Co-Infection with *M. tuberculosis* and *M. leprae*-Case Report and Systematic Review

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**Summary**

The relationship between *M. tuberculosis* and *M. leprae* remains enigmatic with evidence to support relative protection to predisposition cited in the literature. With the near eradication of *M. leprae*, recognition of new cases may be delayed with poor outcomes. We describe a case of drug-resistant extra-pulmonary tuberculosis co-infection with tuberculosis leprosy. We also discuss the findings of our comprehensive literature review on clinical features, treatment and outcomes of dual infections. We hope that this manuscript serves as a timely reminder and ready reckoner of findings of this rare situation.

**Abstract**

**Background:** Co-infection with *Mycobacterium tuberculosis* and *M. leprae* is infrequent and conflicting views on their interaction exist.

**Methods:** We describe an immunocompetent male with simultaneously diagnosed primary multi-drug resistant extra-pulmonary tuberculosis and borderline lepromatous leprosy; we also review all cases of dual infection reported in English literature.

**Results:** Our search yielded 156 cases of dual infections. Most dual infections were reported in middle-aged males. The sentinel infection was leprosy in 90.4%. Most affected patients had lepromatous leprosy (52.5%) but tuberculosis occurred throughout the disease spectrum of leprosy. The time to development of the second infection varied from 1 month-25 years (median 1.5 years). Tuberculosis was reported to occur in 2.5-13.5% of cases in six series of patients with lepromatous leprosy. Most patients were diagnosed by sputum smears and radiography. Co-morbid conditions predisposed to development of tuberculosis in most patients. The most common pre-disposing factor was malnutrition (92.5%). Dual infections were associated with high mortality (37.2%) and morbidity (5.3%).

**Conclusions:** Dual mycobacterial infections occur despite partial cross-immunity between both species. Directly observed treatment for tuberculosis with intensive medical monitoring is required to prevent poor outcomes during management of these complex patients.

**Keywords:** Mycobacterium tuberculosis; Mycobacterium leprae; Leprosy; Tuberculosis; Drug-resistant extra-pulmonary tuberculosis

**Case Report**

A 55-year-old male farmer presented with swelling and purulent discharge from his right foot for six months. There was no history of fever, cough, and foot trauma or weight loss. He denied any smoking, alcohol and substance abuse. He had received several courses of oral antibiotics with no reduction in the ulcer or discharge. He denied any contact with patients having tuberculosis or leprosy. General physical examination showed a firm 6 x 5 centimeters nodular swelling on the dorsum of the right foot, with discharging sinuses. Two punched out ulcers, about 3 x 3 centimeters, with clean base and pale granulation tissue were seen. The discharge was about 5-10 mL/ day, mucopurulent and without any granules. Multiple hypopigmented anesthetic macules over the trunk and limbs along with ichthyosis and scaling were also noticed. No deformity or digit resorption was observed. Neurological examination revealed thickened ulnar and peroneal nerves with loss of touch, vibration and joint position till ankle. Respiratory examination was normal. Investigations showed normal hemoglobin (12.3 g/dL) and peripheral smear. Renal function tests, serum electrolytes and liver function tests were normal. Chest radiograph was normal and radiographs of the right foot did not show any evidence of osteomyelitis. Fasting serum glucose was 130 mg/dL and HbA1c was 6.5%. Human Immunodeficiency virus ELISA was non-reactive and Mantoux test was negative (four millimeters, 1 TU at 48 hours). Pus from the right foot ulcer was sterile by aerobic bacterial cultures. Stains for nocardia and actinomyces were negative. Zehl-Neelson’s staining showed acid-fast bacilli. Biopsy form edge of ulcer showed granulomatous inflammation with necrosis; multiple langhans giant cells, histiocytes and lymphocytes were present. BACTEC culture showed *M. tuberculosis* and he was initiated on isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1250 mg and ethambutol 1 gm/day. Biopsy from the hypo-anaesthetic patches showed features of tuberculosis leprosy; six site slit smears were negative. He was also initiated on regimen for multi-bacillary leprosy with dapson 100 mg/day and clofazamine 50 mg/day and monthly clofazamine 300 mg. Metformin 1 gram/day

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**Received May 25, 2012; Accepted June 14, 2012; Published June 16, 2012**

**Citation:** Rajagopala S, Devraj U, D’Souza G, V Aithal V (2012) Co-Infection with *M. tuberculosis* and *M. leprae*-Case Report and Systematic Review. J Mycobac Dis 2:118. doi:10.4172/2161-1068.1000118

