Original Article

Histopathologic Analysis of Female Genital Tuberculosis with Clinical Correlation: A Fifteen Year Study in a Tertiary Hospital of India

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ABSTRACT

Background: Tuberculosis remains a global health problem and is an important cause of morbidity and mortality. Female genital tuberculosis (FGTB), though rare in western world, is relevant in developing countries like India. **Aims and Objective:** The aim of this study was to determine histologic findings of different parts of female genital tract affected by TB and to correlate it with clinical and other features. **Materials and Methods:** A total number of 110 cases of FGTB from 92 patients were included over a period of 15 years. (April, 1997 to March, 2012) The age range of the patients was 17 to 45 years with mean of 26.3 years. The diagnostic procedures used were curettage biopsy, hysterectomy, histologic examination, culture, *Mycobacterium* tuberculosis-polymerase chain reaction, laparoscopy, hysterosalpingography, and ultrasonography. Patients of FGTB presented with infertility (65-70%), pelvic/ abdominal pain (50-55%), and menstrual disturbances (20-25%). **Results:** FGTB involved vulva (2), vagina (1), cervix (5), endometrium (66), fallopian tube (24), and ovaries (12). Out of 66 endometrial TB, proliferative, secretory endometrium, and atrophic endometrium were seen in 53, 09, and 04 cases. HIV co-infection was found only in 5 cases, and acid-fast bacilli in tissue sections were detected in 7 cases. **Conclusions:** FGTB is not uncommon in developing countries and is an important cause of infertility. Though fallopian tube was the most common site in many studies, in this study, endometrium emerges as the commonest site.

KEY WORDS: Female genital tuberculosis, histopathology, HIV

INTRODUCTION

Morgagni first described genital tuberculosis in the mid eighteenth century, and tuberculous bacillus was discovered in 1882 by Koch.[1]

Tuberculosis is the second most common cause of death worldwide amongst communicable diseases. It kills nearly 2 million people each year, and developing countries are mostly affected.[2] Genital tuberculosis in females occurs secondary to primary disease in the lung, lymph nodes, urinary tract, bones, joints, and bowel. The spread is usually by hematogenous or lymphatic route. Sexual transmission of FGTB has been reported, but direct spread from other intraperitoneal foci is very rare.[2]

The exact incidence of FGTB cannot be determined with certainty as some cases are asymptomatic and are detected incidentally during investigation of infertility. In developing countries, FGTB accounts for ≥3% of patients with infertility.[1]

Access this article online	
Quick Response Code	Website: www.jbcrs.org
	DOI: 10.4103/2278-960X.104292

MATERIALS AND METHODS

A retrospective study on FGTB was done over a period of 15 years in our institute from April, 1997 to March, 2012. Detailed clinical information, radiologic and other relevant investigations were recorded from case sheets. The clinical information included age of the patients, signs and symptoms, socio-economic background, history of tuberculosis (lung/ non-genital), and HIV in the patient and family. Radiologic investigations include chest X-ray, ultrasonography (USG) of abdomen/pelvis, hysterosalpingography (HSG) and computed tomography (CT) scan. Information regarding other relevant investigations like Mantoux test/purified protein derivative (PPD) skin tests, erythrocyte sedimentation rate (ESR) etc. were also recorded.

Histologic examination of tissue biopsies was done in the pathology department, and reports were collected. Slides

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were stained by Hematoxylin and Eosin (HandE) stain and Zeihl-Neelsen (ZN) stain routinely. Periodic Acid Schiff (PAS) and other special stains like Gomori's methanamine silver stain were done whenever necessary to exclude fungal etiology. Other diagnostic procedures included in this study were microbiological culture after *Mycobacterium* tuberculosis polymerase chain reaction (MTB-PCR) for a definitive diagnosis of mycobacterium tuberculosis.

A total of 110 cases of FGTB were retrieved during this 15 years period from 92 patients. The age range of the patients was 17-45 years with a median age of 26.3 years. Most common specimens in this study were endometrial curettage and biopsy for evaluation of infertility, followed by tubo-ovarian mass and hysterectomy. In 8 cases, specimens of total hysterectomy with bilateral salpingo-ophorectomy were submitted with lesions involving multiple sites.

