A rare case of ethambutol induced pulmonary eosinophilia

Kaushik Saha, Ankan Bandyopadhyay[1], Amitabha Sengupta[2], Debraj Jash[2]

Department of Pulmonary Medicine, Burdwan Medical College and Hospital, Burdwan [2]Department of Pulmonary Medicine, NRS Medical College and Hospital, Shealdah, Kolkata, West Bengal, [1]Department of Pulmonary Medicine, R G Kar Medical College, Kolkata India

ABSTRACT

Antitubercular drug (ATD) induced eosinophilic lung disease is a rare phenomenon. It usually occurs due to isoniazid and para amino salicylic acid. A 34-year-male of sputum positive pulmonary tuberculosis, on antitubercular drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide) for last 3 weeks, presented with generalized arthralgia and maculopapular rash for last 2 weeks and shortness of breath for last 1 week. Chest X-ray and High resolution computerized tomographic scan thorax showed bilateral peripheral airspace opacification. Bronchoalveolar lavage revealed 51% eosinophils of total cellularity (1200/cmm) confirming the diagnosis of pulmonary eosinophilia. ATD was stopped for 2 weeks and then reintroduced one by one. Patient again developed similar kind of symptoms with reintroduction of ethambutol. According to criteria for drug induced pulmonary eosinophilia, he was diagnosed as a case of ethambutol induced pulmonary eosinophilia.

Key words: Antitubercular drug, ethambutol, pulmonary eosinophilia

INTRODUCTION

Eosinophilic lung disease can be caused by a number of drugs. Diagnosis of drug or toxin induced eosinophilic pneumonia is based upon a careful review of drug and other exposures like non-prescription drugs, herbal preparations, street drugs etc. A concomitant skin rash and pleural effusion can support the diagnosis of drug induced eosinophilic lung disease.[1] Antitubercular drug (ATD) induced eosinophilic lung disease is rare.[2,3] Here, we report a rare case of ethambutol induced pulmonary eosinophilia in a patient of sputum positive pulmonary tuberculosis.

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.119724

CASE REPORT

A 34-year-male was admitted in our department with generalized arthralgia without any joint swelling and maculopapular rash for last 2 weeks; dry cough and progressive grade 3 shortness of breath according to Modified Medical Research Council for last 1 week [Figure 1]. He was a diagnosed case of sputum smear positive pulmonary tuberculosis and on ATD, i.e., rifampicin, isoniazid, ethambutol and pyrazinamide according to his body weight for last 3 weeks on daily doses. His sputum for mycobacterial tuberculosis culture was also positive and was sensitive to all first line ATD. He had no history of addiction to smoking, alcohol or drugs and not receiving any other medication except ATD. Examination of respiratory system revealed bilateral vesicular breath sound with prolonged expiration and bibasal inspiratory crackles. Chest X-ray (CXR) during starting of ATD showed right lower zone alveolar opacity [Figure 2a]. His blood examination showed total leukocyte count 12000/cmm of which eosinophil count was 19%. His absolute eosinophil count was 2500. His CXR showed radiological deterioration with predominant

Address for correspondence:
Kaushik Saha, Rabindra Pally, 1st Lane, P.O. - Nimta, Kolkata - 700 049, West Bengal, India. E-mail: doctorkaushiksaha@gmail.com

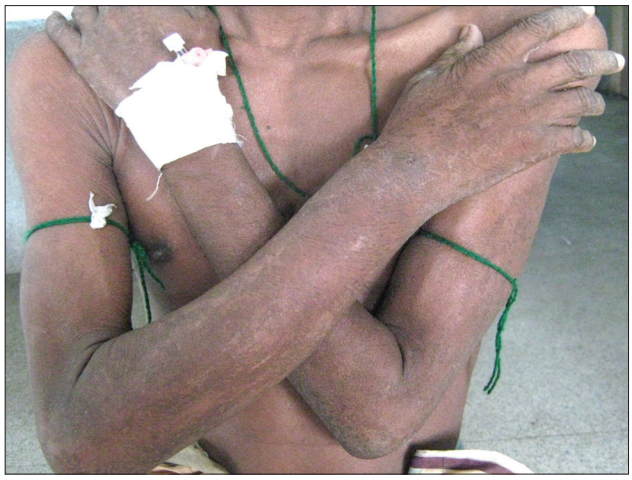

Figure 1: Maculopapular rash with erythema and desquamation involving the trunk and upper limbs

