

## ***Embolia cutis medicamentosa*: an unusual adverse reaction to terlipressin**

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### **Abstract**

Terlipressin is a synthetic long-acting analog of vasopressin widely used to control variceal bleeding by lowering portal venous pressure. We report an unusual adverse reaction to terlipressin in a 78-year-old patient with esophageal variceal bleeding who developed skin necrosis soon after treatment initiation. Skin biopsy revealed *embolia cutis medicamentosa*.

**Keywords** Terlipressin, *embolia cutis medicamentosa*, skin necrosis, Nicolau syndrome, esophageal variceal bleeding

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### **Introduction**

The initial management of variceal bleeding is vasoactive pharmacological therapy with octreotide, somatostatin, terlipressin, or vasopressin. We report a case of terlipressin-induced extensive skin necrosis in a 78-year-old female with cirrhosis and esophageal variceal bleeding.

### **Case report**

A 78-year-old Caucasian female presented with hematemesis. She was obese and cirrhotic as a result of non-alcoholic steatohepatitis. Clinical examination revealed confusion, blood pressure 90/42 mmHg, heart rate 135 beats/min, and respiratory rate 18 breaths/min. Laboratory

findings included anemia, with hemoglobin 5.2 g/dL (normal range 12.0-15.0 g/dL), international normalized ratio 1.56 (normal range 0.90-1.20), blood glucose 571 mg/dL (normal range 74-106 mg/dL) and blood creatinine 1.3 mg/dL (normal range 0.5-0.9 mg/dL). Bilirubin, transaminases and cholestatic enzymes were within their normal range.

Variceal bleeding was suspected and the patient received two units of red blood cells, terlipressin 2 mg (Glypressin<sup>®</sup>, Ferring Pharmaceutical Hellas, Greece) and ceftriaxone 1 g iv (Rocephin<sup>®</sup>, Roche Hellas, Greece). Upper gastrointestinal endoscopy under anesthesia identified actively bleeding esophageal varices, ligated endoscopically.

Two hours after the third 2 mg dose of terlipressin iv (doses given every 4 h), the patient developed purpuric skin lesions on her left arm (Fig. 1A), both breasts (Fig. 1C) and lower abdomen (Fig. 1B, D). Terlipressin treatment was terminated. The lesions evolved rapidly (Fig. 2) to necrosis and a cutaneous biopsy performed 48 h after the start of treatment led to the diagnosis of *embolia cutis medicamentosa* (ECM) or Nicolau syndrome (Fig. 3). The patient died from sepsis 8 days after her admission.

### **Discussion**

Terlipressin doses of 1-2 mg iv, bolus and every 4-6 h thereafter, effectively reduce the portal venous pressure and induce marked splanchnic vasoconstriction. Common adverse effects of terlipressin include headache, bradycardia, peripheral vasoconstriction, peripheral ischemia, facial pallor, hypertension, transient abdominal cramps and transient diarrhea, while skin necrosis is reported as an adverse reaction of unknown frequency.

ECM, also known as Nicolau syndrome or livedoid dermatitis, is a rare cutaneous adverse reaction to certain

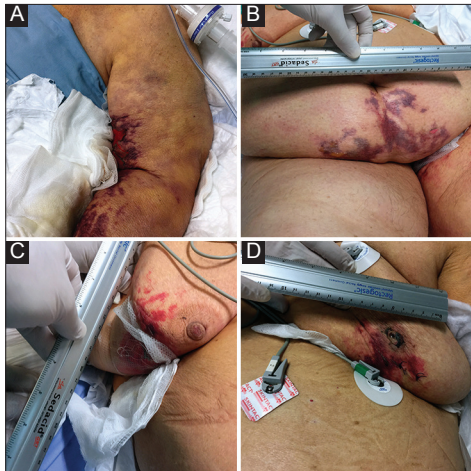
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Conflict of Interest: None

