Clinical Case Report

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Allopurinol-induced toxic epidermal necrolysis featuring almost 60% skin detachment

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Abstract

Rationale: Toxic epidermal necrolysis (TEN) is a life-threatening, immunologically mediated, and usually drug-induced disease. Rarely, clinical pharmacists participating in finding the etiology have been reported.

Patients concerns: A 33-year-old male presented to the emergency department with a 1-day history of fever and rash. The patient, being newly diagnosed with gout 10 days ago, received allopurinol at a dose of 250 mg by mouth daily. After 10 days' exposure to allopurinol, the patient manifested with an "influenza-like" prodromal phase (fever of 38°C, throat pains), which was treated with amoxicillin and nonsteroidal anti-inflammatory drugs of the oxicam type. The next day, he developed a worsening fever of 39.5°C, accompanied by a pruriginous rash all over his body.

Diagnosis: On physical examination, we observed coalescing dusky red macules over >60% of his body surface area, with blisters and detachment of large sheets of necrolytic epidermis all over his chest and face. The diagnosis of TEN was confirmed.

Interventions: The patient recovered following treatment with short-term high-dose methylprednisolone sodium succinate, immunoglobulin therapy, topical medication, and supportive therapy.

Outcomes: He showed a slow but progressive improvement both in symptoms and cutaneous manifestations. Reepithelization of the skin was achieved after 3 weeks.

Lessons: Drug-induced-TEN is potentially fatal. This case underlines the necessity of asking medication history in detail and detecting related drug gene to correctly identify the cause of TEN.

Abbreviations: SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis; TEN = toxic epidermal necrolysis.

Keywords: toxic epidermal necrolysis, HLA genes, allopurinol

1. Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a life-threatening, immunologically mediated, and usually drug-induced disease with a high burden on individuals, which is characterized by a rapidly developing blistering exanthema of purpuric macules and targetoid lesions accompanied by mucosal involvement and variable skin detachment.[1–3] SJS/TEN is thought to be the same disease across a spectrum of severity defined by the percentage of skin detachment related to the body surface area (BSA) comprising SJS (<10%), SJS/TEN overlap (10%–30%), and TEN (>30%).[4–6]

SJS/TEN is a rare disease and usually, but not exclusively, represents a drug reaction. Drugs with a high confirmed risk of causing SJS/TEN are anti-infective sulfonamides, allopurinol, carbamazapine, phenobarbital, phenytoin, non-steroidal antiinflammatory drugs of the oxicam type, nevirapine, and chlormezanone. TEN is a rare skin condition, most often drug-induced, known for its skin detachment and high mortality.[7–9] TEN, a T-cell mediated type IV hypersensitivity disorder, mostly results from a cumulative effect of risks from the drug structure, drug metabolism, T cell clonotypes and HLA alleles.[10–12] Apoptosis or necroptosis causes keratinocytes to lose their shape and adhesion, and subsequently total epidermal necrosis separates the epidermis from the dermis.[13]

2. Case presentation

A 33-year-old male presented to the emergency department with a 1-day history of fever and rash. The patient, being newly diagnosed with gout 10 days ago, received allopurinol at a dose of 250 mg by mouth daily. After 10 days' exposure to allopurinol, the patient manifest with an "influenza-like" prodromal phase (fever of 38°C, throat pains), which was treated with amoxicillin and non-steroidal anti-inflammatory drugs of the oxicam type. The next day, he developed a worsening fever of 39.5°C, accompanied by a pruriginous rash all over his body. It was noted that dusky erythematous, purpuric, and irregularly shaped

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macules, and spots were on patient's trunk, face, and palms. Some lesions have the appearance of atypical flat target lesions with 2 concentric rings around a necrotic center. The next day, the erythema begins to blister and coalesce to become fluid-filled bullae. Owing to unstability of the epidermis in these involved areas, tangential digital pressure on the skin causes the epidermis to shear off and detach. The patient is transferred to dermatology department to optimize wound care and dressing application to extensive and complex anatomic areas.

