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Daignosis of female genital TB (FGTB)

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Tuberculosis (TB) is one of the world's major health problems. It affected an estimated global total of 10.6 million people (95% uncertainty interval [UI]: 9.9–11 million) fell ill with TB in 2021, equivalent to 134 cases (95% UI: 125–143) per 100 000 populations and caused approximately 1.5 million deaths.[1] Geographically, most TB cases in 2021 were in the WHO regions of South-East Asia region

The SAARC region, with an estimated incidence of 4.0 million TB cases, carried 38% of the Global burden of TB in 2021.

Female genital TB (FGTB) is an essential factor for infertility in countries with a high TB prevalence. This type of TB usually occurs secondary to primary pulmonary TB.

The incidence of FGTB is increasing among young women globally. It is almost always secondary to a focus elsewhere in the body. Fallopian tubes are the first and the most commonly affected genitalorgans, followed by endometrium, ovary and cervix.[2] Occasionally, other sites may also be affected. A number of patients may remain asymptomatic and the disease may also be discovered incidentally.[3]The last century has witnessed changing trends in incidence of FGTB, initially due to improvement in economic standards in developed countries and subsequently by the global pandemic of the human immunodeficiency virus [HIV] infection.[3] However the risk of TB and its after effects are or increasingover the years. Emergence of multidrug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB] is a cause of serious concern.[1] FGTB can also cause abnormal uterine bleeding and postmenopausal bleeding and involves genital organs as observed on laparoscopy in pulmonary TB cases.[4,5] FGTB affects younger women in developing and under developed countries but FGTB affectsolder women in western world mostly in 40–50 years age group. Female genital TB is less common in postmenopausal women.

Epidemiology

The available Epidemiological and clinical data on FGTB cases is mostly from tertiary care centers or from individual studies published over decades. The exact prevalence and incidence of FGTB is unknown. The incidence is very high in developing countries compared to developed countries.Extrapulmonary TB represented about 16% of the 7.1 million incident cases in 2019, ranging from 8% in the WHO Western Pacific region to 24% in the Eastern Mediterranean region. Twentieth century witnessed dramatic reduction of FGTB cases in the developed world. However, in the developing countries the trend is different and it is on the higher side.

Pathogenesis

Genital tract TB is almost always secondary to TB infection elsewhere in the body. Although pulmonary TB is most common, extrapulmonary organs, such as, kidneys, gastrointestinal tract, bone or joints may also be theprimary source of infection. In patients with miliary TB, genital organs may be one of the many organs involved. Primary genital TB, though extremely rare, has been described in the female partners of males affected by active genitourinary TB through their semen.[6] The route of M. tuberculosis infection of FGTB is usually through the hematogenous or lymphatic spreadfrom pulmonary TB and possibly by direct spread from infected pelvic organs. Tuberculosis affects everypart of the female reproductive tract. In India, the frequency

of female genital organs affected by TB are fallopian tubes (95–100%); uterine endometrium (50–60%); ovaries (20–30%); cervix (5–15%); uterine myometrium (2.5%); and vagina and/or vulva (1%).[2]

Diagnosis

As genital TB is a paucibacillary disease, it is not possible to demonstrate M.tuberculosis in every case.So a comprehensive battery of investigations is carried out by the specialists based on the clinical suspicion and after clearly considering the various differential diagnoses. Some of the investigations carried outafter suspecting clinically are as follows

General investigations: Routine Blood and urine examination Chest X ray.

Site specific investigations: Imaging procedures: hystero-salpingography, Hysteroscopy Endoscopy procedures: Laparoscopy, ultrasonography of pelvic organs, computed tomography [CT] and Magnetic Resonance Imaging [MRI]

Pathological examination: Endometrial biopsy, tubal biopsy Endometrial histologyEndometrial aspirate smear Cervix Biopsy for Exfoliative cytology Vagina and vulva Biopsy for histopathological examination

Microbiological tests: peritoneal fluid smear for AFB and mycobacterial culture, Endometrial aspirate smear for AFB and mycobacterial culture Menstrual blood culture for Mycobacterium tuberculosisCervix Biopsy for AFB and for Detection of M.tuberculosis by Genexpert.

