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Case Report

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ALLOPURINOL INDUCED TOXIC EPIDERMAL NECROLYSIS: A CASE REPORT

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ABSTRACT

Toxic epidermal necrolysis is a rare but potentially life threatening disorder. Many drugs known to cause such fatal reactions are Lamotrigine, Carbamazepine, Allopurinol, Sulfonamide antibiotics, Nevirapine etc. Here we report one such case of Allopurinol induced Toxic Epidermal Necrolysis (TEN). The patient was taking Tab Allopurinol 300 mg OD since 15 days for Gouty Arthritis after which he developed boils and blisters all over the body associated with severe itching, redness of eyes and mouth ulcers. It was diagnosed as a case of drug induced TEN and Naranjo score for adverse drug reaction was seven, thereby making it a probable ADR. Patient was managed symptomatically and the offending drug was withdrawn. We are presenting this case to highlight the serious adverse reactions occurring with Allopurinol.

KEYWORDS: Allopurinol, Toxic Epidermal Necrolysis (TEN), Adverse Drug Reaction.

INTRODUCTION

Adverse drug reaction (ADR) is defined as "any noxious change which is suspected to be due to a drug occurring at doses normally used in man and requires treatment or decrease in dose or indicates caution in the future use of the same drug".

Allopurinol is a purine analog. It is a structural isomer of hypoxanthine (a naturally occurring purine in the body) and is an inhibitor of the enzyme xanthine oxidase. Xanthine Oxidase is responsible for the successive oxidation of hypoxanthine & xanthine resulting in the production of uric acid, a product of human purine metabolism.[1]

Common side effects when taken orally are rashes with itching, fever, malaise, muscle pain, gastric irritation, headache, nausea and dizziness. Side effects when used intravenous are vomiting and kidney problems.[1]

Here, we report a case of Allopurinol induced Toxic Epidermal Necrolysis (TEN) a clinical association that has been reported previously in a very few Indian population. Toxic epidermal necrolysis also known as Lyell's syndrome is a rare but potentially life-threatening condition. Early indications are fever & flu like symptoms. Few days' later skin begins to blister & peel forming painful raw erupted lesions. Mucous membrane of the oral cavity is also commonly involved.[2]

CASE REPORT

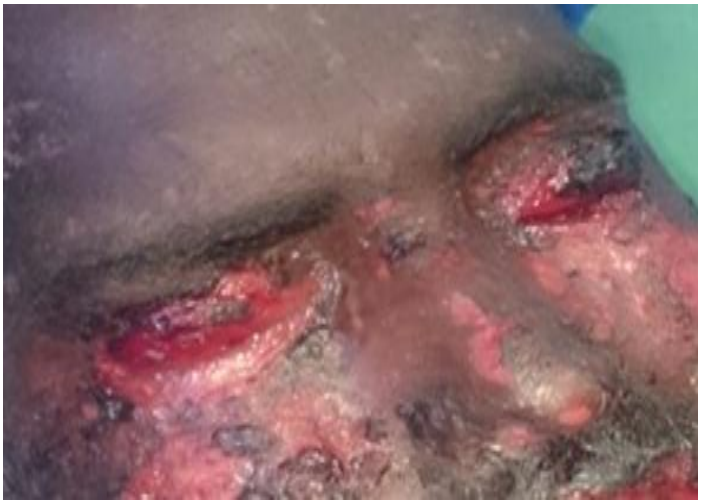
Patient was apparently asymptomatic 15 days back when gradually he started developing mouth ulcers in the buccal cavity which increased in number, so he had difficulty in eating.(Figure 1) Ten days back, he started developing small blisters over abdomen & back which were reddish in color then it spread all over the body involving whole trunk, extremities and face. (Figure 2,3). Simultaneously he started developing pain in eye, redness, irritation, burning sensation, swelling followed by whitish colored discharge from eyes.(Figure 4) Gradually he also started developing dyspnoea, chest pain and high grade fever. He was brought to the emergency department with these complaints.

