Successful treatment of a bleeding esophageal sclerotherapy ulcer with endoscopic injection of granulocyte-macrophage colony-stimulating factor

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Endoscopic sclerotherapy is a well-established treatment for esophageal variceal hemorrhage and prevention of recurrent variceal bleeding.1-3 Nevertheless, complications of sclerotherapy are common and may be acute, intermediate, or late.4-7 One of the most frequent is ulceration of the esophagus, which occurs in 25% to 75% of patients after sclerotherapy. These ulcerations can lead to chronic strictures, dysmotility, and recurrent hemorrhage.7 This is a report of the first successful treatment of a chronic esophageal ulcer after sclerotherapy for recurrent variceal hemorrhage in a patient with liver cirrhosis, thrombocytopenia, hemophilia A, and insulin-dependent diabetes mellitus (IDDM) with local endoscopic submucosal injection of granulocyte-macrophage colony-stimulating factor (GM-CSF).

CASE REPORT

A 45-year-old man was admitted for further evaluation after treatment at another hospital of a first episode of esophageal variceal hemorrhage by sclerotherapy with polidocanol. He was known to have liver cirrhosis (Child-Pugh A) of unknown etiology. He tested negative for all viral markers and human immunodeficiency virus; he was not an alcoholic and no other common cause of chronic liver disease was identified. Liver biopsy revealed micronodular cirrhosis without fatty changes or increased storage of iron or copper. The patient also had IDDM, intermittent thrombocytopenia, and hereditary hemophilia A, for which he had been treated repeatedly with factor VIII replacement.

Endoscopy showed grade III to IV esophageal varices, portal hypertensive gastropathy, gastric varices, and duodenal varices. To prevent a recurrence of bleeding, band ligation was performed by using a multiband ligator to eradicate esophageal varices. Treatment at discharge included orally administered propanolol and omeprazole. Esophageal variceal bleeding recurred 1 week later and the patient underwent further sclerotherapy at his local hospital.

Because of recurrent hemorrhages and the failure of endoscopic therapy in combination with coexisting hemophilia and good liver function, a transjugular intrahepatic portosystemic shunt (TIPS) was established.8-11 The TIPS procedure was performed 3 weeks after the second episode of bleeding. Subsequent endoscopy revealed a reduction in the esophageal varices to grade I and disappearance of the gastric and duodenal varices.

Sixteen months after the TIPS procedure, the patient experienced 2 further episodes of esophageal variceal hemorrhage. He underwent emergency sclerotherapy followed by balloon tamponade at his local hospital. Subsequent endoscopy in our department disclosed a 2-cm diameter ulcer covered by a coagulum in the distal esophagus (Fig. 1). Removal of the coagulum resulted in immediate bleeding, which stopped after local injection of epi-nephrine and then band ligation. Angiography revealed occlusion of the TIPS as the cause of the recurrent hemorrhage, and the stent was dilated. Endoscopy 4 and 8 days later disclosed persistence of the 2-cm ulcer but no varices. To prevent another occlusion of the stent the patient was treated at this time with the platelet-aggregation inhibitor clopidogrel.

Two weeks later the patient was readmitted to his local hospital with another acute episode of upper GI hemorrhage. At emergency endoscopy the previously noted ulcer was found to be the site of bleeding. Endoscopy in our unit confirmed the presence of low-grade persistent bleeding from the ulcer; argon-plasma-coagulation was performed and treatment with clopidogrel discontinued. Sixteen days later, while still in the hospital, the patient again had a subacute episode of bleeding and required a blood transfusion. Endoscopy revealed the ulcer to be unchanged with signs of bleeding and a large amount of blood in the stomach. To achieve hemostasis, the ulcer was again treated by argon-plasma-coagulation.

Endoscopy 1 week later revealed the same persistent ulcer covered by a large coagulum with evidence of ongoing subclinical bleeding. It was evident that without
healing of the ulcer, which had persisted for 6 weeks, hemostasis would not be achieved. Because of our awareness of the favorable results of treatment of chronic skin ulcers with GM-CSF, it was suggested to the patient that the esophageal ulcer be treated with this agent.

By using a standard sclerotherapy catheter with a retractable 25-gauge 5-mm needle, 400 \( \mu g/4.44 \) million IU of GM-CSF were injected submucosally in 4 quadrants close to the border of the ulcer (Fig. 2). A commercially available and registered GM-CSF preparation was used in a dosage of 400 \( \mu g/4.44 \) million IU/1 mL (Leucomax, Aesca Inc., Traiskirchen, Austria). The total dose of 400 \( \mu g \) GM-CSF was diluted with normal saline solution to a total volume of 8 mL. Each of the 4 quadrant injections consisted of 100 \( \mu g \) GM-CSF, diluted with normal saline solution to 2 mL. At endoscopy 5 days later the diameter of the ulcer was reduced by 50% and there were no signs of bleeding. Another 400 \( \mu g/4.44 \) million IU of GM-CSF were injected as above. Two days later the ulcer had almost disappeared (Fig. 3), and another 7 days later only a small scar could be identified at the ulcer site (Fig. 4). At follow-up 18 months later, there had been no further episodes of bleeding, the patient had not experienced dysphagia, and there was no evidence of stricture formation.

**DISCUSSION**

Chronic esophageal ulcer is a well-known complication after sclerotherapy for variceal hemorrhage. Occurring in 25% to 75% of patients, it is the most frequent complication of the procedure and often leads to chronic strictures and dysmotility of the esophagus. These strictures usually require repeated dilation despite the higher complication rate for dilation procedures in patients with portal hypertension as compared with patients without cirrhosis.

Two additional factors were present in our patient that crucially influenced the clinical course. The first was hereditary hemophilia A and intermittent thrombocytopenia, which, in addition to portal hypertension, was the most important risk factor for recurrent ulcer bleeding. The second was IDDM, which probably caused delayed ulcer healing. The adverse effect of IDDM on tissue healing has long been recognized, and the disease is known to be associated with delayed healing of ulcers in the GI tract as well as an increased risk for ulcer bleeding.

GM-CSF is a well-established treatment for chronic ulcers of the skin. Chronic leg ulcers in diabetic necrobiosis lipoidica have been successfully treated with topically applied GM-CSF. In patients who are nondiabetic with ulcers caused by chronic venous insufficiency, and in patients with chronic ulcers caused by pressure necrosis, the results of topical treatment with GM-CSF have been excellent.

For mucosal ulcers of the mouth, such as those that occur after radiotherapy or chemotherapy, or aphthous ulcerations in patients with acquired immunodeficiency syndrome, the data for local GM-CSF treatment are also promising. However, there has been no report of local endoscopic treatment of ulcers in the GI tract. To our knowledge, this is the first report of local GM-CSF injection as treatment for a chronic benign ulcer of the GI tract.
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Because several methods of treatment were unsuccessful in healing the esophageal ulcer in our patient, local endoscopic injection of GM-CSF was performed. The rapid decrease in ulcer size after the first injection and the complete and sustained healing obtained after only 2 injections of 400 µg GM-CSF were surprising. Moreover, follow-up at 18 months did not show any evidence of recurrent ulcer, hemorrhage, stricture, or dysmotility. It is our belief that these results strongly warrant further investigation of this form of treatment in large groups of patients including controlled, randomized trials.

REFERENCES