CASE REPORT

Allopurinol induced Stevens - Johnson syndrome in a Nigerian woman with chronic lymphocytic leukaemia

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Received: March 29th, 2015
Accepted: May 19th, 2015

DISCLOSURES: NONE

ABSTRACT

Stevens-Johnson syndrome is an adverse muco-cutaneous complication arising from a number of conditions which include the administration of some drugs. A female Nigerian with chronic lymphocytic leukaemia, (Binet stage C) who developed Stevens-Johnson syndrome following commencement of allopurinol is presented. She was treated with intravenous fluids, steroid, antihistamine, antibiotics, skin emollient along with oral care, while allopurinol was discontinued. She attained full recovery and was re-commenced on cyclophosphamide (without allopurinol), with no further sequelae.

Conclusion: Stevens-Johnson syndrome could occur in patients on allopurinol, this is the first of such report (to the author's best knowledge) from South-East Nigeria. Drug withdrawal and supportive management are associated with clinical recovery.

Keywords: *Adverse skin reactions, lymphoid malignancy, steroids*

INTRODUCTION

Stevens-Johnson syndrome (SJS) is a muco-cutaneous adverse reaction seen in a number of conditions which includes the administration of some drugs (or other chemicals). It was first described in 1922 by Albert Stevens and Frank Johnson.[1] It is typically characterized by generalized macular rash with vesicular and bullous eruptions (which could be painful), fever, purulent conjunctivitis and stomatitis.[1] The annual incidence of SJS has been reported to range from 2 to 6 cases per million people per year.[2] It is closely related to a more severe

disease, known as toxic epidermal necrolysis (TEN), which is also characterized by severe muco-cutaneous adverse reactions.

The rashes of SJS usually start around the face, neck, and upper trunk 4-14 days after commencement of the offending drug, and gradually, spread to other parts of the body. These could progress in severe cases to extensive bullae which may slough off, particularly at pressure points, exposing weepy and painful underlying skin (Nikolsky's sign).[3] In addition, kerato-conjunctivitis, pulmonary edema with hypoxemia, glomerulonephritis and hepatitis may also occur, depending on the severity.[3] In some instances, however, onset of symptoms may be delayed up to 2months following the administration of the offending drug.[3]

This syndrome has been traced to a number of infectious agents (such as *Mycoplasma pneumoniae* and herpes virus) and a number of drugs such as anti-convulsants, sulfonamides, some antibiotics, non-steroidal anti-inflammatory drugs, anti-fungals, anti-malarials, and allopurinol.[3] Similarly, organ or bone marrow transplantation, and certain vaccines including those for smallpox, anthrax and tetanus have also been implicated in its aetiology.[4]

We report a case of SJS in a female Nigerian, diagnosed of chronic lymphocytic leukaemia (CLL) who was on allopurinol, which, to the authors' best knowledge, is the first of such report (i.e. allopurinol induced SJS in the setting of CLL) in literature from South-East Nigeria.

CASE REPORT

The patient was a 70-year old, female, petty trader who was diagnosed with chronic lymphocytic leukaemia (CLL), Binet stage-C in May 2013. She was commenced on chlorambucil, allopurinol (100mg tds) and haematinics, after due pre-chemotherapy work-up. She was a known diabetic and hypertensive for more than 5years; both of which diseases were well controlled with glucophage and lisinopril, respectively.

She presented to the emergency room of the Nnamdi Azikiwe University Teaching Hospital, Nnewi, one month, later, with complaints of generalized skin rashes and dysphagia which started about one week earlier. The rashes appeared initially on both arms but gradually involved the whole body, and were associated with itching and skin excoriation. There was a history of redness of the eyes, with purulent discharge and swelling of both eye lids (*Figure 1*). She developed multiple sores in the mouth, associated with painful swallowing, drooling of saliva and fever, about 3days after the appearance of rashes. No history of bleeding diathesis, prior transfusion, use of tobacco products, jaundice or use of medications aside those prescribed from our facility.

Figure 1. Patient at presentation with generalized muculo-papular rashes

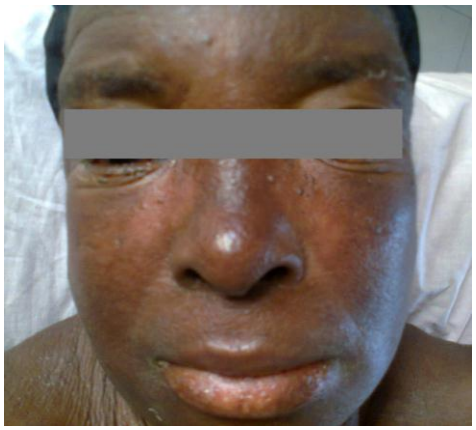
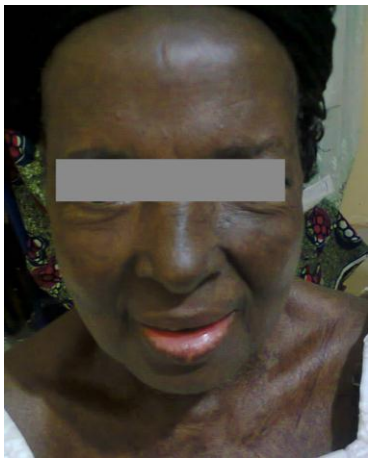