On taking history patient's attendant told that he was a case of Gouty arthritis & was taking Tab Allopurinol 300 mg OD from last 1 month. Fifteen days after taking medication he started developing these complaints. He was diagnosed as a case of drug induced Toxic Epidermal Necrolysis. Treatment was started with intravenous Dexamethasone, Avil (anti histaminic), injection Pan-40 (proton pump inhibitor), injection Metrogyl and Ceftriaxone. Gradually the symptoms started resolving.

Causality assessment was done and according to Naranjo scale it came to be seven thus was a Probable ADR.

(Figure 1).

(Figure 2, 3).



(Figure 4).

DISCUSSION

Toxic epidermal necrolysis (TEN) also known as Lyell's syndrome is a rare but potentially life-threatening condition with widespread epidermal detachment and mucosal erosions.[2] TEN represents the most severe form in the broad spectrum of erythema multiforme (EM), the

other forms being erythema multiforme minor and erythema multiforme major or Stevens Johnson syndrome (SJS).[3]
There are 3 grade classification of SJS/TEN spectrum of diseases.[4]

- SJS includes cases with mucosal erosions plus widespread purpuric macules and epidermal detachment up to 10%
- Transitional SJS-TEN represents epidermal detachment between 10 to 30%
- TEN represents skin detachment of more than 30% of the body surface areas (BSA).

Drugs that are suspected to cause TEN includes antibiotics, anticonvulsants and nonsteroidal anti-inflammatory drugs (NSAIDs).[5]

Exact pathogenesis of Toxic Epidermal Necrolysis is not clear. Keratinocytes play a major role in the pathogenesis. They represent the initial protagonists in TEN epidermal destruction.[6] Toxic epidermal necrolysis (TEN) lead to full destruction of the epidermis and epithelial mucosa.

At an early stage of the disease epidermal lesions demonstrated that keratinocytes undergo apoptosis followed by necrosis of the epidermal cells. First, keratinocytes are increasingly recognized for their metabolic activity through various transport-associated and detoxifying enzymes.[6]

SJS and TEN are specific drug hypersensitivity reactions, in which cytotoxic T lymphocytes (CTL) play an important role. In early phase of disease, blister fluid contains mainly cytotoxic CD8+T lymphocytes suggesting that a major histocompatibility (MHC) class-I restricted drug presentation leads to clonal expansion of CD8+ CTLs.[7,8]

Constitutive presence of the cytochrome fraction of CYP450-3A and the potential induction of CYP450-1A are well documented in the human epidermis.[9] Overexpression of different proapoptotic systems by TEN keratinocytes, including tumor necrosis factor alpha(TNF-α) were seen.[10] Thus indicating that activated T lymphocytes and macrophages undoubtedly participate in the TEN epidermal destruction.

Proapoptotic Concept
There is overexpression of different proapoptotic systems by TEN keratinocytes, including tumor necrosis factor alpha (TNFα) and Fas receptor/Fas ligand (Fas L) (CD95R/CD95L).[11]

L1 Protein Concept
The cytosolic complex calprotectin (L1-protein) is also almost always expressed both in clinically involved and apparently uninvolved TEN epidermis.[12] The L1-protein results from calcium (Ca++)-related process. Its presence in normal-looking epidermis of TEN patients in the absence of inflammatory cells suggests that an increase in Ca++ concentration inside the keratinocytes is one of the earliest biological events disclosed in the process of TEN destruction following the drug metabolite formation.

Evidence suggests a key contribution of the cytotoxic molecules FasL and granulysin as molecules responsible for the disseminated keratinocyte apoptosis in SJS/TEN.[13,14]

CONCLUSION

TEN is usually Drug-induced. Allopurinol, used for gouty arthritis is one of the drug reported to cause TEN/ SJS. Early recognition and treatment of symptoms of Drug induced TEN, improves the outcome. Patient education regarding the possibility of adverse drug reaction is essential to minimize the use of over the counter drug, to be vigilant in obtaining treatment as it is a serious ADR and may be lethal.

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