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Case Report Open Access

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

Srinivas Rajagopala[1]*, Uma Devaraj[2], George D'Souza[3] and Vijay V Aithal[4]

[1]*Division of Chest diseases, Department of Medicine, St John's Medical College Hospital, India*
[2]*Division of Chest diseases, Department of Medicine, St John's Medical College Hospital, India*
[3]*Division of Chest diseases, Department of Medicine, St John's Medical College Hospital, India*
[4]*Department of Dermatology, St John's Medical College Hospital, India*

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 tuberculoid 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 icythosis 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. Zeihl-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 tuberculoid leprosy; six site slit smears were negative. He was also initiated on regimen for multi-bacillary leprosy with dapsone 100 mg/day and clofazamine 50 mg/day and monthly clofazamine 300 mg. Metformin 1 gram/day

***Corresponding author:** Srinivas Rajagopala, Assistant Professor, Division of Chest diseases, Department of Medicine, St John's Medical College Hospital, Sarjapur Road, Bangalore, India-560034, Tel: +91 80 22065353; Fax: +91 80 25501144; E-mail: visitsrinivasan@gmail.com

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Reference	Year	Number (if series)	Age/ sex	First infection	Time between the two infections	Leprosy spectrum Jopling)	Clinical presentation of tuberculosis	Mode of diagnosis of tuberculosis	Aggravating co-morbidity	Clinical features at diagnosis	Out come
Gajwani et al	1968	3	60/M	Tuberculosis	6 months; diagnosed simultaneously	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	Lepra reaction, better
			25/F	Leprosy	6 months; diagnosed simultaneously				Euthyroid nodular goitre	Fever, Cough, expectoration	Better
Agnihotri 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			None	Cough, expectoration, hemoptysis	
			30/F	Leprosy	1 month	TT			None	Cough	
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	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 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	NA
Gatner 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-8; SN-7	Sputum smear; chest radiograph	Malnutrition	Screening	10/15 improved; rest NA

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 NA	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	LL	Pulmonary tuberculosis (SP)	Sputum, chest radiograph	Malnutrition	Screening	NA
Patki et al	1990	1	35/F	Leprosy	5 years	BL	Multicentric lupus vugaris	Histopathology	None	Swelling	Better
Pinto et al	1991	1	36/M	Simultaneous occurrence		BT	Cutaneous tuberculosis	Histopathology	Thorn 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 leflunomide	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 ulnar neuritis	Cough, expectoration, chest pain	Better
					2 years	LL	Pulmonary tuberculosis (SP)		Prednisolone, thalidomide	Fever, cough	

Abbreviations: Male (M), Female (F), Sputum positive (SP), Sputum negative (SN), Not available (NA), Left against medical advice (LAMA), Erythema nodosum leprae (ENL), Tuberculoid leprosy (TT), Borderline tuberculoid 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

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

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 completed one year of dual treatment and multi-bacillary leprosy treatment was stopped with no recurrences. MDR-TB regimen was stopped at 22 months. He remains asymptomatic four months after completion of this regimen.

Patients and Methods

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 [(12:3 (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

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)

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

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 tuberculosis has been debated for over a century. They share common antigens as evidenced by conversion of lepromin intradermal tests after the administration of Bacille-Calmette-Guerin (BCG) and the partial protection offered by BCG against leprosy [23]. Though an increased frequency of pulmonary tuberculosis in patients with lepromatous leprosy may occur as a result of malnutrition, tuberculosis occurs across the spectrum of leprosy [20]. An inherent impaired immunity against both mycobacterial organisms has been postulated as the etiology for dual infection; however, it appears that the anergy in leprosy is pathogen-specific [24]. Some investigators have speculated that leprosy and tuberculosis are antagonistic diseases on the basis of immunologic, clinical, and epidemiologic data [25]. Low rates of leprosy have been observed in areas which have high rates of tuberculosis despite large scale migration of patients with leprosy into them. The historical high rates of tuberculosis have also been postulated as one reason for the decline of leprosy in Europe. Recent analysis of bone material from human remains at sites in Israel, Egypt and Europe showed DNA traces of both *M. tuberculosis* and *M. leprae* infection in 42% of the samples. Since tuberculosis is a more aggressive illness than leprosy, the authors suggest that patients with tuberculosis and leprosy were more likely to have died faster, reducing the reservoir for *M. leprae* [26]. The relationship between the two mycobacterial diseases continues to be enigmatic despite decades of research.

Our review shows that while co-infection is not uncommon in high endemic areas, it has been reported from throughout the globe. Though pulmonary tuberculosis has been reported in the vast majority, extra-pulmonary tuberculosis is also described (3.2%) The association of tuberculoid leprosy and tuberculosis (26.2%) and simultaneous occurrence of dual mycobacterial infections suggests a mycobacterial genera-specific anergy as a predisposing factor. Dual infections are associated with high mortality (37.2%) and major morbidity (5.5%). Management of these patients requires inter-disciplinary management and social support.

In conclusion, dual mycobacterial infections occur despite partial cross-immunity between both species. Recognition of tuberculosis is important to prevent emergence of rifampicin-resistant tuberculosis during treatment of leprosy. Directly observed treatment for tuberculosis with intensive medical monitoring is required to prevent poor outcomes during management.

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