

Is Tuberculosis Still a Threat in the Developed World? Two Cases of Tuberculosis Masquerading as Gynecologic Cancers

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Abstract

Summary: Two cases of Filipina women with tuberculosis mimicking gynecologic cancers remind physicians to include tuberculosis in the differential diagnosis, especially for patients from endemic areas.

Background: Tuberculosis is difficult to diagnosis and can mimic gynecologic cancers. Distinguishing these diseases is important in patient management.

Case 1: A 55-year-old female Filipina immigrant presented with pelvic pain. She had an elevated CA-125, ascites, abdomino-pelvic nodules, and pulmonary nodules. She underwent surgery for suspected metastatic ovarian cancer and was diagnosed with tuberculosis.

Case 2: A 75-year-old female Filipina immigrant presented with gastric burning. She had pyometra, a 0.5x1.0cm cervical mass, and 4.4cm endometrial mass. She underwent surgery for suspected uterine cancer and was diagnosed with tuberculosis.

Conclusion: A high index of suspicion is key to pre-operatively diagnose tuberculosis because its clinical picture overlaps greatly with that of gynecologic cancers in high risk populations. If tuberculosis is suspected, a screening test should be performed.

Teaching points

- ▶ While the prevalence of tuberculosis in the United States has been steadily decreasing, tuberculosis continues to be a significant concern in certain states, such as Hawaii.
- ▶ A high index of suspicion is key to pre-operatively diagnose tuberculosis because its clinical picture overlaps greatly with that of gynecologic cancers in high risk populations.
- ▶ If tuberculosis is suspected, healthcare providers should administer a screening test, such as a purified protein derivative or an interferon-based blood test for patients with a history of Bacille Calmette-Guerin vaccination.

Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis and is an extremely deadly disease that ranks alongside the human immunodeficiency virus as the leading cause of death from an infectious disease [1, 2]. When left untreated, approximately 50% of people with TB will die within 5 years [1, 3].

In 2014, 9.6 million people worldwide were newly infected with TB, and 58% of these cases occurred in South-East Asian and the Western Pacific Regions [2]. While the prevalence of TB in the United States has been steadily decreasing over the last couple of decades [3]. TB continues to be a significant concern in Hawaii, likely due to the state's large Asian and Pacific Island immigrant population. The Hawaii State Department of Health reported a TB rate that was three times higher than the nation's rate of 3.0 per 100,000 individuals [4].

M. tuberculosis most commonly attacks the lungs but can involve any part of the body including the abdomen and female genital tract [1-3, 5]. The abdomen is the sixth most common extrapulmonary site of infection for TB after the lymph nodes, pleura, osteoarticular system, genitourinary tract, and meninges [6]. Although abdominal TB is rare in developed nations, it remains common in underdeveloped nations and accounts for 10% of intestinal obstructions in India and Nepal [5]. Abdominal TB poses a unique challenge for physicians given its wide range of presentations: constitutional symptoms,

vague abdominal pain, abdominal swelling, abdominal masses, gastrointestinal obstruction, and even gastrointestinal bleeding [5]. On rare occasions, abdominal tuberculosis may masquerade as metastatic ovarian cancer with an abdomino-pelvic mass, ascites, and elevated tumor marker CA-125 [7-10]. Pre-operative diagnosis of abdominal TB remains rather difficult, and most diagnoses are discovered intraoperatively [10].

Female genital TB (FGTB) is responsible for 9% of extrapulmonary tuberculosis [11]. When present, the infection may involve the fallopian tubes (100%), endometrium (79%), cervix (24%), ovaries (11%), and the vulva and vagina (0.07%) [12]. TB is a significant cause of infertility and pelvic inflammatory disease in developing nations. Infertility is the most common presenting symptom of FGTB, followed by abdominal pain, oligomenorrhea, amenorrhea, menorrhagia, and dysmenorrhea [13]. Extremely rare presentations include abdomino-pelvic masses and ascites [14]. Both FGTB and abdominal TB present diagnostic dilemmas.

We report two cases of suspected gynecologic cancer in women who migrated from the Philippines and were ultimately diagnosed with TB. These cases are significant because they highlight an unusual presentation and remind physicians to maintain a high index of suspicion when patients migrate from endemic areas. We also provide a literature review on distinguishing TB from gynecologic cancer.

Case presentation 1

A 55-year-old woman, who emigrated from the Philippines to Hawaii 11 years ago, presented with 3 weeks of intermittent sharp pelvic pain and dark tarry stools. Physical exam was benign, and review of systems was negative for weight loss, fever, and night sweats. CA-125 was 186 U/mL. Colonoscopy and biopsy results were unremarkable. Pelvic ultrasonography revealed ascites with no evidence of gynecologic abnormalities. Computerized tomography (CT) of the chest-abdomen-pelvis with contrast revealed a 10 x 8 mm right pericardiophrenic lymph node with scattered 4 to 8 mm omental nodules, small pleural effusions, and right upper lobe nodules (Figure 1). In addition, there was wall thickening of the cecum and ascending colon and small nodular opacities within the right upper lobe. She underwent a robotic-assisted hysterectomy and bilateral salpingo-oophorectomy for suspected metastatic ovarian cancer. Intraoperative pathology revealed necrotizing granulomatous inflammation on frozen section and was later confirmed on permanent section (Figure 2). A diagnosis of abdominal and pulmonary TB was confirmed via *M. tuberculosis* complex DNA and sputum culture. The patient was referred for directly observed anti-TB therapy and is doing well.

