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Case Report

Pharmacology Section

Carbamazepine-induced Life-threatening Stevens-Johnson Syndrome and Agranulocytosis: The Maiden Case

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ABSTRACT

Stevens-Johnson syndrome is one of the few dermatological emergencies in clinical practice. The syndrome is often secondary to the usage of drugs, of which allopurinol, penicillins, sulfa drugs, ibuprofen, sodium valproate, phenytoin, lamotrigine and carbamazepine are commonly implicated. Agranulocytosis is the existence of a clinically significant reduction in neutrophil count.This condition is a serious threat to the patient, as he/she is at a greater risk of contracting bacterial or fungal infections, which may prove to be fatal. The co-existence of Stevens-Johnson syndrome and agranulocytosis in the same patient further increases the risk of morbidity and mortality. To the best of our knowledge, there are no reports available in the existing literature, of cases that were reported with both these life-threatening conditions in a single patient, at the same point of time. This is a case narrative of a patient who presented with both Stevens-Johnson syndrome and agranulocytosis, following the administration of carbamazepine The patient's differential leucocyte count revealed a neutrophil proportion of 2.33%. A causality assessment done using Naranjo's algorithm showed that carbamazepine "definitely" caused Agranulocytosis and "probably" caused Stevens-Johnson syndrome.

Keywords: Anticonvulsant, Antiepileptic, Hypersensitivity, Rash, Skin

CASE REPORT

A 63-year-old male farmer was brought to the emergency room of our tertiary care hospital (day 1), with complaints of rashes all over the body (started 12 days ago), associated with fever, altered sensorium and breathlessness. The patient had been prescribed oral tablets of carbamazepine 200 mg twice daily for trigeminal neuralgia 20 days ago. Rashes started over his forearms, 8 days after starting carbamazepine. Subsequently, the rashes spread all over his upper limbs, trunk and thighs, associated with erosions of the buccal and labial mucosa. The lesions were erythematous and target-like. The patient was also diagnosed to be suffering from MRSA (Methicillin-Resistant *Staphylococcus aureus*) Pneumonia and Cellulitis of his right upper limb, based on microbiological culture reports. Since his breathlessness worsened, he was intubated and started on mechanical ventilation.

Blood samples were collected. Total leucocyte count on admission was 600cells/cu.mm. Differential leucocyte count showed 1 neutrophil out of 43 (2.33%); 35 lymphocytes out of 43 (81.39%); and 7 monocytes out of 43 cells (16.28%). Based on this neutropenic picture, the patient was diagnosed to have Agranulocytosis.

An opinion was obtained from the dermatologists, who diagnosed it as a case of Stevens-Johnson Syndrome (SJS) with a SCORTEN score of 1, and the patient was treated with intravenous hydrocortisone 100mg thrice daily and liquid paraffin local application twice daily. Carbamazepine was stopped with immediate effect, and replaced with oral tablets of amitriptyline 25mg and pregabalin 75mg, both given once daily at bed-time. The lesions become hyperpigmented, with scaling and crusting. Erosions of the buccal and labial mucosa also started regressing. Hence, the dermatologists advised against a skin biopsy.

Simultaneously, in order to manage cellulitis and MRSA pneumonia, the patient was started on amoxicillin: clavulanic acid (fixed dose combination) 1.2 g thrice daily, cloxacillin 1 g twice daily, teicoplanin 400 mg thrice a day and meropenem 500 mg thrice daily, all given intravenously.

Seven days after admission, the patient was weaned off ventilation, and extubated. His rashes had subsided and leucocyte counts were normal, as shown in [Table/Fig-1]. Based on Naranjo's causality algorithm, the score for SJS was 7, falling under the "probable" category. Similarly, for agranulocytosis, the Naranjo score was 9, making it a "definite" adverse event due to carbamazepine.

DISCUSSION

Stevens-Johnson Syndrome

SJS is a rare but life-threatening reaction, almost always associated with drugs. The average annual incidence was estimated to be around 1.2 to 6 cases per million in the United States, with a male to female ratio of 1.5:1. However, the study conducted by Patel TK et al., showed that there were no significant differences based on age and sex in the Indian population [1]. On the contrary, another Indian study showed a clear male preponderance, and an age group predominance of 46 to 60 years [2]. The mortality rate of SJS varies, with a recent study showing a rate as high as 16.39% in the Indian population [1].

SJS is more likely to affect high-risk groups like slow acetylators, immunosuppressed population and patients with HLA associations [3]. Individuals with HLA-B*1502 allele are at a higher risk of developing carbamazepine-induced SJS. US-FDA has also issued a labeling change for carbamazepine regarding this association. Although this allele is found commonly in the Chinese and Korean populations, a study has shown that 1 to 6% of Indians possess this allele [4]. Similar associations have been identified for drugs like abacavir (HLA-B*5701) and allopurinol (HLA-B*5801) [5].

More than a hundred drugs have been reported to cause SJS/TEN (Toxic Epidermal Necrolysis) [6]. Drugs that are commonly implicated in SJS are NSAIDs, allopurinol, antiepileptics and antibiotics [3,7,8]. Of the antiepileptics, there are reports of SJS

Day	Total leucocyte count (cells/cu.mm.)	Different leucocyte count (%)
1	600	N – 2.33, L – 81.39, M – 16.28
2	600	N – 2.38, L – 80.95, M – 16.67
3	1100	N – 16.25, L – 70.0, M – 13.75
5	6200	N – 49.0, L – 49.5, M – 1.0, E –0.5

[Table/Fig-1]: Blood counts of the patient during the hospital stay (N – neutrophils, L – lymphocytes, E – eosinophils, M – monocytes).

