Female genital tuberculosis

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Abstract

Mycobacterium tuberculosis has been identified as the aetiological agent of tuberculosis for many centuries. Genital tuberculosis is a chronic disease and often has low-grade symptomatology, with very few specific complaints. A study from South Africa found an incidence of 6% of culture-positive tuberculosis in an infertile population. The fallopian tubes are involved in most cases of genital tuberculosis and, together with endometrial involvement, cause infertility in patients. Many patients present with a symptom complex similar to that of ovarian carcinoma, i.e. abdominal distension, pelvic tumour and ascites, which may easily be confused with ovarian carcinoma. Biopsies should be obtained by either laparoscopy or laparotomy if examination of the ascitic fluid could not confirm the diagnosis. Genital tuberculosis is an elusive diagnosis and requires a high index of suspicion as a first step in the diagnostic process. Excellent cure rates are reported on all of the standard treatment regimens.

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Introduction

Mycobacterium tuberculosis and *Mycobacterium lepra* have been recognised for many centuries as aetiological agents of tuberculosis and leprosy respectively. The term "consumption" was first used in the 14th century to describe a fatal wasting disease. A condition called "tuberculosis" was first described in 1860 and a few years later, in 1882, Robert Koch identified the causative agent in the form of rod-shaped bacteria. Tuberculosis is widely represented in the arts. One of the most tragic references comes from the opera La Traviata by Giuseppe Verdi, which describes the eventual death (from tuberculosis) of the heroine Violetta.

Mycobacterium tuberculosis is a slow-growing bacterium and only doubles its population every 18 to 24 hours. This slow doubling time partly explains the chronic nature of the disease and may allow dissemination of the disease before acute symptoms develop. Transmission usually occurs when infectious people cough, sneeze, talk or spit and thereby propel the tuberculosis bacilli. It is only necessary to inhale a small number of these mycobacteria to be infected. During primary infection, organisms may spread systemically and, at a later stage, may be activated at a genital site. Genital tuberculosis may be sexually transmitted, as confirmed by restriction fragment length polymorphism (RFLP) analysis.[1] The most common mode of transmission to the genital tract is through haematogenous spread from pulmonary or other sites of tuberculosis.

Prevention

Primary prevention of the disease includes strategies to reduce the risk of exposure to disease-causing organisms. It is therefore important to educate and inform patients with confirmed cases to be cautious with spitting, coughing or sneezing in public places to curtail the spread of tuberculosis. A well-meaning kiss of affection may spread mycobacteria to uninfected individuals. In the specific scenario of genital tuberculosis, safe sexual practices may reduce the incidence of genital infection.

Immunisation with Bacille Calmette-Guérin (BCG) is a preventative strategy used in many countries with a high prevalence of tuberculosis. BCG is prepared from a strain of live-attenuated bovine tuberculosis bacillus, *Mycobacterium bovis*. The bacilli have retained enough antigenicity to become a partially effective vaccine for the prevention of human tuberculosis. The BCG vaccine is up to 80% effective in preventing tuberculosis; however, its protective effect appears to vary according to geography.

Incidence

On the basis of a 10-year study, Hassoun et al. reported that 1.8% of all tuberculosis cases may have a genito-urinary site.[2] A study from South Africa found an incidence of 6% of culture-positive tuberculosis in an infertile population.[3] The reported incidence of genital tuberculosis and the age distribution of such cases vary between geographic areas. Cases occur more frequently (62%) in postmenopausal women in developed countries than in developing countries, where only 28% of cases are in the postmenopausal category.[4] The prevalence of genital tuberculosis is directly proportional to the incidence of pulmonary tuberculosis in an area. An interesting observation from Spain showed that very high incidences of pulmonary tuberculosis during the Spanish Civil War and World War II declined very quickly after 1961, followed only years later by a corresponding decline in genital tuberculosis.[5] The delay in the decline of the incidence of genital tuberculosis was possibly due to the late diagnosis of this asymptomatic condition.