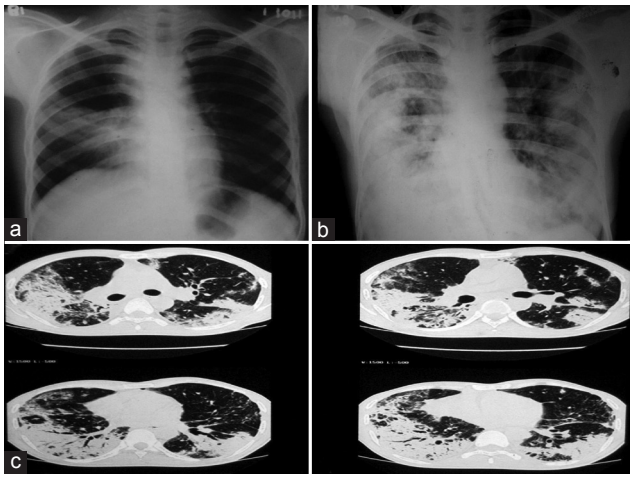

Figure 2: Chest X-ray PA view showing right lower zone alveolar opacity before starting antitubercular drug (ATD) (a) and bilateral peripheral consolidation in upper and mid zones of lung mimicking photographic negative of pulmonary edema after three weeks of starting ATD (b) High resolution computerised tomography of thorax showing bilateral diffuse air space opacification predominantly in the peripheral lung field along with some ground glass opacity suggestive of eosinophilic pneumonia (c)

involvement of periphery of lung field mimicking photographic negative of pulmonary edema [Figure 2b]. High resolution computerized tomographic scan (HRCT) of thorax showed diffuse bilateral air space opacification predominantly in the peripheral area along with some ground glass opacity [Figure 2c]. We suspected the case to be eosinophilic lung disease. All ATD were stopped. His stool examination for ova, parasite and cysts for three consecutive days was negative. Blood for c-ANCA (Antinuclear cytoplasmic antibody), p-ANCA, echinococcal immunoglobulin (Ig) M antibody and collagen vascular profile were negative. Immediate skin hypersensitivity to aspergillus antigen and aspergillus specific IgE were negative. Fiber-optic bronchoscopy guided bronchoalveolar lavage (BAL) fluid showed 51% eosinophil of total cellularity (1200/cmm). BAL fluid for acid fast bacilli (AFB) stain, fungal stain, Papanicolaou (PAP) stain, fungal culture and mycobacterial culture were negative. Patient was put on oral prednisolone (40 mg/day). The patient showed marked improvement of respiratory symptoms within 48 h and significant radiological clearance occurred within two weeks. Complete resolution of skin lesions and respiratory symptoms also took place within 2 weeks. Diagnosis of eosinophilic pneumonia was established on the basis of clinico-radiological picture and BAL fluid cytology. ATD was planned to reintroduce after complete resolution of skin lesions at 2nd week in order of rifampicin, pyrazinamide, ethambutol and isoniazid at a small challenge dose followed by gradual increase to full therapeutic dose. After reintroduction of ethambutol patient again developed shortness of breath, fever and skin rash within 24 h. His absolute eosinophil count in peripheral blood was 1800/cmm. Ethambutol was suspected to be the offending drug and it was stopped immediately. Then we started isoniazid in a small challenge dose followed by full therapeutic dose with previous two ATD, i.e., rifampicin and pyrazinamide. We added ofloxacin to the above ATD regimen. His absolute blood eosinophil count became normal within 2 days; dyspnoea and skin rash improved within 7 days. He was discharged with ATD comprising of rifampicin 450 mg/day, isoniazid 300 mg/day, pyrazinamide 1250 mg/day and ofloxacin 800 mg/day along with oral prednisolone 40 mg/day. On follow-up visit, after 1 month, prednisolone was tapered gradually over a period of 2 months and then stopped. His CXR and peripheral blood absolute eosinophil count were normal and patient was asymptomatic at that time. After 2 months sputum for acid fast bacilli and mycobacterial culture were negative. Ofloxacin and pyrazinamide were stopped at that time and rifampicin and isoniazid continued for another 4 months. The case was diagnosed to be ethambutol induced pulmonary eosinophilia in a patient of sputum positive pulmonary tuberculosis.

