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Case Report

Drug Induced Exanthem Secondary to Sulfasalazine: A Case Report

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ABSTRACT

Introduction: Adverse drug reactions are a challenge in modern healthcare. With the increasing complexity of therapeutics, and rising multi-morbidity, it is worth emphasizing the importance of pharmacovigilance and rationale pharmacotherapy. Drug hypersensitivity syndrome (DHS) induced by Sulfasalazine is a serious systemic delayed adverse drug reaction, which is associated with significant morbidity and mortality. Patient concerns: A 42-year-old women who was a known case of Chronic Hypertension and Type 2 Diabetes Mellitus was hospitalised in Dermatology ward of Silchar Medical College and Hospital for developing erythematous macules, patches and papule all over face, both forearms, hands, palms and soles, 10 days after taking sulfasalazine for treatment of knee pain. **Diagnosis**: The patient was diagnosed with drug induced exanthem secondary to sulfasalazine based on her drug history, clinical manifestations, and laboratory test results. **Interventions**: The patient was administered intravenous glucocorticoids. The patient's condition improved after treatment with IM Pheniramine and antihistaminics. **Outcomes**: After receiving combination therapy of glucocorticoid with antihistaminics, IM pheniramine and calamine lotion the whole-body pruritus and erythematous rashes disappeared, and no new rash appeared. **Conclusion**: Despite the significant amount of data on sulfasalazine-induced drug exanthem, due to the diversity in its clinical presentation, proper diagnostic criteria and management protocol have not been well described and physicians rely on case reports majorly for in-depth understanding of this hypersensitivity reaction hence, here, a case report on drug induced exanthem secondary to sulfasalazine has been presented.

Keywords: Sulfasalazine, DRESS, Sulfasalazine-induced hypersensitivity syndrome, ADR.

INTRODUCTION

Adverse drug reactions (ADRs) as defined by WHO, 'a response to a drug that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'[1]. ADRs are a challenge in modern healthcare because of the increasing complexity of therapeutics, an ageing population and rising multimorbidity. Also ADRs, are a major clinical issue and account for approximately 5% of hospital admissions.[2] Sulfasalazine is an anti inflammatory drug which has immunosuppressive properties. Sulfasalazine, firstly synthesized in 1930, was created by combining an anti-inflammatory agent (5-aminosalicylic acid) with a sulfonamide antibiotic (sulfapyridine) joined by an azo bond, to treat joint inflammation. 5-aminosalicylic acid (5-ASA), is the active therapeutic compound, and sulfapyridine, which serves as a carrier molecule. Sulphasalazine was initially used more than 50 yrs ago to treat inflammatory arthritis but fell into disuse, only to be revived 25 yrs ago for rheumatoid arthritis. Since then its place as a second-line agent has been established and its toxicity profile has been outlined.[3] Common adverse effects associated with sulfasalazine are gastrointestinal upset (nausea, vomiting, diarrhoea, abdominal pain), headaches, dizziness, decreased appetite, fever, arthralgias and rash particularly in the first 3–6 months.[4] But in some cases, as reported in recent years, it can be associated with Sulfasalazine-induced hypersensitivity syndrome (SIHS), which is a drug-specific variant of the syndrome known as drug reaction with eosinophilia and systemic symptoms (DRESS).[5] SIHS is a rare, potentially life-threatening delayed hypersensitivity reaction (Type IVb) occurring 2–6 weeks after starting

sulfasalazine. It is driven by the activation of drug-specific CD4+ and CD8+ T cells, often triggered by metabolic intermediates (sulfapyridine) with reactivation of human herpesvirus-6 (HHV-6).[6] While the precise, singular etiology is not fully understood, but the causes can be multifactorial including genetic predisposition, pharmacokinetic or metabolic variations and immune dysfunctions. Even though SIHS presents with wide variety of clinical manifestation some of the common symptoms include high fever (>38°C), morbilliform rash, facial edema, lymphadenopathy, and multi-organ involvement.[7] Due to the lack of a clear, single mechanism, diagnosis is usually made on clinical presentation, exclusion of other causes, and improvement after drug withdrawal. Despite the serious nature, there is still no consensus regarding its management, and current approaches are based on case reports. In the lack of proper RCTs due to rarity, and unpredictability of this condition, case reports are essential to deepen our understanding of this complex reaction.