Adults	Children
Nevirapine (1 in 1000)	Nevirapine (3 in 1000)
Lamotrigine (1 in 1000)	Lamotrigine (3 in 1000)
Carbamazepine (14 in 100,000)	Sulfonamides
Sulfadoxine-Pyrimethamine (10 in 100,000)	Acetaminophen
Cotrimoxazole (1 to 3 in 100,000)	Other anti-epileptics

[Table/Fig-2]: Incidence of SJS/TEN with the most commonly implicated drugs.

following the use of phenytoin, carbamazepine, valproic acid, lamotrigine, levetiracetam, etc., [9,10]. In the study conducted by Sasidharanpillai et al., phenytoin was the most common drug involved, followed by carbamazepine [2]. In a retrospective analysis, it was shown that anticonvulsants were the most common cause in the Indian population [11].

Based on age, the most commonly implicated drugs in SJS/TEN (with incidence in parentheses) are as in [Table/Fig-2] [6].

European data indicate that allopurinol could be the most frequently implicated drug in the continent [6]. Also, seasonal variation has been noted, especially with cotrimoxazole, which is more common during spring [12]. However, the same with respect to the other causative drugs has not been illustrated. According to a study done by Vertieva et al., in Russia, the severity of SJS was maximal with sulfamethoxazole, methimazole and carbamazepine [13].

Literature review suggests that the maximal incidence of SJS/TEN is in the initial two months of starting the offending medication, with a sharp dip in the incidence rate after a period of two months [14]. In our case, the features developed in the first month of initiation of carbamazepine.

The most common clinical features of SJS include fever, flu-like symptoms, skin eruptions (which are initially macular, and later transform into bullous target-like lesions) and affectation of the mucous membranes (may not be seen in all patients). Diagnosis can be made with the typical clinical picture and a skin biopsy [6]. In the current case, a typical clinical picture was observed.

The SCORTEN scale introduced in 2000 is the most common algorithm used to predict the mortality rate of the SJS/TEN patients. It takes into account the age of the patient, extent of lesions, tachycardia, associated malignancies, metabolic derangements and renal failure. A score of 0-1 indicates a mortality of 3.2% (which was the scenario in our case), while a maximal score of 5 or above is associated with a mortality rate of 90% [5,6].

Managing a patient of SJS/TEN typically mirrors that of a patient with burns. Fluid and metabolic corrections have to be done, although the deficit is less when compared with that seen in burns. Ideal management requires the admission of the patient to a dedicated burns unit, or to an ICU. However, the chances of spread of infections are significantly high with the latter option [6].

The initial management is the immediate withdrawal of the offending drug, which was followed in the present case as well. This is followed by corticosteroids (either intravenously or orally), and if required, intravenous immunoglobulins in severe cases [2,11]. The use of systemic corticosteroids is controversial due to several reasons:

a. Risk of developing infections.

b. Chances of masking septicaemia.

c. Delay in skin epithelialization.

d. Lack of controlled trials proving the benefits of steroids.

However, there is considerable proof that corticosteroids can prevent or delay the ocular complications that may arise from the disease spectrum. Hence, the use of corticosteroids is left to the clinical acumen of the physician and the status of the patient [6,15].

Further, in case of desquamation of the skin and mucosa, skin grafting and amniotic membrane ocular transplant may be performed [16]. In our case, such procedures were not required. A major step in managing the patient includes reporting of the adverse reaction through an appropriate pharmacovigilance programme existing in the locality [17]. The current case was reported to the Uppsala Monitoring Centre.

Agranulocytosis

Agranulocytosis is a life-threatening condition, which is characterized by a granulocyte count of less than 0.5 x 10^3/μL. The aetiology is multifactorial, with drugs playing a significant part [18]. Drugs commonly cited include antipsychotics (clozapine, chlorpromazine), antiepileptics (carbamazepine), antithyroid drugs, beta lactam antibiotics, etc., [19,20]. The mortality rate is about 5%, with adequate management [21]. The mechanism by which carbamazepine causes agranulocytosis is unclear. However, it has been reported that granulocyte colony stimulating factor is inhibited by carbamazepine. Further, concurrent co-administration of lithium (a potent stimulator of colony stimulating factor) has been shown to reverse the changes produced by carbamazepine, thus elucidating this hypothesis [22].

Management chiefly comprises discontinuation of the causative agent, followed by courses of intravenous broad spectrum antibiotics to prevent or treat infections. If required, haematopoietic growth factors can be instituted [21]. This was not required in our case, as the patient improved on discontinuation of carbamazepine.

Although carbamazepine is known to cause agranulocytosis, there are no reports available that show the co-existence of SJS and agranulocytosis due to carbamazepine, to the best of our knowledge.

CONCLUSION

SJS and TEN are rare but serious dermatological conditions. Since drugs play a major role in the aetiopathogenesis of SJS, it is absolutely essential to obtain a detailed medication history in the patient, prior to initiation of drugs that are known to cause SJS. Carbamazepine is widely used as an antiepileptic or as treatment for neuralgias, because it is cheap and well tolerated. Caution has to be exercised when starting carbamazepine. Also, physicians must educate the patients on the clinical features of SJS, and ask them to report to a medical facility in case of such drug eruptions. Further, monitoring of blood counts is essential during carbamazepine therapy, as identification of Agranulocytosis can result in reversal of blood counts, which might prevent the onset of serious infections.

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