CASE REPORT

Lamotrigine, a Miscreant in Toxic Epidermal Necrolysis: a Rare Case Report

Mahima MAKHIJA[1], Alka BANSAL[1], Deepak Raj SAKHNANI[2]

Abstract

This case report is about a rural 39 years old female of Asian origin and laborer by profession who developed Toxic Epidermal Necrolysis (TEN) with lamotrigine. She was a known case of Bipolar Affective Disorder Type 1 with psychosis on treatment with quetiapine, duloxetine, escitalopram, and etizolam for the last one and a half years and had no history of adverse effects with those drugs. Recently Lamotrigine was added to her regimen at a dose of 50 mg/day. She developed Stevens-Johnson syndrome (SJ syndrome) within two weeks of adding lamotrigine which progressed to Toxic Epidermal Necrolysis (TEN), SCORTEN scores 3, in the next 3-4 days. The sequence of events, reports of laboratory investigations, and management of TEN have been elaborated in this case report. On the Naranjo scale of causality, the suspected adverse drug reaction was established as 'probable' because the suspected culprit drug discontinuation led to improvement in the patient's condition but a rechallenge was not tried.

Keywords: Adverse drug reaction (ADR), Case report, Lamotrigine, Stevens-Johnson syndrome (SJ syndrome), Toxic Epidermal Necrolysis (TEN).

INTRODUCTION

Lamotrigine has been approved for the first-line treatment of focal-onset tonic-clonic seizures, simple partial seizures, complex partial seizures, and Lennox-Gestault syndrome. Also, it is used as maintenance therapy in bipolar affective disorder type I, to prevent basilar migraine with aura, and to treat panic disorders and binge-eating disorders.[1]

Lamotrigine frequently causes headaches, nausea, vomiting, trembling, anxiety, and sleeplessness as a side effect. In 3–10% of users, a mild to moderate skin rash is seen[2]. However, lamotrigine, occasionally (0.03-0.08% cases) causes serious skin responses such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), necessitating the drug's withdrawal and careful toxicity management.

SJS/TEN are a subset of the illness spectrum and are not distinct entities. SJS affects less than 10% of the body surface, whereas TEN impacts more than 30% with extensive damage to the mucous membranes[3]. SJS/TEN overlap is defined as 10–30% of the body surface covered by skin detachment often accompanied by systemic symptoms[4]. More than 80 percent of cases are triggered by medication and SCORTEN is a severity-of-illness score to indicate the severity of TEN[5,6,7].

CASE REPORT

A 39-year-old rural female patient presented to the emergency complaining of high temperature, shortness of breath, and restlessness. Detailed history revealed that she was a known case of Bipolar Affective Disorder Type 1 with psychiatric symptoms and was receiving quetiapine, duloxetine, escitalopram, and etizolam for the past one-and-a-half years on prescription. No significant previous history of food/ drug allergy or reaction was found. Recently lamotrigine 50mg per day was added to her regimen. It was further discovered that after two weeks of adding lamotrigine, the patient began to experience localized burning, minor rashes, and itching. She saw a dermatologist to treat the symp-

[1]RUHS College of Medical Sciences, Jaipur, India
[2]SMS Medical College, Jaipur

Corresponding author:
Deepak Raj SAKHNANI, Kaveri Path Mansarovar, Jaipur, India
E-mail: doctordeepakraj@gmail.com

toms, who recommended calamine lotion & levocetirizine, but the condition worsened.

In the next three to four days, she developed extensive rashes, blisters, itching all over the body, multiple oral ulcers, redness of eyes, and genital ulceration [Figure 1 (a, b)].