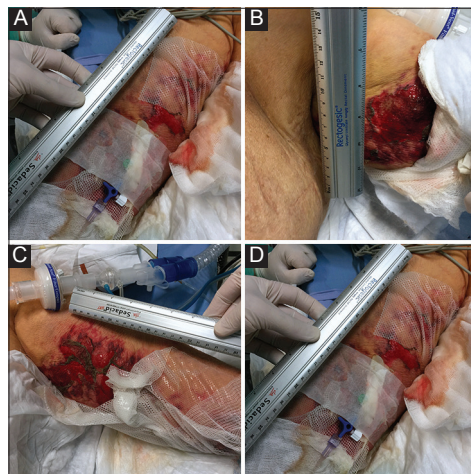
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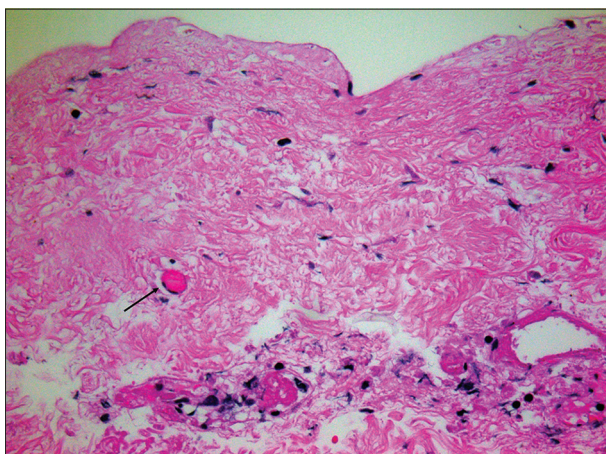
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**Figure 1** Fourteen hours after initiation of terlipressin treatment skin purpuric lesions developed on the (A) left arm, (B) lower abdomen and (C, D) breasts



**Figure 2** The evolution of skin lesions on the patient's left arm: (A) 24 h following initiation of terlipressin treatment; (B, C, D) 36 h following treatment initiation



**Figure 3** Histology of a cutaneous specimen that disclosed complete absence of the epidermis, as well as the presence of a few fibrin plugs within dermal capillaries (arrow), with no essential inflammation and IgG, IgA, IgM or C3 complement immunohistochemical component

medications, such as penicillins, non-steroidal anti-inflammatory drugs, local anesthetics and corticosteroids. It is characterized clinically by severe pain immediately after the injection, followed by an erythematous, reticular patch that may result in a necrotic ulcer and scarring. Histopathological examination reveals necrosis of the epidermis, dermis, subcutaneous tissue and muscle, with focal thrombosis of small and medium blood vessels.

A PubMed search using the terms “terlipressin”, “skin necrosis”, “skin ischemia”, “*embolia cutis medicamentosa*” and “Nicolau syndrome” returned 21 reports of skin necrosis in patients treated with terlipressin, either for variceal bleeding or for hepatorenal syndrome. In addition, the pharmacovigilance department of Ferring Pharmaceutical Hellas, the local terlipressin distributor, referred us to a case of an alcoholic patient who experienced extensive epidermal necrosis following treatment with terlipressin for “stomach bleeding”; however, this case could not be matched with the aforementioned cases because additional patient data were lacking.

Among the reported cases with histological confirmation of terlipressin-induced skin necrosis (n=14), a diagnosis compatible with Nicolau syndrome was made in 6 [1-5] (Table 1), while in the rest no capillary emboli were detected. It is difficult to clarify whether these two distinct histologic types are associated with different mechanisms or stages of terlipressin's action in the skin capillaries, with different affected skin areas (corpus vs. extremities), with the co-administration of other medication, or with the patients' background.

More specifically, our patient developed skin lesions 14 h after terlipressin treatment initiation, whereas in all but one (time lag not specified, no histology available [6]) of the cases found in PubMed the lesions developed up to 264 h later. Moreover, in the 2 cases where lesions occurred within 24 h following treatment initiation [1,4], ECM was detected. Although ischemic skin lesions related to terlipressin administration usually affect the extremities (fingers, scrotum, lower legs and toes), our patient's extremities were spared.

