Recurrent heart failure in pulmonary tuberculosis patients on antitubercular therapy: A case of protector turning predator!

Animesh Ray[a], Vivek Nangia[b], RS Chatterji[c], Navin Dalal[a], Ruchismita Satpathy Ray[d]

Anti-tubercular drugs are associated some common and uncommon adverse effects. We report the association between cardiomyopathy and the use of anti-tubercular drugs. In the two cases described in the case report the different causes of cardiomyopathy are ruled out leading to the diagnosis of drug induced cardiomyopathy. The report also throws light on the various aspects of this association and the clinical implications.

Egypt J Bronchol 2017 11:288–291

Egyptian Journal of Bronchology 2017 11:288–291

Keywords: anti-tubercular therapy, cardiomyopathy, heart failure, tuberculosis

[a]Consultant, Department of Pulmonary Critical Care & Sleep Medicine, Fortis Hospital, Vasant Kunj, New Delhi, [b]Senior Consultant & HOD, Department of Pulmonary Critical Care & Sleep Medicine, Fortis Hospital, Vasant Kunj, New Delhi, [c]Senior Consultant, Department of Pulmonary Critical Care & Sleep Medicine, Fortis Hospital, Vasant Kunj, New Delhi, [d]Consultant, Department of Radiodiagnosis, The Mission Hospital, Durgapur, West Bengal

Correspondence to Animesh Ray, MD, DNB, MRCP, DM, 290 Parnasree, Kolkata 700060, India;
e-mail: doctoranimeshray@gmail.com

Received 28 November 2016 **Accepted** 16 December 2016

Case 1

A 20-year-old woman who was diagnosed as a case of sputum positive pulmonary tuberculosis and was on anti-tubercular therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months followed by isoniazid and rifampicin in standard daily dose) for the past 3.5 months presented to us with complaints of progressively increasing breathlessness, cough with whitish expectoration, and generalized body swelling for the past 3 months. On examination, the patient had SpO_2 of 90% on room air, tachycardia, tachypnea, edema (periorbital, parietal, and pedal), and raised jugular venous pressure. Examination of the cardiovascular and gastrointestinal system revealed cardiomegaly with S3 and tender soft hepatomegaly with ascites, respectively. Lab investigations revealed hemoglobin of 7 g/dl and raised liver enzymes (alanine aminotransferase of 230 U/l). Chest radiography (Fig. 1) and, subsequently, computed tomography thorax (Fig. 2) were performed, and they showed features suggestive of pulmonary edema. Ascitic fluid analysis showed high serum ascitic albumin gradient (1.4 g/dl) with normal cell count. Two dimensional echocardiography showed global left ventricular hypokinesia with ejection fraction of 20%.

The patient was started on antiheart failure treatment with diuretics, fluid restriction, and angiotensin receptor blockers. The patient improved on the above treatment and her breathlessness (from New York Heart Association IV to New York Heart Association II) and oxygen saturation improved, and edema subsided. As her liver enzymes became normal, she was restarted on isoniazid and rifampicin. However, within 48 h of restarting antitubercular drugs she had recurrence of frank heart failure with decreasing oxygen saturation and other telltale signs of heart failure, including worsening of the chest radiograph (Fig. 3). Antifailure treatment was further increased and antituberculosis therapy (ATT) was stopped. After this, the patient's condition again improved. A thorough investigation to evaluate the sudden deterioration was done, including bronchoscopy with bronchial lavage for stains and geneXpert, connective tissue markers (antinuclear antibody, antineutrophilic cytoplasmic antibody, anti-histone antibody), and HIV serology, which were all negative. There was no evidence of viral prodrome, any other infections, electrolyte abnormalities, or ischemic heart disease. The fluid input/output charts were reviewed to rule out any unaccounted fluid administration to the patient and proper drug administration was confirmed. Although the echocardiography showed unchanged ejection fraction of 20%, the inferior vena cava showed minimal respiratory variation (initially after treatment the inferior vena cava had shown normal respiratory variation). All the evidence pointed toward a worsening heart failure, the reason of which eluded us. Her ATT was subsequently stopped (she had completed 5.5 months of treatment and had no signs of active tuberculosis).

