CASE REPORT

TJG
The Turkish Journal of Gastroenterology

Ischemic skin necrosis following terlipressin therapy: Report of two cases and review of the literature

Türker TAŞLIYURT[1], Faruk KUTLUTÜRK[1], Fikret ERDEMİR[2], Berna Murat YELKEN[1], Abdulkerim YILMAZ[1], Bünyamin KISACIK[1], Pelin AYTAN[1], Reşit Doğan KÖSEOĞLU[3]

Departments of [1]Internal Medicine, [2]Urology and [3]Pathology, Tokat Gaziosmanpaşa University School of Medicine, Tokat

Terlipressin is a synthetic vasopressin analogue that is used in the treatment of bleeding esophageal varices and hepatorenal syndrome in patients with cirrhosis. Hepatorenal syndrome is a form of renal failure seen in patients with cirrhosis, with fatal outcomes. Ischemic adverse effects related to terlipressin are rarely observed. Herein, two cases who developed ischemic skin necrosis due to terlipressin usage are presented. Terlipressin therapy was started in two cirrhotic patients with presumptive hepatorenal syndrome. During the therapy, ecchymotic and necrotic changes were observed on the scrotal regions of both patients. Skin lesions were relieved after terlipressin therapy. Biopsy results were consistent with ischemia. Even if seen rarely, possible emergence of ischemic complications must be considered.

Key words: Terlipressin, skin necrosis, hepatorenal syndrome, adverse effect

Terlipresin tedavisi sonrasında gelişen iskemik cilt nekrozu: İki olgu sunumu ve literatürün gözden geçirilmesi

Terlipresin bir sentetik vazopressin analoğu olup, sirotik hastalarda özofagus varis kanamalarında ve hepatorenal sendrom tedavisinde kullanılmaktadır. Hepatorenal sendrom sirozlu hastalarda görülen ve mortal seyredebilen bir böbrek yetmezliği tablosudur. Terlipresin'e bağlı iskemik yan etkiler oldukça nadir olarak görülmektedir. Burada terlipresin kullanımına bağlı iskemik cilt nekrozu gelişen iki olgu sunulmaktadır. İki sirotik hastada da hepatorenal sendrom düşünülerek terlipresin tedavisine başlandı. Tedavi devam ederken her iki hastada da skrotal bölgede ekimotik ve nekrotik değişiklikler olduğu gözlendi. Terlipresin tedavisi kesildikten sonra cilt lezyonları düzeldi. Biyopsi sonucu da iskemi ile uyumlu geldi. Her ne kadar oldukça nadir olarak görülse de terlipresin tedavisi sırasında iskemik komplikasyonların ortaya çıkabileceği daima göz önünde bulundurulmalıdır.

Anahtar kelimeler: Terlipresin, cilt nekrozu, hepatorenal sendrom, yan etki

INTRODUCTION

Hepatorenal syndrome is a serious complication of chronic liver disease presenting with clinical manifestations of renal failure, with potential mortal outcomes. Even if its pathogenesis has not been fully elucidated, hypoperfusion resulting from vasodilation and a decrease in vascular resistance in the splanchnic region have been conceived as probable etiologic factors (1). Terlipressin, which is a synthetic analogue of vasopressin, is used commonly in the treatment of gastrointestinal hemorrhages, mainly of bleeding esophageal varices, and hepatorenal syndrome (2-4). When compared with other vasopressin analogues like ornipressin, terlipressin–related ischemic adverse effects have been reported rarely.

Address for correspondence: Türker TAŞLIYURT
Department of Internal Medicine, Tokat Gaziosmanpaşa University, School of Medicine, Tokat, Turkey
E-mail: turtasliyurt@hotmail.com

Manuscript received: 10.01.2012 **Accepted:** 02.02.2012

Turk J Gastroenterol 2012; 23 (6): 788-791
doi: 10.4318/tjg.2012.0490

In this report, two cases who developed ischemic skin lesions on the scrotal region due to terlipressin usage are presented with the relevant literature.