One of the confounding factors in the causative relation leading to adverse events after a treatment is co-administered medication. Antibiotic administration has been related to ECM, and our patient received ceftriaxone for infection prophylaxis, as per guidelines. There are no literature reports of ECM associated with ceftriaxone use, and a safety search of the Roche Medical Information Department following our request detected no such signal. However, colleagues from India have reported Nicolau syndrome (without histological confirmation) in a child treated with ceftriaxone for Dengue fever [7]. Finally, there is no reported association of ECM with the use of propofol (Propofol®, Fresenius Kabi Hellas, Greece) or midazolam (Midazolam/B. Braun®, Bioser, Greece), which were administered to our patient during endoscopy.

The majority of cases of skin necrosis associated with terlipressin use occurred in alcoholic cirrhotics suffering from hepatorenal syndrome or variceal bleeding. Several predisposing factors for skin necrosis in these patients have been reported, including obesity [3,5], hypovolemia [4,5],

**Table 1** Skin necrosis cases associated with terlipressin treatment

Case ID	Sex, age (years)	Underlying condition	Condition under treatment	Predisposing factor	Terlipressin dose	Area affected	Onset lag time	Capillary thrombi	Skin lesion outcome	Patient outcome
Oh JE, <i>et al</i> 2008 [1]	Male, 71	Alcoholic CI	Variceal bleeding	None	1 mg/6 h	Abdomen, thighs, scrotum	24 h	Yes	Resolved	Death due to hepatic failure and re-bleeding
Mégarbané H, <i>et al</i> 2009 [2]	Male, 68	Alcoholic CI	Hepatorenal syndrome	Sepsis, vasoconstrictors	1 mg/6 h	Trunk, tongue, legs, scrotum	72 h	Yes	Evolved	Died from sepsis
Mégarbané H, <i>et al</i> 2009 [2]	Male, 74	Liver metastasis	"Pseudo-hepatorenal syndrome"	CVD	0.5 mg/h, infusion	Scalp	96 h	Yes	NA	Death due to tumor progression
Yefet, <i>et al</i> 2011 [3]	Male, 66	Alcoholic CI	Upper GI bleeding	Obesity, hypertension, hypovolemia	2 mg/4 h	Thighs, calves, abdomen, arms	120 h	Yes	NA	Death
Lu YY, <i>et al</i> 2012 [4]	Male, 75	Hepatitis C	Variceal bleeding	Hypertension, hypovolemia	1 mg/6 h	Abdomen, buttocks, thighs	24 h	Yes	Healed	Death due to multi-organ failure
Coscun BDO, <i>et al</i> 2014 [5]	Male, 65	NAFLD	Variceal bleeding	CVD, hypertension, hypovolemia, overweight	1 mg/6 h	Forearm	48 h	Yes	Worsened	NA

NA, not available; SBP, spontaneous bacterial peritonitis; CVD, cardiovascular disease; CI, cirrhosis; NAFLD, nonalcoholic fatty liver disease; CI, cirrhosis

use of vasoconstrictive agents (apart from terlipressin) [2], ischemic vascular disease [2,5] and sepsis [2]. Our patient was non-alcoholic, obese, and hypovolemic at presentation. Although our histology findings were not associated with *Staphylococcus capitis* skin infection, the possibility of this microbe being implicated in the pathogenesis and/or evolution of ECM cannot be firmly excluded.

The vasopressin analog terlipressin releases von Willebrand factor via activation of  $V_2$  receptors in endothelial cells and enhances platelet aggregation. This may lead to capillary thrombosis, especially under intense or prolonged peripheral vasoconstriction [8], which is the case in hepatorenal syndrome and in severe variceal bleeding.

Based on its pharmacology and mechanism of action, literature reports, histological findings and chronological association, we conclude that terlipressin may cause acute-onset ECM with extensive ischemic skin necrosis. It remains to be proven whether ECM is a different entity than skin necrosis without capillary thrombi. Moreover, we cannot exclude the possibility that specific patient background, co-medication and skin infections might also have been involved in the evolution of this rare adverse drug reaction.

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