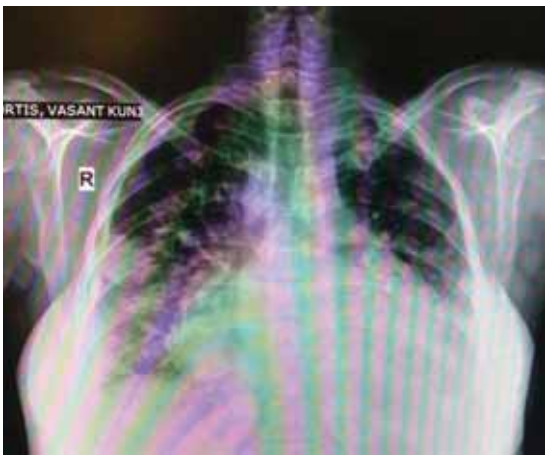
Case II

A 40-year-old man diagnosed as a case of pulmonary tuberculosis (on the basis of symptoms of long-drawn fever with cough and suggestive chest radiography) and

 DOI: 10.4103/1687-8426.211400

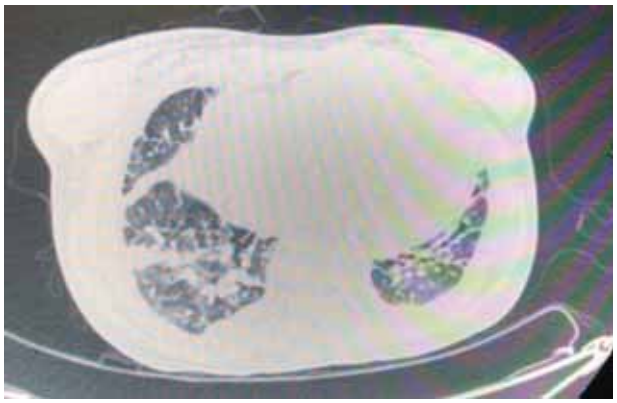
who was on antitubercular therapy for the past 1.5 months presented to us with complaints of shortness of breath and pedal swelling for the past 15 days. On examination, he had hypotension (80/40 mmHg), raised jugular venous pressure, hepatomegaly, and bilateral end inspiratory crepitations. Echocardiography showed ejection fraction of 15% with global hypokinesia of the left ventricle. Chest radiography and computed tomography thorax showed bilateral pulmonary edema with cardiomegaly (Figs 4 and 5). Blood investigations showed direct hyperbilirubinemia with transaminitis. Ultrasonography (USG) abdomen showed ascites (low protein) with hepatomegaly. A central line was inserted (initial central venous pressure 25 mmHg) and inotropes were started along with management of heart failure in the form of diuretics, fluid restriction, and noninvasive ventilator support. His antitubercular therapy was stopped, and levofloxacin (L), ethambutol, and streptomycin (S) were started. Sputum showed acid-fast bacilli with geneXpert positive for tubercle bacilli but negative for rifampicin resistance. The patient recovered and could be weaned off the inotropes and noninvasive ventilator. Subsequently, when the liver function test improved, he was restarted on isoniazid, rifampicin, pyrazinamide, ethambutol. Within 2 days, he had recurrence of similar symptoms with worsening of oxygen saturation and frank pulmonary edema on the chest radiography (Fig. 6). His central venous pressure, which had come down to 10 mmHg on therapy, increased further to 22 mmHg with reappearance of derangement in the liver function. His ATT was stopped and LSE (Levofloxacin, Streptomycin, Ethambutol) was started with intensification of the antiheart failure management. Investigations performed to reveal any precipitating cause for heart failure were all negative. Subsequently, ATT was restarted once the patient

Figure 1



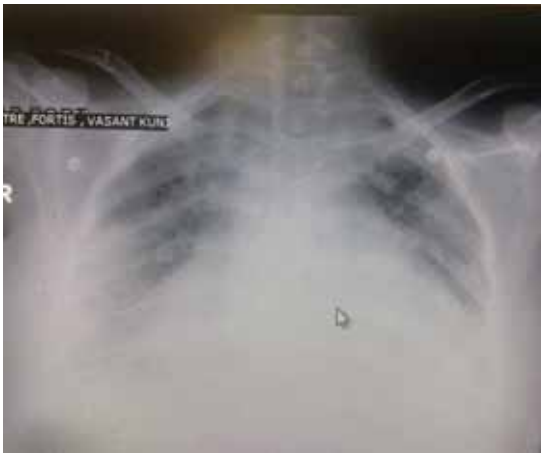
Chest radiograph showing cardiomegaly with bilateral alveolar infiltrates.

