Case Report

FATAL CIPROFLOXACIN-INDUCED TOXIC EPIDERMAL NECROLYSIS (LYELL SYNDROME): A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Toxic epidermal necrolysis (TEN) is one of the most dramatic and severe adverse cutaneous drug reactions. Ciprofloxacin is a frequently prescribed fluoroquinolone and can induce TEN occasionally. A review of the English literature revealed 7 ciprofloxacin-associated TEN cases in the past 10 years. A well-documented fatal case of ciprofloxacin induced TEN is presented. This case report adds to the evidence that ciprofloxacin is associated with TEN in rare cases. All healthcare practitioners should be alert for signs of TEN in patients taking ciprofloxacin and discontinue the drug immediately. Because of the similarity of TEN to an extensive partial-thickness burn besides multiorgan involvement or complications, transfer of the patient to a burn unit in the shortest time is vital.

Key Words : Toxic epidermal necrolysis, Ciprofloxacin, Quinolones, Adverse drug reactions.

INTRODUCTION

Toxic epidermal necrolysis (TEN) or Lyell's syndrome is an idiosyncratic severe systemic disease characterized by extensive full-thickness epidermal exfoliation (30-100 % total body surface area), fever, conjunctivitis, and mucous membrane involvement (1). TEN has a significant morbidity and high mortality (mean 30%) with an average incidence of about 1 per million persons in Western countries (2).

The most frequent cause for TEN is drugs, with most series showing over 90 % of patients with a probable drug cause (3). Antibacterial sulfonamides (cotrimoxazole), aromatic anticonvulsants (phenobarbital, phenytoin, carbamazepine), some antibiotics (aminopenicillins, quinolines, cephalosporins), some nonsteroidal anti-inflammatory drugs (tenoxicam, piroxicam), chlormezanone and allopurinol were all confirmed as culprit drugs for TEN in a case-control study held in Europe by Roujeau et al (4). It is noteworthy that corticosteroid use was also associated with the development of TEN in that study.

Nondrug causes of TEN are uncommon but include acute graft-versus-host reaction, hepatitis, viral, bacterial and fungal infections. Patients with acquired immunodeficiency syndrome (AIDS) have a higher incidence of TEN (2, 5). Some cases of TEN have no detectable cause (2, 3).

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The exact immunopathologic mechanism of TEN is yet to be determined. It is postulated that a reactive metabolite produced by alteration in the detoxification process complexes with class I major histocompatibility complex on the keratinocyte, causing a cell-mediated immune response with cytotoxic T lymphocytes, and cytokines causing keratinocyte damage (3).

A strong association between quinolones and TEN or Stevens-Johnson syndrome (SJS) has been previously reported (4). Seven cases of ciprofloxacin-associated TEN were reported in the English literature in the past 10 years (6-11). Presented herein is another rare case of ciprofloxacin-induced TEN.

CASE REPORT

A 63-year-old female suffering extensive, full-thickness epidermal loss was admitted to the burn unit. She had first sought medical attention 20 days prior to admission for urinary infection, and she was treated with ciprofloxacin (p.o.500 mg b.i.d.) on an outpatient basis for 10 days. On the tenth day, she presented at the outpatient department of another hospital with a two-day history of fever, vomiting, and a day history of erythema of her face and neck. A tentative diagnosis of allergy to the medication was made and the drug was discontinued; treatment was started with cetrizine dihydrochlorure (p.o.10 mg a day). One day after, she presented at the emergency department of another hospital with a high temperature, irresistible itching, and extended maculopapular erythematous rash over the trunk. A tentative diagnosis of Stevens-Johnson syndrome was made and prednisolone (p.o.40 mg b.i.d.) and cefazoline sodium (IV 1 gm b.i.d.) were initiated. Over the next 5 days, erythema and blistering spread to involve almost the entire body, sparing only the scalp, and some places in the anterior part of the thorax and abdomen. It was noted that the skin would peel off in sheets with very slight digital pressure (Nikolsky's sign). At this time a diagnosis of toxic epidermal necrolysis was made, and she was transferred to our burn unit.

