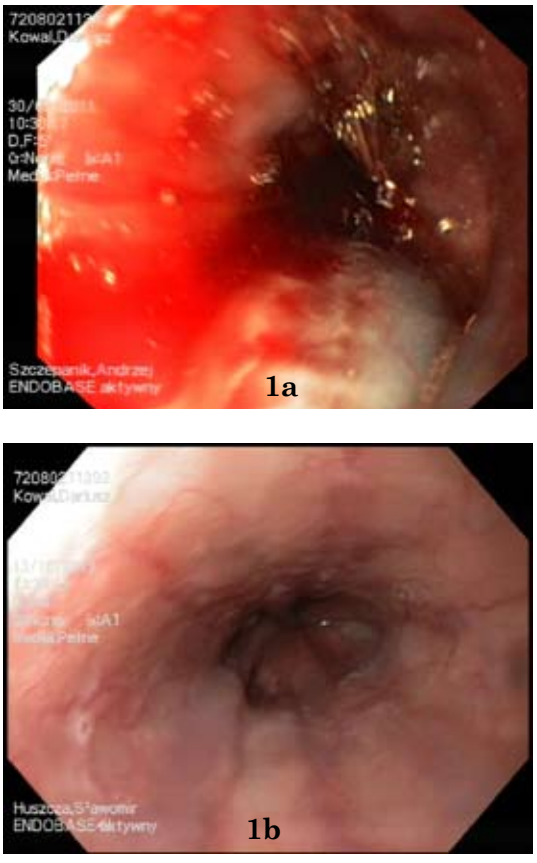

Fig. 1a, b. Esophageal varices before (1a) and after sclerotherapy (1b)

Table 1. Treatment characteristics of injection sclerotherapy (IS) procedures

IS nr	Time sequence (days)	Bypasing therapy	Initial bolus dose	Number of doses	Treatment duration (days)	Total dose (U or mg)	Average daily dose (U/kg or mg/kg)	RBC transfusion (units)	Hemostatic outcome
1	0	aPCC	72,5 U/kg	17	5	67 000 U	162 U/kg	5	excellent
2	6	aPCC	43,5 U/kg	12	4	33 000 U	120 U/kg	2	excellent
3	25	aPCC	72,5 U/kg	6	3	30 000 U	145 U/kg	0	excellent
4	46	rFVIIa	116 μg/kg	17	3	104 mg	0,5 mg/kg	0	excellent
5	112	rFVIIa	116 μg/kg	17	3	104 mg	0,5 mg/kg	0	excellent

inhibitor which indicated that a three-day replacement therapy is sufficient (6).

Bypassing therapy after emergency sclerotherapy was of longer duration than after elective procedure, and an average daily dose of 162 U/kg was also higher. We also applied different dosage of FEIBA® following each of the elective sclerotherapy procedures, which proved equally effective. Initial dose before the second procedure was lower (43,5 U/kg) as compared to the third one, in which we applied the same dosage i.e. 72.5 U/kg. Average daily doses following elective procedures were different; 120 U k/g and 145 U/kg respectively. Hemostasis achieved with FEIBA® infusions following all three procedures, regardless the differences in dosage regimen, was excellent and there were no intra-procedure haemostatic complications or thromboembolic events.

To achieved total eradication of esophageal varices the patient required a fourth and fifth sclerotherapy procedure which were covered by NovoSeven ®. Initial dose of 116 μg/kg and the next doses of 87 μg/kg were consistent with those recommended for minor surgical procedures, though the frequency of administration was higher on procedure day (12). Excellent hemostasis was achieved with Novoseven® following both procedures and there were no intra-procedure haemostatic complications.

Literature data revealed that the overall efficacy of inhibitor bypassing therapy with aPCC and rFVIIa ranges from 80-90% (13, 14). In the presented case haemostatic efficacy was excellent and the doses which we administered were in general consistent with international consensus recommendations (12,15). FEIBA® and NovoSeven® therapy were well tolerated by patients with no hemorrhagic complications and clinical evidence of disseminated intravascular coagulation or any other thromboembolic adverse events following any of the five procedures. The bypassing therapy regimen which we applied has been shown to be safe and effective in this patient subjected to sclerotherapy procedures.

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