Figure 2



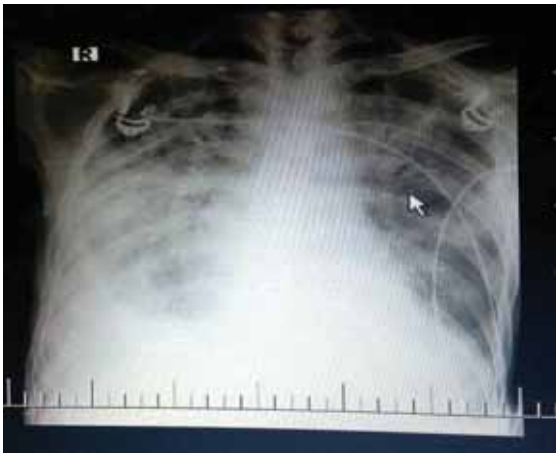
Computed tomography thorax showing bilateral pleural effusion with ground glass opacities and centrilobular infiltrates.

Figure 3



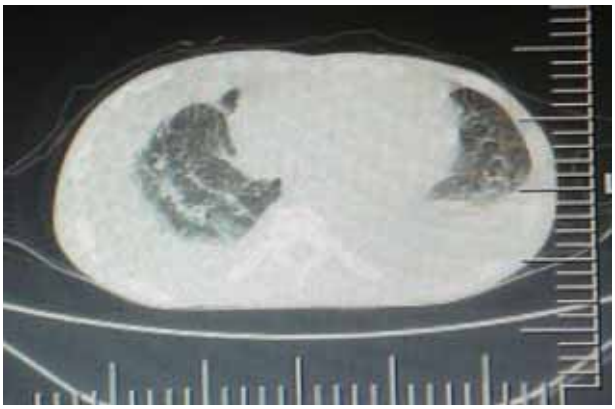
Chest radiograph showing cardiomegaly and bilateral alveolar infiltrates.

Figure 4



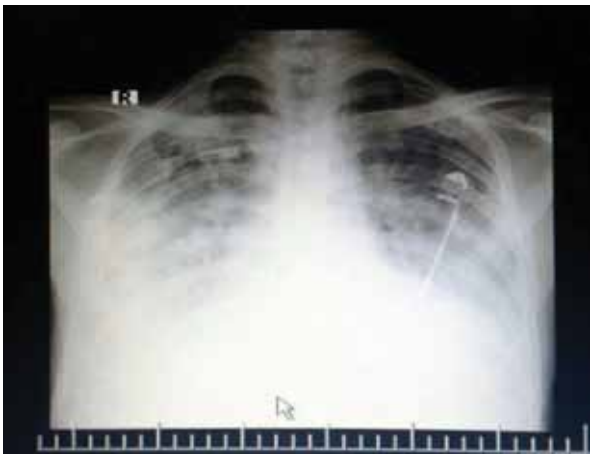
Chest radiograph showing bilateral consolidation with right pleural effusion.

Figure 5



Computed tomography thorax showing bilateral pleural effusion and centrilobular nodules.

Figure 6



Chest radiograph showing recurrence of pulmonary edema.

stabilized with the cover of steroids (prednisolone 30 mg). This time the patient tolerated the medication and could be shifted out of the ICU. However, once the steroid was tapered to 10 mg over 2 weeks, he again developed frank heart failure, which subsequently responded to an increasing dose of steroids. He was continued on steroids 20 mg for 1 month and then tapered slowly to 10 mg with continuation of antitubercular drugs. The patient completed his ATT and was symptom-free at 6 months of follow-up. Repeat echocardiography at 6 months showed no improvement of the ejection fraction.