Symptoms

Genital tuberculosis is a chronic disease and often has low-grade symptomatology with very few specific complaints. However, Sutherland reported that 44% of patients with genital tuberculosis reported infertility.[6] Pelvic pain was present in 25% and abnormal vaginal bleeding in 18% of individuals. Amenorrhoea and vaginal discharge were present in about 5% of cases, while post-menopausal bleeding accounted for 2% of patients presenting with genital tuberculosis. Rare symptoms included an abdominal mass or unexplained ascites. Genital tuberculosis may mimic a tumour or ovarian abscess and may also present with vague abdominal distension.

Physical examination

Most cases of confirmed genital tuberculosis will have a perfectly normal clinical examination (43%), while about a quarter of cases will present with an adnexal mass (23.6%).[7] Other common findings are the presence of pelvic tumour on imaging, which may look like fibroids (23.6%) or an irregular uterus (1.4%). On gynaecological examination, adnexal tenderness is found in less than 5% of cases, while uterine prolapse or a cervical polyp-like lesion may be present (1.4%).

Diagnosis

Genital tuberculosis is an elusive diagnosis and a high index of suspicion is the first step in the diagnostic process. A careful history with specific mention of previous exposure to or active tuberculosis is of importance. Taking a detailed drug and treatment history in patients who had previous treatment for active tuberculosis is important to establish compliance and possible resistance patterns. A high erythrocyte sedimentation rate (ESR) may help in the diagnosis, while a test for human immune deficiency virus (HIV) may identify a high-risk population.

Many patients present with a symptom complex similar to that of ovarian carcinoma, i.e. abdominal distension, pelvic tumour and ascites, and a CA 125 level (it is a marker after of non-mucinous epithelial ovarian cancer) may be done in the diagnostic work-up. CA 125, however, is very often raised above an empiric cut-off point of 35 IU/ml in patients with any peritoneal infectious process like tuberculosis. The raised CA 125 in patients with active tuberculosis may be misinterpreted as being diagnostic for ovarian cancer.

A Mantoux or Heaf test may be useful in populations where tuberculosis is a rare disease. The Mantoux test may show sensitivity of up to 55% for the accurate diagnosis of genital tuberculosis in populations with a low incidence.[8] Raut et al., using laparoscopic findings only, reported specificity as high as 80%.[8] The Mantoux test may be negative in patients with active tuberculosis if the patient has overwhelming clinical disease, is severely immune compromised, has co-incidental viral infection or is malnourished. The validity of the Mantoux test, therefore, is variable. In populations with a high incidence of tuberculosis and where BCG is given routinely, the Mantoux test is often falsely positive. The Mantoux test may, in rare cases of genital tuberculosis, elicit a systemic reaction, where a local abdomino-pelvic reaction in the form of lower abdomen pain, tender adnexae and increased discharge from the cervix may be noted for 24 to 48 hours after the injection of tuberculin.

More than 75% of the patients with active, culture-proven genital tuberculosis have a normal chest X-ray. It is important not to use a chest X-ray as exclusion for the diagnosis of genital tuberculosis. The gold standard remains the proof of acid-fast bacilli in biological specimens or culture. In patients presenting with sub-fertility and/or abnormal bleeding, a culture of menstrual fluid may be the most useful strategy.[9] Obtaining menstrual fluid for culture need not be a difficult procedure. The patient is invited to attend the out-patient clinic during the second day of her normal menstruation, when she will be put in the lithotomy position and a sterile speculum is passed. About 10 to 20 ml of normal saline is instilled into the vagina with a sterile syringe and the normal saline is mixed with the menstrual blood. It is then aspirated and sent for culture. This approach has a good yield for positive cultures. Culture of mycobacterium tuberculosis on Lowenstein-Jensen medium is the most accurate diagnostic method. Microscopic examination of acid-fast bacilli (AFB) requires the presence of at least 10 000 organisms per millilitre in the sample. Culture is more sensitive, requiring only 100 organisms per millilitre. However, culture may take up to eight weeks to grow on LJ medium. Polymerase chain reaction (PCR) is a rapid and sensitive molecular biological method for detecting tuberculosis DNA.[10] A commercial PCR assay, COBAS Amplicor MTB, is FDA approved for sputum, but may be used on a variety of specimen types. The assay detects the *Mycobacterium tuberculosis* complex.