Ethics and methods

- Written informed consent was obtained from the the patient before collection of personal details.
- All procedures described in this case report involving the patient were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

CASE PRESENTATION

A 40 yrs old female patient, was admitted to the dermatology ward of Silchar Medical college and hospital on 17 December 2025 with chief complaint of erythematous macules and papules over her face, back, neck, both forearms, hands and legs which started after intake of Sulfasalazine. She was prescribed tab Sulfasalazine 1gm twice daily for 5 days for the treatment of knee pain.

10 days after the intake of last medication, itching started over her feet which was sudden in onset and gradually progressed to involve head, face, neck, back, and arms with facial swelling in a span of 1 day. Then these areas were covered with , red, elevated macules and papules which progressed in size and number over the next 3 days.

Sulfasalazine was discontinued but the lesions did not regress so she was admitted to Dermatology ward of SMCH, and was diagnosed with Drug Induced Exanthem secondary to Sulfasalazine. She was a known case of chronic hypertension and Type 2 Diabetes Mellitus and she was already on medication for the same. Laboratory parameters were within normal range except for mild lymphocytosis and elevated RBS (398mg/dl).

In the ward, she was administered administered Inj. Dexamethasone 2cc IV once daily for 3 days and Inj. Pheniramine maleate 1 amp as and when needed along with concomitant medications such as Tab Levoceterizine and Mometasone lotion. The leisons and swelling started to regress and after 3 days the patient was discharged on Tab. Prednisolone 10 mg. When she was followed up after 2 weeks the whole-body pruritus have disappeared, and no new rash appeared.

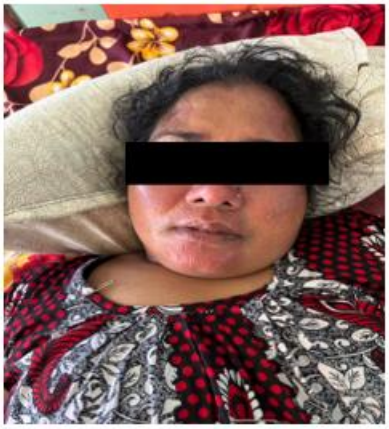

Fig1. Facial edema.

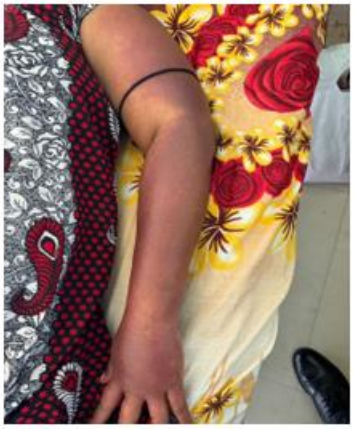

Fig2. Erythematous macules with swelling of left arm

Fig3. Erythematous macules with swelling of left arm

DISCUSSION

Sulfasalazine is widely used in the treatment of autoimmune diseases such as Inflammatory Bowel disease and Rheumatoid Arthritis as it has immunomodulatory properties but general knee pain is not a proper indication to sulfasalazine use.[8] The clinical pattern of injury with sulfasalazine suggests a drug-allergy or hypersensitivity mechanism, perhaps through the metabolism of the sulfonamide component to a toxic, reactive or antigenic metabolite.[9] Specific human leukocyte antigens (HLA), such as HLA-B08:01 and HLA-A31:01, have been associated with an increased risk of developing this

hypersensitivity reaction, particularly in cases involving agranulocytosis.[11] Based on an analysis of the FDA Adverse Event Reporting System (FAERS) database up to the fourth quarter of 2023, the United States reported the highest number of adverse event (AE) reports related to sulfasalazine, which includes hypersensitivity reactions like DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms).[10] While the US has the highest absolute number of reported cases, a literature review of 39 severe sulfasalazine-induced DRESS/DIHS cases indicated a higher concentration of reported cases in Asia (43.6%) compared to Europe (30.8%) and America (12.8%) in that specific study cohort.[10]