On physical examination, we observed coalescing dusky red macules over >60% of his BSA, with blisters and detachment of large sheets of necrolytic epidermis all over his chest and face. The diagnosis of TEN was confirmed. Upon physical examination, his temperature was 38.9°C, arterial blood pressure was 143/91 mm Hg, and heart rate was 121 beats/minute. Three days later, further confluence of bullae and the blistered skin on the back leads formation of larger flaccid bullae and, ultimately, to spontaneous sheet-like detachment of necrotic epidermis, leaving painful raw areas of glistening bright red dermis exposed throughout the back (Fig. 1). In the meantime, erosions and sloughing of the mucous membranes, involving the lips, oropharynx, genitalia, the esophagus, the remainder of the gastrointestinal tract, and the tracheobronchial surfaces, had also been progressing. Aggressive involvement of his, lips, and oropharynx (Fig. 2), with odynophagia, erosions, and bleeding and severe pain, incapacitated him to drink or eat. The lips typically become crusted with dried blood. A nonblanching, petechial rash was noted on the palms of his feet (Fig. 3). Sloughing of the skin caused several erosions to appear on the scrotum (Fig. 4).

Laboratory examination showed markedly elevated C-reactive protein and hepatic enzymes levels, with renal within normal limits. Laboratory investigations on admission revealed the following: white blood cells, 13.7×10^9 cells/L (normal, 3.5–9.5); neutrophils, 87.5% (normal, 40%–75%); lymphocytes, 8.9% (normal, 20%–50%); monocytes, 3.1% (normal, 3%–10%); eosinophils, 0.1% (normal, 0.4%–8%); basophils, 0.4% (normal, 0–1%); aspartate aminotransferase, 110 U/L (normal, 15–40); alanine aminotransferase, 149 U/L(normal, 9–50); serum creatinine, 94.3 μmol/L (normal, 57–97); total protein, 104.5 g/L (normal, 65–85); and C-reactive protein, 27.80 mg/dL (normal, <0.8). The patient was treated with intravenous immunoglobulin at a dose of 50 g/day, intravenous corticosteroids (tapered methylprednisolone starting with 40 mg daily, then changing to 80 mg daily), and levofloxacin lactate at a dose of 0.5 g/day. After treatment, the laboratory examination returned to normal. He showed a slow but progressive improvement both in symptoms and cutaneous manifestations. Reepithelization of the skin was achieved after 3 weeks.