Discussion

These two cases posed several questions to us:

(1) Were antitubercular drugs responsible for myocardial injury, which resulted in the patients having heart failure and further worsening on reintroduction?
(2) If yes, which one of the drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) were responsible?
(3) What is the best line of management in such a case? Is it to stop the drugs (as in case 1) and start alternate drugs or to continue the drugs under cover of steroids (as in case 2)?
(4) How to pre-empt the development of this condition in patients?
(5) Whether the involvement of the heart is reversible?

Numerous drugs are known to cause myocardial injury and cardiomyopathy [1]. However, none of the antitubercular drugs are commonly mentioned. However, there have been rare reports of myocardial damage by antitubercular drugs. In the case report by Zhang *et al.* [2], they had described a 42-year-old man who suffered from isoniazid-induced myocardial damage as a part of drug rash with eosinophilia and systemic symptoms. Agarwal *et al.* [3] had described a 25-year-old woman diagnosed and treated as a case of sputum positive tuberculosis who after 2.5 months of therapy had cough, dyspnea, and low-grade fever (for 1 week). Echo showed left ventricular global hypokinesia, and subsequent postmortem cardiac biopsy showed myocardial caseous necrosis and acid-fast bacilli suggestive of tubercular myocardial damage. What was relevant was that the patient after initiation of treatment had been well for about 2 months and then developed symptoms of left ventricular failure, leading the author to suggest that a 'paradoxical reaction' had occurred in which the immunogenicity of the host had been enhanced to the tubercle bacilli. Our patients had more or less the same features – diagnosis of tuberculosis antitubercular drugs initiated frank heart failure. Although we could not perform a myocardial biopsy or magnetic resonance imaging of the heart because of financial constraints, the circumstantial evidence (worsening of heart failure on reintroduction of antitubercular drugs in the absence of other precipitating factors) suggests that it was a drug-related phenomenon. As it happens with other drugs, there is myocardial inflammation and myocytolysis resulting in myocardial necrosis and later on fibrosis [4].

As case 1 had received isoniazid, rifampicin and case 2 had received isoniazid, rifampicin, pyrazinamide, ethambutol during reintroduction that resulted in reappearance of symptoms and signs of heart failure, it is plausible that either isoniazid or rifampicin (or both) was responsible. Zhang *et al.* [2] had suggested that isoniazid was responsible for drug rash with eosinophilia and systemic symptoms in their

patient, but to resolve this issue scientifically we would require more data.

Zhang *et al.* [2] had stopped isoniazid in their patient. Agarwal *et al.* [3] had suggested that steroids might be helpful in controlling the heightened immunogenicity leading to the paradoxical reaction in their patient. Paradoxical reactions in the form of tubercular pleural effusion and tubercular lymphadenopathy may respond well to steroids (5), but whether the same holds true for 'myocardial toxicity' needs to be deduced from well-planned studies.

Finally, we believe that to pre-empt this condition what is important is to consider the possibility of ATT-induced myocardial toxicity in patients presenting with features akin to the cases discussed above. With reporting of more such cases, clearer perception about this condition and its intricacies will emerge.

The available literature does not show much light on this. In both our patients, the condition persisted even after a year or so of follow-up. However, the natural history of the disease will become clear only after more such cases are reported.

These two cases thus highlight a seemingly uncommon complication of the antitubercular drug – dilated cardiomyopathy – and the different nuances associated with the same condition. The putative link between the use of antitubercular drugs and cardiomyopathy should attract more research on this area to further enunciate the different aspects of this issue.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Ansari A, Maron BJ, Berntson DG. Drug-induced toxic myocarditis. *Tex Heart Inst J* 2003; **30**:76–79.

2 Zhang SN, He QX, Yang NB, Ni SL, Lu MQ. Isoniazid-induced drug rash with eosinophilia and systemic symptoms (DRESS) syndrome presenting as acute eosinophilic myocarditis. *Intern Med* 2015; **54**: 1227–1230.

3 Agarwal R, Malhotra P, Awasthi A, Kakkar N, Gupta D. Tuberculous dilated cardiomyopathy: an under-recognized entity? *BMC Infect Dis* 2005; **5**:29.

4 Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000; **343**: 1388–1398.