case report

A fatal case of cutaneous adverse drug-induced toxic epidermal necrolysis associated with severe rhabdomyolysis

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Toxic epidermal necrolysis represents an immunologic reaction to a foreign antigen and is most often caused by drugs. Atorvastatin, a blood cholesterol–lowering agent, is a recognized cause of rhabdomyolysis; while naproxen, a widely used nonsteroidal anti-inflammatory drug, is a known cause of photo-induced skin lesions. We report the first fatal case of drug-induced toxic epidermal necrolysis associated with severe muscle necrosis due to the use of a nonsteroidal anti-inflammatory drug and a statin with very high levels of creatine phosphokinase leading to acute kidney injury, disseminated intravascular coagulation, and complete skin necrosis leading to death.

Toxic epidermal necrolysis (TEN) is a cutaneous drug-induced reaction characterized by a widespread exfoliation and necrosis of the epidermis, involving more than 30% of body surface area. Rhabdomyolysis and necrosis of smooth muscle fibers have never been reported with TEN. We report the first case of a non–photo-induced, fatal skin necrolysis accompanied by severe rhabdomyolysis due to naproxen and atorvastatin use in a 61-year-old woman.

CASE

A 61-year-old female patient presented with complaints of breathing difficulties, vomiting, and diarrhea that started 2 days prior to admission; she also complained of right hemithoracic pain. Her medical history revealed arterial hypertension, hypercholesterolemia, arthritis, and type 2 diabetes. She did not consume alcohol and was a nonsmoker. She had allergy to molds. Her medications consisted of metformin 500 mg once daily, co-lisinopril (lisinopil and hydrochlorothiaride) 20/12.5 mg once daily, tramadol 100 mg twice daily as needed, atorvastatin 10 mg once daily, allopurinol 300 mg once daily, ranitidine 500 mg once daily, and quinine sulfate 100 mg once daily. She was taking naproxen 500 mg three times a day and as needed for arthritis, 10 days prior to admission. On the day of admission, she had consumed 1.5 g of naproxen for her arthritis and chest pain.

On examination, she was restless with breathing difficulties; she was pale and hypotensive (65/10), and had sinus tachycardia (120/min). The arterial blood gas revealed a pH of 7.27; pCO_2, 23 mm Hg; paO_2, 154 mm Hg (at room air), with a base excess of -17.5; serum bicarbonate 11 mEq/L; potassium 3.14 mEq/L; and lactate, 55 mg/dL. The patient had marbled legs and thorax and complained of thirst. She was admitted to the intensive care unit (ICU) and fluid resuscitation was pursued, with a central venous pressure of 14 mm Hg, $ScVO_2$ of 52%, and low urine output [<0.5 mL/(kg per h)]. A few hours after admission to the ICU, she suddenly became bradycardic with cardiac arrest. The patient rapidly developed multiple organ failure with respiratory failure (PaO_2/FiO_2 <150 mm Hg), renal failure requiring continuous renal support, liver failure with increased bilirubinemia, and coagulopathy. Inotropes and broad-spectrum antibiotics such as amoxicillin-clavulanic acid, amikacin with a quick shift toward meropenem, vancomycin, and fluconazole

Figure 1. Massive erythematous and bullous eruptions with skin necrosis and a positive Nikolsky sign, involving 80% of body surface.
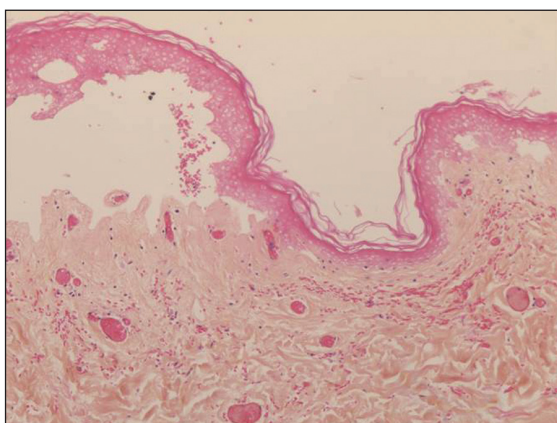
Figure 2a. Skin with a cell-poor, subepidermal blister and epidermal necrosis with the presence of fibrinous thrombi in the dermal capillaries (Hematoxylin-eosin-safron, ×100).
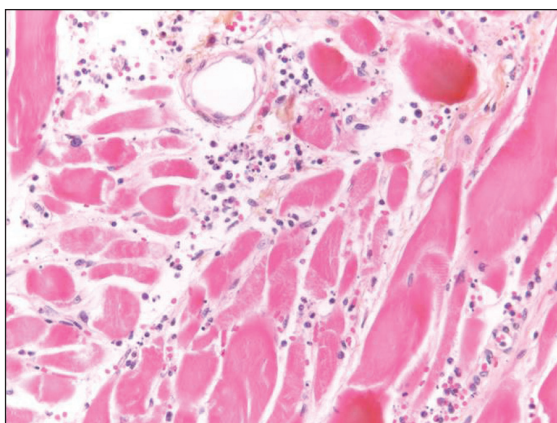
Figure 2b. Recent necrosis of striated oesophageal muscle with inflammatory infiltration (Hematoxylin-eosin-safron, ×200).

Table 1. Laboratory tests on admission.