Clinicians should pay special attention to its possible serious systemic adverse reactions, associated with Drug-induced hypersensitivity syndrome (DIHS). Even though DIHS are rare but sometimes can be life threatening and almost 10% of DHS cases can be fatal.[11]

Due to rarity, and unpredictability of this condition, proper randomised control trials are not feasible and so uniformly recognized worldwide diagnostic criteria are lacking. There is no gold standard for DIHS diagnosis and in India it is diagnosed using international criteria (RegiSCAR or Japanese criteria) focused on a triad of: rash (usually appearing 2–8 weeks after starting), fever (>38∘C), and multi-organ involvement (typically hepatitis or renal dysfunction).[13]

In our case report the patient was a female and a study of the FAERS database (2004–2023) showed that 68.06% of reported adverse reactions to sulfasalazine involved females, while only 26.41% were male. This higher prevalence in women may be linked to the fact that sulfasalazine is frequently prescribed for autoimmune conditions (like rheumatoid arthritis) that are more common in women.

The patient was treated with IV steroids which is similar to the Literature review of the clinical features of sulfasalazine-induced drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS) by Liu et al where most of the patients were administered steroids.[5] Steroids are given in sulfasalazine-induced hypersensitivity syndrome (including DRESS/DIHS) because they are the gold standard treatment for suppressing the intense, widespread systemic inflammation, autoimmune-like response, and organ damage caused by this potentially fatal reaction. In the treatment of DRESS/DIHS resulting from SSZ, the immediate cessation of SSZ is paramount. Following this, systemic administration of corticosteroids is essential.[14]

In some case reports like Chen et al.Medicine (2022) IV gamma globulin was used for treatment of SIHS.[15] Glucocorticoids and gamma globulin are the main drugs used to treat DHS. In recent years, immunoglobulin has been widely used for the treatment of severe drug eruptions. Immunoglobulin can significantly relieve symptoms, reduce the risk of infection, reduce the glucocorticoid dosage, and improve rescue and cure rates.[16]

CONCLUSION

Case reports play a vital role in identifying and understanding rare adverse reactions like sulfasalazine-induced hypersensitivity, which manifests as drug reaction with eosinophilia and systemic symptoms (DRESS) or similar syndromes. They provide detailed clinical insights into unpredictable events that clinical trials often miss due to low incidence.[17]

These reports boost recognition among clinicians, aiding faster diagnosis amid mimics like systemic juvenile idiopathic arthritis or hemophagocytic lymphohistiocytosis. For instance, they detail effective treatments like glucocorticoids, while noting risks like 13% mortality or need for liver transplant in severe cases.[7]

Physicians should be careful while prescribing sulfasalazine and it should always be prescribed for proper indications after proper history taking from the patient as re-prescribing sulfasalazine to a patient with prior sulfasalazine-induced hypersensitivity syndrome (SIHS) is highly dangerous and contraindicated. It typically triggers a rapid, more severe recurrence of symptoms, often within hours to days, due to immune memory and potential reactivation of human herpesvirus 6 (HHV-6) and mortality can exceed 10% in severe cases. As of now physicians are more or less dependant on case reports and literature review studies for the understanding of this hypersensitivity reaction. In the future it is hoped that advancement in pharmacogenetics will provide a clearer picture and open the scope of personalised medicine for drug induced hypersensitivity syndromes.

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