In patients with active genital ulceration, particularly on the vulva, a simple impression on a glass slide may reveal AFBs. In cases of suspected pelvic or abdominal tuberculosis, several biopsies should be taken during laparotomy for histology and swabs should also be taken for bacilli culture. Biopsies may show the typical histology, which includes granulomas and positive acid-fast stain. Other typical features of tuberculosis on histology are epitheloid cell granulomas with or without Langerhans's giant cells. Caseating necrosis is rare in specimens from the genital tract.

Laparoscopy may be a very good way of diagnosing active genital tuberculosis. In a study in India, Tripathy and Tripathy showed that 59% of patients with pulmonary tuberculosis may have tubal damage.[11] A total of 24% of patients with pulmonary tuberculosis had tubercles on the genital organs. In a study in South Africa, laparoscopic examinations in patients with genital tuberculosis showed that 53% of the patients had abnormal tubes.[9] Other imaging techniques may be of diagnostic importance. Hysterosalpingogram is a fairly simple test with a high yield. Hysterosalpingogram in more than 70% of patients showed:

- Coronal or fimbrial block
- Beaded tube
- Hydrosalpinx

Ultrasound findings included:

- Adnexal mass
- Thickened omentum
- Ascites

Other endoscopic investigations, such as hysteroscopy, may improve the diagnostic yield, and an endometrial biopsy may be cultured for acid-fast bacilli.

Pathology

The fallopian tube is affected in nearly all patients with active genital-site tuberculosis. The endometrium is involved in 50 to 60% of all patients and the ovary in 20% to 30% of cases.[7] Cervical, vulval and vaginal disease are rare, but on very careful investigation it may be

found that tuberculosis from these sites is under-diagnosed.[7] In a large descriptive study of 1 426 cases collected at a pathology laboratory over a 31-year period, Nogales-Ortiz et al. reported involvement of the fallopian tubes in all the cases studied.[5] In this series, all the patients had *bilateral* tubal involvement. Epitheloid granulomas were found throughout the endometrium; however, the density was higher in the superficial layers and decreased towards the myometrium. Acid-fast bacilli were only demonstrated in less than 2% of these lesions. The myometrium was involved in only 20% of cases and cervical involvement was a rare occurrence. If the cervix was involved, it was mainly in the endocervical canal (72.5%), and if the ectocervix was involved, the changes were mostly hyperplastic mucosal changes. Vaginal and vulval tuberculosis presented with ulcers with a rolled edge.

Pregnancy

Female genital tuberculosis is usually associated with infertility, although a small number of cases have been reported in the literature where an intra-uterine or ectopic pregnancy co-exists with female genital tuberculosis.[5] Congenital transmission of tuberculosis has also been reported.[2]

Tuberculosis of the vulva

Tuberculosis of the skin presents in many different ways. On the vulva, tuberculosis is usually associated with ulceration and has an appearance very similar to that of a chancre (tuberculous chancre). The lesion may appear brown or red and may have a surrounding area of induration. There is often a slightly raised edge around the central ulcer. If chronic ulceration on the vulva does not respond to adequate antibiotic therapy, a biopsy should be taken for histological investigation. A simple impression on a glass slide may reveal AFBs.

Cervical tuberculosis

Cervical tuberculosis is a rare disease, although under-diagnosis is very likely. A total of 2% to 24% of cases of genital tuberculosis have cervical involvement.[2,5] The patients present with postmenopausal bleeding and/or chronic discharge. On inspection of the cervix, there is often ulceration and necrosis that can easily be confused with a cervical carcinoma. Histology, however, is very typical, with granulomas and possibly acid-fast bacilli. Growths on the cervix are often assumed to be cervical cancer, hence histological proof is of the utmost importance. Other conditions that may cause granulomatous disease of the cervix are summarised in Table I.

