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Case Report

Rifampicin- and allopurinol-induced Stevens-Johnson syndrome: A case series

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ABSTRACT

Stevens-Johnson syndrome (SJS) is a rare, serious disorder and may be life threatening affecting mainly mucocutaneous tissues. It is a type of generalised, multisystemic hypersensitivity reaction directly linked to the drug intake. It is one of the few serious adverse effects of drugs involving skin and mucous membranes which are characterised by rash, bullae and blisters spread on skin, mucous membranes, swelling with erosive lesions on lips and face and hyperpigmentation. Normally, SJS is a self-resolving condition but it has potential to be converted into life-threatening disease. Here, we describe and present a case series of SJS inflicted by rifampicin and allopurinol. First one is a 28-year-old-female and second case is a 50-year-old male, both received rifampicin for pulmonary tuberculosis. Third patient is a 22-year-old young male taken allopurinol for hyperuricemia. All these patients noticed a severe skin reaction which is a part of erythema multiforme spectrum. Causality assessment was done in these patients with the help of Naranjo's algorithm and diagnosed as cases of SJS.

Keywords: Stevens-Johnson syndrome, Hypersensitivity, Rifampicin, Allopurinol

INTRODUCTION

Stevens-Johnson syndrome (SJS) is a worrying unfavourable drug reaction initially affecting mucous membranes and skin. This is categorised as an immune-mediated hypersensitivity reaction[1] and almost all cases of SJS commonly associated with inflicting drug exposure.[2] Rifampicin is the first-line antitubercular drug prescribed most commonly for tuberculosis. It is a bactericidal drug, having high efficacy against tubercle bacilli. Allopurinol is another common drug given for the treatment of hyperuricemia or gout. It reduces synthesis of uric acid by inhibiting xanthine oxidase enzyme. Both the above-mentioned medications are considered safer drugs, but uninvited, inconvenient adverse effects, especially in the form of mucocutaneous hypersensitivity reactions, have been reported only in very few occurrences due to these medications.[3,4]

CASE PRESENTATION

Case 1

A 28-year-old female patient presented in dermatology OPD with complaints of rapidly progressive multiple eruptions all over her body. These rashes also involved her face, hands, back and adhesion of tongue and also the palate. These rashes converted into haemorrhagic bullae with scaling. She was diagnosed as a case of pulmonary tuberculosis and prescribed first-line

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antitubercular drugs rifampicin, isoniazid and pyrazinamide. On the 5th day morning, she noticed rashes all over her body in a manner described above. After that, she did not take any other first-line antitubercular drug prescribed to him.

On the examination of patient, she was conscious, well-oriented and stable with febrile (39.5°C) and hypotensive (98/70 mmHg) condition. Respiratory rate was 22/min while pulse rate was 80 bpm. Blister and rashes converted into haemorrhagic bullae involving major parts of her body. Erosion and crusting also involved her lips. There was no lymphadenopathy detected on clinical examination.

Her haemoglobin value was 8.4 g/dl, while platelets were in normal range and total white blood cells count was 7.02 × 10^9/L. On the basis of liver function test, we found that aspartate aminotransferase (420 U/L), alanine aminotransferase (170.4 U/L) and serum alkaline phosphatase (400.5 U/L) levels were raised. Blood urea and serum creatinine were 110.2 mg/dl and 2.29 mg/dl, respectively. ESR was elevated to 54 mm/h. The patient was a known case of cholecystitis and pancreatitis. Systemic examinations did not reveal any other noteworthy conclusions.

On the basis of detailed history from patient, clinical examinations and relevant findings, this patient was diagnosed as a case of rifampicin-induced SJS by dermatologist. After that, the patient was admitted and treatment started with intravenous dexamethasone (4 mg/day in divided doses), antihistamines and ursodeoxycholic acid 300 mg, twice a day. About 2% fusidic acid cream was applied topically. Intravenous fluid therapy to overcome fluid loss, supportive and symptomatic treatment had been given for optimal benefit of the patient. Despite the treatment given, her condition deteriorated and ultimately she died after 3 days.

Case 2

A 50-year-old male patient came to the emergency department in the hospital with generalised severe body rashes with itching and swelling on her lips. Some blisters and erosions were also present on some parts of his body. It started on the 6th day after he was initiated the treatment of directly observed treatment short-course category I regimen prescribed for pulmonary tuberculosis. These rashes first appeared on the trunk and then rapidly progressed to involve the upper and lower extremities, oral cavity and lips. These rashes were initially popular in character and converted into erythematous eruptions later on with some hyperpigmented lesions. On the basis of detailed clinical examinations, findings and relevant medical history, this patient was diagnosed of SJS inflicted by first-line antitubercular bactericidal drug rifampicin. His blood investigations revealed normal range of platelets and haemoglobin value of 12.3 g/dl. The total leucocytes were also with in normal range (9.3 × 10^9/L). His hepatorenal functions were at desired level while ESR reading was 30 mm/h. We did not find any other relevant findings on systemic examinations.

After that, the patient was admitted and treated for 1 week with intravenous fluid therapy for maintaining proper hydration, injection amoxicillin 500 mg, 8 h, to prevent secondary bacterial infections, injection hydrocortisone 100 mg, 12 h IV, injection pantoprazole 1 ampoule twice a day, tablet levocetirizine 5 mg OD and mupirocin ointment (2% w/w) applied topically on the skin. The condition of patient improved progressively and he was discharged later on.

