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Tuberculosis in gynecologic oncology: still a diagnostic dilemma

Abstract

Tuberculosis is an ancient disease, as old as mankind. It has many profound impacts on society and represents a major socioeconomic burden. Despite the availability of anti-tuberculosis therapy, it still remains a major health problem and is one of the leading causes of morbidity and mortality in many developing countries. Tuberculosis most commonly affects the lungs, but it can affect virtually any organ. It is accepted as one of the great mimickers in medicine. The abdominopelvic cavity is one of the common sites for extra-pulmonary tuberculosis. The preoperative misdiagnosis of peritoneal tuberculosis as ovarian cancer is common because of overlapping signs and symptoms. In this review, we address the diagnostic difficulties in distinguishing between these two pathologies.

Keywords: tuberculosis, pelvic tuberculosis, ovarian cancer, peritoneal carcinomatosis

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Abbreviations: HIV, human immunodeficiency virus; WHO, world health organization

Introduction

Tuberculosis is caused by *Mycobacterium tuberculosis*, a slow-growing obligate aerobe and a facultative intracellular bacterium. Humans are the only known reservoir for this microorganism. Various factors help to determine whether tuberculosis is likely to be transmitted: the number of organisms expelled the concentration of organisms, the length of exposure time to contaminated air and the immune status of the exposed individual. The major risk factors for tuberculosis are human immunodeficiency virus infection (HIV), intravenous drug abuse, alcoholism, diabetes mellitus, immunosuppressive therapies, underlying malignant conditions, chronic renal diseases, smoking, close contact with a tuberculosis patient and immigration.

It is estimated that one third of the world population is latently infected with *M. tuberculosis*. According to the World Health Organization (WHO), there were 8.8 million incident cases in 2010 and nearly 1.5 million deaths from tuberculosis worldwide.[1] It was declared to be the emergent public health issue in 1993 by WHO after the threat of global pandemic occurred in the late 1980s and early 1990s.[2] Tuberculosis resurgence can be ascribed to the emergence of multi-drug resistance and the increasing numbers of immune-compromised individuals and immigrants from developing countries.

Tuberculosis can affect all the systems or organs in body. The lungs are the most common sites for the development of disease. Although transdermal and gastrointestinal transmission have been reported, *M. tuberculosis* is spread primarily as an airborne aerosol from an individual who has active infection. The typical tuberculosis lesion is an epithelioid granuloma with central caseation necrosis. The most common site of the primary lesion is within alveolar macrophages in the subpleural regions of the lung. Bacilli proliferate locally and spread through the lymphatics to a hilar node, forming the Ghon complex. Initial lesions may heal and the infection become latent before symptomatic disease occurs.

Extrapulmonary tuberculosis

The term extra pulmonary tuberculosis has been used to describe the isolated occurrence of tuberculosis at body sites other than the lungs. Although mycobacteria are spread by the blood throughout the body during initial infection, primary extra pulmonary disease is rare except in immuno-compromised hosts. Extra pulmonary tuberculosis has become more common since the advent of human HIV infection.[3] Infants, older persons or otherwise immuno-suppressed hosts are unable to control mycobacterial growth and develop disseminated tuberculosis. Patients, who become immuno-compromised months to years after primary infection can also develop late, generalized disease.

The most common extra pulmonary sites for tuberculosis are lymph nodes, the genito-urinary system, vertebral bodies, adrenal glands, meninges and the gastrointestinal tract. Despite increasing awareness and the availability of better imaging and other diagnostic methods, extra pulmonary tuberculosis remains a difficult diagnosis to make. Due to its non-specific and protean manifestations, the actual incidence of extra pulmonary tuberculosis is underreported because of such difficulties in diagnosis and its vague presentation. When an extra pulmonary focus is evident in a patient with pulmonary tuberculosis, such patients have been categorized under pulmonary tuberculosis as per the guidelines of WHO.[4]

Female genital and peritoneal tuberculosis

Abdominal tuberculosis is the term used to encompass tuberculosis of the abdominal cavity including the gastrointestinal tract, solid visceral organs (liver, spleen, kidney, or pancreas), genital organs, peritoneum, lymph node, or in any combination of these.[5]

Abdominal tuberculosis can occur at any age but is predominantly a disease of young adults.[6] It constitutes 3% of all tuberculosis cases and its association with pulmonary tuberculosis is not well defined. Abdominal tuberculosis can be characterized by acute, sub-acute, and chronic presentations and it may be an incidental finding during laparotomy for other diseases. The clinical presentation depends upon the site and type of involvement.