DISCUSSION

Numerous drugs are implicated in causation of pulmonary infiltrates or pulmonary eosinophilia. Common causative drugs are antibiotics, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitor, angiotensin converting enzyme inhibitors, anticonvulsants, antidepressants, beta-blockers, amiodarone etc.[1] Among antitubercular drugs isoniazid, para-aminosalicylic acid can produce eosinophilic lung disease.[2,3] Ethambutol very rarely can cause drug induced eosinophilia.[4] Drug induced pulmonary eosinophilia have an acute or subacute onset with nonspecific presentation. In most cases patients present with either pulmonary manifestations compatible with idiopathic chronic eosinophilic pneumonia or features characteristic of idiopathic acute eosinophilic pneumonia. Interstitial or alveolar infiltrate are typically seen on chest X-ray. On HRCT scan thorax, bilateral consolidation and ground glass opacities with predominant peripheral

distribution are seen.[5] A concomitant skin rash and pleural effusion can support the diagnosis of drug induced eosinophilic pneumonia.[1] Although, the most certain way to determine whether a patient has drug-induced eosinophilic lung disease is for the eosinophilia to resolve after discontinuation of medication and then recur after re-challenging the patient with the same drug. However, this can be risky and should be avoided in most cases.[1] More practically, for diagnosis of drug-induced eosinophilic lung disease, five criteria should be met. The patient should: (1) have no other likely cause of lung disease, (2) have symptoms consistent with the suspect drug, (3) have a time course compatible with drug-induced lung disease, (4) have tissue or BAL findings compatible with drug-induced lung disease and (5) improve after the drug is discontinued. Patients who have all five of these criteria can be considered as having definite drug induced eosinophilic lung disease, patients who meet four criteria can be considered as having probable disease and those who meet three criteria are suspected to have the disease.[1] Our patient satisfied all five criteria required for diagnosis of drug induced eosinophilic lung disease. Elimination of drug or other toxins usually leads to resolution of symptoms, eosinophilia, pulmonary infiltrates and normalization of lung function within a month. Supplemental therapy with corticosteroids is useful as a palliative measure.[6]

Acute eosinophilic pneumonia (AEP) may be associated with various skin manifestations like pruritic rash, which may be raised or serpiginous; splinter hemorrhages and evidence of vascular occlusion. The widespread skin rash made up of redness, little bumps (papules) and sometimes blisters (vesicles) and pustules. The rash can last many weeks and may be progress to erythroderma or exfoliative dermatitis, where all the skin peels off. Our case was an AEP associated with skin eruption due to ethambutol. Systemic allergic reaction, such as skin rash, may coexist with AEP. As a result, the diagnosis of drug rash, eosinophilia and systemic symptoms syndrome (DRESS) is a possibility. DRESS is defined by fever, skin eruption, enlarged lymph nodes, visceral involvement, haematological abnormalities (hypereosinophilia and lymphocytosis) and viral reactivation, in particular human herpes virus-6 and Epstein–Barr virus.[7] DRESS syndrome has a clinical variable presentation and was considered possible in the present case, according to the new European registry of severe cutaneous adverse reactions to drugs and collection of biological samples (RegiSCAR) group's criteria, but not definite.[8,9] Multi visceral involvement in DRESS is what differentiates it from more common cutaneous drug reactions.

ATD induced eosinophilic lung disease is itself rare. Among ATD, isoniazid is common to cause this, but ethambutol is very rare causative agent. Here we reported a rare case of ethambutol induced pulmonary eosinophilia, which satisfied all the criteria required for diagnosis of drug induced eosinophilic lung disease. Only one case was reported, but it was not presented as classical radiological photographic negative of pulmonary edema like our case.[4] Prompt suspicion, diagnosis and withdrawal of the causative drug are needed to save the patient.

REFERENCES

1. Allen JN. Drug-induced eosinophilic lung disease. Clin Chest Med 2004; 25:77-88.
2. Perreau P, fresneau M, boumard B, lebrizaut Y. Pulmonary infiltrate with Eosinophilia during treatment with isoniazid. Press Med 1955; 63:1454-6.
3. Cuthbert RJ. Loffler's syndrome occurring during streptomycin and PAS therapy. Br Med J 1954;2:398-9.
4. Wong PC, Yew WW, Wong CF, Choi HY. Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. Eur Respir J 1995;8:866-8.
5. Johkoh T, Müller NL, Akira M, Ichikado K, Suga M, Ando M, *et al*. Eosinophilic lung diseases: Diagnostic accuracy of thin-section CT in 111 patients. Radiology 2000;216:773-80.
6. Kroegel C, Reissig A, Mock B. Eosinophilic pneumonia. In: Gibson GJ, editor. Respiratory medicine. 3rd ed. Edinburgh: Elsevier science Ltd.; 2003. p. 1643-59.
7. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome DRESS. Semin Cutan Med Surg 1996;15:250-7.
8. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: A retrospective study of 60 cases. Arch Dermatol 2010;146:1373-9.
9. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.

How to cite this article: Saha K, Bandyopadhyay A, Sengupta A, Jash D. A rare case of ethambutol induced pulmonary eosinophilia. J Pharmacol Pharmacother 2013;4:300-2.

Source of Support: Nil, **Conflict of Interest:** None declared.