

Cotrimoxazole Induced Toxic Epidermal Necrolysis in a Suspected Case of *Pneumocystis Carinii Pneumonia* with Human Immuno Deficiency Virus Infection

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Toxic epidermal necrolysis due to trimethoprim sulpha-methoxazole therapy in a subject of HIV with suspected *pneumocystis carinii pneumonia*, is reported, because of its rarity in Indian conditions. Patient showed excellent recovery on corticosteroid therapy.

Key words : *Human immuno deficiency virus infection, Pneumocystis carinii pneumonia, Toxic epidermal necrolysis.*

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Toxic epidermal necrolysis is a severe and potentially life threatening form of the Stevens-Johnson syndrome, affecting both skin and mucous membranes.

An international group of dermatologists proposed a classification based on the pattern of erythema multiforme like lesions and on the extent of epidermal detachment.

1. *Overlap Stevens-Johnson syndrome-toxic epidermal necrolysis.* Detachment between 10% and 30% of the body surface area plus widespread purpuric macules or flat atypical targets¹.
2. *Toxic epidermal necrolysis with spots.* Detachment above 30% of body surface area, plus widespread macules or flat atypical targets.
3. *Toxic epidermal necrolysis without spots.* Detachment above 10% of body surface area with large epidermal sheets and without any purpuric macules or targets.

We present here a case of toxic epidermal necrolysis, which developed fifteen days after starting the therapy with trimethoprim sulphamethoxazole in a subject of HIV infection with suspected *pneumocystis carinii pneumonia*.

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Case Report

A 23-year-old female presented with complaints of cough with mucoid expectoration and intermittent low grade fever for four months. She also complained of occasional streaky haemoptysis, grade II exertional dyspnoea, difficulty in swallowing and loss of appetite present for the last three months.

On examination, the patient was emaciated. There was absence of cyanosis, clubbing, jaundice, oedema or generalized lymphadenopathy. There were multiple molluscum contagiosum present on the back. On auscultation, there were high pitched discontinuous crackles at both bases. Vital data revealed respiratory rate : 28/min, pulse rate : 88/min, blood pressure : 110/70 mmHg and oxygen saturation : 86 percent. Haemogram was essentially normal with an absolute lymphocyte count of 1920 cells per microlitre. Her renal parameters were within normal limits. HbsAg was negative and diagnosis of HIV was made by ELISA test which was reactive on two occasions with two different antigen-kits and confirmed by immunocomb test².

Chest radiograph showed bilateral basal reticulo-nodular opacities. A diagnosis of *pneumocystis carinii pneumonia (PCP)* was considered and patient was started on cotrimoxazole (trimethoprim/sulfamethoxazole) double strength two tablets thrice daily.

Two weeks after commencing the therapy with cotrimoxazole, the patient developed a generalized cutaneous eruption, pain in the eye and mouth ulcers. After 48 hours, the patient developed bullous lesions all over the body with extensive lesions in the oral and nasal mucosa as well as in the eyes.

On examination, she had developed multiple flacid bullae with clear fluid all over the body. A few erosive lesions were also seen. Nikolsky's sign was positive (Fig. 1). Oral cavity showed extensive erosions and crusted lesions over the upper lip and erosions with purulent discharge from lower lip. Angular stomatitis, oral *candidiasis* with multiple erosions over soft palate and buccal mucosa were also present. Vulval erosions were also seen. Examination of the eyes revealed hyperemia with severe seropurulent discharge in both the eyes.

The patient was haemodynamically stable with a pulse rate of 90 per/min and a blood pressure of 150/90 mmHg. The chest was clear and the abdomen was soft and non-tender.

A diagnosis of cotrimoxazole induced toxic epidermal necrolysis was made on the basis of bilateral conjunctivitis, buccal and nasal mucositis and wide spread bullous dermatosis.

Cotrimoxazole therapy was stopped immediately and patient was started on oral prednisolone 100 mg twice daily antacids, saline and condys compresses to oral and eye lesions.