On the day of admission the skin resembled a recent scald, which covered 95 percent of the body surface (Figs. 1 and 2). Her weight was 95 kg and oral temperature was 38,3°C. Physical examination revealed bloody, crusted erosions over almost the entire body, the perioral region and oro-nasal mucosa, sparing only the scalp and some places on the anterior part of the torso.

A skin biopsy demonstrated full-thickness epidermal necrosis. There was only sparse lymphohistiocytic infiltrate, papillary dermal edema and dilatation of the dermal vessels. Focal separation of the epidermis from the dermis beneath the basal layer was consistent with a diagnosis of toxic epidermal necrolysis.

Laboratory values obtained on the day of admission showed leukopenia (white blood cell count $2.3x10^3/\mu l$, reference range 4.4-$11.3x10^3/\mu l$), elevated lactate dehydrogenase of 783 U/l (reference range 0-450 U/l) and, elevated liver enzymes (AST 50 U/l, reference range 5-40 U/l).

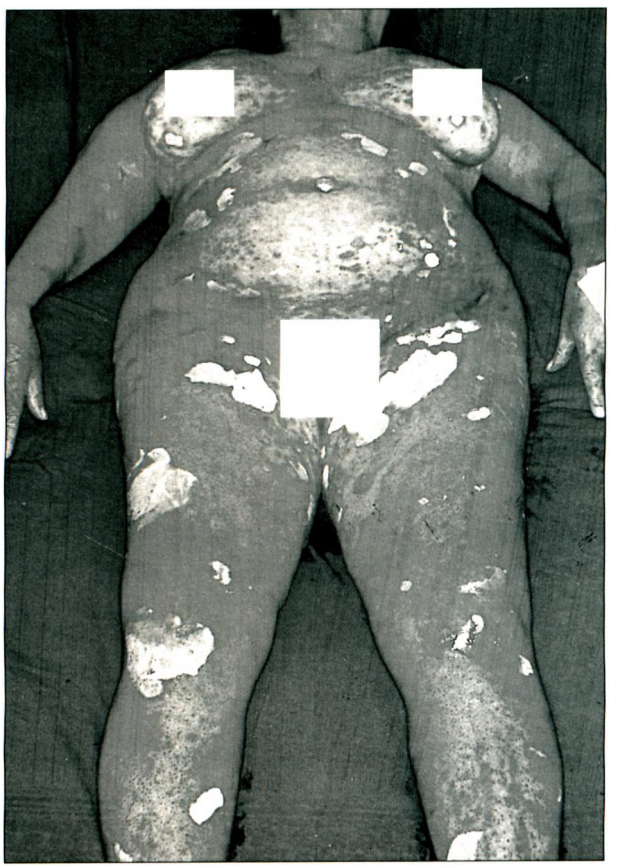

Fig. 1: Extensive skin slough of a 63-year-old woman suffering toxic epidermal necrolysis.

