

Healing of Leg Ulcers Associated With Transjugular Intrahepatic Portosystemic Shunt in Decompensated Cirrhosis: Case Series of a Possible Hepatodermal Syndrome

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Abstract: The occurrence of leg ulcers in patients with cirrhosis is not well documented in the literature. In this case series, we describe 4 patients with cirrhosis complicated by leg ulceration that failed all conventional therapy, yet healed completely following the placement of transjugular intrahepatic portosystemic shunt. The course of disease and the possibility of a hepatodermal syndrome underlying this observation are discussed.

The most common cause of leg ulcers is venous stasis, and the underlying mechanism is venous hypertension secondary to venous thrombosis or valvular incompetence.¹⁻³ Patients with decompensated cirrhosis can develop leg ulcers, the treatment of which is difficult and usually supportive; however, there is no published information regarding this complication in patients with liver disease.

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure used to treat complications of portal hypertension, including uncontrolled or recurrent variceal bleeding and refractory ascites.^{4,5} In this case series, we describe 4 patients with decompensated cirrhosis who presented with refractory leg ulcers, which healed in association with decompression of the portal system associated with TIPS placement.

Patient 1

A 61-year-old man managed weekly with large-volume paracentesis presented with ascites refractory to diuretics. The patient had a history of a venous leg ulcer on the lateral side of the distal third of the right leg that had been attributed to unilateral varicose veins. The ulcer had measured 2.8 cm (with clean margins) and had been given several local treatments, including frequent ulcer dressings, which had been associated with only partial healing over the several months prior to the patient's presentation with ascites. Upon his presentation, the patient was listed for orthotopic liver transplantation (OLT), and TIPS was placed for the management of ascites. Over the first several weeks following placement of TIPS, healing of the ulcer was observed and appeared to be complete by approximately the fifth week after the procedure. No antibiotics were administered to the patient. Three months later the patient underwent OLT, but 1 month after surgery he developed ascites in association with the recurrence of the leg ulceration. The ulcer was managed with local therapy. Six weeks post-OLT, the patient had a massive upper gastrointestinal bleed from grade IV esophageal varices, which was refractory to obliterative therapy. As the patient had recurrent episodes of variceal bleeding, an angiogram was performed and revealed extensive portal vein thrombosis as a cause for the development of portal hypertension.

Patient 2

A 54-year-old man with chronic hepatitis C and cirrhosis complicated by recurrent variceal bleeding and mild ascites had a chronic venous leg ulcer in the absence of edema of the lower extremities. The ulcer measured 2.4 cm on the lateral aspect of the right ankle. No signs of infection or cellulitis were documented. Apart from local dressing of the ulcer site, the patient received antibiotics only on one occasion approximately 1 year prior to the patient's referral for TIPS. The patient underwent TIPS for prevention of further variceal bleeding and was placed on the waiting list for OLT. The leg ulcer healed completely over the 6 weeks following the placement of TIPS. Over the subsequent 2 years, during which the patient was followed at our hospital and patency of the TIPS was documented sonographically, no ulcer recurrence was noted.

Patient 3

A 52-year-old woman had a 1.8-cm venous ulcer on the dorsum of the left foot for several years. A vascular surgeon treated her ulcer with conventional local therapy, including dressings, for more than 2 years. The patient



Figure 1. Leg of Patient 4 revealing an ulcer prior to the placement of a transjugular intrahepatic portosystemic shunt.

was diagnosed with autoimmune hepatitis in the absence of clinical signs for portal hypertension. Several weeks after the diagnosis was made, the patient had a massive bleed from esophageal varices, which was not controlled with variceal banding and sclerotherapy; thus, TIPS was placed. In the subsequent 2 months, the leg ulcer healed completely, and no antibiotics were administered. Over the following 5 years, the patient has undergone periodic sonographic surveillance of her TIPS, which required revision due to stenosis on two occasions. Six years following the placement of TIPS, the leg ulcer recurred. Compressive treatment and skin grafting were undertaken without response. The recurrence of the ulcer coincided with a screening sonogram that showed that the TIPS was completely occluded. Placement of a new TIPS was associated with a precipitous drop in the portal pressure gradient to 13 mm Hg. Four weeks following this procedure, the ulcer exhibited appreciable evidence of healing. Subsequently, for over 2 years the TIPS has remained patent, and the ulcer has been healed.

