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ORIGINAL ARTICLE

Drug resistance in intestinal tuberculosis: A reason to worry?

Ajinkya Sonambekar,* Devendra Desai,* Philip Abraham,* Vatsal Mehta,* Hrishikesh Samant,† Anand Joshi,* Tarun Gupta* and Camilla Rodrigues‡

Division of *Gastroenterology, ‡Microbiology, P D Hinduja Hospital and Medical Research Centre, Mumbai, India and †Division of Hepatology, LSU Health Sciences Center, Shreveport, Louisiana, USA

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Correspondence
Dr Devendra Desai, Division of Gastroenterology, P D Hinduja Hospital and Medical Research Centre, Veer Savarkar Marg, Mahim, Mumbai 400016, India. Email: devendracdesai@gmail.com

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Abstract

Background and Aim: Emergence of drug resistance in intestinal tuberculosis (ITB) makes the treatment of this condition challenging. While there is growing evidence of multiple and extensive drug resistance in pulmonary and glandular tuberculosis (TB), literature regarding susceptibility and resistance patterns in ITB is scarce. The aim of the current paper was to study the prevalence of drug resistance in patients with ITB.

Methods: Among patients presenting to a tertiary care hospital in Mumbai between 2008 and 2016, records of all patients with ITB, whose mucosal biopsy (obtained at ileocolonoscopy) tissue culture was positive for *Mycobacterium tuberculosis* and in whom drug sensitivity testing was performed, were retrospectively analyzed. Sensitivity and resistance to single or multiple anti-TB drugs were noted.

Results: A total of 43 patients were included, of whom 10 (23.2%) patients were diagnosed to have resistance to at least one first-line anti-TB drug. Resistance to isoniazid was the most common (nine patients), followed by rifampicin (six), pyrazinamide (five), streptomycin and ethionamide (four each), ethambutol, moxifloxacin and ofloxacin (three each), and *p*-amino salicylic acid (one). Six patients (13.9%) had multidrug-resistant TB and needed second-line anti-TB therapy as per drug sensitivity pattern. There was no patient with extensive drug-resistant TB.

Conclusion: Twenty-three percent of our patients with ITB tested for drug resistance had drug resistance, 13.9% being multidrug resistant and needing second-line anti-TB therapy.

Introduction

Drug resistance is well known in pulmonary and glandular tuberculosis (TB).[1] However, resistance in intestinal TB (ITB) is believed to be uncommon.[2–4] Apart from treatment difficulties, drug resistance presents a unique challenge in ITB. In endemic areas for TB, where the prevalence of Crohn's disease is also on the rise,[5,6] when the differentiation between Crohn's disease and ITB is not clear, empirical first-line anti-tubercular therapy (ATT) is often administered. If treatment failure/recurrence occurs, differentiating drug-resistant ITB from Crohn's disease becomes difficult.

Culture of acid-fast bacilli (AFB) is the gold standard for a positive diagnosis of ITB.[7–9] However, a positive yield of *Mycobacterium tuberculosis* (MTB) complex is obtained in only 25–50% of cases on culture of intestinal biopsy tissue,[4,7–9] making it difficult to test for drug resistance.

There is paucity of literature on drug resistance in ITB.[8,9] We update our experience on drug resistance patterns in the MTB isolates obtained from intestinal biopsies in 43 patients.

Methods

We retrospectively analyzed the data of patients with culture-positive ITB seen in the Gastroenterology Division of our tertiary care private sector hospital between 2008 and 2016. Some of these data have been reported earlier, as part of a report on abdominal TB.[4] Our hospital laboratory is certified by the College of American Pathologists and the National Accreditation Board for Testing and Calibration of Laboratories; it is also accredited by the Central TB Division, Government of India as an Intermediate Referral Lab for TB culture and drug sensitivity testing.

Patients in whom antibiogram was not available were excluded from the analysis. Demographic features, clinical presentation, investigations, and treatment offered were noted. The Institutional Ethics Committee approved the analysis and, as it was a retrospective analysis of data, granted waiver of consent.

A diagnosis of drug-resistant ITB was made when MTB complex grown on culture of intestinal biopsy sample (obtained at ileocolonoscopy) showed resistance to any of the first-line or second-line anti-TB drugs. Multidrug-resistant TB (MDR TB)

was defined as resistance to at least rifampicin and isoniazid. Extensive drug resistance was defined as resistance to isoniazid and rifampicin, plus any fluoroquinolone, and at least one of the three injectable second-line drugs (i.e. amikacin, kanamycin, or capreomycin).