CASE REPORTS

CASE 1

A 79-year-old male patient diagnosed as alcoholic cirrhosis presented to our clinic with manifestations of advanced ascites and acute renal failure. He had no bleeding episode, with the following laboratory parameters: hemoglobin (Hgb): 10.3 g/dl, platelets (PLT): 142000/mm^3, prothrombin time (PT): 28 sec, activated partial thromboplastin time (aPTT): 52 sec, international normalized ratio (INR): 2.64, alanine aminotransferase (ALT): 116 U/L, aspartate aminotransferase (AST): 141 U/L, alkaline phosphatase (ALP): 118 U/L, gamma-glutamyl transpeptidase (GGT): 29.2 U/L, albumin: 2.7 g/dl, creatinine: 1.8 mg/dl, sodium (Na): 129 mmol/L, and potassium (K): 4.02 mmol/L. His viral serologic tests and tests for autoimmune hepatitis did not reveal any abnormality. In abdominal ultrasonography, an extremely enlarged liver with irregular contours, coarse and granular parenchyma, splenomegaly, and widespread free intraabdominal fluid were detected without any renal abnormality. Despite treatment, his renal functions deteriorated further in time and his disease state criteria were consistent with hepatorenal syndrome. The patient received terlipressin as pulsatile daily doses of 4x1 mg intravenous (iv). Concomitantly, albumin therapy was maintained. On the 2nd day of the treatment, ecchymotic and necrotic changes on his scrotal skin were noted (Figure 1). In consideration of rarely reported ischemic adverse effects of terlipressin, the drug was discontinued as a probable culprit of these ischemic complications. Skin biopsy material revealed a dermal ulceration, necrosis, and nonspecific inflammation, which were considered to be consistent with ischemic changes (Figure 2). After cessation of the therapy, the ischemic lesions regressed. However, the patient died due to gastrointestinal system bleeding and advanced renal failure.

CASE 2

A 65-year-old man diagnosed as cirrhosis caused by hepatitis B admitted to our clinic with the manifestation of acute renal failure. He had ascites without any bleeding episode with the following laboratory test results: Hgb: 10.3 g/dl, PLT:

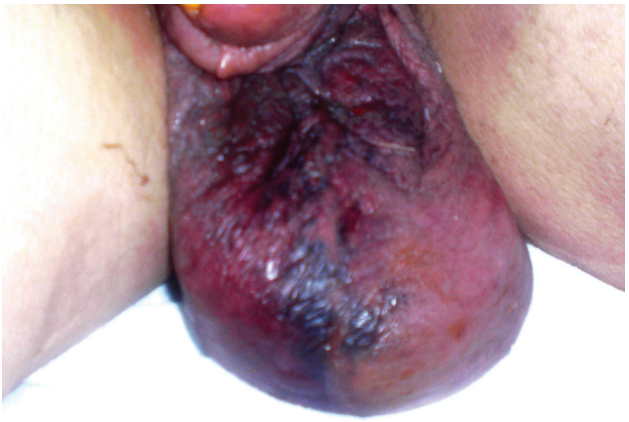

Figure 1. An ischemic skin necrosis is seen in the scrotal area after terlipressin therapy.

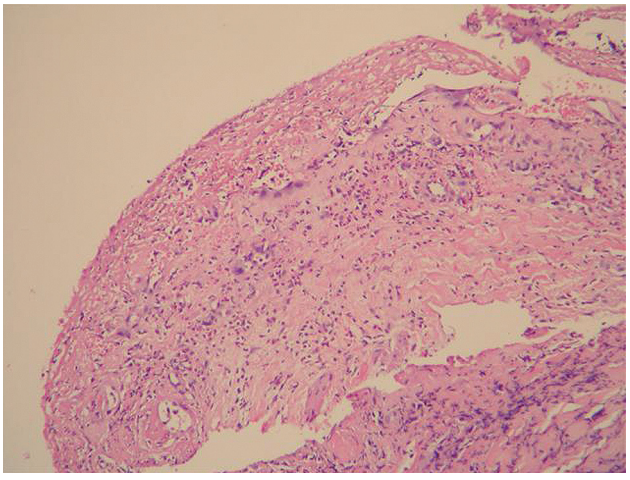

Figure 2. Ulcerated surface covered by inflamed fibrin material and dermal nonspecific inflammatory infiltration are seen on the skin punch biopsy sample.