RESULTS

During the 15-year study period, we received 110 cases of FGTB, of which endometrium TB was 60% (66/110) cases, fallopian tube 21.8% (24/110) cases, ovarian 10.9% (12/110) cases, cervix 4.5% (5/110) cases, vulva 1.8% (2/110) cases, and vagina 0.9% (1/110) cases [Table 1]. Most of the endometrium TB cases were in proliferative phase 83.3% (53/66), followed by secretory phase 13.6% (9/66) and atrophic endometrium 6.1% (4/66). Bilateral involvement was seen in 18 out of 24 cases of fallopian tube TB and in 7 out of 12 cases of ovarian TB. HIV co-infection was seen in 5 cases, and caseous necrosis was found in 16 cases. Acid-fast bacilli (AFB) in tissue section were detected in 7 cases after special staining (ZN stain).

The main histologic finding in endometrial TB was presence of epithelioid cell granulomas in different stages. Most of these granulomas were small to medium-sized, isolated, and scattered through the functionalis layer [Figure 1]. Confluent granulomas were not detected in endometrial TB. Multinucleated giant cells of both Langhans and foreign-body type were present in some cases (11/66), and disruption of endometrial glands was seen in 3 cases. Plasma cells were found in 5 cases where secondary infection was also present. Caseous necrosis was rarely found in endometrial TB (2/66), and both of these patients were post-menopausal. AFB were also rarely detected (2/66) [Figure 2].

Fallopian tubes were involved by TB, it appeared to be enlarged and slightly edematous grossly (23/24). External surface was irregular due to adhesions (17/24). In 5 cases, the fimbria was everted with a patent orifice, imparting characteristic "tobacco pouch" appearance. On cut open, serosanguinous fluid was found in 9 cases, blood in 2 cases, caseous material in 5 cases, clear fluid /hydrosalpinx in 5 cases, and pus in 3 cases. Diffuse or focal mucosal ulceration were noted in most of the cases (21/24). Microscopically, the features were of chronic salpingitis with occasional non-caseating granulomas in early stage (7/24). Plical adhesion with follicular salpingitis was seen in the early stage [Figure 3]. In the late advanced stage (17/24), single and/or multiple confluent epithelioid granulomas were present in the lamina propri. Involvement of muscularis layer (4/24) and serosa (2/24) were seen occasionally. Caseous necrosis (9/24) and AFB in tissue sections (4/24) were found in a number of cases.

Ovarian tuberculosis presented as tubo-ovarian mass and usually a sequel of tuberculous salpingitis [Figure 4]. The granulomas were seen in cortical area in the majority of cases (3/12). Caseous necrosis was seen in 3 cases, of which 1 showed AFB in tissue sections.

Cervical TB grossly appeared as red, enlarged, ulcerated, and friable with clinical misdiagnosis of cervical cancer in 3 cases. Commonest site of involvement was mucosa of endocervical canal. As in other sites, epithelioid granulomas were present, but caseous necrosis was absent in all the 5 cases. Vulva (2 cases) and vagina (1 case) were rarely involved, and like in cervical TB, caseation and AFB were absent.

Table 1: Tuberculosis of different anatomical sites and percentage

Site	No. of cases	Percentage	HIV co–infection	Caseation present	AFB present in tissue section (ZN stain)
Vulva	2	1.81	–	–	–
Vagina	1	0.91	–	–	–
Cervix	5	4.54	–	–	–
Endometrium	66	60	3	2	2
Proliferative	53	48.18	–	–	–
Secretory	09	8.18	–	–	–
Atrophic	04	3.64	–	–	–
Fallopian tube	24	21.82	1	9	4
Bilateral	18	16.36	–	–	–
Unilateral	06	5.45	–	–	–
Ovaries	12	10.91	1	3	1
Bilateral	07	6.36	–	–	–
Unilateral	05	4.54	–	–	–
Total	110	100	5	14	7

Diagnosis of FGTB was done by microscopic examination, mycobacterical culture on Lowenstein Jensen medium/ BACTEC culture, and by MTB-PCR (positive band of 123 bp DNA fragment of IS 6110 gene of M. Tuberculosis).