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| Reference          | Year | Number (if series) | Age/sex | First infection | Time between two infections | Leprosy spectrum (Jopling) | Clinical presentation of tuberculosis | Mode of diagnosis of tuberculosis | Aggravating co-morbidity | Clinical features at diagnosis | Outcome |
|--------------------|------|--------------------|---------|----------------|----------------------------|----------------------------|-------------------------------------|-----------------------------------|----------------------------------|---------------------------------|----------|
| Gajwani et al      | 1968 | 3                  | 60/M    | Tuberculosis    | 6 months; diagnosed simultane-ously | BT                         | Pulmonary tuberculosis (SP)       | Sputum smear                       | Malnutrition                     | Fever, cough, hemoptysis         | NA       |
|                    |      |                    | 30/M    | Leprosy         | 2 years; diagnosed simultaneously | TT                         | Pulmonary tuberculosis (SP)       | Sputum smear                       |                                  | Fever, cough                   | NA       |
|                    |      |                    | 60/M    | Tuberculosis    | 2 years; diagnosed simultaneously | BT                         | Pulmonary tuberculosis (SP)       | Sputum smear                       |                                  | Cough, expectoration             | NA       |
| Gupta et al        | 1971 | 2                  | 50/M    | Leprosy         | 1 year; diagnosed simultaneously | TT                         | Pulmonary tuberculosis (SP)       | Sputum smear/ culture              | Diabetes, CAD                    | Asymptomatic Leprosy reaction, better | NA       |
|                    |      |                    | 25/F    | Leprosy         | 6 months; diagnosed simultaneously |                             |                                      |                                  | Euthyroid nodular goitre           | Fever, cough, expectoration      | Better   |
| Agnihoti et al     | 1973 | 3                  | 65/M    | Tuberculosis    | 1 year; diagnosed simultaneously | TT                         | Pulmonary tuberculosis (SP)-relapse | Sputum smear                       | Malnutrition                     | Fever, emaciation                | Better   |
|                    |      |                    | 18/M    | Tuberculosis    | 4 year; relapse simultaneously diagnosed | TT                         | Pulmonary tuberculosis (SP)       | Sputum smear                       | None                             | Cough, expectoration, hemoptysis | NA       |
|                    |      |                    | 30/F    | Leprosy         | 1 month | TT                        |                             |                                      | None                             | Cough                           | NA       |
| Bhargava et al     | 1976 | 4                  | 39/M    | Leprosy         | 3 years | LL                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Fever, cough                    | NA       |
|                    |      |                    | 50/M    | Leprosy         | 1 year | LL                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Cough, weakness                 | NA       |
|                    |      |                    | 45/M    | Leprosy         | 4 years | LL                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | Cough, expectoration              | NA       |
|                    |      |                    | 35/M    | Leprosy         | 15 years | LL                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Cough, expectoration             | NA       |
| Premnath et al     | 1976 | 40 (in 2 years)    | Median 27; range 21-64 years | Leprosy | 1-25 years; individual data NA | LL (72.5%); BL (27.5%) | Pulmonary tuberculosis (SP) | Sputum smear | Malnutrition | Cough, expectoration (87.5%), fever (57.5%), and weight loss (35%) | Died (30%), LAMA (20%), Improved (50%) |
| Ganapathi et al    | 1976 | 1                  | 30/M    | Leprosy         | NA      | LL                        | Cutaneous (lupus vulgaris)       | Histopathology                     | None                             | NA                               | NA       |
| Vachharajani et al | 1977 | 4                  | 50/M    | Tuberculosis    | 4 months | TT                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Hypopigmented anesthetic patches | Better   |
|                    |      |                    | 26/M    | Tuberculosis    | 4 months | TT                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Single hypopigmented anesthetic patch | Better   |
|                    |      |                    | 30/M    | Tuberculosis    | 2 months | LL                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Macular rash                    | Better   |
|                    |      |                    | 29/M    | Tuberculosis    | 1.5 months | TT                        | Pulmonary tuberculosis (SP)     | Sputum smear                       | None                             | Multiple patches                | Better   |
| Nigam et al        | 1979 | 20 (2.5% of 793)   | 16-58, mean 28.4; M(15); F(5) | Leprosy | 10-15 years | LL (15), BL (3), TT (2) | Pulmonary tuberculosis (SP-16, SN-4); pleural effusion (2) | Sputum smear(16); chest radiograph (4) | Malnutrition | Cough, expectoration (100%), fever (80%), weight loss (60%), hemoptysis (25%) | Died (4); LAMA (5) | Better (11) |
| Kaur et al         | 1979 | 2 out of 25 (8%)   | Age, Sex NA | Leprosy | 4.2 years | LL (2) | SP-1 Pulmonary tuberculosis; SN-1 | Sputum smear; chest radiograph | Malnutrition | Individual data | NA |
| Gatnar et al       | 1980 | 13.4% (15 of 112 active; 8 healed) | Age, Sex NA | Leprosy | NA | LL(4), BL (3), BB(1)| BT(7) | Pulmonary tuberculosis SP-6; SN-7 | Sputum smear; chest radiograph | Malnutrition | Screening | 10/15 improved; rest NA |