Microbiology. A Mycobacterial Growth Indicator Tubes (MGIT) system (BACTEC MGIT 960 TB; Becton Dickinson Biosciences, Sparks, MD, USA) was used for mycobacterial culture. In this automated system, processed specimens were inoculated into MGIT that contain 7 mL of modified Middlebrook as liquid culture media, a growth supplement, and antimicrobial substance. Tubes were incubated at 37°C for 6 weeks in automated MGIT instruments. At the bottom of the tube, there is a fluorescent compound embedded in silicone; this compound is sensitive to dissolved oxygen in broth. As the actively growing bacteria consume the dissolved oxygen, the fluorescence is unmasked and can be observed in the tube under long-wave ultraviolet light. MTP64 antigen is used for confirmation of the MTB complex in the tubes.

Drug susceptibility testing was carried out on the MTB growth in 1:10 dilutions with positive and negative controls. The tested drugs and their critical concentrations (in μg/mL) were as follows: streptomycin 1.0, isoniazid 0.1, rifampicin 1.0, ethambutol 5.0, pyrazinamide 100, kanamycin 2.5, ethionamide 5, *p*-amino salicylic acid 4, ofloxacin 2, moxifloxacin 0.5 and 2.0 (higher dose), amikacin 1, clofazimine 0.5, capreomycin 2.5, and linezolid 1.0.

Statistical analysis. Descriptive analysis was performed for demographic characteristics; results are presented as mean (SD) and percentage for continuous variables, and number and percentage for categorical variables.

Results

A total of 43 patients (mean age: 37 [SD: 30] years; 27 female [52%]) were detected with culture-positive ITB during the study period.

Drug sensitivity and resistance pattern. Samples of 33 patients (76.7%) were susceptible to all drugs; 10 (23.2%) showed resistance to at least one first-line anti-TB drug, isoniazid being most common (9 patients), followed by rifampicin (6), pyrazinamide (5), streptomycin and ethionamide (4 each), ethambutol, moxifloxacin and ofloxacin (3 each), and *p*-amino salicylic acid (1). Four patients (9.3%) showed resistance to a single drug, three of them to isoniazid and one to pyrazinamide. The other six (13.9%) were MDR. Resistance to each drug is mentioned in Table 1.

Table 1 Anti-TB drug resistance in patients with intestinal TB

Drug	Number of resistant patients[†]
Isoniazid	9
Rifampicin	6
Pyrazinamide	5
Ethambutol	3
Streptomycin	4
Moxifloxacin	3
Ethionamide	4
p-Amino salicylic acid	1
Ofloxacin	3

[†]Not mutually exclusive.
TB, tuberculosis.

Table 2 Drug resistance pattern in individual patients

Sr. no.	Resistance	Treatment received
1	INH, RMP, SM, moxifloxacin, ofloxacin	Second-line ATT
2	INH	First-line ATT
3	INH, RMP, ETM, ethionamide	Second-line ATT
4	INH, RMP, PZA, ETM, SM, moxifloxacin, ofloxacin, ethionamide	Second-line ATT
5	INH	First-line ATT
6	INH	First-line ATT
7	INH, RMP, PZA, ethionamide	Second-line ATT
8	INH, RMP, PZA, ETM, SM, moxifloxacin, ofloxacin, ethionamide, PAS	Second-line ATT
9	INH, RMP, PZA, SM	Second-line ATT
10	PZA	First-line ATT

ATT, anti-tubercular therapy; ETM, ethambutol; INH, isoniazid; PAS, *p*-amino salicylic acid; PZA, pyrazinamide; RMP, rifampicin; SM, streptomycin.

Among the second-line drugs, ethionamide and fluoroquinolone resistance was common (Table 2). These patients received second-line anti-TB therapy depending on the pattern of drug sensitivity.

No resistance was observed to amikacin, kanamycin, linezolid, clofazimine, and capreomycin. There was no patient with extensive drug-resistant TB.