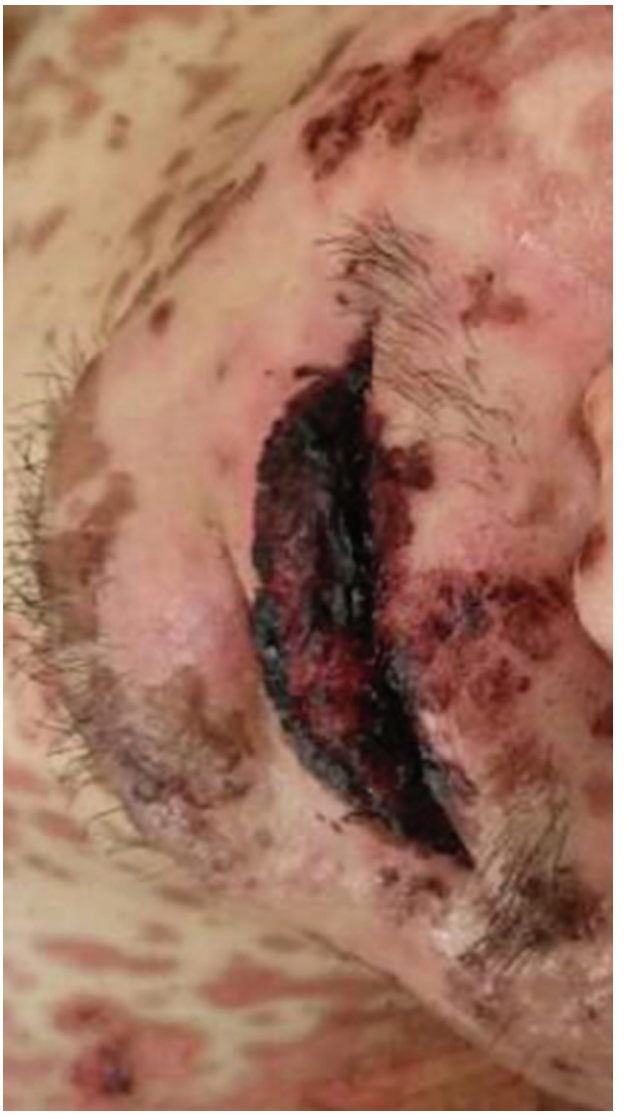

Figure 2. Aggressive involvement of his lips and oropharynx in the case report.

In the case presented, testing for HLA-B*5801 was positive, which more definitely confirmed allopurinol as the causative drug of SJS/TEN. Many results revealed that there were strong

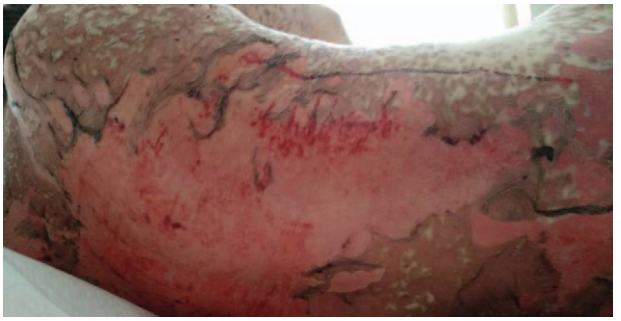

Figure 1. Extensive skin detachment on the back in the case report.

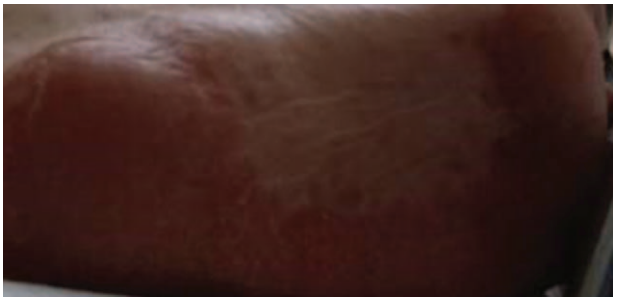

Figure 3. Petechial rash on the palms of his feet in the case report.

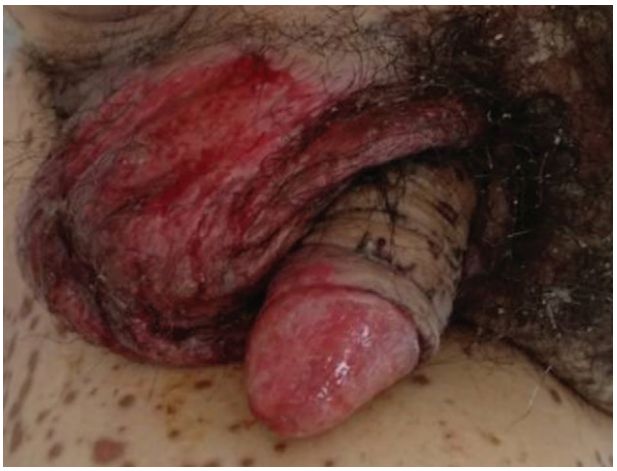

Figure 4. Genital mucosal invovement in the case report.

relationships between 2 specific HLA alleles and SJS/TEN in Han-Chinese, which were HLA-B*58:01 with allopurinol-induced SJS/TEN and HLA-B*15:02 with carbamazepine-induced SJS/TEN. Therefore, HLA-B*5801 and HLA-B*15:02 testing was of great importance because physicians would not intend to use allopurinol and carbamazepine in patients who are HLA alleles positive. The 2 HLA alleles frequency of patients in our hospital was shown in table (Table 1).

