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Isolated lower limb gangrene: a caveat of terlipressin therapy

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Sir,

Terlipressin is a synthetic analogue of the natural hormone arginine–vasopressin. It is often employed for the management of bleeding esophageal varices (BEV) and hepatorenal syndrome (HRS), both of which are catastrophic complications of advanced liver disease. Being a vasoconstrictor with preferential action on the splanchnic circulation, it aids the lowering of portal venous pressure. Terlipressin usage during BEV has been shown to decrease mortality, the failure rate of initial hemostasis, as well as the number of emergency procedures to stop uncontrolled bleeding or rebleeding [1]. In spite of its relatively safer pharmacological profile as compared to vasopressin, complications attributed to systemic vasoconstrictor properties have been occasionally reported. We encountered a case of isolated lower-limb gangrene following terlipressin therapy and wish to report it after obtaining informed written consent from the relatives.

A 67-year-old male patient with a history of alcohol-related chronic liver disease (CLD) and portal hypertension (7 years duration) was admitted to our ICU following one episode of haemetemesis, deteriorating sensorium and reduced urine output (approx. 300 mL day^{-1}) during the previous 48 hours. The patient was an active smoker with a history of 45 pack-years. His daily intake of alcohol had been 150 g for 38 years. He had discontinued alcohol consumption 7 years ago following the initial identification of alcohol-related cirrhosis. On admission, the patient was afebrile, haemodynamically stable and icteric. After initial examination and investigations, patient was diagnosed provisionally as acute-on-chronic liver disease with decompensation and HRS. Since the concern of aspiration existed due to an ongoing oesophageal bleed and depressed sensorium secondary to hepatic encephalopathy, the patient was intubated and put on mechanical ventilation using the Continous Positive Airway Pressure (CPAP) mode.

Subsequently, endoscopic variceal band ligation (EVL) was attempted but the procedure failed due to a persistent haemorrhage. Therefore, terlipressin therapy was considered. The patient was administered an initial bolus of terlipressin (2 mg stat) followed by 1 mg every 4 hours. Concomitantly, a 20% albumin solution infusion was commenced at a dose of 1 g kg^{-1} day^{-1} for the 1st day followed by 20 g day^{-1} in view of HRS. Packed Red Blood Cells (PRBCs) and blood products were transfused based on existing haemoglobin levels, the coagulation profile and thromboelastography. After the initial conservative measures had stabilised the patient, EVL was again attempted on the 3rd day and was carried out successfully.

On the 4th day, however, a new onset of blackish discolouration of the skin of all the toes of the left foot, along

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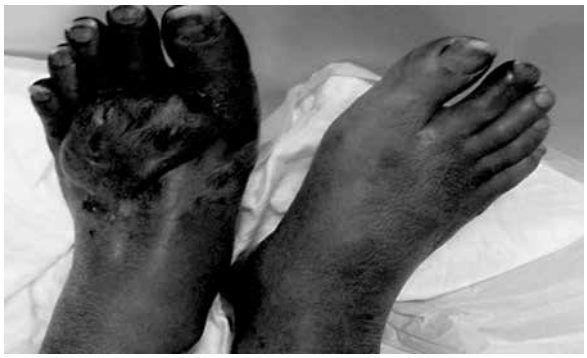

Figure 1. Blackish discolouration of skin of all the toes of the left foot, along with distal part of the same foot. Similar changes, but of lesser magnitude, may also be noticed on the great toe and 2nd toe of the right foot

with the distal part of the foot on both the dorsal and ventral aspects, were noticed. Similar changes, but of a lesser magnitude were also noticed on the great toe and the 2nd toe of the right foot (Fig. 1). An urgent Doppler ultrasound was performed which demonstrated normal blood flow in the major arteries (superficial femoral, popliteal, anterior tibial, posterior tibial, peroneal and dorsalis pedis) of both lower limbs, while also confirming the patency of the venous channels. Such changes were, however, absent on other body parts. Terlipressin injections were stopped immediately and oral sildenafil (50 mg twice a day) was started on the same day. However, the gangrenous changes did not resolve until the 14th day when the patient expired due to systemic complications of ongoing severe sepsis and acute respiratory distress syndrome (ARDS).

Since its introduction in the early 1990s, terlipressin has emerged as a frontline therapy in order to manage BEV and HRS. Its advantages include its potency, prolonged half-life (6 hours), relative safety and easy administration in intravenous boluses. While terlipressin acts selectively on the splanchnic circulation, it can exert vasoconstrictor effects on the systemic circulation. Therefore, systemic sequelae ranging from mild ischaemic complications to serious complications like ischaemic colitis, myocardial infarction and skin necrosis can be attributed to terlipressin usage. The frequency of ischaemic complications after terlipressin therapy for HRS is reported to be 5% [2]. Le Moine *et al.* [3] reported the absence of ischaemic complications following high doses of terlipressin (1 mg every 4 hours) administration to a patient with HRS over 2 months. Conversely, gangrenous changes on the toes have been reported to appear on the very first day of terlipressin therapy [4]. Ischaemic events, therefore, are probably independent of the duration of terlipressin therapy. This necessitates the recognition of certain risk factors like hypovolemia, the concomitant administration of pressor drugs and the mode of terlipressin administration [5]. Generally, continuous intravenous infusion of terlipressin is not recommended as the mode of administration, since it causes cutaneous (at the infusion site) and scrotal necrosis [6]. The ischaemic complications secondary to terlipressin therapy are probably related to the particular distribution of the target receptor of terlipressin — the vasopressin receptor type 1 (V_1 receptor) — which is located in the smooth muscles of the blood vessels, mainly in the territory of the splanchnic circulation, kidney, myometrium, bladder, adipocytes and skin circulation [7]. However, preferential involvement of a particular site has not yet been fully explained.

In our case, terlipressin was administered as an intravenous bolus while the risk factors involved were chronic alcoholism and smoking. The peripheral vasoconstrictive changes secondary to prolonged smoking may have exaggerated and accelerated the development of limb gangrene.

Terlipressin should be stopped immediately once the ischaemic events are suspected. Ischaemic changes in both the lower limbs have been reported to have regressed and recovered in 2 weeks after the discontinuation of terlipressin [8]. In contrast, Coskun *et al.* [1] reported that skin necrosis on the forearm progressed for 1 week even after terlipressin discontinuation. Thus, cessation of terlipressin does not always necessarily result in the regression of gangrenous changes.

Various vasodilators have been tried as rescue therapy with variable success rates. These include alprostadil (PGE1 analogue) [9], sildenafil [10] and nitrates [11] as reported by various authors. Nevertheless, amputation remains the last resort in limb gangrene. In our patient, terlipressin-induced ischemia led to necrosis and gangrene of both feet. Despite the timely cessation of terlipressin and the initiation of vasodilator therapy, gangrene did not subside in our patient until his death on the 14th day.

This case suggests that despite its rarity, the possibility of ischaemic complications caused by terlipressin, must be borne in mind by clinicians. Recognising the risk factors, the immediate cessation of terlipressin and concomitant initiation of vasodilators can be helpful, albeit not always successful forms of treatment.

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