The acceptable specimen for Microbiological and pathology tests are:

- Endometrial biopsy/ curettage/aspiration.
- Menstrual Blood within 12 hours of onset.
- Biopsy from TO mass.
- Peritoneal fluid/ biopsy
- Cervix or Vaginal secretion.
- Other supportive samples
- Sputum for ABF smear/ Culture/ Molecular tests
- Radiological Imaging, endoscopic procedures are combined with histopathology examination of
- endometrial material is commonly used for establishing the diagnosis of FGTB.
- Mycobacterial detection bySmear Microscopy, Culture for mycobacteria also remains themost
- commonly used procedure for the diagnosis of FGTB in tertiary care centers .

Microbiological Tests:

Role of smear microscopy in FGTB is very minimal. Even though it is done on all extra pulmonary specimen the yield positivity is less. Sensitivity is low. Acid-fast [Ziehl–Neelsen (ZN), Kinyon] staining or fluorescent (auramine, rhodamine) staining is generally used. For ZN staining to yield a positive result, a sample should contain approx. 10000 bacilli/ml. LED Microscopy using fluorescent stains is good and rapid,sensitivity is adequate in symptomatic extra pulmonary TB cases.

Culture

Culture for Mycobacterium.tuberculosis is the gold standard test for confirming the diagnosis.It is more sensitive and requires 10-100 bacilli/ml of tissue/fluid sample for the positive culture. The diagnosis of TB is confirmed based on the identification of M. tuberculosis rapid identification tests on positive growth in the cultures. Solid cultures are usually performed on the egg-based Lowenstein–Jensen (LJ) medium or agar-based Middlebrook 7H10 medium. The solid media based culture procedure is time consuming and take 4-8 weeks for taking the decision on the culture results hence rarely used in the present times. The liquid culture is performed using automated BACTEC Mycobacterial Growth Indicator Tube 960(MGIT 960) based on modified Middlebrook 7H9 Broth with an oxygen-sensitive fluorescent detection technology. Liquid culture test more rapid and requires at least 9-10 days for positive results and six weeks for being considered negative. The sensitivityis also higher than solid media based culture tests.

Some Experts recommendthat bacteriologic examination of menstrual blood for smear and culture for M.tb for the diagnosis of FGTB. But the collection and handling of menstrual blood is not only cumbersome but also sensitivity of these tests is very low. However, for the diagnostic tests on menstrual blood, menstrual fluid can be collected from the vagina on the first day of menstruation. An acid-fast staining of the endometrial curettings can also be beneficial for diagnostic process.

Molecular Methods: Molecular techniques for the detection of TB are increasingly used nowadays. The nucleic-acid amplification tests (NAAT) provide results in a few hours. The commonly used test is Cartridge-based nucleic acid amplification tests [CBNAAT]. The Xpert MTB/RIF® is a new fully automated diagnostic molecular test with an analytic sensitivity of five genome copies of purified deoxyribonucleic acid [DNA] and 131 colony-forming units [cfu]/mL of Mtb in sputum. The Xpert MBT/RIF is also able to detect more than 99.5% rifampicin resistance mutations, an indicator of multidrug-resistant TB in less than two hours' time . There are several PCR assays available across the continent. Most of these PCR is a rapid molecular method are used for identification of nucleic acid sequencesspecific to M. tuberculosis and other mycobacteria in tissue samples of patients with FGTB. PCR can detect <10 bacilli/ml including dead bacilli and has a testing time of 8-12

hrs. Sensitivity of PCR is higher than culture and histopathology and specificity may be as high as 100 per cent in detecting FGTB (18).But WHO endorsed only the following molecular tests for use in clinical Practice and for use in TB control programmes are as follows:(Low complexity automated NAATs for detection of resistance to isoniazid are Xpert MTB/RIF Ultra and Truenat assays and for detection of resistance to Second-line anti-TB agents also is Xpert MTB/XDR (Cepheid) (Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid are Abbott RealTime MTB and Abbott RealTime MTB RIF/INH (Abbott)BD MAX MDR-TB (Becton Dickinson) cobas MTB and cobas MTB-RIF/INH (Roche)FluoroType MTBDR and FluoroType MTB (Bruker/Hain Lifescience).[4]

Serology: WHO has banned the usage of serological tests in individuals suspected of any form of active TB, regardless of their HIV status but most of the clinicians use it in their clinical practice. Role of Skin tests for TB is not useful for establishing an active TB diagnosis, as such they can only be used for screening purposes or as an add on test only for other advanced and more reliable tests.The recently published evidence-based INDEX-TB guidelines . specifiesAdvanced genital TB is diagnosed by the presence of palpable tubo-ovarian masses and histopathologicor bacteriologic evidence of TB.

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