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was started for newly detected diabetes mellitus. He had significant reduction in the number of cutaneous patches at two months follow-up; however ulcers continued to discharge. Drug susceptibility testing of BACTEC cultures was reported as 

M. tuberculosis resistant to isoniazid and rifampicin. The patient denied any contact with patients diagnosed with multi-drug resistant tuberculosis (MDR-TB). His regimen was modified to observed levofloxacin 750 mg/day, kanamycin 750 mg/day, ethionamide 250 mg and cycloserine 250 mg thrice a day. He had resolution of discharge from these ulcers with healing at two months follow-up. Kanamycin was continued till 6 months and stopped. He resolved reduction in the number of cutaneous patches at two months follow-up. Kanamycin was continued till 6 months and stopped. He resolved

Two of the authors (R.S and U.D) independently performed a MEDLINE search using the free text terms tuberculosis and leprosy, M. tuberculosis and M. leprae in the English literature. This was further supplemented by direct search of the references and our personal databases. Both abstracts and full text articles, where available, were reviewed and only those articles which documented both infections by microbiological criteria were included for analysis. Data was extracted regarding the clinical features, first infection, time to development of second infection, leprosy spectrum of patients, mode of diagnosis, co-morbidities, site of tuberculosis and outcomes where available (Table 1).

**Results**

Our search yielded 2194 citations. These included 22 citations [1-22], including 156 cases of dual infection. Full text was available for all cases in the articles reviewed (Table 1). Dual infections have been reported from throughout the globe. The mean age was 37.8 (N=87) years (Table 2). Males accounted for 81.25% of cases ([123 (N=64)]). The first infection was leprosy in most patients (90.4%) but tuberculosis was diagnosed prior to symptoms of leprosy in 5.7% of patients [1,2,3]. In some instances, symptoms of both the mycobacterial infections occurred simultaneously:[4-8] Most affected patients

### Table 1: Summary of all reported cases of co-infection with leprosy and tuberculosis (English literature).

| Authors | Year | Total | Gender | First Infection | Second Infection | First Infection Duration | Second Infection Duration | Symptoms | Treatments |
|---------|------|-------|--------|----------------|----------------|--------------------------|--------------------------|---------|------------|
| Kumar et al | 1982 | 9 (7.7% of 117) | NA | Leprosy | NA | LL (4), BL (3) TT (2) | Pulmonary tuberculosis (SP-3, SN-6) | Sputum smear (3), chest radiograph (6) | NA | Screening | NA |
| Singh et al | 1987 | 25 (2.9% of 846) | NA | Leprosy | NA | Individual data | Pulmonary tuberculosis | Sputum, chest radiograph | NA | Screening | NA |
| Saha et al | 1989 | 18 of 133 (13.5%) | 15(M); 3(F) | 15-65 | Leprosy | NA | Pulmonary tuberculosis (SP) | Sputum, chest radiograph | Malnutrition | Screening | NA |
| Patki et al | 1990 | 1 | 35/F | Leprosy | 5 years | BL | Multicentric lupus vulgaris | Histopathology | None | Swelling | Better |
| Pinto et al | 1991 | 1 | 36/M | Simultaneous occurrence | BT | Cutaneous tuberculosis | Histopathology | Thom prick | Warty lesion | Jaundice |
| Inamadar et al | 1994 | 1 | 23/M | Simultaneous occurrence | TT | Cutaneous and pulmonary tuberculosis (SP) | Sputum smear | None | Patch, ulcer and discharge | Type 1 reaction, better |
| Arora et al | 1994 | 1 | 40/M | Simultaneous re-occurrence due to HIV | BL | Lymph nodal tuberculosis | Histopathology | HIV | Patch, sinus | Better |
| Agarwal et al | 2000 | 1 | 40/M | Simultaneous occurrence | LL | Pulmonary tuberculosis (SP) | Sputum smear/culture | CKD, transplantation, immunosuppression | Fever, cough, anesthetic patch | Reaction, resolved |
| Srilakshmi et al | 2003 | 1 | 32/M | Leprosy | 10 years | LL | Pulmonary tuberculosis (SP) | Sputum smear | Nil | Fever, cough | Dead |
| Lee et al | 2003 | 1 | 62/M | Tuberculosis | 6 months | BL | Pulmonary tuberculosis (SP) | Sputum smear/culture | Nil | Cough, expectoration | Type I reversal reaction, better |
| Agarwal et al | 2007 | 1 | 36/F | Simultaneous occurrence | BL | Pulmonary tuberculosis (SP) | Sputum smear | Rheumatoid arthritis, methotrexate, steroids, lefunomide | Fever, weight loss | ENL, better |
| Sreerama Reddy et al | 2007 | 2 | 65/M | Leprosy | 3 months | BL | Pulmonary tuberculosis (SP), pleural effusion | Sputum smear | Steroids for ulcer neuritis | Cough, expectoration, chest pain | Better |