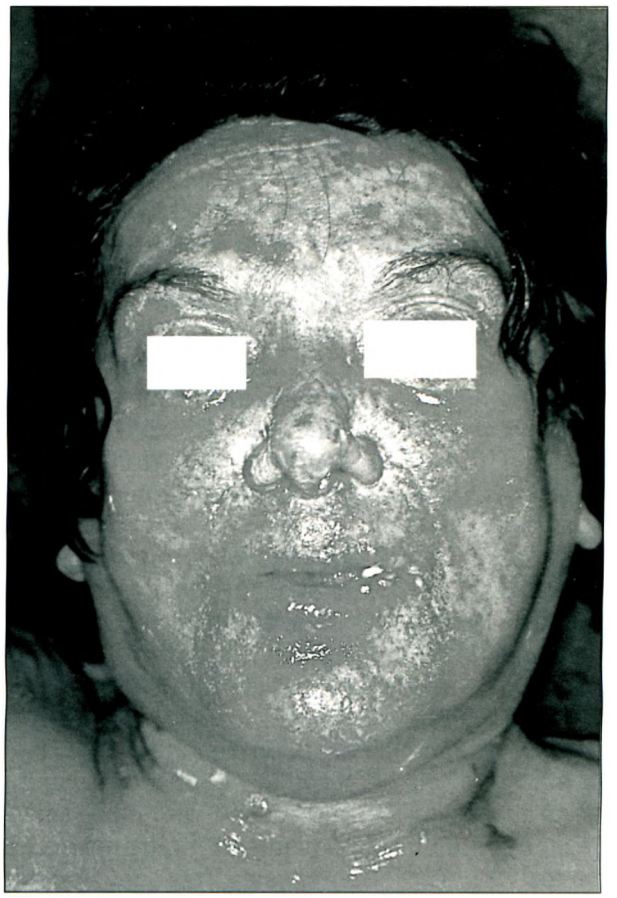

Fig.2: Face of the same patient.

A set of blood and wound cultures drawn early in her hospital course grew Methicillin-resistant *Staphylococcus aureus* (MRSA); the patient was started on broad-spectrum antibiotic coverage including amikacin (iv 500 mg b.i.d.) and vancomycin.(iv 500 mg q.i.d.) and prednisolone therapy was stopped. Each day the wounds were covered with chlorhexidine and white petrolatum saturated occlusive dressing, following cleaning of the wounds in the washing tank. The severe conjunctiva inflammation was treated with dexamethasone ophthalmic solution. Eye care was provided every 1 to 2 hours and included saline rinses. Chest physiotherapy and gastrointestinal tube feeding and other supportive measures were begun immediately after admission to the burn unit.

The patient's general condition deteriorated due to sepsis and other complications of TEN. Hemodynamic instability with persistent fever developed; pulmonary status worsened, with decreasing oxygen saturation and a decrease in pulmonary compliance requiring increased ventilatory support. Although a total of about 8 L/day fluids were given to the patient and 1.8 L/day urine output was maintained, the patient developed acute renal failure. Urine output decreased and blood urea level raised to 161 mg/dL (reference range 15-44 mg/dL) and total bilirubin was 15.4 mg/dL (reference range 0.2-1 mg/dL). Haemodialysis was attempted but the patient expired on the twelfth day after the first cutaneous signs appeared and on the fourth day of burn unit admission.

DISCUSSION

Fluoroquinolones have been used for 10 years all over the world. Ciprofloxacin is one of the most prescribed fluoroquinolone. Major adverse effects due to ciprofloxacin and other fluoroquinolones such as gastrointestinal disorders, hypersensitivity reactions, central nervous system disorders, hepatic disorders and hemolytic disorders were reported (11-14).

There is no reliable test to prove the link between a single case of TEN and a specific drug (15). The usefulness of patch tests in TEN seems to be weak (16). On the other hand, determination of a single precipitating factor in drug-related TEN is often difficult, because patients might be taking more than one medication. Guillaume et al. have utilized an adaptation of the adverse drug surveillance system to implicate drugs associated with TEN (17). Under this system drugs are assessed for culpability based on the following criteria: 1- time interval between drug administration and onset of symptoms, 2- improvement in the patient's condition after withdrawal of the drug, 3- disease recurrence with re-exposure to the drug, and 4- exclusion of other causes of TEN including other drugs and TEN-associated diseases. The time interval from drug administration to bullous eruption is highly suggestive of an adverse drug reaction when the eruption begins 7-21 days after first administration of the drug, or the eruption begins within 48 h of administration of the drug if it has previously caused a similar reaction in the patient. Situations incompatible with adverse drug reaction in this case include: drugs administered after the onset of cutaneous or