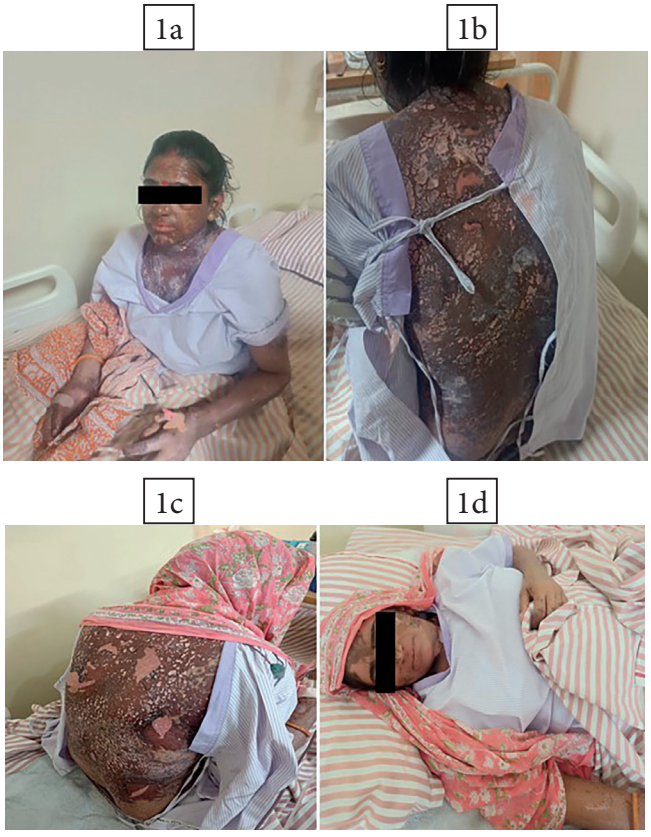

Figure 1. (a, b): Day 1 showing the front and back of the patient with severe mucocutaneous involvement, blisters, and erythema with crusting
(c): Day 7 post-treatment showing improvement
(d): Day 10 post-treatment with healed lesions

She continued taking lamotrigine. The mucocutaneous involvement worsened and systemic symptoms of fever, breathlessness, and restlessness also developed making her land in an emergency. Based on their medical history and physical examination, she was diagnosed to be a case of TEN with a Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) score of "3" [7]. By the Naranjo scale of causality, lamotrigine was suspected to be the probable reason.

SCORTEN score considers age ≥ 40 years, associated cancer, heart rate ≥ 120 beats/min, serum blood urea nitrogen > 28 mg/dL, detached or compromised body surface ≥ 10%, serum bicarbonate < 20 mEq/L and serum glucose > 250 mg/dL as significant risk factors and assigns mark 1 for the presence of each risk factor. A higher score indicates a higher mortality rate, varying from 3.2% at score 0-1 to >90% at score 5-6.

At the time of admission, her vitals were: body temperature, 102.6 F; blood pressure, 102/64 mm Hg; heart rate, 122 beats/min; respiratory rate, 22 breaths/min; and oxygen saturation (SPO2) of 93%. The laboratory test findings from day 1 of admission till discharge on day 10 are shown in Table 1.

For managing the case, the suspected offending drug lamotrigine was stopped and O2 at 2L/min via an oxygen mask was started immediately. She was also prescribed antiemetics, antihistaminics, fluids, topical steroids, anti-inflammatory eye drops, and topical moisturizers. Antibiotics amoxiclav (1.2 g iv q8hr), linezolid (600mg iv q12hr), cyclosporine (3.0 mg/kg/day) and systemic steroids (methylprednisolone; 1 g/day for 5 days and subsequent tapering) were given. All aseptic precautions were taken and close ICU monitoring was done.

Her condition improved gradually and finally on day 10, she fully recovered with all deranged blood cells and biochemical parameters returning to normal (Table 1).

DISCUSSION

Chemically lamotrigine is a phenyltriazine that acts by blocking voltage-activated-sodium-channels and thereby preventing the presynaptic release of the excitatory glutamate neurotransmitters[8]. It is extensively metabolized in the liver by N-glucuronidation.

Although the exact mechanism of developing SJ/TEN with lamotrigine remains elusive, it is believed that failure to clear reactive metabolites in some patients triggers a CD8+T-cell-mediated, cytotoxic response (type IV hypersensitivity) to drug antigens within keratinocytes causing blister formation which then progresses to painful red or purple burned/peeled off skin, mucous membrane[9,10].

SJS often starts with a fever and shows flu-like symptoms. The increased risk of manifesting SJS/TEN reactions is largely confined to the first 8 weeks of initiating the treatment[11]. Studies have proved that female gender, concomitant anti-psychotic drugs, high starting dose and Asiatic origin of the patient are associated with increased risk of SJS/TEN with lamotrigine.