DISCUSSION

Most of the cases of tuberculosis (95%) occur in developing countries.[1] However, recently the prevalence of TB in developed countries has increased due to HIV infection, immigration, and the development of drugs-resistant strains of *Mycobacterium* tuberculosis.[3,4] Patients suffering from latent TB are more prone to have active TB if co-infected with HIV (20 times more risk than HIV-negative patients.) HIV infection causes recent tuberculous infection as well.[5] In our study, 5 cases of HIV co-infection were present amongst 110 cases of FGTB (4.5%). According to current report, nearly 5.1 million people in India are HIV-positive and 60% of these patients also have tuberculosis.[6]

Patient of FGTB are usually in the reproductive age group. The most common presentation reported were infertility (44%), pelvic pain (25%), vaginal bleeding (18%), amenorrhea (5%), vaginal discharge (4%), and post-menopausal bleeding (2%).[7,8] Less common presentations are ascitis, abdominal mass, tubo-ovarian abscess, and vague abdominal distention.[8] In our study, 3 common presentations were infertility (65-70%), pelvic abdominal pain (50-55%), and menstrual disturbances (20-25%). In most of the studies, the fallopian tubes are affected in 100% cases followed by endometrium (50%), ovaries (20%), cervix (5%), and vulva and vagina (< 1%).[5,9] But in our study, endometrium was the most common site (60%) followed by fallopian tube (21.82%), ovaries (10.9%), cervix (4.54%), vulva (1.81%), and vagina (0.91%). The higher incidence of endometrial TB in our study might be explained by the fact that most of the

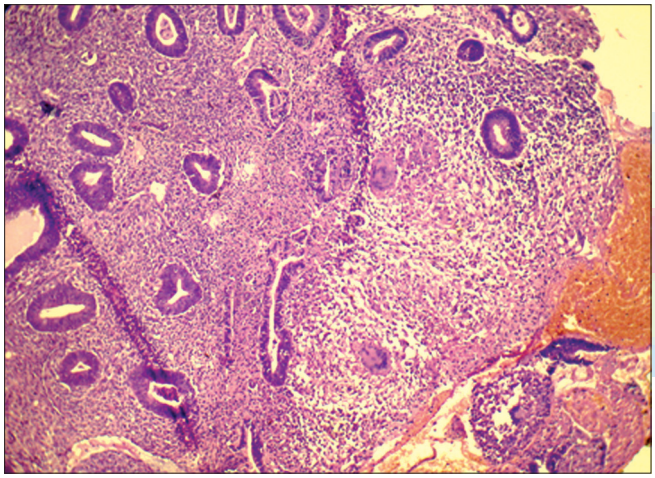

Figure 1: Photomicrograph showing epithelioid granulomas of tuberculosis in the proliferative endometrium. Both Langhans and foreign body type of giant cells are also present. (Hematoxylin and Eosin, ×100)

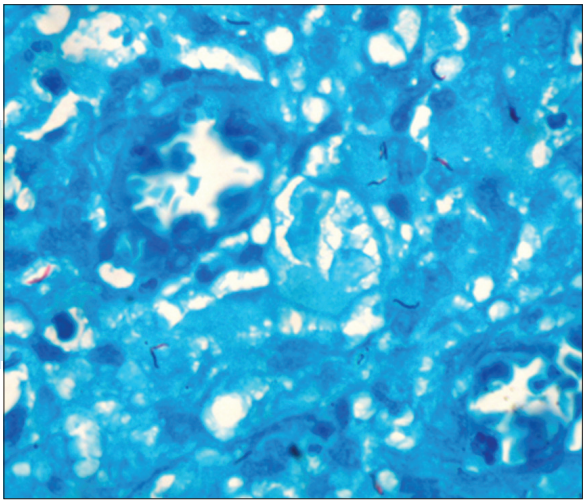

Figure 2: Zeihl-Neelsen (ZN) stain showing bacilli of *tuberculous mycobacterium* in the same endometrium. (ZN, ×1000)

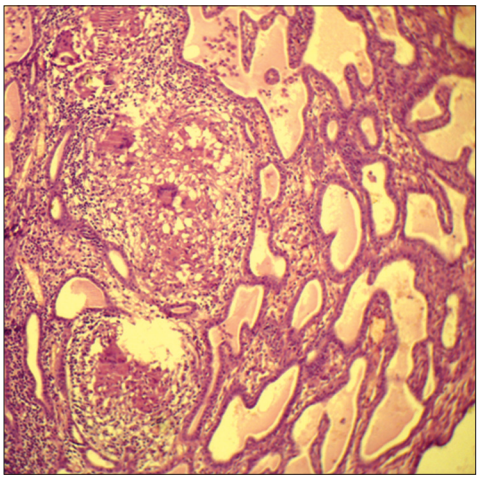

Figure 3: Photomicrograph showing tuberculous granulomas in the mucosal layer of fallopian tube and fused plica. (Hematoxylin and Eosin, ×100)