mucosal signs, drugs that cause eruptions within 24 h of administration and cases of lesions presenting more than 21 days after first administration unless the drug has prolonged pharmacokinetics (7, 10, 17). In the presented case, the patient was placed on the offending drug 8 days before prodrome and early acute symptoms began approximately 9 days before marked cutaneous manifestations presented. To our knowledge this was the patient's first exposure to ciprofloxacin and hence the time period (according to the Guillaume criteria) strongly implicates this fluoroquinolone antibiotic as casual for TEN. The patient's only known medical illness was nephrolithiasis . This medical condition has not been reported to be associated with TEN. Cetrizine dihydrochlorure , cefazoline sodium and prednisolone were prescribed after the symptoms of the prodrome and the acute phase of TEN had appeared.

Garcia-Doval et al reported that if there is a strong suspicion that a patient may have SJS or TEN, prompt withdrawal of drug treatment will reduce the risk of death by about 30% per day (18). In spite of timely cessation of the drug and initiation of corticosteroid in our case, the clinical picture progressed to TEN in a few days.

Of the various treatments advocated to modify the extent of skin detachment, the one that remains the most controversial is the use of systemic corticosteroids. Although there is a lack of double-blind randomized controlled trials that support or exclude the benefits of corticosteroids, recent data suggest that corticosteroids are more detrimental than useful in TEN and should be avoided (2). Plasmapheresis, cyclosporine, cyclophosphamide, N-acetylcysteine, monoclonal antibodies against cytokines and intravenous immunoglobulin have been used in the treatment of TEN but they all need well-controlled clinical trials (19, 20).

The main causes of mortality in TEN are sepsis and multiple organ failure, either related to sepsis or to adult respiratory distress syndrome besides pulmonary, renal and gastrointestinal complications (2, 3). The most important prognostic factors are the age of the patient, the percentage of skin slough, serum urea nitrogen level, and visceral involvement (2). The presented patient was 63 years old, the percentage of denuded skin was 95, MRSA sepsis was developed and serum urea nitrogen level was high. These factors were all poor prognostic factors. The patient was referred to our burn unit 11 days after the onset of cutaneous symptoms. Thus she missed the opportunity to remove the sloughing skin and to apply xenograft, cadaveric skin or other biological or synthetic dressings when the wounds were still relatively clean without bacterial contaminants. Acute epidermal exfoliation seen in TEN resembles a partial thickness burn and a significant amount of heat and fluid can be lost from the denuded skin. If viable dermis can be protected from toxic detergents, desiccation, mechanical trauma, and wound infection, then spontaneous epithelialization in 1-3 weeks without scarring is the rule (2, 21). The aims of local treatment methods used for TEN are; to minimize heat and fluid loss from the wound, to prevent wound infection, to reduce pain and to provide moist and clean wound environment for promoting re-epithelialization. It has been reported that the overall rate of bacteremia, septicemia, and mortality is significantly reduced with early (< 7 days) referral of TEN patients to a regional burn center (22, 23). Rasmussen has developed recommendations for hospital management of patients with the spectrum of disease process ranging from erythema multiforme minor to toxic epidermal necrolysis. He suggests admission to a burn center or intensive care unit is appropriate when more than 10 % of the total body surface area is blistered or if there is oral or mucosal involvement (24).

It is noteworthy that 6 of the 8 patients, who developed ciprofloxacin-associated TEN, were older than 50 years and all died while the other 2 young patients survived (6-11). Although TEN occurs in all age groups, the incidence of TEN increases sharply with age. This increase is correlated to the more frequent drug intake in the elderly (25, 26).

As a conclusion, ciprofloxacin is associated with TEN in rare cases. All healthcare practitioners should be alert for signs of TEN in patients taking ciprofloxacin and discontinue the drug immediately. Because of the similarity of TEN to an extensive partial-thickness burn besides multiorgan involvement or complications, transfer

of the patient to a burn unit in the shortest time is vital.

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