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Case Report

Tailoring antituberculosis treatment regimen in a patient with serious adverse drug reactions to multiple drugs

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Abstract

Stevens–Johnson syndrome (SJS) and hepatitis are serious adverse drug reactions following the administration of anti-tuberculosis treatment (ATT). Here, we report a case of a young woman who developed hepatitis and SJS following ATT. Identifying the culprit drug and tailoring the appropriate regimen is a challenge to the clinicians. We described the clinical features, laboratory findings, hospital course and follow-up in a young female with tuberculosis, SJS and hepatitis in the case report. After the resolution of hepatitis, we confirmed the diagnosis of extrapulmonary tuberculosis and treated her after a cautious rechallenge with antitubercular drugs.

Keywords: Tuberculosis, treatment, hepatitis, Stevens–Johnson syndrome

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INTRODUCTION

Hepatitis and Stevens–Johnson syndrome (SJS) are of great concern in the treatment with anti-tuberculosis drugs. Hepatitis following anti-tuberculosis treatment (ATT) is due to either an idiosyncratic reaction or may be related to dose. ATT, including ethambutol, isoniazid, rifampicin, pyrazinamide, streptomycin and thiacetazone, has been reported to cause SJS and toxic epidermal necrolysis.[1] We report a case of severe adverse drug reactions to ATT and reintroduction of ATT.

CASE REPORT

A 27-year-old female presented with moderate-grade fever with evening rise of temperature along with weight loss of 20 days duration. The patient was found to have left-sided pleural effusion which was analysed elsewhere in April 2012 and was found to be straw-coloured, exudative, lymphocytic predominant and with raised adenosine deaminase levels. She was started on isoniazid, rifampicin, pyrazinamide and ethambutol. After 1 week, the patient had headache, vomiting and gradually worsening sensorium. She was readmitted to another hospital where magnetic resonance venogram was suggestive of cortical sinus venous thrombosis and the patient was managed with anticoagulants, phenytoin along with ATT, and was shifted to another hospital. In the 3rd hospital, hepatitis was noticed and ATT was stopped. She was started on fluoroquinolones along with ethambutol and amikacin. Two days later, the patient developed an erythematous rash, which became confluent and progressed to all over the body. As the patient was deteriorating, she was referred to our institute hospital.

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On examination at admission in the emergency medicine department, there was deep icterus, severe keratoconjunctivitis, rash all over the body [Figure 1] and mucositis involving the oral mucosa and anus along with oral candidiasis. A possibility of SJS was entertained in view of extensive involvement of the skin and mucosa. ATT, fluoroquinolones and phenytoin were stopped. She was started on lubricant eyedrops for 1 week. The patient also received emollients to the skin and barrier precautions to prevent cross infections. The patient showed symptomatic improvement with a reduction of rash and icterus. During hospital stay, the patient developed two pustular lesions on the thigh due to methicillin-sensitive *Staphylococcus aureus* and treated with cloxacillin intravenously followed by oral administration for 10 days. The patient was discharged and managed on an outpatient basis. During regular follow-up, liver enzymes returned to normal levels after 8 months of discharge [Table 1].

Table 1: Liver function test results during follow-up

Parameter	At admission	After 6 months	After 8 months	After 9 months
AST (IU/L)	143	101	20	23
ALT (IU/L)	169	223	30	30
ALP (IU/L)	1581	1191	233	228
Total serum bilirubin (mg/dL)	15.3	1	0.4	0.9
Conjugated bilirubin (mg/dL)	13.1	0.7	–	–

AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase

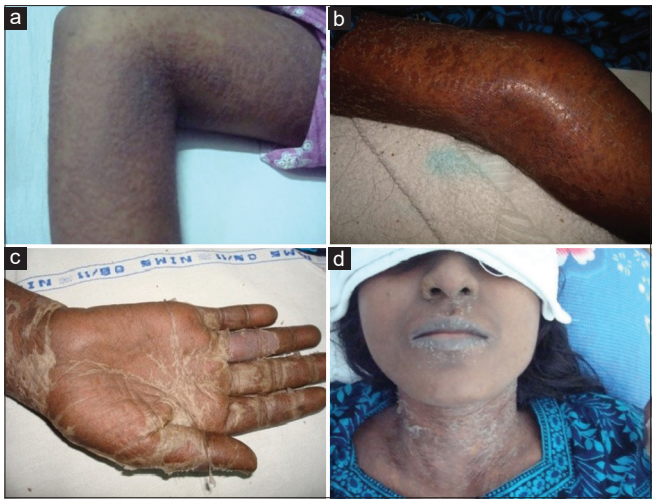

Figure 1: Severe maculopapular rash involving arms, forearms (a, b). Desquamating lesions on the hands, neck and lips (c, d)

During follow-up after the resolution of skin lesions, review high-resolution computed tomography (HRCT) of the chest was done. repeat HRCT chest showed two well-defined pleural-based soft tissue density lesions noted in the basal segment of the left lower lobe, which was aspirated under computed tomography guidance [Figure 2]. Fine-needle aspiration and cytopathology of the lesion were suggestive of necrotising granulomatous inflammation.