Patient 4

A 49-year-old man with chronic liver disease due to chronic hepatitis C infection presented with a ruptured umbilical hernia secondary to tense ascites. The patient had marked venous stasis and a 4-cm ulcer on the medial aspect of the distal third of the right leg (Figure 1). The



Figure 2. Leg of Patient 4 several months after the placement of a transjugular intrahepatic portosystemic shunt. A scarred area is revealed where the ulcer had previously been present.

ulcer had appeared 3 months prior to hospitalization. Various local therapies had no effect on the ulcer prior to the patient's referral to our institution. Six weeks following TIPS placement for refractory ascites, the ulcer healed almost completely, though ascites remained detectable. The patient did not receive antibiotics in association with ulcer healing. One year after TIPS placement, the ulcer has remained healed (Figure 2).

Discussion

We have described 4 patients with leg ulcers that preceded complications of portal hypertension (ie, variceal bleed

and ascites; Table 1). In all 4 patients, a dramatic healing of the ulcer occurred within 5–8 weeks following the placement of TIPS, and in 2 patients, the recurrence of the ulcer was associated with stenosis or occlusion of the graft. Patients 1–3 were followed at one of our institutions, and vascular assessment did not reveal evidence of ischemia. (Patient 4 was transferred from a community hospital because of refractory ascites.) Only in Patient 2 were antibiotics used during treatment of the ulcer (1 year prior to the placement of TIPS), with no effect on healing noted.

Venous ulcers are the most common type of leg ulcers and a significant cause of morbidity and hospitalizations.¹⁻³ Venous insufficiency is caused by venous hypertension due to venous occlusion or valvular incompetence.¹⁻³ In addition to local anatomic abnormalities, healing may be impaired by increased local levels of pro-inflammatory mediators or deficiency of certain growth factors.^{6,7} Although portal hypertension alone may be insufficient to cause ulcers, associated risk factors (eg, varicose veins) may potentiate the development of ulcers and delay in their healing.

Growth factors secreted by the enterocyte, including hepatocyte growth factor (HGF), transforming growth factor, and epidermal growth factor,^{8,9} promote regeneration and healing of the skin and other tissues. We hypothesize that in severe portal hypertension the local concentration of these growth factors or their receptors may be insufficient to support the regenerative function of dermatocytes. Support of this hypothesis comes from the reports of decreased activity of endogenous HGF in chronic leg ulcers,⁶ in which the topical use of HGF has been associated with ulcer healing.⁷

Table 1. Cases of Decompensated Cirrhosis Presenting With Refractory Leg Ulcers

	Etiology of liver disease	Leg ulcer	Ulcer size, cm	Complication of portal hypertension	Time to ulcer healing after TIPS placement, wks	Post-TIPS resolution of ascites or recurrence of bleeding	Ulcer recurrence after restenosis of TIPS?
Patient 1	Alcohol	Preceded ascites	2.8	Ascites	5	Partial	Yes
Patient 2	Hepatitis C	Preceded bleeding	2.4	Variceal bleed	6	No recurrence	NA
Patient 3	Autoimmune hepatitis	Preceded bleeding	1.8	Variceal bleed	8	No recurrence	Yes
Patient 4	Hepatitis C	Preceded ascites	4.0	Ascites	6	Partial	NA

NA=not applicable; TIPS= transjugular intrahepatic portosystemic shunt.

