



Contents lists available at ScienceDirect

## Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Document heading

doi:10.1016/S2222-1808(14)60315-7

© 2014 by the Asian Pacific Journal of Tropical Disease. All rights reserved.

## Co-infection of visceral leishmaniasis and pulmonary tuberculosis: a case study

Shweta<sup>1\*</sup>, Surabhi Bhatnagar<sup>1</sup>, Ashok Kumar Gupta<sup>2</sup>, Krishna Murti<sup>2</sup>, Krishna Pandey<sup>3</sup><sup>1</sup>National Institute of Pharmaceutical Education and Research, Hajipur, India<sup>2</sup>Faculty of Pharmacy, National Institute of Pharmaceutical Education and Research, Hajipur, India<sup>3</sup>Assistant Director, Rajendra Memorial Research Institute of Medical Sciences, Patna, India

## PEER REVIEW

## Peer reviewer

Dr. Sokindra Kumar, Professor and Principal, R.V. Northland Institute, Greater Noida, Phase-II, Dadri, G.B Nagar, Uttar Pradesh, India.

Tel: +91-120-2666444

+91-120-2666 445

E-mail: sokindra\_kumar@yahoo.co.in.

## Comments

This is a good endeavor by the authors who have undertaken the case study of a person with visceral leishmaniasis and latent tuberculosis. They concluded that co-infection of visceral leishmaniasis and pulmonary tuberculosis is a real threat in developing countries. These types of co-infection inhibit host's immune system. There is a need of cost effective diagnostic and therapeutic facilities for these co-infections.

Details on Page 60

## ABSTRACT

Co-infection of visceral leishmaniasis and pulmonary tuberculosis are increasing public health problem in eastern region of country. A large number of clinical cases of leishmaniasis and tuberculosis have been reported in Sudan. Such type of co-infections lead to decreased host's immune system. This is a case report of 48 years old male with visceral leishmaniasis and pulmonary tuberculosis. He arrived at hospital with complaints of fever with rigor, abdominal pain, weakness, loss of appetite, yellowish discoloration of urine and sclerosis at lower back. Bone marrow aspiration cytology revealed the presence of *Leishmania donovani* bodies (2+). His treatment was initiated with amphotericin B deoxycholate (inj. Fungizone) 15 infusions on alternate days with 5% dextrose. He had 20 years past history of pulmonary tuberculosis. His chest X-ray showed increased bronchovascular marking encysted pleural effusion on lower segment of right lung. Ultrasonography guided fine needle aspiration cytology of pleural fluid for protein, sugar, lactate dehydrogenase, adenosine deaminase, cell type and cell count. Cytological reports confirmed pulmonary tuberculosis. Antitubercular therapy (four drug regimen: rifampicin, isoniazid, ethambutal, and pyrazinamide) was started. Co-infection of visceral leishmaniasis and pulmonary tuberculosis is a real threat in developing countries. There is a need of cost effective diagnostic and therapeutic facilities for these co-infections.

## KEYWORDS

Visceral leishmaniasis, *Leishmania donovani*, Pulmonary tuberculosis, Co-infection, Amphotericin B deoxycholate, Fine needle aspiration cytology, Anti-tubercular therapy

### 1. Introduction

Leishmaniasis is a parasitic disease which is caused by intracellular protozoans of genus *Leishmania*. These protozoans are transmitted through bite of infected female phlebotomine sandflies. There are three main types of leishmaniasis: (a) cutaneous leishmaniasis, (b)

mucocutaneous leishmaniasis, (c) visceral leishmaniasis (kala azar). Cutaneous leishmaniasis is a localized reaction (skin ulcers, scars) which is caused by *Leishmania tropica* and *Leishmania aethiopica*. It is most commonly found in Brazil, Iran, Syria. Mucocutaneous leishmaniasis (espundia or uta) starts with bite of sandflies and go into mucous membrane through

\*Corresponding author: Shweta, National Institute Pharmaceutical Education and Research, Hajipur, Bihar-844102, India.  
E-mail: shweta01214@gmail.com

## Article history:

Received 23 Oct 2013

Received in revised form 29 Oct, 2nd revised 12 Nov, 3rd revised form 18 Nov 2013