As a kind of abdominal tuberculosis, peritoneal tuberculosis is the second most common form of extra pulmonary disease after lymph node tuberculosis.[7] It may develop from reactivation of latent foci in the peritoneal cavity or from hematogenous spread from a primary pulmonary infection. Tuberculous peritonitis has been described in three form: 'wet type' with free or loculated ascites; 'dry or plastic type' with caseous nodules, fibrous peritoneal reaction and dense adhesions; and 'fibrotic fixed type' with mass formation of omentum and bowel loops with occasional loculated ascites.[8] Patients characterize with abdominal pain, weight loss, fever and insidious onset ascites. While the frequency of each symptom varies, abdominal pain is a common presenting symptom and is frequently accompanied by abdominal distension. It is usually non-localized and vague in nature. The pain is largely due to the inflammation of the peritoneum and mesentery. Less often, it could be a manifestation of intermittent sub-acute intestinal obstruction. The features of peritoneal tuberculosis such as ascites, irregular abdominal masses and omental involvement are also detected in other diseases such as primary malignant tumors, lymphoma, and peritonitis.[9] The radiologic differential diagnosis includes carcinomatosis, malignant mesothelioma, and nontuberculous peritonitis. Dirty appearance of omentum is more commonly seen with tuberculous peritonitis, and a nodular or caked appearance with peritoneal carcinomatosis.[8] Because of its nonspecific features, discriminating between some gastrointestinal and gynecologic conditions such as malignancy, bacterial infectious disease, and inflammatory disease can be extremely difficult.[10] A main step in early diagnosis is the identification of patients at high risk. Thorough questioning of the patient is of great value. Suspicion should be raised if a patient has a personal history of latent tuberculosis infection or previous contact with persons suffering from tuberculosis.

The genital system is rarely the primary site of tuberculosis. Genital tuberculosis affects nearly 12.1% of patients with pulmonary tuberculosis and constitutes 15-20% of extra-pulmonary tuberculosis depending on the country.[11] Furthermore, the coexistence of pulmonary and genital tuberculosis has been reported in 8-15% of the cases in different studies.[12] In the majority of cases, genital tuberculosis presents as a secondary complication acquired from an extra-genital source like pulmonary or abdominal tuberculosis.[13] Primary infection may also occur if the male partner has active genito-urinary tuberculosis, and transmission might occur through sexual intercourse.

Infection of vulva, vagina and cervix may result from direct inoculation with ascending infection to other genital organs. The fallopian tubes are involved in almost all cases of genital tuberculosis (90-100%) and the involvement is almost always bilateral. From the endosalpinx, it spreads to the endometrium, ovaries, occasionally to the cervix, but rarely to the vagina.[14] Among the various clinical presentations of tuberculosis, female genital tuberculosis poses serious concern because of various associated complications like oligomenorrhea, amenorrhea, primary or secondary infertility, chronic pelvic pain, pelvic mass and significant mortality.[13] The most common presenting symptoms of genital tuberculosis were reported to be abdominal distension (96%), abdominal pain (82%), weight loss (80%), weakness (76%), loss of appetite (73%) and fever (69%).[15] Given that the genital system becomes susceptible for *M. tuberculosis* after puberty, disease is mostly seen in women during the reproductive years.[16] Because of the low symptomatic or asymptomatic nature of the disease and the underreporting, the exact prevalence is not known.

Tuberculous endometritis in advanced stage may mimic severe uterine adhesions as seen in Asherman syndrome. Computerized tomography allows for the evaluation of the adnexa, which may show tubo-ovarian abscesses and chronic calcifications. MRI better demonstrates changes such as uterine adhesions, hydrosalpinx, and tubo-ovarian abscess.[8] The most common gynecological complication of tuberculosis is infertility and most cases are diagnosed incidentally during infertility work-up.[17] Infertility is attributed to tubal damage and adhesions created in the course of the chronic inflammatory process. Patients may also present with chronic lower abdominal pain or alterations in the menstrual pattern.

Tuberculosis and gynecological cancers

Tuberculosis is one of the great mimickers in medicine, with nonspecific clinical and radiological manifestations that may present in various atypical manners masquerading, as conditions like ovarian and endometrial malignancy, pelvic abscess, vulvar or vaginal ulcer, cervicitis, and even carcinoma of the cervix.[18] Ozat et al.[19] presented the presence of extra-ovarian diseases mimicking ovarian carcinoma in 5.11% of patients that preoperatively diagnosed as having ovarian carcinoma and peritoneal tuberculosis was the leading cause in 37.1% of these patients. Peritoneal tuberculosis is a diagnostic challenge along with risk factors like liver cirrhosis, renal failure with peritoneal dialysis, diabetes mellitus, malignancy, HIV infection and the administration of systemic corticosteroids, particularly in the absence of evidence of pulmonary infection. It can be confused easily with ovarian or peritoneal cancer especially if high levels of Cancer Antigen-125 (CA-125) and ascites exist. Although the CA-125 level is a useful tumor marker in the treatment monitoring of epithelial ovarian or peritoneal cancer, it can also be elevated in a series of benign gynecological conditions such as pelvic infections, tuberculosis, Meig's syndrome and endometriosis.[20] Once a definitive diagnosis has been made, CA-125 should instead be utilized to track treatment response, as patients with tuberculous peritonitis have been shown to have rapid declines in CA-125 levels paralleling clinical response and resolution of ascites after anti-tuberculosis treatment.[21] Ascites develops secondary to exudation of proteinaceous fluid from the tubercles, similar to the mechanism leading to ascites in patients with peritoneal carcinomatosis.[22] Peritoneal tuberculosis is similar to ovarian and peritoneal cancers in terms of routine laboratory findings.[23] There are number of tests to help in differentiating these conditions. Tuberculin testing with purified protein derivative is positive in approximately 70% of patients with tuberculosis; however, a negative result is of no help in excluding the disease.[24] Examination of the peritoneal fluid can be helpful in raising suspicion for the diagnosis. The majority of patients have an ascetic leukocyte count of 150 to 4000 per mm3, with a relative lymphocytic pleocytosis.[24,25] The polymerase chain reaction of ascetic fluid is other method used for differentiation, but it has not yet been well established because of its high risk of false positive results due to common laboratory contamination or presence of killed or dormant bacilli in the patient specimens.[26,27] The adenosine deaminase (ADA) activity of ascetic