Overexpression of inducible nitric oxide synthase and increased nitric oxide (NO) generation have been implicated in the hyperdynamic circulation of patients with cirrhosis.¹⁰ The role of NO has also been studied in the context of venous leg ulcers.^{11,12} Increased NO production is considered to mediate, in part, pathologic changes in many inflammatory conditions via peroxynitrite, a potential oxidant produced by NO-induced reduction of superoxide anion.¹¹ Increased expression of NO may be involved directly or indirectly in the pathogenesis of chronic venous ulcers as a consequence of the effects of peroxynitrite on vasculature, inflammation, and collagen deposition.^{12,13}

This is the first report of an observation that appears to link portal hypertension to a subset of venous leg ulcerations in patients with cirrhosis. Although it may be reasonable to implicate nutritional deficiencies in the impaired healing of leg ulcers in patients with advanced cirrhosis, the ulcers in our patients occurred with normal or close to normal serum albumin. In addition, although tense ascites may impair venous drainage from the lower extremities, in all of these patients the leg ulcers preceded the onset of appreciable ascites and in 2 patients, ulcer recurrence occurred prior to the worsening of ascites from occlusion of the shunt.

Conclusion

We describe the association between refractory leg ulcers and portal hypertension with complete healing of the ulcers following decompression of the portal circulation by TIPSs. This observation, together with the recurrence of ulcers associated with an increase in portal pressure, strongly implicates the role of portal hypertension in

the pathogenesis and perpetuation of a subset of venous leg ulcers in patients with cirrhosis. We believe that this observation suggests the existence of a hepatodermal axis, which may be modulated by portal hypertension, and the possibility of chronic venous leg ulcers as a manifestation of a hepatodermal syndrome.

References

1. Abbade LP, Lastoria S. Venous ulcer: epidemiology, physiology, diagnosis, and treatment. *Int J Dermatol*. 2005;44:449-456.
2. Simon DA, Dix FP, McCollum CN. Management of venous leg ulcers. *BMJ*. 2004;328:1358-1362.
3. Kantor J, Margolis DJ. Management of leg ulcers. *Semin Cutan Med Surg*. 2003;22:212-221.
4. Moller S, Bendsten F, Hendrikson JH. Pathophysiological basis of pharmacotherapy in the hepatorenal syndrome. *Scan J Gastroenterol*. 2005;40:491-500.
5. Ochs A. Transjugular intrahepatic portosystemic shunt. *Dig Dis*. 2005;23:56-64.
6. Nayeri F, Olsson H, Peterson C, Sundqvist T. Hepatocyte growth factor: expression, concentration, and biological activity in chronic leg ulcers. *J Dermatol Sci*. 2005;37:75-85.
7. Nayeri F, Stromberg T, Larsson M, Brudin L, Soderstrom C, Forsberg P. Hepatocyte growth factor may accelerate healing in chronic leg ulcers: a pilot study. *J Dermatolog Treat*. 2002;13:81-86.
8. Murphy MS. Growth factors and the gastrointestinal tract. *Nutrition*. 1998;14:771-774.
9. Jiang WG, Hiscox S. Hepatocyte growth factor/scatter factor, a cytokine playing multiple and converse roles. *Histol Histopathol*. 1997;12:537-555.
10. Ferguson JW, Dover AR, Chia S, Cruden NL, Hayes PC, Newby DE. Inducible nitric oxide synthase activity contributes to the regulation of peripheral vascular tone in patients with cirrhosis and ascites. *Gut*. 2006;55:542-546.
11. Kandemir O, Polat A, Kaya A. Inducible nitric oxide synthase expression in chronic viral hepatitis and its relation with histological severity of disease. *J Viral Hepat*. 2002;9:419-423.
12. Abd-El-Aleem SA, Ferguson MW, Appleton I, Kairsingh S, Jude EB, et al. Expression of nitric oxide synthase isoforms and arginase in normal human skin and chronic venous leg ulcers. *J Pathol*. 2000;191:434-442.
13. Jude EB, Boulton AJ, Ferguson MW, Appleton I. The role of nitric oxide synthase isoforms and arginase in the pathogenesis of diabetic foot ulcers: possible modulatory effects by transforming growth factor beta 1. *Diabetologia*. 1999;42:748-757.