Test	Value (normal range)
C-reactive protein (mg/dL)	45.5 (<1)
Creatine phosphokinase (IU/L)	3739 rose to 145 518 (<167)
D-Dimers (ng/mL)	>8000 (0-500)
Fibrinogen (mg/dL)	298 (160-415)
Partial thromboplastin (%)	50 (70-100)
Potassium (mEq/L)	3.1 (3.5-4.8)
Bicarbonate (mEq/L)	11 (23-30)
Urea (mg/dL)	93 (13-40)
Uric acid (mg/dL)	8.1 (2.5-6.0)
Creatinine (mg/dL)	2.90 (0.55-0.96)
Glomerular filtration rate (mL/min)	17 (>60)
Aspartate aminotransferase (IU/L)	73 (15-40)
Alanine aminotransferase (IU/L)	44 (10-35)
Gamma glutamyl transferase (IU/L)	154 (5-36)
Total bilirubin (mg/dL)	2.7 (0.2-1.2)
Conjugated bilirubin (mg/dL)	1.9 (<0.4)
Glucose (mg/dL)	95 (<100)
Lactic acid (mg/dL)	117 (6-18)
Platelets (mL)	159 000 reduced to 125 000 (150-440 000).

were initiated. Her SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores were 21 and 38, respectively.

Dermatologic examination showed a marbled skin pattern on the thorax on admission, rapidly progressing to petechial lesions over the next 6 hours, the latter becoming confluent over the following 24 hours and changing into erythematous and bullous eruptions located on the upper chest and lower and upper extremities (**Figure 1**). The Nikolsky sign was positive. The extent of involvement was 80% of the body surface. The skin biopsy revealed an extensive epidermal necrosis (**Figure 2a**), while the muscle biopsy showed necrosis of striated (**Figure 2b**) and smooth muscle fibers. The laboratory tests yielded the pathological changes on admission (**Table 1**). Chest x-ray, electrocardiogram, lumbar puncture, urine, and blood cultures were unremarkable on admission. A thoracoabdominal CT scan was also normal, and a skin swab did not identify any pathological microorganisms.

With regard to medications, the lymphocyte transformation test (LTT) was significantly positive with naproxen. There was no response to LTTs for either her home medications (co-lisinopril, allopurinol, and quinine) or the antibiotics prescribed on admission (amikacin, metronidazole, meropenem, amoxicillin-clavulanic acid, and fluconazole). Anti-skin, anti-skeletal muscle antibodies were absent; antineutrophil cytoplasmic antibody, anti-glomerular basement membrane, anti-Jo1, and anti-scl70 antibodies were also absent. Serologies for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and hepatitis (hepatitis A virus, hepatitis B virus, hepatitis C virus) were all negative. Naproxen was discontinued, and intravenous methylprednisolone at a dose of 1200 mg was administered. She died the following day despite broad-spectrum systemic antibiotics and supportive measures.

DISCUSSION

Only two cases of TEN due to naproxen are repoted in published studies.[1,2] To the best of our knowledge, this is the first case report of non–photo-induced TEN due to naproxen use associated with rhabdomyolysis. Acute kidney injury (AKI) and rhabdomyolysis were present on admission to the hospital before the skin lesions became confluent and generalized. Such a presentation of TEN is rare, with a picture of diffuse cutaneo-hemorrhagic aspects (**Figure 1**). The autopsy examination confirmed the clinical diagnosis of TEN as well as renal infarct. The pathogenesis of this renal failure may be explained by initial acute tubular necrosis, caused by an initial sepsis-like syndrome combined with dehydration, muscle necrosis, and drug-induced toxicity of a loading dose of 1.5 g of naproxen.

Animal studies have shown that matrix metalloproteinases (MMPs) have been incriminated in the pathogenesis of AKI, most particularly with increased expression of MMP-2 and MMP-9 in glomerular and tubular cells in ischemia reperfusion injury models.[3] The tubulointerstitial damage may be due to a down-regulation of MMP-9.[4] Paquet et al suggested that keratinocytes are key initiator cells in the pathogenesis of TEN, and the combined effects of tumor necrosis factor alpha (TNF-alpha), and oxidative stress on keratinocytes are responsible for apoptotic and necrotic events.[5]

In patients with a high-uric acid turnover (polycythemia vera and hemolytic anemias), nucleotides are released rapidly, leading to a fast increase in serum uric acid by the liver, and this has been reported in rhabdomyolysis.[4,6] Our patient on admission had an elevated uric acid level and was taking atorvastatin, which could explain drug-induced rhabdomyolysis leading to AKI, disseminated intravascular coagulation, and complete skin necrosis. However, hyperuricemia is frequently encountered in ICU patients with acute renal failure of any etiology, and is not a prominent feature or a major pathophysiological element in the renal failures of non-hematology/oncology patients.[6]

No gold-standard therapy exists; also no evidence exists indicating the superiority of monotherapy with corticosteroids, cyclosporine, or intravenous immunoglobulins over supportive care for patients with TEN.[1] Although Gubinelli et al have described a successful treatment with etanercept, this drug was not considered as an option.[7] The pathogenesis of TEN supports the administration of a combination of antiapoptotic/antinecrotic drugs such as anti-TNF-alpha antibodies and N-acetylcysteine targeting different levels of the keratinocyte failure.[5]

In conclusion, we report the first fatal case of drug-induced TEN associated with severe muscle necrosis due to the use of an nonsteroidal anti-inflammatory drug and a statin leading to AKI and complete skin necrosis. The rapid onset of lesions after a loading dose of naproxen favors an immunopathogenesis of skin and muscle necrosis.

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