

Levofloxacin-induced Toxic Epidermal Necrolysis Treated with Intravenous Immunoglobulin

Dear Editor,

Toxic Epidermal Necrolysis (TEN) is a rare, fulminating rash with a mortality rate of 35%.¹ It is predominantly medication-induced; allopurinol, ampicillins, anti-convulsants and non-steroidal anti-inflammatory drugs are commonly implicated.

Fluoroquinolones are widely used, have a broad coverage and have a low incidence of serious adverse effects. Levofloxacin, a L-racemic isomer of ofloxacin, has one of the most favourable adverse reaction profiles.² The first case of levofloxacin induced TEN was reported in 2002.³ A total of 4 cases of TEN with levofloxacin as the implicated drug have been reported in the literature, of which 2 cases proved fatal.⁴⁻⁶

We present a patient with levofloxacin-induced TEN. A 76-year-old Indian lady had undergone an open anterior resection for sigmoid colon cancer a month ago. She was prescribed oral levofloxacin for post-operative nosocomial pneumonia and was subsequently developed an asymptomatic maculopapular rash 11 days later. Blisters subsequently developed over the next 4 days, along with fever, conjunctival injection, oral and vaginal labial ulcers. On day 4 of the rash, levofloxacin was stopped and she was referred to the dermatologist. She had no known drug allergy.

Clinical examination revealed widespread dusky red skin with vesicles and bullae, over the chest, abdomen, back and the groin, with 40% of the total body surface area (BSA) involvement and 15% of the denuded skin. The Nikolsky sign was positive (Fig. 1). There was superficial abdominal wound dehiscence. She was haemodynamically stable. The laboratory results were normal apart from a raised ESR of 50. A calculated SCORTEN⁷ value of 4 predicted a 58.3% mortality rate.

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The clinical diagnosis was consistent with Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis (SJS-TEN) overlap with 15% body surface area epidermal detachment.

Intravenous immunoglobulin (IVIG) infusion at 1 mg/kg/day for 3 days was initiated on admission, along with hourly parameters, strict input-output monitoring, IV fluids

The implicated culprit drug was levofloxacin. Skin biopsy showed near transepidermal keratinocyte necrosis and group apoptosis associated with mild lymphocytic exocytosis, confirming TEN (Fig. 2).



Fig. 1. Widespread dusky red confluent bullae and erosions, with positive Nikolsky sign (top layer of skin slips from lower layers when rubbed) over the chest, abdomen, back and the groin.



Fig. 2. Near transepidermal keratinocyte necrosis and group apoptosis associated with mild lymphocytic exocytosis, confirming TEN.

and dressings. She was managed in an isolation room in the general ward. Ophthalmology review revealed mild ocular inflammation. Progression to 40% BSA epidermal detachment occurred over the next 40 hours. Greenish wound discharge was noted on day 4 of admission, and IV aztreonam (for 5 days) and acetic acid compresses were administered for presumed *Pseudomonas Aeruginosa* infection. Subsequent clinical/biochemical markers, blood and urine cultures were negative for infection. Wound cultures grew Methicillin Resistant *Staphylococcus Aureus* (MRSA) and multi-drug resistant *Klebsiella*. Re-epithelialisation occurred on day 8 of hospitalisation. She was discharged after 16 days, with complete re-epithelialisation.

The fluoroquinolones have a low incidence of TEN.⁶ Levofloxacin has comparable clinical and microbiologic success rates in the treatment of nosocomial pneumonia and is preferred over other quinolones for its favourable side effects profile and once daily dosing.⁸

It is important for the physician to be aware of levofloxacin-induced TEN, in the light of the previous 2 fatalities (50%) of cases. It is important to caution patients to stop the drug once a rash develops. In this patient, medical attention was not sought immediately and the patient continued on levofloxacin till day 4 of the rash. The key prognostic marker in TEN is the prompt identification and withdrawal of the causative drug.

High-dose IVIG is a controversial therapeutic approach for TEN—it blocks the Fas-Fas ligand interaction responsible for epidermal cell apoptosis.⁹ Three of the previously reported cases were treated with fluid resuscitation and IV antibiotics, 1 patient was treated with IV methylprednisolone (with a fatal outcome). Two local case series feature the use of IVIG in TEN. In a study by Tan AW et al,¹⁰ the survival rate was 91.6%. The authors concluded that high-dose IVIG may be a safe and effective therapy for Asian patients with TEN. A case series by Teo L et al¹¹ involving TEN patients treated with IVIG, none of the patients experienced adverse events related to IVIG. Our patient was treated with IVIG with a good outcome. Non-comparative studies have suggested the benefits of IVIG treatment. However, the lack of blind, multicentric randomised trials of pharmacologic agents in TEN¹² emphasise the difficulties in evaluating the efficacy of such therapeutic modalities.

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REFERENCES

1. Borchers AT, Lee JL, Naguwa SM, Cheema GS, Gershwin ME. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev* 2008;7:598-605.
2. Carbon C. Comparison of side effects of levofloxacin versus other fluoroquinolones. *Chemotherapy* 2001;47 Suppl 3:9-14; discussion 44-8.
3. Digwood-Lettieri S, Reilly KJ, Haith LR Jr, Patton ML, Guilday RJ, Cawley MJ, Ackerman BH. Levofloxacin-induced toxic epidermal necrolysis in an elderly patient. *Pharmacotherapy* 2002;22:789-93.
4. Islam AF, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. *Ann Pharmacother* 2005;39:1136-7.
5. Davila G, Ruiz-Hornillos J, Rojas P, De Castro F, Zubeldia JM. Toxic epidermal necrolysis induced by levofloxacin. *Ann Allergy Asthma Immunol* 2009;102:441-2.
6. Christie MJ, Wong K, Ting RH, Tam PY, Sikaneta TG. Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005;39:953-5.
7. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000;115:149-53.
8. West M, Boulanger BR, Fogarty C, Tennenberg A, Wiesinger B, Oross M, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003;25:485-506.
9. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol* 2007;56:181-200.
10. Tan AW, Thong BY, Yip LW, Chng HH, Ng SK. High-dose intravenous immunoglobulins in the treatment of toxic epidermal necrolysis: an Asian series. *J Dermatol* 2005;32:1-6.
11. Teo L, Tay Y K, Liu T T, Kwok C. Stevens-Johnson syndrome and toxic epidermal necrolysis: efficacy of intravenous immunoglobulin and a review of treatment options. *Singapore Med J* 2009;50:29-33.
12. Stern RS. Improving the outcome of patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Arch Dermatol* 2000;136:410-1.

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