He did not give any history of drug allergy before rifampicin intake. Other blistering dermatological conditions which mimic SJS such as bullous pemphigoid and pemphigus vulgaris were excluded on the basis of clinical grounds. Rechallenging is neither possible nor desirable due to fatal outcome of drug reactions and ethical issues.

Hence, SJS in this case has a strong sequential association to rifampicin ingestion by the patient. According to causality evaluation and assessment of suspected adverse drug reactions,[5] this case can be considered as probable/likely adverse drug reaction due to rifampicin.

Case 3

A 22-year-old male came to dermatology OPD with complaining of blister and rashes over his face and thorax after taking tablet zyloric (allopurinol 100 mg, BD) prescribed by physician after he was diagnosed of hyperuricemia. He came on the 3rd day since start of medication. After this untoward event, causative drug was withdrawn immediately from his prescription. The patient was admitted in the ward and supportive treatment was initiated as given in the first two cases of SJS for optimal care of the patient. He was a known case of hypertension and was taking tablet Revelol AM (amlodipine 5 mg + metoprolol succinate 50 mg) once a day for 2 years.

His haemoglobin was 11.9 g/dl while total leucocytes count was 8.5× 10^9/L. His biochemical parameters of liver function test as well as renal function test were mildly elevated and ESR was 28 mm/h. No abnormalities were detected in other biochemical tests or in systemic examinations.

On the basis of a history of causative drug administration, clinical examination and associated findings, he was diagnosed as a case of SJS. In this case, ingestion of allopurinol was strongly associated with emergence of SJS.

DISCUSSION

SJSs pathophysiology is not well known, although it is considered to be immune-mediated hypersensitivity response. The immunological, histopathological and clinical findings in SJS support the theory that SJS is a precise drug-

induced hypersensitivity adverse reactions in which cytotoxic T cells play a major part in the initiation phase.[6] SJS is highly unusual incidence but serious adverse skin reactions that cause substantial morbidity and mortality. In the general population, the estimated incidence of SJS is known to be 1–6/million persons while the mortality rate was estimated at 1–5%.[7,8]

A standard procedure to validate the aetiology of the drug does not exist. Positive history of intake of inflicting agent is the most strong evidence as not having any confirmatory research tools sufficient to identify the causative agent. Hence, identification of the first incident of adverse drug reaction is based on the probability estimation and evaluation. Here, the existence and temporal relationship of the drug or pharmacological agent with the clinical initiation of the disease phase is identified.

Most of the cases begin within a week with fever, malaise and non-specific symptoms. It is accompanied by burning sensation. Lip and buccal mucosal erythema and erythematous macules that are quickly necrosed in the centre with vesicle development are also present. Sometimes, bullae formation and denudation of the ear, trunk and limbs are also present.

Among the first-line antitubercular drugs, rifampicin has maximum potential to cause SJS. In this case series, the first patient of pulmonary Koch's was died due to severity and complications of adverse drug reactions on the 3rd day of admission. The second patient of pulmonary Koch's survived and discharge successfully from hospital. In this patient, rifampicin was stopped and other first-line antitubercular drugs were continued at the time of discharge and no hypersensitivity reactions or any other dermatological reactions were noticed further in follow-up.

Antibiotics are the most common cause of SJS, followed by analgesics, cough and cold medications, antipsychotics, antiepileptics and allopurinol in the general population.[9] In our third case, allopurinol is the causative agent. It is commonly prescribed drug for hyperuricemia, gout and gouty arthritis. This patient was treated and discharged successfully later on with advice that not to take allopurinol in future. Allopurinol has very strong causative relationship with SJS. The idea behind this case series is to create awareness among healthcare professionals and in general population about drug-induced SJS which can be fatal and devastating due to rifampicin and allopurinol, which are used in the treatment of pulmonary Koch's and hyperuricemia, respectively.

CONCLUSION

Thus, SJS needs a high index of scepticism, experience of the situation and method of care by healthcare professionals. Those who administer first-line anti-TB medications that are lifesaving should be extra careful. Health professionals who prescribe allopurinol for hyperuricemia, gout and other conditions should take extra precaution. Timely identification and diagnosis of SJS and initiation of therapy in the form of systemic steroid and supportive care and medications proved to be useful in the optimal management of these patients. An early and important approach is to withdraw the offending medication immediately and initiation of supportive care.

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Authors' contributions

Gunjita Belwal collected the data and details about cases, Zafar Masood Ansari drafted the case series, Renu Khanchandani analysed the case series while Bhavana Srivastava and Reena Bhardwaj contributed in critical revision of the manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: A multicentric retrospective study. J Postgrad Med 2011;57:115-9.
2. Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthonpalin P. Stevens-Johnson syndrome and toxic epidermal necrolysis in Thailand. Int J Dermatol 1993;32:428-31.
3. Badar VA, Mishra D, Deshmukh S, Chaudhari S. A case of Stevens-Johnson syndrome due to rifampicin. Int J Basic Clin Pharmacol 2014;3:239-41.
4. Nyirenda R, Gill GV. Stevens-Johnson syndrome due to rifampicin. Br Med J 1977;2:1189.
5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet 2000;356:1255-9.
6. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+lymphocyte involvement. Arch

Dermatol 1993;129:466-8.
7. Chan HL, Stern RS, Arndt KA, Arndt KA, Langlois J, Jick SS, *et al*. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990;126:43-7.
8. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. New Engl J Med 1994;331:1272-85.
9. Melde SL. Ofloxacin: A probable cause of toxic epidermal necrolysis. Ann Pharmacother 2001;35:1388-90.

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