Table 1: Reports of Laboratory Tests

Test Name	Day 1	Day 3	Day 7	Day 8	Day 10	Unit	Reference Range
Haemoglobin	12.5	12.3	**11.0**	**11.5**	12.6	gm/dl	12-16
Red Blood Count	4.83	4.85	4.39	4.45	4.92	millions/cumm	3.5-5.5
Total Leukocyte Count	**15900**	6400	9700	5200	6300	cells/cumm	4,000-11,000
Platelet	3.14	3.82	4.02	4.74	4.67	lakhs/cmm	1.5-4.5
Blood Urea	**48.97**	42.6	20.90	19.20	18.73	mg/dl	15-36
S.Creatinine	**1.56**	1.42	0.73	0.79	0.65	mg/dl	0.4-1.25
Uric Acid	3.60	3.86	3.96	3.62	3.47	mg/dl	2.4-8.5
Sodium	128.9	**132.0**	**133.5**	135.8	138	mmol/L	135-145
Potassium	4.13	3.89	4.48	4.74	4.75	mmol/L	3.5-5.1
Chloride	104.5	101.2	98.5	99.5	103.9	mmol/L	98-107
Blood Sugar Random	**174.4**	98	96	78	82	mg/dl	90-140
ESR	**60**		**42**		18		0-20
CRP Quantitative	**100.2**		**71.66**		25.58	mg/L	0.0-0.6
HBA1c		5.6				%	
Serum Bilirubin (Total)	0.88		0.88			mg/dl	0.2-1.3
Serum Bilirubin (Direct)	0.26		0.27			mg/dl	0.0-0.4
Serum Bilirubin (Indirect)	0.62		0.61			mg/dl	0.0-1.0
SGOT(AST)	**153.3**		28.69		22.23	U/L	15-46
SGPT(ALT)	**231.1**		**41.85**		28.62	U/L	13-34
Alkaline Phosphatase	**127.1**		65.73		62.49	U/L	38-126
Total Protein	7.22		**5.71**		7.58	g/dL	6.3-8.2
Albumin	4.19		**3.49**		4.22	g/dL	3.5-5.0
Globulin	3.03		2.22		3.36	g/dL	0-5
Albumin Globulin Ratio	1.38		1.57		1.25	Ratio	1.0-2.3
Blood urea nitrogen	22.85					mg/dl	

CONCLUSION

Lamotrigine can precipitate TEN, a possibly fatal skin reaction in occasional cases thereby requiring awareness and vigilant supervision while prescribing and quality of care with faster management in case the reaction develops.

References

1. Betchel NT, Fariba KA, Saadabadi A. Lamotrigine. [Updated 2022 May 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470442/
2. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epider mal necrolysis during first weeks of antiepileptic therapy: a case-control study. Vols. 353, The Lancet. 1999. pp. 2190-4.

3. Stevens-Johnson syndrome/toxic epidermal necrolysis - About the. [Internet]. [Cited 2022Oct.27]. Available from: https://rarediseases.info.nih.gov/diseases/7700/stevens-johnson-syndrome-toxic-epidermal-necrolysis/
4. Fouchard N, Bertocchi M, Roujeau J-C, Revuz J, Wolkenstein P, Bastuji-Garin S. SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis. Vols. 115, Journal of Investigative Dermatology. 2000. pp. 149-53.
5. Stevens-Johnson syndrome - Symptoms and causes - Mayo Clinic [Internet]. [Cited 2022Oct.27]. Available from: https://www.mayoclinic.org/diseases-conditions/stevens-johnson-syndrome/symptoms-causes/syc-20355936
6. Stevens - Johnson syndrome (SJS): Causes and Treatments [Internet]. [Cited 2022Oct.27]. Available from: https://www.webmd.com/skin-problems-and-treatments/stevens-johnson-syndrome
7. Table: Severity-of-Illness Score for Toxic Epidermal Necrolysis . [Internet]. [cited 2022Oct.31]. Available from: https://www.msdmanuals.com/professional/multimedia/table/severity-of-illness-score-for-toxic-epidermal-necrolysis-scorten
8. Johannessen SI. Therapeutic drug monitoring of antiepileptic drugs. Handbook of Analytical Separations [Internet]. 2004 [cited 2022Oct.27]; 221-53. Available from: https://www.sciencedirect.com/science/article/abs/pii/S156771920480010X
9. Beattie K, Phadke G, Novakovic J. Lamotrigine. Profiles of Drug Substances, Excipients and Related Methodology. 2012. pp. 245-8.
10. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis . [Internet]. [Cited 2022Oct.27]. Available from: https://www.msdmanuals.com/professional/dermatologic-disorders/hypersensitivity-and-reactive-skin-disorders/stevens-johnson-syndrome-sjs-and-toxic-epidermal-necrolysis-ten
11. Stevens–Johnson syndrome - Wikipedia [Internet]. [Cited 2022 Oct.27]. Available from: https://en.wikipedia.org/wiki/Stevens%E2%80%93Johnson_syndrome