Fig. 1. Toxic epidermal necrolysis in a suspected case of pneumocystis carinii pneumonia with HIV.

After ten days, the eruptions began to clear. Re-epithelialization of the previously sloughed areas occurred and the general condition of the patient remained satisfactory. She was discharged after four weeks by which time the skin had healed with extensive post-inflammatory hypopigmentation. However, the ocular and mucosal lesions cleared completely.

Discussion

Toxic epidermal necrolysis is rare, with an overall incidence of 1-2 cases per million population per year. Patients with the acquired immunodeficiency syndrome (AIDS) appear to be at increased risk for adverse drug reactions especially from sulphonamides including cotrimoxazole³. A review of charts at the HIV treatment center of North-Western University at Chicago revealed that 40.3% of patients treated with cotrimoxazole could not tolerate the medication. Prophylactic use had a 40 times higher risk than single dose therapeutic use. In developing countries with mainly single dosage administration, the risk of developing severe cutaneous adverse reactions (SCAR) is estimated to be 0.1 per million population, whereas in Europe and North America with mainly prophylactic administration, the risk was 10 and 36

per million population, respectively. The mortality from Stevens-Johnson syndrome is 5% and toxic epidermal necrolysis is 25-30%, while many survivors suffer potentially disabling sequelae⁴.

Our patient developed Toxic Epidermal Necrolysis' as a consequence of Cotrimoxazole therapy. Skin biopsy to exclude other dermatological disorders was considered unnecessary in this case as the history in presence of bullous lesions and mucosal involvement satisfied the clinical criteria for the diagnosis. Other disease characterized by excessive desquamation include staphylococcal scalded skin syndrome (SSSS) and toxic shock syndrome (TSS)⁵.

The pathogenesis and the risk factors for cutaneous hypersensitivity reactions in HIV-infected patients are poorly understood. These kind of reactions, however, seem to occur more often in patients with a more advanced immunodeficiency state. Some immunological, non allergic factors may also facilitate eruptions in patients with AIDS on trimethoprim/sulphanethoxazole therapy. The pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis is attributed to antiphospholipid antibodies, slow acetylator phenotype and glutathione enzyme deficiency. Hereditary and acquired enzyme deficiency and variations in metabolic pathways may delay drug metabolism and cause non-allergic toxic side effects. Such a mechanism is known to occur in patients with a low acetylation rate on sulfonamide treatment⁶. HIV positive individuals have a systemic glutathione deficiency, resulting in a decreased capacity to scavenge hydroxylamine derivatives of sulphamethaxazole, which have been proposed as the reactive metabolites responsible for adverse reaction to this drug³.

Recently, the pathogenesis of epidermal necrolysis has been postulated to be mediated by a lymphocytotoxic reaction. Immunological studies have demonstrated that the dermal cellular infiltrate consists mainly of CD4 + T lymphocytes, where as a predominance of CD8+ T lymphocytes are found in the epidermis and in blister fluid. CD4+ macrophages are found in both the dermal and epidermal infiltrates. This pattern of CD8+ T lymphocytes acting as effector cells in an acute cell-mediated reaction against allogenic antigens is similar to that of skin graft rejection⁷.

The mortality rate from toxic epidermal necrolysis remains significant despite improvements in the care of patients with acute renal failure. The main prognostic factors are age, area of necrolysis and elevated blood urea.

The role of corticosteroids in the management of toxic epidermal necrolysis in HIV individuals is controversial due to the potential risk of further immunosuppression in these already immunodeficient patients with the use of corticosteroids⁸.

In our case, CD4+ and CD8+ T cell counts could not be done. However, the absolute lymphocyte count was 1920 cells per microlitre. Our patient tolerated high corticosteroid doses which were tapered over a period of three weeks. There

appears to be no difference in immunosuppression by steroids for toxic epidermal necrolysis as compared to HIV negative cases.

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