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Multi drug resistant female genital tuberculosis: A preliminary report

J.B. Sharma[a,*], Alka Kriplani[a], Eshani Sharma[a], Sangeeta Sharma[b], Sona Dharmendra[a], Sunesh Kumar[a], P. Vanamail[c], S.K. Sharma[d]

[a] Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi 110029, India
[b] Department of Pediatrics, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India
[c] Department of Biostatistics and Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India
[d] Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Objective: Evaluation of 6 patients presenting with tubo-ovarian mass or infertility with multi drug resistant (MDR) female genital tuberculosis (FGTB).
Study design: It was an observational study in a tertiary referral centre, India on subjects with MDR FGTB on clinical examination and investigations. All patients were given category IV drugs using kanamycin (intramuscular), levofloxacin, pyrazinamide, cycloserine, ethionamide and ethambutol (or para aminosalicylic acid [PAS] for ethambutol resistant cases) for 6 months intensive phase followed by oral levofloxacin, cycloserine, ethionamide and ethambutol (or PAS for ethambutol resistant cases) for 18 months continuation phase.
Patients were evaluated for primary end points (complete cure, partial response, no response, treatment completed) and secondary end points (recurrence rate, pregnancy rate) during treatment.
Results: There were 2 (33.3%) primary MDR FGTB patients and 4 (66.6%) secondary MDR FGTB (three pulmonary MDR and one MDR lymphadenitis) patients. Mean age was 23.6 years. Presenting features were menstrual dysfunction in all patients (100%) especially oligomenorrhea in 4 (66.6%) patients, weight loss in all the patients (100%), cough with expectoration in three patients (50%), tubo-ovarian masses in five (83.3%) patients. Endometrial biopsy showed positive culture for AFB with rifampicin and isoniazid (INH) resistance in both primary MDR FGTB patients and in two secondary MDR FGTB patients who were sexually active. In secondary MDR FGTB, three pulmonary MDR patients had positive sputum AFB culture, while the patient with MDR lymphadenitis had lymph node aspirate for AFB culture positive with all showing resistance to rifampicin and isonioazid.
Gene Xpert on endometrial biopsy or sputum was positive in 5 (83.3%) patients. Three (50%) patients (one primary and two secondary) have completed therapy while other 3 (50%) are in continuation phase. All patients are asymptomatic with one having 12 weeks ongoing successful pregnancy.
Conclusion: MDR FGTB should be thought of in women of FGTB with tubo- ovarian masses who are not responding to first line drugs. Gene Xpert can be used in early diagnosis of MDR FGTB.

Introduction

According to Global TB Report 2016, there were an estimated 10.4 million new TB cases worldwide, of which 3.5 million (34%) occurred in women [1]. India has one of the highest incidence of tuberculosis in the world [2]. Emergence of multi drug resistant TB (MDR TB) and extensively drug resistant TB (XDR TB) is a serious cause of concern [3,4,5]. Multidrug resistant TB is defined as Mycobacterium tuberculosis strain resistant to the main primary drugs rifampicin and isoniazid. MDR TB occurs either due to poorly developed regimen, use of substandard drugs, inadequate dose and poor compliance [5–8]. A person can also acquire MDR TB due to transmission of drug resistant TB from one person to another which means acquisition of MDR TB in the first place [1,3]. Usually MDR genital TB is a part of disseminated MDR TB in lungs, lymph nodes, skeletal system or gastrointestinal tract. However, sometimes it can be primary MDR FGTB with no evidence of disease elsewhere in the body [9].

Female genital tuberculosis is usually secondary to tuberculosis elsewhere in the body [6]. It can rarely be transmitted from infected semen of the male partner from TB of epididymis [10].

* Corresponding author at: Department of Obstetrics and Gynecology All India Institute of Medical Sciences Ansari Nagar, New Delhi 110029, India.
E-mail address: jbsharma2000@gmail.com (J.B. Sharma).

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Diagnosis of FGTB is by endometrial biopsy for acid fast bacilli (AFB), polymerase chain reaction (PCR), microscopy and culture and histopathology [9,11].

Radiological methods like magnetic resonance imaging (MRI) and positron emission tomography (PET) have role in tubercular tubo-ovarian masses [12,13]. Laparoscopy can directly visualize TB lesions like tubercles, caseous nodules, shaggy areas, adhesions, beading of tubes etc, and a directed biopsy can be taken [14]. Hysteroscopy can also be useful showing tubercles, pale endometrium and adhesions [15]. Combination of tests is often used to make diagnosis [16,17].

Diagnosis of pulmonary MDR, is by positive sputum culture while for extra pulmonary tuberculosis (EPTB) MDR it's by culture positivity on biopsy from the specimen from extra-pulmonary site [5,8,9]. Conventional drug susceptibility testing (DST) is the gold standard to diagnose MDR but takes 70 days [8]. Line probe assay (LPA), liquid culture (Mycobacterial Growth Indicator Tube [MGIT]) have also been used. Recently, gene Xpert and genotype MTB DR plus assays have been used as adjuvants in early diagnosis of EPTB MDR [18–23]. Drug sensitivity FGTB is generally treated by 6 months course of anti-tubercular drugs [24].