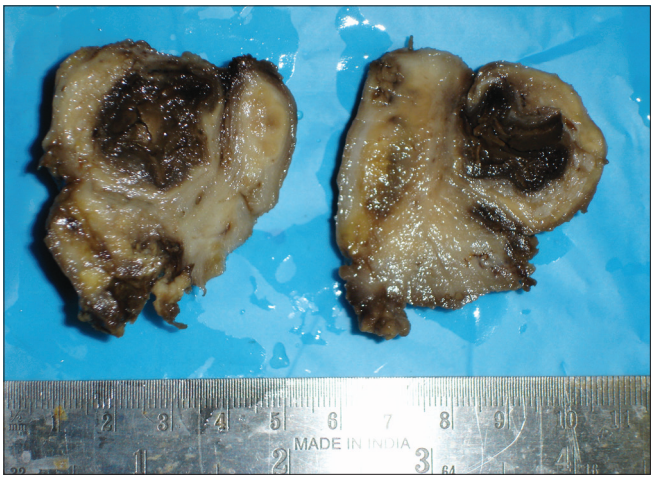

Figure 4: Gross photograph showing tubo-ovarian mass, which was the presenting feature in a case of ovarian tuberculosis

specimens we received were endometrial curettage during work-up of infertile women.

During the reproductive age group, caseous necrosis is rare in tuberculous endometritis.[10] But, in postmenopausal women, tuberculous granulomas get enough time to develop caseous necrosis as there is no periodic loss of endometrium of menstruation. In our study also, both the patient of tuberculous endometritis with caseous necrosis were postmenopausal. In the reproductive age, tuberculous granulomas have to regenerate from basal layer after menstrual shedding of functionalis layer. The granulomas become well-developed and numerous as the menstrual cycle progresses. So, biopsy is recommended just before menstruation (or late secretory phase) as the granulomas get longest possible time to develop and greater chance of providing accurate diagnosis.[9] In most of the studies, endometrial TB occurs mainly in women of reproductive age group, but Falk V *et al* found most cases in the postmenopausal group.[11] In postmenopausal women, genital TB is rare and comprises 1% of cases of postmenopausal bleeding.[12] The exact cause of low incidence of the disease in this age group is not known. Most authors believe that an atrophic endometrium is a poor milieu for the growth of *Mycobacterium* tuberculosis bacilli.[13]

Pelvic tuberculosis may mimic ovarian malignancy, and CA- 125 may be falsely elevated.[14,15] After successful treatment of TB, CA-125 returned to normal level. FGTB usually occur as a result of seeding of bacilli immediately after puberty as blood supply to pelvic organ increases. As a result, more bacilli can reach these organs and infect them.[16] Primary infection may also occur if the male partner has active genito-urinary TB, and transmission may occur through sexual intercourse. Infection of vulva, vagina, and cervix may result from direct inoculation and ascending infection to other genital organs.[16,17] In most of the series of FGTB, vulva and vagina are uncommon sites of infection.[18] In our study also, incidence of vulva and vaginal TB was 1.81% and 0.91%, respectively.

The diagnosis of FGTB is challenging as it is rarely pinpointed by clinical symptoms because of their low specificity. Elaborate examination (pelvic ultrasound, chest X-rays, bacteriological culture, ZN stain, PCR analysis, histopathologic examination) should be carried out for accurate diagnosis. Microscopic examination of AFB on ZN stain requires the presence of at least $10^{[4]}$ organisms/ml in the sample, whereas culture is more sensitive, requiring as little as $10^{[2]}$ organisms/ml as pointed out by Bates in 1979. Recently, PCR has emerged as a rapid, sensitive, and specific molecular method to diagnose female genital TB with a turnaround time of 1-2 days.[19]

There are scant prospective data regarding optimal management of FGTB. In our patients, anti-TB drugs, which included isoniazid, rifampicin, pyrazinamide, and ethambutal, were given for a 2-month period and first 2 agents for an additional 4 months.[20]

Surgical therapy usually consists of total abdominal hysterectomy and salpingo-oophorectomy. Persistence of pelvic mass and recurrence of pain or bleeding after 9 months of medical treatment are indications for surgical intervention. Surgery should be attempted at least 6 weeks after initiation of anti-TB regimen because anti-microbial treatment facilitates the surgical procedure and reduces the risk of perioperative complications.[21]