Accepted 27 Dec 2013

Available online 28 Feb 2014

metastasis. Main pathogen involved is *Leishmania braziliensis* and it is found in Brazil, China, and Peru. Visceral leishmaniasis is caused by *Leishmania donovani*, *Leishmania inflatum* and it is mostly prevalent in India, Nepal, Bangladesh and Sudan[1]. *Leishmania* cells have two morphological form: promastigote (with flagella) in the insect host and amastigote form (without flagella) in vertebrate host[2]. *Leishmania* parasites invade and multiply within host macrophages and decrease cell mediated immune response. They neutralize complement component and prevent the release of macrophage superoxide and nitric oxide and suppress the induction of CD4 and T lymphocytes[3]. It is characterized by fever, hepatosplenomegaly, pancytopenia, loss of appetite, and anaemia. On the basis of symptoms, physical examinations are performed. Enlarged spleen (5–15 cm) below costal margin and haemoglobin concentration (5–9 g/dL), white blood cell count (2000–4000/mm<sup>3</sup>), platelet count (100 000–200 000/mm<sup>3</sup>) are typical in visceral leishmaniasis. Amphotericin B is a systemic antifungal agent, also used for treatment of visceral leishmaniasis in India. Due to resistance to antimonials, it is used as alternative drug. But it is highly toxic[4]. Fifteen infusions of 1 mg/kg of amphotericin B are given on alternate days (total dose 15 mg/kg) for treatment of visceral leishmaniasis. After several months or years of initial treatment of visceral leishmaniasis, a cutaneous complication *i.e.* post kala azar dermal leishmaniasis may occur[5].

Both visceral leishmaniasis and tuberculosis are increasing in eastern region of country. Although their etiology and transmission mechanism are different, they share several features. Tuberculosis is immunosuppressive condition that causes progression of latent leishmaniasis to clinical leishmaniasis, and visceral leishmaniasis can produce latent tuberculosis. Treatment of leishmaniasis depends on development of effective immune response which activates macrophages to produce nitric oxide for killing intracellular amastigotes.

## 2. Case report

A 48 years old male was admitted to Rajendra Memorial Research Institute of Medical Sciences in Bihar, India on 1st April, 2013 with fever associated with rigor, abdominal pain, weakness, headache, loss of appetite, yellowish discoloration of urine and sclerosis at lower back. He had 20 years back history of pulmonary tuberculosis. On physical examination, patient was conscious, oriented,

pulse (84 beats/min), blood pressure (120/80 mmHg) and pallor (+). There was vesicular breath sound from chest and heart sound (s1s2) was audible. His liver and spleen were palpable and enlarged (2 cm). On Day 10, he had difficulty in breathing. His chest X-ray was done, but nothing was found. Clinical laboratory examinations were normal except serum glutamic-oxaloacetic transaminase *i.e.* 58 U/L (normal range is upto 34 U/L) and serum glutamic pyruvic transaminase was 55 U/L (normal range is upto 45 U/L). After 2 d, bone marrow aspiration was done and revealed amastigote of *Leishmania* and smear was positive for *Leishmania donovani* bodies (2+). His treatment was initiated with 15 infusions of amphotericin B deoxycholate (inj. Fungizone 58 mg or 11.6 mL) with 5% dextrose on alternate days. Laboratory tests were performed after 15 d from admission, serum creatinine was raised to 1.9 mg/dL (normal range: 0.7–1.4 mg/dL) and investigations revealed pancytopenia (red blood cell count: 2.85 million/mm<sup>3</sup>, white blood cell count: 2100/μL, and platelet count: 106 000/μL) and anaemia (haemoglobin: 7.6 g/dL). As his serum creatinine was increased, inj. fungizone was withheld until serum creatinine reached to normal level.

On 21st April, X-ray chest showed increased bronchovascular marking encysted pleural effusion on lower side of right lung. Ultrasonography guided fine needle aspiration cytology of right pleural fluid. Pleural fluid was straw in color, hazy in appearance, and fibrin coagulum was present in pleural fluid. Sputum smear showed predominantly mature lymphocytes and few histiocytes (macrophages) in a hemorrhagic background with lysed red blood cells. There was no atypical/malignant cell in smear. Protein (4.65 g/dL), lactate dehydrogenase (198 U/L), sugar (79 mg/dL), adenosine deaminase (18 U/L), cell count (540/mm<sup>3</sup>), and cell was polymorphonuclear. There was cyst seen in right kidney. Due to this, his renal function was deranging gradually. Cytological reports and sputum smear were positive for pulmonary tuberculosis in the patient. Antitubercular therapy was started. AKT-FD (four drug regimen: isoniazid 100 mg, rifampicin 150 mg, pyrazinamide 500 mg, ethambutol 267 mg) was prescribed three tablet once in an empty stomach in morning. B-long (pyridoxine sustained release 100 mg) was also prescribed alongwith antitubercular drugs.