However, treatment for MDR (both pulmonary and extra pulmonary) is by use of category IV regimen with 6 drugs for 6 months of intensive phase followed by 4 drugs for 18 months of continuation phase. We present our results of six patients of MDR FGTB who presented to gynecology department with either infertility or tubo-ovarian masses.

Materials and methods

It was a prospective study over 4 $^{1}/_{2}$ years between January 2012 to July 2016. The study was part of our ongoing study on female genital tuberculosis which was granted ethical approval by the institutional ethical committee. Patients gave written informed consent to participate in the study and the study was done in accordance with the Helsinki declaration.

Primary MDR FGTB was defined as patient having isolated MDR FGTB on endometrial biopsy without evidence of tuberculosis elsewhere in the body.

Secondary MDR FGTB was defined as patients with MDR FGTB on endometrial biopsy or evidence of FGTB in uterus or adnexa on ultrasound, computerized axial tomography or positive positron emission tomography (PET) along with pulmonary or extra pulmonary MDR.

Detailed history of all the patients was taken including age, socioeconomic status, complaints including menstrual history and other symptoms. Detailed physical examination, heart and chest auscultation, abdominal examination was performed in all patients. Vaginal examination was performed in sexually active patients (not done in patients who had not resumed sexual activity). Ultrasound scan was done in all patients whereas CT scan of abdomen and PET scan were done wherever possible. On PET, any area of focal increased FDG uptake in the suspicious region (like adnexa) more than FDG uptake of liver was considered abnormal and was used in this study as defined by Kumar et al [25]. Hysterosalpinography, diagnostic laparoscopy and hysteroscopy were not done routinely in MDR FGTB, but were done only in patients of infertility as routine test for tubal patency where diagnosis of FGTB was not made.

Sputum examination, endometrial biopsy (except in adolescent girls who had not resumed sexual activity) and fine needle aspiration cytology (FNAC) of lymph node were performed wherever required for acid fast bacilli (AFB) microscopy, AFB culture including drug sensitivity testing, line probe assay for smear positive samples and liquid culture [MGIT] for smear negative samples, gene Xpert (which detects rifampicin resistance) and histopathology for any epithelioid granuloma. Drug sensitivity testing (DST) was performed for first line drugs like rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin.

All patients found to have multidrug resistant TB (primary or secondary) were started category IV treatment under DOTS plus strategy of Revised National Tuberculosis Control Programme of India (RNTCP) with quality assured second line drugs given under direct observation of health care provider free of cost as shown in Appendix A.

Repeat sputum examination, endometrial biopsy and lymph node FNAC were performed at 6 months of intensive phase for any persistent disease.

Patients were followed up in TB clinic and gynae clinic every 3 months for relief of symptoms and any adverse effects of drugs. Repeat cultures were done as per WHO and RNTCP guidelines [1,2]. All of them were advised to avoid conception during antitubercular therapy with category IV drugs due to possible teratogenicity. However, they were allowed to try conception after completion of therapy. Patients were followed up further after completion of therapy for pregnancy outcome. All patients were also given pyridoxine (to prevent neuropathy). and ranitidine (to prevent gastritis and acidity) Liver function tests, kidney function tests, complete blood count, thyroid function tests, HIV testing (after informed consent) and hearing tests were performed at the start of the treatment and as and when required.

Statistical analysis

Data analyses method for small sample sizes that vary between 5 and 30 were adopted. Since there were only six study patients,

Table 1
Characteristics of patients.

S. No	Name	Age in (Years)	Sexual activity	Menstrual Symptoms	Other complaints
	Primary MDR FGTB				
1	NJ	28	Sexually active	Oligomenorrhea with irregular periods	Primary infertility, anorexia, weight loss (5 kg), mild fever
2	SK	30	Sexually active	Hypomenorrhea	Primary infertility, anorexia, weight loss (6 kg), mild fever
	Secondary MDR FGTB				
3	KD	14	Sexual activity not yet resumed	Primary amenorrhea	Anorexia, weight loss (7 kg), cough with expectoration (3 weeks), fever, abdominal pain
4	SD	26	Sexually active	Oligomenorrhea	Anorexia, weight loss (6 kg), cough with expectoration, fever(1 month), Primary infertility
5	RR	16	Sexual activity not yet resumed	Secondary amenorrhea	Anorexia, weight loss (5 kg), swelling in neck, fever(2 months)
6	PD	25	Sexually active	Oligomenorrhea with hypomenorrhea	Anorexia, weight loss (10 kg), cough with expectoration, abdominal pain, primary infertility, diarrhea, fever (one month)