REFERENCES

1. Chow TW, Lim BK, Vallipuram S. The masquerades of female pelvic tuberculosis:case reports and review of literature on clinical presentations and diognasis. J Obstet Gynaecol Res 2002;28:203-10.
2. Akhan O, Pringot J. Imaging of abdominal tuberculosis. Eur Radiol 2002;12:312-23.
3. Global tuberculosis control:Survillance, planning, financing. WHO report, 2007. Geneva: World Health Organisation; 2007.
4. Muttarak M, Ching Mai WN, Lojanpiwat B. Tuberculosis of the genitourinary tract: image features with pathological correlation. Singapore Med J 2005;46:568-74.
5. Antonucci G, Girardi E, Raviglione C, Ippolito G. Risk factors for tuberculosis in HIV infected persons: a prospective cohort study. J Am Med Assoc 1995;274:143-8.
6. Government of India. Annual Report 2005-06. New Delhi: Ministry of Health and Family Welfare; 2006.
7. Samal S, Gupta U, Agarwal P. Menstrual disorders in genital tuberculosis. J Indian Med Assoc 2000;98:126-7.
8. Carter JR. Unusual presentation of genital tract tuberculosis. Int J Gynecol Obstet 1990;33:171-6.
9. Nogales-Ortiz F, Taracon I, Nogales FF Jr. The pathology of female genital tuberculosis: A 31 year study of 1436 cases. Obstet Gynecol 1976;53:422-8.
10. Roy A, Mukherjee S, Bhattachrya S, Adhya S, Chakraborty P. Tuberculous Endometritis in hills of Derjeeling: A clinicopathological and bacteriological study. Indian J Pathol Microbiol 1993;36:361-9.
11. Falk V, Ludriksson K, Agren G. Genital tuberculosis in women-analysis of 187 newly diagnosed cases from 47 Swedish hospitals during the ten year period 1968 to1977. Am J Obstet Gynecol 1980;138:974-7.
12. Gungorduk K, Ulker V, Sahbaz A, Ark C, Tekirdag AI. Post menopausal tuberculous endometritis. Infect Dis Obstet Gynecol 2007;2007:27028.
13. Maestre MA, Manzano CD, Lopez RM. Postmenopausal endometrial tuberculosis. Int J Gynecol Obstet 2004;86:405-6.
14. Kawatra V, Kohli K, Khurana N. Pelvic tuberculosis mimicking ovarian malignancy: A case report. J Reprod Med 2010,55:449-51.
15. Bilgin T, Karabay A, Dolar E, Develioglu OH. Peritoneal tuberculosis with pelvic abdominal mass, ascites and elevated CA125 mimicking advanced ovarian carcinoma: A series of 10 cases. Int J Gynecol Cancer 2001;11:290-4.
16. Duggal S, Duggal N, Hans C, Mahajan RK. Female genital TB and HIV co-infection. Indian J Med Microbiol 2009;27:361-72.
17. Hass DW. Mycobacterial disease. In: Mandell GL, Bennet JE, Dolin R, editors. Principles and practice of infectious disease. Philadelphia, PA: Churchil Livingstone; 2000. p. 2576-607.
18. Buppasiri P, Temtanakitpaisan T, Somboonporn W. Tuberculosis at vulva and vagina. J Med Assoc Thai 2010;93:613-5.
19. Bhanu NV, Singh UB, Chakraborty M, Suresh N, Arora J, Rana T *et al*.

Improved diagnostic value of PCR in the diagnosis of female genital tuberculosis leading to infertility. J Med Microbiol 2005;54:927-31.
20. Onyebujoh PC, Ribeiro I, Whalen CC. Treatment options for HIV-associated tuberculosis. J Infect Dis2007;196:35-45.
21. Sutherland AM. Surgical treatment of tuberculosis of the genital tract. Br J Obstet Gynecol 1980;87:610-12.

How to cite this article: Mondal SK, Dutta TK, Nag DR, Biswas PK, Sinha MG. Histopathologic analysis of female genital tuberculosis with clinical correlation: A fifteen year study in a tertiary hospital of India. J Basic Clin Reprod Sci 2012;1:25-9.

Source of Support: Nil, **Conflict of Interest:** None declared

ISSN - 0000-0000

JOURNAL OF BASIC and CLINICAL REPRODUCTIVE SCIENCES

Official Publication of Society of Reproductive Biologist of Nigeria

Volume 1 / Issue 1 / Year 2012

www.jbcrs.org