Discussion

Drug resistance in pulmonary TB is known. In a high-burden country like India, 10–15% of patients are reported to be isoniazid resistant, while 2–3% are MDR.[10] Single-drug resistance of 27% and multidrug resistance of 19% have been reported for extra-pulmonary (glandular and pleural) TB.[11] Data on presence of resistance and its pattern in ITB are sparse.

Ye *et al.*[9] from Korea identified resistance to at least one anti-TB drug in 13 (17.6%) patients, and MDR TB was diagnosed in 2 (2.7%) of the 74 patients in whom drug susceptibility testing was performed. We had earlier reported[8] single-drug resistance and multidrug resistance in three (25%) patients each in ITB. The higher rates were probably due to the smaller number of patients in that analysis or due to true resistance pattern in that population sample. Our current data are comparable to those reported by Ye *et al.*,[9] but show higher percentage of MDR cases (Table 3). These rates are lower than that reported by Dusthackeer *et al.*[11] in pulmonary (single-drug resistance in 23.8% and MDR in 21%) and extra-pulmonary (27.5% and 19%, respectively) TB.

Table 3 Reported anti-TB drug resistance rates in intestinal TB

	Samant *et al.*[8]	Ye *et al.*[9]	Current study
Sample size	12	74	43
Pan susceptible	6 (50%)	59 (79.7%)	33 (76.7%)
Single-drug resistance	3 (25%)	13 (17.6%)	4 (9.3%)
Multidrug resistance	3 (25%)	2 (2.7%)	6 (13.9%)

TB, tuberculosis.

Our report adds to the sparse data on resistance pattern in ITB. We limited our analysis to cases of ITB, a condition that closely mimics Crohn's disease. This is however a single-center study and in a predominantly urban population. Higher anti-TB drug resistance rates in pulmonary TB have been reported from urban than from rural populations. Almeida *et al.*[1] reported 51% resistance rate in pulmonary TB in Mumbai as compared with 2% in a rural center. They hypothesized that the difference was due to less access to multiple drugs, and less likelihood of transmission of drug-resistant strains in rural areas with low population densities.

Studies from more centers, urban and rural, are needed to obtain a more comprehensive estimate of the prevalence of drug resistance in ITB. It is clear though that testing for drug sensitivity in patients with ITB will become increasingly imperative.

In conclusion, drug resistance in ITB is a cause for concern; 4 of 45 (9.3%) patients had single-drug resistance and 6 of 45 (13.9%) had multidrug resistance. Drug sensitivity should be tested in all culture-positive cases.

References

1 Almeida D, Rodrigues C, Udwadia ZF *et al*. Incidence of multidrug-resistant tuberculosis in urban and rural India and implications for prevention. *Clin. Infect. Dis.* 2003; **36**: 152–4.
2 Pai CG, Khandige GK. Is Crohn's disease rare in India? *Indian J. Gastroenterol.* 2000; **19**: 17–20.
3 Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India: is it related to improved sanitation? *Indian J. Gastroenterol.* 2005; **24**: 23–4.
4 Leung VK, Law ST, Lam CW *et al*. Intestinal tuberculosis in a regional hospital in Hong Kong: a 10-year experience. *Hong Kong Med. J.* 2006; **12**: 264–71.
5 Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J. Gastroenterol.* 2008; **14**: 741–6.
6 Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am. J. Gastroenterol.* 2009; **104**: 1003–12.
7 Tandon HD, Prakash A. Pathology of intestinal tuberculosis and its distinction from Crohn's disease. *Gut*. 1972; **13**: 260–9.
8 Samant H, Desai D, Abraham P, George S. Acid-fast bacilli culture positivity and drug resistance in abdominal tuberculosis in Mumbai, India. *Indian J. Gastroenterol.* 2014; **33**: 414–9.
9 Ye BD, Yang S-K, Kim D *et al*. Diagnostic sensitivity of culture and drug resistance patterns in Korean patients with intestinal tuberculosis. *Int. J. Tuberc. Lung Dis.* 2012; **16**: 799–804.
10 Ramachandran R, Nalini S, Chandrasekar V *et al*. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int. J. Tuberc. Lung Dis.* 2009; **13**: 1154–60.
11 Dusthackeer A, Sekar G, Chidambaram S, Kumar V, Mehta P, Swaminathan S. Drug resistance among extrapulmonary TB patients: six years experience from a supranational reference laboratory. *Indian J. Med. Res.* 2015; **142**: 568–74.