3. Discussion

SJS/TEN appears most commonly between 4 days and 4 weeks after exposure to the drug. There is usually an initial nonspecific prodromal illness lasting 2 or 3 days that may feature malaise and fatigue, rhinitis, sore throat, fever, and pruritus, or irritation of the eyes and skin. Patients often take, or are prescribed a medication for these symptoms, which is then erroneously implicated as the causative drug once the cutaneous manifestations appear and the diagnosis of SJS/TEN becomes apparent.[14,15] We present the case of a 33-year-old male patient who developed TEN while receiving allopurinol for being newly diagnosed with hyperuricemia. After 10 days' exposure to allopurinol, the patient manifested with an "influenza-like" prodromal phase (fever, throat pains), followed by painful cutaneous and mucous membrane (ocular, oral, and genital). In the period, the patient received amoxicillin and nonsteroidal anti-inflammatory drugs of the oxicam type, which had been erroneously implicated as the causative drug. In the course, clinical pharmacist plays an important role in finding the etiology, which has been mistaken by the doctor because of the inattention of the consultation process. Given that allopurinol-induced SJS/TEN has serious life-threatening consequences, and long term-0sequelae after development, such as cornea opacity and blindness, and that there are available drug alternatives to allopurinol, testing for HLA-B*5801 before allopurinol initiation may be justifiable and valuable to prevent TEN/SJS caused by allopurinol.[16]

The experience of the drug regulatory authority illustrates some of the benefits and challenges of implementing genetic screening to reduce the incidence of SJS/TEN. There are specific HLA alleles that are associated with a high risk for SJS/TEN. The strongest of HLA associations are HLA-B*58:01 with allopurinol-induced hypersensitivity syndrome and SJS/TEN in Asian populations.[17] HLA-B*58:01 in patients of all ethnicities administered with allopurinol are at high risk for SJS/TEN. Allopurinol, a xanthine oxidase inhibitor that blocks uric acid production, is used for the treatment of chronic gout, uric acid nephrolithiasis, and hyperuricemia secondary to tumor lysis syndrome. Allopurinol as a major cause of SJS/TEN was studied extensively in terms of genetic linkage.

Intravenous immunoglobulin (IVIG) and short-term high-dose corticosteroids were regarded as the most promising treatments for TEN in a comprehensive review of all reported TEN cases.[18] Concerns about the use of glucocorticoids in SJS/TEN patients were mainly related to the high rate of bacterial infection/sepsis in SJS/TEN and the slow rate of reepithelialization of the affected skin. IVIG products lead to inhibition of Fas-mediated keratinocyte apoptosis when applied on keratinocytes in vitro. The proposed mechanism of action of IVIG was that it contained anti-Fas antibodies which could inhibit the Fas/Fas ligand (FasL) interaction, preventing further apoptosis of keratinocytes, and arresting the progression of TEN. It is reasonable to think that the best timing for IVIG intervention is before this detachment occurs, and the earlier the better to limit further apoptosis of keratinocytes and arrest progression of the disease.

Table 1

The 2 HLA alleles frequency of patients in our hospital.

Drugs	Gene detection site	Patient number	The HLA-B*5801 allelic frequency
Allopurinol	HLA-B*58:01	2257	8%
Carbamazepine	HLA-B*15:02	180	1%

4. Conclusion

SJS/TEN is considered a delayed-type hypersensitivity reaction to drugs, including nonsteroidal anti-inflammatory drugs of the oxicam type, anti-infective sulfonamides, anti-epileptic drugs, nevirapine, allopurinol, and chlormezanone. The role of drug-specific cytotoxicity mediated by T cells, genetic linkage with HLA and non-HLA genes, TCR restriction, and cytotoxicity mechanisms in SJS/TEN is quite clear. The acute management of SJS/TEN requires a multi-disciplinary approach, immediate withdrawal of potentially causative drugs and prompt referral to an appropriate medical center for supportive treatment. This case underlines the necessity of asking medication history in detail to correctly identify the cause of TEN.

Author contributions

Conceptualization: Feifei Wang, Lihong Liu.
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Validation: Zhuo Ma, Xinan Wu.
Visualization: Zhuo Ma, Xinan Wu.
Writing – original draft: Feifei Wang, Zhuo Ma.
Writing – review & editing: Zhuo Ma, Xinan Wu, Lihong Liu.

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