Abbreviations: Male (M), Female (F), Sputum positive (SP), Sputum negative (SN), Not available (NA), Left against medical advice (LAMA), Erythema nodosum lepra (ENL), Tuberculosis leprosy (TT), Borderline tuberculosis leprosy (BT), Mid-borderline leprosy (BB) Borderline lepromatous leprosy (BL), Lepromatous leprosy (LL)

*The numerator is the number of cases in males and the denominator is the total number of cases reported
suffered from borderline lepromatous leprosy [9-14] (20.5%) and lepromatous leprosy [7,9,11,14-19] (52.5%), but tuberculosis occurred throughout the disease spectrum [3,5,10,20]. The time to development of the second infection varied from 1 month to 25 years (median 1.5 years). When series of lepromatous leprosy in which screening for tuberculosis was done were examined, tuberculosis has been reported to complicate leprosy in 2.5-13.5% of cases in endemic areas. [9-11,18,20,21] Most patients presented with cough, expectoration, weight loss and fever. The site of tuberculosis was reported as lung (96.7%); cutaneous [4,5,12,16] and lymph nodal tuberculosis [6] have also been reported in association with leprosy. Most patients were diagnosed by sputum smears and radiography. Co-morbid conditions predisposed to development of tuberculosis in most patients (67.9%). Malnutrition was the most common pre-disposing factor (85.8%) in the development of tuberculosis [18]; human immunodeficiency virus infection [6], diabetes mellitus type 2 [22], systemic steroid use [14] and immunosuppressive therapies [8] and chronic kidney disease [7] have also been implicated. Dual infections were associated with high mortality [9,10,19] (37.2%). Leprosy reversal reactions [22], both type 1 [5,7,13] and type 2 [8], and jaundice [4] also complicated 4.25% of treatments for dual infections.

**Discussion**

The exact nature of the interaction between leprosy and tubercul-

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**Table 2:** Summary of findings of co-infection with leprosy and tuberculosis (English literature).

| Parameter                        | Value                                    |
|----------------------------------|------------------------------------------|
| Total number of cases            | N=156                                    |
| Age (Mean)                       | 37.8 (N=87)                              |
| Sex (M:F)                        | 12:3 (N=64)                              |
| First infection                  | Tuberculosis 5.7% (9/156)                |
|                                 | Leprosy 90.4% (141/156)                 |
|                                 | Simultaneous diagnosis 3.9% (6/156)      |
| Time from first infection diagnosis to the second | Median 1.5 years (range 1 month-25 years) |
| Leprosy spectrum (Data available N=122/156) | TT 10.6% (13/122)                        |
|                                 | BT 15.6% (19/122)                       |
|                                 | BB 0.8% (1/122)                         |
|                                 | BL 20.5% (25/122)                       |
|                                 | LL 52.5% (64/122)                       |
| Clinical presentation of tuberculosis | Pulmonary tuberculosis 96.7% (151/156) |
|                                 | Extra-pulmonary tuberculosis 2.6% (4/156) |
|                                 | Both 0.8% (1/122)                       |
|                                 | Cutaneous tuberculosis 2.6% (4/156)      |
|                                 | Lymph-nodal tuberculosis 0.6% (1/156)    |
| Co-morbidity                     | 67.9% (N=106/156)                       |
|                                 | Malnutrition 85.8 % (91/106)            |
|                                 | HIV 0.9% (1/106)                        |
|                                 | Steroid treatment/ Immunosuppression 3.6% (4/106) |
|                                 | Chronic kidney disease 0.9% (1/106)     |
|                                 | Diabetes 0.9% (1/106)                   |
|                                 | Goiter 0.9% (1/106)                     |
| Outcome                          | Died 37.2% (35/94)                      |
|                                 | Better 72.8% (59/94)                    |
|                                 | Reactions 4.2% (4/94)                   |
|                                 | Jaundice 1.1% (1/94)                    |

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