Table I: Differential diagnosis of granulomatous disease of the cervix[12]

Amoebiasis	Sarcoidosis
Schistosomiasis	Foreign body reaction
Brucellosis	Tuberculosis
Tularaemia	

Endometrial tuberculosis

Endometrial tuberculosis often goes undiagnosed because it is either asymptomatic or presents with non-specific symptoms in most affected women. In women of reproductive age, the most common presenting symptoms are menstrual disturbance, oligo-amenorrhea or pelvic pain. Postmenopausal women may present with postmenopausal bleeding, pyometra or leucorrhea.[13,14]

Although imaging is not diagnostic, it may raise the index of suspicion. Transvaginal ultrasound may illustrate a thickened endometrium or pyometra.[13] Features on hysterosalpingogram include a distorted contour of the uterine cavity due to scarring, venous and lymphatic intravasation or synechiae with well-demarcated borders.[15] Hysteroscopy can allow visualisation of granulomas in cases of non-caseating granulomatous endometritis.[13,16] Biopsy of such lesions is mandatory to get histological confirmation of the typical non-caseating lesion consistent with tuberculosis. Recovery of mycobacteria from granulomas or other endometrial biopsies is highly specific, but culture from menstrual fluid, as described earlier in this article, is more sensitive for the identification of genital tract tuberculosis.[3,17]

Tuberculosis of the fallopian tubes and infertility

Infertility is one of the leading presenting symptoms of patients with genital tuberculosis.[18] The fallopian tubes are involved in most cases of genital tuberculosis and, together with endometrial involvement, cause these patients to become infertile. It is reported that 44% to 78% of women with genital tuberculosis will be infertile.[3,7,18,19] The prevalence of genital tuberculosis in the infertile population in developing countries is between 5% and 20% and it is even higher among patients with tubal factor infertility (39% to 41%).[3,5,7,9,17,18,19,20] Genital tuberculosis should therefore always be considered as a probable cause in the diagnostic work-up of infertile couples, especially in populations with a high prevalence of tuberculosis – even in the absence of a previous history of tuberculosis.[18] As the diagnostic work-up of infertile women includes a hysterosalpingogram and/or hysteroscopy and laparoscopy with chromopertubation, clinicians should be familiar with the features associated with genital tuberculosis when doing these investigations.

Tubal involvement has a variety of hysterosalpingographic appearances.[15,19] The various features illustrated in a review are listed in Table II.

Table II: Hysterosalpingographic findings

Calcifications showing as linear streaks
Tufted tubal outline or tubal diverticula
Tubal occlusion, especially at the transition between the isthmus and ampulla, multiple occlusions causing a beaded appearance or a rigid "pipe-stem" appearance
Hydrosalpinx showing as tubal dilatation with thick mucosal folds
Peritubal adhesions giving the tube a "corkscrew" appearance, a peritubal halo or loculated spillage of contrast medium[15]
The rare finding of enterotubal fistulae – most common between the sigmoid colon and fallopian tube[21]

Although laparoscopy is a more invasive procedure, it not only allows for visualisation of the fallopian tubes, ovaries and peritoneal cavity, but also gives the opportunity to biopsy tuberculous lesions and to restore the anatomy in the pelvis where appropriate. One or more of the following features may be found on laparoscopy (see Table III):

Table III: Laparoscopy findings

Tubercles on the peritoneal surface
Inflamed or blue-coloured uterus
Salpingitis, oophoritis or a tubo-ovarian mass
Tubal occlusion with hydrosalpinx Dye dripping (instead of free flowing) from the fimbreal opening on chromopertubation
Free peritoneal fluid looking like blood
Caseation in the Pouch of Douglas
"Frozen pelvis"
Omental adhesions

Many of the aforementioned laparoscopic findings may be caused by non-tuberculous pelvic infections. Therefore, laboratory confirmation of the diagnosis is essential. Although many would argue that microbiological proof is essential, most authorities now accept histopathological proof of the typical granuloma to confirm the diagnosis.[18]

Hysteroscopy should be combined with laparoscopy to exclude/confirm endometrial involvement. Synechiae formed after endometrial tuberculosis may require intervention in the form of lysis of the synechiae and priming of the endometrium with oestrogen.