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fluid has been proposed as a useful non-culture method of detecting tuberculous peritonitis.[28] Also it is presented that ADA determination was a relatively sensitive and specific test for the diagnosis.[29] Furthermore, according to a recent meta-analysis, IFN-γ in the ascetic fluid might be a sensitive and specific marker for the accurate diagnosis of peritoneal tuberculosis[30] Concomitant peritoneal and hepatic involvement of tuberculosis may result in false elevation of multiple tumor markers of gynecological cancers and thus lead to the mismanagement of patients. Regarding the differential diagnosis between malignancy and peritoneal tuberculosis, it is generally accepted that the efficacy of the majority of imaging techniques including ultrasonography, computerized tomography and magnetic resonance imaging is limited. It is mandatory to differentiate between these distinct conditions because of their quite different treatments.

Peritoneal tuberculosis requires conservative quadruple anti-tuberculosis medication with Rifampicin (10mg/kg/j), Isoniazid (5mg/kg/j), Ethambutol (20mg/kg/j) and Pyrazinamide (25mg/kg/j) for two months and a double-agent maintenance regimen with Rifampicin (10mg/kg/j) and Isoniazid (5mg/kg/j) for an additional four months[31] and the prognosis depends on the degree of the detrimental effects of tuberculous infection before the appropriate therapy. On the other hand, ovarian or peritoneal cancers require extended debulking surgery and combined chemotherapy with platinum and taxane agents if indicated. The Even for experienced hands, it is impossible to distinguish the pelvic peritoneal tuberculosis grossly from an ovarian cancer or peritoneal cancer during surgery. Starting neoadjuvant therapy without histological confirmation could have harmful effects on patients due to the different management of these diseases.[32] Thus the definitive diagnosis in such cases can only be achieved by tissue biopsy.

Image-guided percutaneous peritoneal biopsy was presented as a safe and adequate method for the diagnosis of peritoneal tuberculosis. Oge et al.[33] were preferred the ultrasound guided tru-cut biopsy as the first-line approach especially in young aged patients and they achieved definitive diagnoses with histopathological evaluation. Laparoscopy is an ideal method for early diagnosis in peritoneal tuberculosis with a sensitivity of 93% and a specificity of 98% when macroscopic appearance and combined histological findings are used.[34] Macroscopic signs suggestive of peritoneal tuberculosis during laparoscopy were miliary granulations over the peritoneum, inflammatory adhesions on the visceral or parietal surfaces, thickening, hyperemia, and retraction of the greater omentum. Laparotomy might be the preferred choice in patients with preoperatively diagnosed severe ascites and a huge abdominal mass with highly elevated CA 125 levels.[33]

Although an accurate diagnosis of genital tract tuberculosis is by the isolation of M. tuberculosis from genital tract, unsupported histological diagnosis by demonstration of granulomas has been universally accepted.[35] Other causes of granulomatous reactions like foreign body reactions to suture material, Crohn's disease, previous diathermy, postoperative necrotizing reaction, endometriosis, tubo-ovarian abscess, sarcoidosis and fungal infections should be kept in mind when making differential diagnosis. In the majority of reports, peritoneal tuberculosis is diagnosed intra-operatively via frozen-section in conjunction with clinical features. Frozen-section analysis has shown a high success rate in positive tuberculosis diagnosis and seems to be the gold standard for differentiation.[36]

Especially in endemic regions, clinicians should always consider tuberculosis as a differential diagnosis when encountering clinical presentations of ovarian tumor or ascites, and a frozen-section must be done before performing a surgical procedure like hysterectomy or oophorectomy, which would have profound effects on the quality of life. Increasing awareness could accelerate the diagnostic decision-making process and markedly reduce the time lag in starting anti-tuberculosis therapy.

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Conflict of interest

The authors declare that there is no conflict of interest.

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