## 3. Discussion

Kala azar is a vectorborne parasitic disease. Approximately 500 000 cases of visceral leishmaniasis

worldwide affect rural population of India, Nepal, Bangladesh, and Sudan. Paromomycin is an aminoglycoside antibiotic given intramuscularly for treatment of kala azar at a dose of 12, 20 mg/kg for 21 d. Sodium stibogluconate is a pentavalent antimonial compound used for treatment of visceral leishmaniasis, but is no longer useful in Bihar because of resistance[6]. Amphotericin B is polyene antibiotic used for treatment of kala-azar, but it causes electrolyte imbalance. Amphotericin B induced hypokalemia is dose-dependent. During amphotericin B therapy, there is defect in distal tubule  $H^+K^+ATPase$  which increases  $K^+$  elimination results in hypokalemia[7]. A total of 5% dextrose is also infused with amphotericin B to reduce hypokalemia.

Co-infections of tuberculosis and parasitic diseases are increasing public health problem in developing countries. Infection with parasitic diseases alters protective immune response to BCG vaccine against tuberculosis[8]. Although their etiology and transmission mechanism are different, they share several features. Tuberculosis is immunosuppressive condition that is caused by mycobacterium tuberculosis. Directly observed treatment short course therapy is provided by government free of cost for TB[9]. Annual risk of tuberculosis is estimated at 1.8% which gives incident rates of TB smear positive cases of 90/100 000 person-year, in which Sudan is highly prevalent for TB.

Patient was treated with 15 infusions of amphotericin B (inj. fungizone 11.6 mL) alongwith 5% dextrose every alternate day. After 6th dose, his serum creatinine was increased above normal, so fungizone was withheld. Rest of doses were continued when serum creatinine reached to normal range. He had 20 years past history of pulmonary tuberculosis. On physical examination, there was vesicular breath sound of chest. He felt difficulty in breathing, so his chest X-ray was done. There was increased bronchovascular marking encysted pleural effusion in lower side of right lung. Fine needle aspiration cytology showed abnormalities in pleural fluid. Pleural fluid was straw in color, hazy in appearance, presence of fibrin coagulum. Cell type was polymorphonuclear and cell count was  $540/mm^3$ . Protein was 4.65 g/dL (normal  $\leq 3$  g/dL) and adenosine deaminase was 18 U/L (normal  $\leq 30$  U/L), sugar was 79 mg/dL. FNAC reports confirmed pulmonary tuberculosis. His antitubercular therapy was started. Combination of isoniazid, rifampicin, pyrazinamide, ethambutal (AKT-FD) was prescribed. This treatment regimen is followed in India under Revised National

Tuberculosis Control Programme (RNTCP 1997). This combination was prescribed three tablet once in morning in an empty stomach. As isoniazid (H) produce toxicity *i.e.* peripheral neuritis (paresthesias, numbness, tingling, mental disturbances, sometimes convulsions). These toxic effects are due to interference with utilization of pyridoxine and increased excretion of pyridoxine in urine. Pyridoxine sustained release tablets 100 mg/d (B-long) was prescribed to reduce isoniazid toxicity.

Visceral leishmaniasis is a chronic infection that results into immunological dysfunction which predisposes to pulmonary infections. Co-infection of visceral leishmaniasis and TB is very common. TB is an immunosuppressive condition that progresses latent leishmaniasis and results in clinical leishmaniasis, and visceral leishmaniasis can reactivate latent tuberculosis. Both infections can be effectively treated. These co-infections are seen in rural population of India. Cost of treatment is very high for such co-infections which most of people in developing countries can not afford. Amphotericin B (15 infusions) should be infused in patient on alternate days. Renal functions (serum creatinine, blood urea) and liver functions (serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum bilirubin) should be monitored before giving amphoterecin B deoxycholate. Due to suppression of CD4 and T lymphocytes of patient, there may be chances of opportunistic infections *i.e.* tuberculosis. Four drug regimen (HRZE combination *i.e.* isoniazid, rifampicin, pyrazinamide, ethambutol) are prescribed for treatment of active pulmonary tuberculosis[10]. Alongwith this combination, pyridoxine 100 mg/d is given to reduce isoniazid toxicity.

### Conflict of interest statement

We declare that we have no conflict of interest.

### Acknowledgements

We express our gratitude to Dr. Pradeep Das, Director, Rajendra Memorial Research Institute of Medical Sciences, Patna, India for permitting us to take cases from the hospital, and also express our gratitude to faculty members at National Institute of Pharmaceutical Education and Research for their constant support and encouragement.