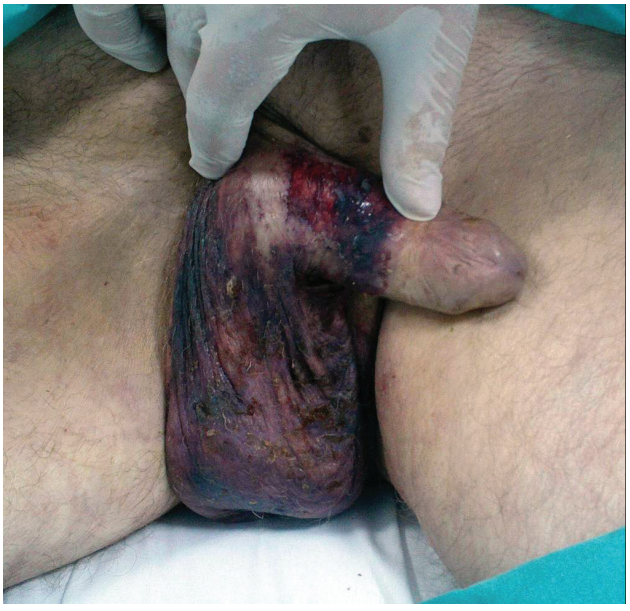

Figure 3. Scrotal skin lesions are seen after terlipressin therapy.

223000/mm^3, PT: 24.9 sec, aPTT: 39.1 sec, INR: 2.28, ALT: 21 U/L, AST: 37 U/L, ALP: 86 U/L, GGT: 72 U/L, albumin: 2.5 g/dl, creatinine: 2.09 mg/dl, Na: 128 mmol/L, and K: 4.68 mmol/L. His disease state suggested the presence of hepatorenal syndrome. Terlipressin therapy at a daily dose of 4x1 mg iv was initiated. Concomitantly, he received albumin, and an increase in his urinary output and a drop in creatinine levels were observed. On the 2nd day of therapy, ecchymotic and necrotic changes were observed on the scrotal skin of the patient (Figure 3). Since these changes were thought to be related to ischemia caused by terlipressin therapy, this treatment was discontinued. Despite regression of the lesions after cessation of the therapy, the patient was lost within a few days because of progressive liver disease and renal failure.

DISCUSSION

Terlipressin is a synthetic vasopressin analogue used widely in the treatment of hepatorenal syndrome and also bleeding esophageal varices in cirrhotic patients. When compared with vasopressin and its other synthetic analogues, adverse effects are relatively rare (1-4). In this context, it has been reported that ischemic adverse effects associated with terlipressin usage were seen at a rate of less than 5% (5,6).

The effectiveness of terlipressin usage in bleeding esophageal varices and its ameliorating effects on renal functions in hepatorenal syndrome have been demonstrated previously in many studies (7,8). Similar to the findings of our study, some studies have revealed an increase in the effectiveness of terlipressin therapy in combination with albumin (6,9). As with other vasopressin analogues, terlipressin manifests its effects on splanchnic circulation. Even if it has selective vasoconstrictive effects, these effects can occur in the systemic circulation as well. Several adverse effects have been reported due to usage of terlipressin, such as headache, hypertension, abdominal pain, skin pallor, and bradycardia. In addition to these adverse effects, serious ischemic side effects have been shown in different studies. Among them, skin lesions on the extremities and abdomen, myocardial infarction and ischemic colitis can be enumerated as well (10-13). In the presented two cases, ischemic complications were observed on the scrotal region, and similar involvements had been reported previously in three cases (14-16). In these cases mentioned in the literature, apart from the scrotal region, involvement of various parts of the body, such as hips, abdominal region, trunk, and legs, has been reported. Interestingly, in our cases, ischemic findings were seen only on the scrotal region, without any other ischemic complications involving other parts of the body. As potential predisposing factors facilitating the occurrence of ischemic side effects, a history of ischemic disease, obesity, venous insufficiency, and spontaneous bacterial peritonitis have been reported (4,15,17). When our cases are evaluated accordingly, the first case was obese; however, no predisposing factor facilitating the development of ischemic lesions could be identified in the second case.

In conclusion, an ischemic skin necrosis secondary to terlipressin usage should be considered in the differential diagnosis of scrotal ischemic pathologies, especially in patients with hepatorenal syndrome.

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