Figure 2. Patient during subsequent follow-up visit after recovery



On clinical examination, she was ill-looking, mildly pale, pyrexic (axillary temperature of 38.1^{0}C) and with significant bilateral axillary lymphadenopathy. There were generalized, maculo-papular, hyperaemic rashes which were exfoliative and exudative, with areas of multiple scratch marks. Oropharyngeal examination showed multiple hyperaemic ulcers in the mouth and pharyngeal mucosae. The conjunctivae appeared injected with associated purulent discharge. The spleen was enlarged, firm and non-tender. She had no significant chest findings.

Full blood count showed moderate anaemia and leukocytosis with a differential picture in keeping with CLL. Liver function tests were within normal limits while renal function tests revealed elevated serum urea and creatinine (25.5mmol/L; *normal range 1.7-9.1mmol/L*) and 133µmol/L; *normal range 76.0-127.0 µmol/L*; respectively).

A diagnosis of Stevens-Johnson syndrome, most probably secondary to allopurinol was thus made and she had intravenous fluids, anti-histamine, antibiotics, systemic steroids, antiseptic mouth wash and skin emollients.
She progressively made a full recovery, with resolution and healing of skin eruptions, eye and mouth lesions, fever and satisfactory re-establishment of oral feeding. She was, subsequently, discharged home after 3weeks on admission and was re-commenced on chemotherapy (cyclophosphamide, without allopurinol) on a subsequent, follow-up visit (*Figure 2*) without any adverse sequelae.

DISCUSSION

This is a report of an elderly woman diagnosed with CLL whose treatment was complicated by the development of SJS, 3weeks after she was commenced on allopurinol and chlorambucil. The time interval between drug commencement and onset of symptoms in this patient is as reported in other literature.[3] In addition, the spectrum of symptomatology at presentation in this patient (fever, painful maculo-papular rashes with peeling of the skin, mouth ulcers, conjunctivitis and renal dysfunction) were all in keeping with previous reports.[3,6]

The pathogenesis of SJS has been traced to cytotoxic T-cells, which induce apoptosis of epidermal keratinocytes via interaction between the Fas receptor (CD 95) and its ligand (FasL).[7] For the above reason, the condition responds to immunosuppression, using systemic steroids or intravenous immunoglobulin (IVIG). Among Thai patients with SJS, steroids were reported as the most commonly prescribed medication (82.2%).[5] This patient was given systemic steroids (dexamethasone 4mg) as part of supportive management, with good result.

A number of reports have implicated both allopurinol and chlorambucil as aetiologic agents of SJS; reports of the former were, however, encountered more frequently than the latter.[3,4,5,6,7,9] Particularly, Limpawattana, *et al,* profiled SJS among Thai patients over a 10-year period and reported that out of 46 patients who developed SJS, allopurinol was the most frequently implicated aetiologic agent (13.3%).[5] On this note, we conclude that allopurinol was the most likely agent that triggered this condition in our patient, even though we could not exclude possible interference of chlorambucil in the causation, with certainty. Due to safety concerns, both agents were, subsequently withdrawn, even when chemotherapy was re-commenced following recovery.

Allopurinol is a xanthine oxidase inhibitor, commonly used to lower serum uric acid levels. In view of its propensity to induce SJS, alternative medications that could be used in its place include, foboxostat (a new xanthine oxidase inhibitor), probenecid (a uricosuric agent), benzbromarone and rasburicase.[8] The use of these alternatives is, however, limited by non-availability and significant organ/system side effect.[8] On account of the above reasons, none of these alternatives could be offered to our patient even when chemotherapy was re-commenced.

Chung, *et al*, studied the spectrum of allopurinol-induced adverse skin reactions and concluded that HLA-B58:01, impaired renal function and high levels of oxypurinol and granulysin (a product of cytotoxic T-cells) were strongly predictive of allopurinol induced SJS and also, of poorer prognosis.[9] The authors then suggested that allopurinol should be avoided in individuals with any of the above factors. Our patient had optimal renal function before commencement of treatment, (however, this became deranged when the patient presented with SJS); HLA typing, assays for serum oxypurinol and granulysin were not done at any time due to lack of facilities for these at the time this patient was seen.

CONCLUSION

Allopurinol is a potential cause of SJS even in this environment; and, a high index of suspicion (particularly in patients who are on medications that are known to potentially trigger this condition) will enable early detection. Drug withdrawal, coupled with systemic steroids and other supportive medications are associated with good result.

LIMITATIONS OF THE STUDY

Even though the authors concluded that the cause of SJS in this study was allopurinol (based on the very high preponderance of allopurinol-induced SJS in literature), we could not categorically rule out possible interference of chlorambucil in disease causation.

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