The conception rate following successful treatment is, unfortunately, as low as 10% to 38% and the live birth rate is 7% to 17%.[9,19] Poor reproductive outcome also holds true for patients who undergo IVF treatment.[20] Factors consistently associated with poor reproductive outcome are elderly age group, long duration of infertility, tubal occlusion and absent or caseating endometrium.[19,20] Some authors are of the opinion that endometrial involvement precludes IVF treatment and that these couples should rather consider other options, like surrogacy or adoption.[20] The risk of ectopic pregnancy and miscarriage is increased in those in whom conception does take place.[19]

Peritoneal tuberculosis

This presentation of genital tuberculosis is often called "the great pretender" because it closely resembles the presentation of advanced ovarian carcinoma. The clinical importance of peritoneal tuberculosis is emphasised by the numerous case reports and case series published over the last decade.[22,23,24,25,26,27]

The most common symptoms that patients present with are abdominal distension due to ascites and abdominal pain. Other symptoms include anorexia and weight loss, night sweats, low-grade fever, malaise and dyspnoea in the presence of a pleural effusion or massive ascites splinting the diaphragm. On clinical examination, ascites can be demonstrated with or without an abdomino-pelvic mass and a possible pleural effusion.

Because it is very difficult to make a firm diagnosis on this non-specific clinical picture, certain special investigations may assist in an effort to do so. Paracentesis should be done when ascites is present and should be sent for biochemistry and cytology, microscopy for AFBs, TB culture and serology. Unfortunately, microscopy for AFBs and TB culture is often negative.[25,28]

The laboratory findings consistent with tuberculous ascites are summarised in Table IV.

Table IV: Tuberculous ascites

Lymphocytic exudates
Absence of malignant cells
High total protein content (>25 g/l)
Small serum-ascites albumin gradient (<11 g/l)
LDH (lactate dehydrogenase) above 90 U/L
ADA (adenosine deaminase) above 30 IU/ml[22,24,25]

Imaging by abdominal ultrasound or abdominal CT-scan is often very non-specific. Findings on imaging include a pelvic mass, ascites, omental involvement, thickening of the small bowel mesentery and parietal peritoneum and retroperitoneal lymphadenopathy.[27,28,29,30]

Serum CA 125 measurement is markedly raised in many cases of peritoneal TB and may further mislead the clinician, because these measures may be elevated in a number of other benign intra-abdominal conditions.[22,23,24,25,28] Serial measurement of CA 125 after the initiation of treatment can be helpful in monitoring response to treatment, since it has been shown to normalise in response to treatment.[31]

Biopsies should be obtained by either laparoscopy or laparotomy if examination of the ascitic fluid could not confirm the diagnosis.[22,24,25,26,32] There is some controversy about the safety of laparoscopy in these patients, but laparoscopy with the open-entry technique should be safe and sufficient in most patients.[23,26,28] Laparotomy can be done when the risk of bowel injury is regarded as being too high to safely perform laparoscopy. Peritoneal TB causes miliary nodules covering almost every surface in the abdomen, peritoneal thickening, an omental cake, adhesions and adnexal pseudo-abscesses, which can easily be mistaken for ovarian carcinoma.[23,24,25,27,32] Biopsy of lesions with intra-operative frozen-section is mandatory to confirm the diagnosis, because the extensive surgical treatment for ovarian carcinoma is very different from the medical treatment for peritoneal TB.[23,24,25,26] Confirmation of the diagnosis of peritoneal TB at this stage saves the patient from having unnecessary major surgery. Samples should also be sent for bacteriology, PCR and histopathology.

Treatment

Standard anti-tuberculous drugs are used to treat genital tuberculosis. A four-drug regimen consisting of isoniazid, ethambutol, rifampicin and pyrazinamide is used for the first two months, followed by triple or dual therapy. The total duration of treatment should be six months to a year.[26, 28, 29] Excellent cure rates are reported for all of the standard treatment regimens.

Conclusion

It is estimated that a third of the world's population is infected with tuberculosis and that a new infection occurs every second.[33] Most of these infections are asymptomatic and may not cause disease. With a high incidence of HIV co-infection, unusual manifestations of tuberculosis, including genital involvement, may be found more frequently.

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