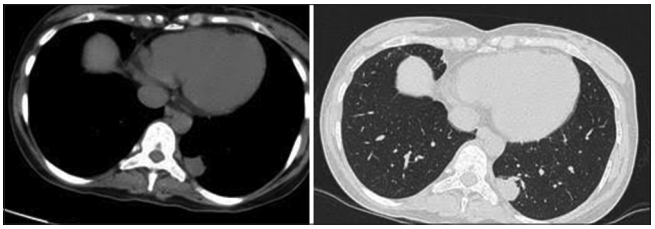

Figure 2: High-resolution computed tomography chest showing solitary pulmonary nodule of the left lower lobe in both mediastinal and lung window

With this evidence, the patient was considered for the treatment with ATT. In view of background severe hepatitis, isoniazid and rifampicin were not started initially. The patient was initially started on streptomycin, ethambutol and ethionamide. She developed maculopapular rash all over the body the following day. All the above medications were stopped and rash subsided. The reaction was thought to be due to ethionamide and the patient was started on intravenous amikacin (750 mg) and ethambutol (800 mg). Again the patient developed rash, amikacin was stopped. Levofloxacin was added to ethambutol, and again the patient developed a rash, levofloxacin was stopped immediately. Rechallenge with rifampicin in escalating doses was done with careful monitoring of liver function tests. Later, pyrazinamide was also added to ethambutol and rifampicin, which was well tolerated by our patient. Subsequently, the patient received rifampicin (600 mg), pyrazinamide (1250 mg) and ethambutol (1000 mg). The patient symptomatically improved, gained weight and rash completely subsided. Liver function tests, haemogram and renal function tests were regularly monitored and were found normal following 5 months of ATT.

DISCUSSION

The occurrence of adverse drug reactions depends on various predisposing factors such as polypharmacy, age, gender, race and genetic factors. Serious adverse reactions to antituberculosis drugs can cause significant morbidity and compromise treatment of tuberculosis.

SJS, otherwise known as erythema multiforme major, is thought to represent a continuum of disease, the most benign type of which is erythema multiforme, whereas toxic epidermal necrolysis is the most severe. It affects mucosal membranes of the mouth, nares, pharynx, oesophagus, urethra and vulvovaginal as well as anal regions.

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Initially, the SJS in our patient was thought to be due to either antitubercular drugs or fluoroquinolones or phenytoin. However, the occurrence of similar cutaneous reactions during ATT rechallenge which included fluoroquinolones led us to confirm the hypersensitivity to isoniazid, ethionamide, aminoglycosides and fluoroquinolones. We did not rechallenge with phenytoin as the patient did not require anticonvulsants during her hospital stay and follow-up.

ATT-induced acute liver failure is the most common drug-induced acute liver failure in South Asia. In a study[2] ATT was found to be the most common cause of acute liver failure contributing to 5.7% of the total 1223 consecutive patients.[2] Drug-induced hepatitis (DIH), the most common serious adverse effect, is defined as a serum aspartate aminotransferase level more than three times the upper limit of normal in the presence of symptoms or more than five times the upper limit of normal in the absence of symptoms.[3] In case of hepatitis, isoniazid, rifampicin and pyrazinamide, which are all potential causes of hepatic injury, should be stopped immediately as it was done in our case. Disruption of intracellular calcium homeostasis, cholestatic damage, interruption of transport pumps and activation of apoptotic pathways are the pathogenic mechanisms involved in ATT-induced hepatotoxicity. Advanced age, female sex, history of alcoholism, underlying liver disease, acetylator phenotype, hepatitis B and C, human immunodeficiency virus infection, extensive disease, hypoalbuminaemia, slow acetylator status of the N-acetyltransferase 2 gene, polymorphism of cytochrome P450 (CYPE21), absence of human leukocyte antigen (HLA)-DQA1 * 0102 and presence of HLA-DQB1 * 0201 have all been observed to be risk factors for the development of DIH.[4] In our patient, the cholestasis was severe and prolonged. Fortunately, the tuberculosis was not so aggressive and gave adequate time for the resolution of drug reaction.

In the event of severe adverse drug reactions, it is important to gradually desensitise and to reintroduce antitubercular drugs in a case of active clinical tuberculosis.[5] Despite severe SJS and hepatitis in our patient, ATT rechallenge was unavoidable as the cytopathology of lung lesions was suggestive of active tuberculosis. We have managed severe SJS and severe cholestatic hepatitis in this patient successfully. We have also identified the culprit drugs in the patient, so that it will be of help to the patient and the physicians managing her for various medical conditions in the future.

Clinicians should be aware of adverse drug reactions before starting the drugs and be ready to identify them early and manage them effectively to reduce morbidity and mortality. It is also important to have knowledge on how to rechallenge drugs like ATT, so that the drugs are used effectively without the development of resistance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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