## Comments

### Background

It is a case report of 48 years old male with complaints of fever with rigor, abdominal pain, weakness, loss of appetite, yellowish discoloration of urine and sclerosis at lower back. His treatment was initiated. X-ray, ultrasonography guided fine needle aspiration cytology and cytological reports confirmed the co-infection of pulmonary tuberculosis and visceral leishmaniasis in the patient.

### Research frontiers

Physical examinations of the patient were done. The felt difficulty in breathing, so his chest X-ray was done. There was increased bronchovascular marking encysted pleural effusion in lower side of right lung. Fine needle aspiration cytology showed abnormalities in pleural fluid. Pleural fluid was straw in color, hazy in appearance, presence of fibrin coagulum. Cell type was polymorphonuclear and cell count was 540/mm<sup>3</sup>. Protein was 4.65 g/dL (normal ≤3 g/dL) and adenosine deaminase was 18 U/L (normal ≤30 U/L), sugar was 79 mg/dL. Physical, microscopic, biochemical investigation of pleural effusion confirmed pulmonary tuberculosis.

### Related reports

Safi et al. studied the infection rates with *Leishmania donovani* and *Mycobacterium tuberculosis* in a village in Sudan. Carlos and Castro carried out a study of *Pneumocystis carinii* pneumonia, pulmonary tuberculosis and visceral leishmaniasis in an adult HIV negative patient.

### Innovations & breakthroughs

The current article highlighted the increasing rate of co-infection of visceral leishmaniasis and pulmonary tuberculosis particularly in rural India. The article also suggests the treatment strategies.

### Applications

Visceral leishmaniasis is a chronic infection that results into immunological dysfunction which predisposes to pulmonary infections. Tuberculosis is an immunosuppressive condition that progresses latent leishmaniasis and results in clinical leishmaniasis and visceral leishmaniasis can reactivate latent tuberculosis. Monitoring of the patient is necessary and proper

treatment strategies are also required.

### Peer review

This is a good endeavor by the authors who have undertaken the case study of a person with visceral leishmaniasis and latent tuberculosis. They concluded that co-infection of visceral leishmaniasis and pulmonary tuberculosis is a real threat in developing countries. These types of co-infection inhibit host's immune system. There is a need of cost effective diagnostic and therapeutic facilities for these co-infections.

## References

- [1] World Health Organization. Report of WHO informal consultation on liposomal amphotericin B in treatment of visceral leishmaniasis. Rome: World Health Organization; 2005. [Online] Available from: [http://www.who.int/neglected\\_diseases/resources/AmBisomeReport.pdf](http://www.who.int/neglected_diseases/resources/AmBisomeReport.pdf). [Accessed on 26th September, 2013]
- [2] Lianet M. Current treatment of leishmaniasis: A review. *Open Antimicrob Agents J* 2009; **1**: 9–19.
- [3] MacMorris-Adix M. Leishmaniasis: a review of disease and debate over the origin and dispersal of causative parasite *Leishmania*. *Macalester Reviews in Biogeography* 2008; **1**: 1–15.
- [4] Freitas-Junior LH, Chatelain E, Kim HA, Siqueira-Neto JL. Visceral leishmaniasis treatment: what do we have, what do we need and how to deliver it? *Int J Parasitol Drugs Drug Resist* 2012; **2**: 11–19.
- [5] Balasegaram M, Ritmeijer K, Lima MA, Burza S, Ortiz Genovese G, Milani B, et al. Liposomal amphotericin B as treatment for human leishmaniasis. *Expert Opin Emerg Drugs* 2012; **17**(4): 493–510.
- [6] Sundar S, Chatterjee M. Visceral leishmaniasis—current therapeutic modalities. *Indian J Med Res* 2006; **123**: 345–352.
- [7] Kim YW. Antimicrobial-induced electrolyte and acid-base disturbances. *Electrolyte Blood Pressure* 2007; **5**: 111–115.
- [8] Li XX, Zhou XN. Co-infection of tuberculosis and parasitic diseases in humans: a systematic review. *Parasit Vectors* 2013; **6**: 79.
- [9] Kehinde AO, Baba A, Bakare RA, Ige OM, Gbadeyanka CF, Adebisi OE. Pulmonary tuberculosis among healthcare workers at two designated DOTS centres in urban city of Ibadan, Nigeria. *Indian J Med Res* 2011; **133**(6): 613–617.
- [10] PubMed Health. Pulmonary tuberculosis. USA: PubMed Health; 2012. [Online] Available from: <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001141>. [Accessed on 26th September, 2013]