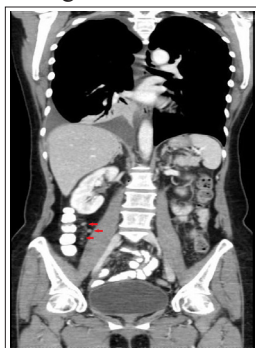


Figure 1: Scattered omental nodules.

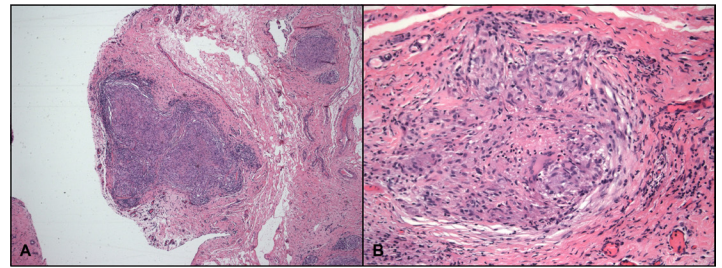


Figure 2: Omental nodule. A: large nodule with necrotizing granulomatous inflammation and serosal inflammation. B: caseous necrosis with nuclear debris, giant cells, and histiocytes.

Case presentation 2

A 75-year-old woman, who emigrated from the Philippines to Hawaii 16 years ago, presented with 1 month of gastric burning refractory to prescription medication. She denied postmenopausal bleeding. On exam, the patient had a 0.5 x 1.0 cm white mass on the posterior lip of the cervix, and biopsy revealed granulomatous inflammation. Pyometra was noted while performing her endometrial biopsy, and pathology was significant for acute and chronic endometritis with rare granulomatous inflammation and extensive necrosis (Figure 3). Pelvic ultrasound revealed a 4.4 cm hypoechoic endometrial mass. She underwent a robotic-assisted hysterectomy and bilateral salpingo-oophorectomy for a suspected uterine malignancy. Operative findings were significant for diffuse 2-3 mm peritoneal nodules which were biopsied and showed granulomatous inflammation (Figure 4). A diagnosis of female genital tract TB was confirmed via QuantiFERON-TB Gold In-Tube Interferon gamma release. The patient was referred for directly observed anti-TB therapy and is doing well.

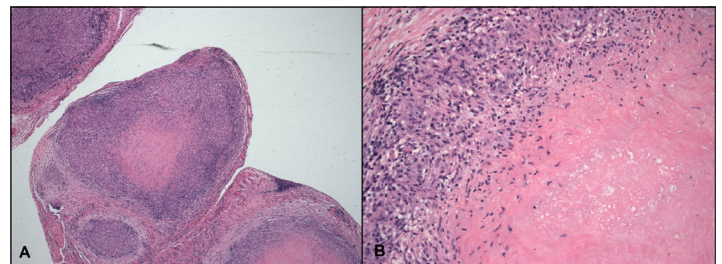


Figure 3: Endometrial biopsy A: necrotizing granulomatous inflammation completely replacing functional endometrium with rare normal glands. B: granulomatous inflammation, residual endometrial gland, and chronic endometritis with plasma cells in the stroma.

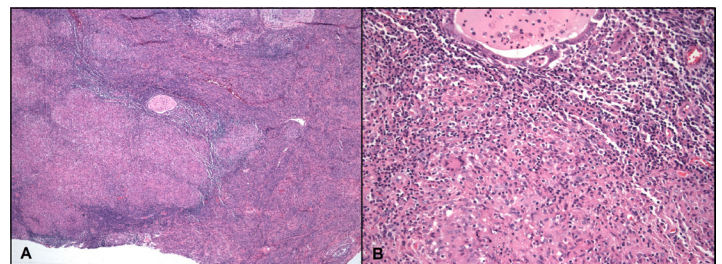


Figure 4: Pelvic mass A: caseous necrosis. B: caseous necrosis.

Discussion

The cases described here exhibit that *M. tuberculosis* remains a public health threat in the developed world. A high index of suspicion, especially in patients from areas with a high prevalence of TB, is necessary to diagnose this highly lethal, yet curable

infectious disease. The Centers for Disease Control and Prevention Division of Global Migration and Quarantine mandates an overseas medical examination for all immigrants and refugees. The medical examination includes a physical exam, mental health evaluation, syphilis serologic testing, review of vaccination records, and chest radiography [15]. While chest radiography is able to identify pulmonary tuberculosis, it fails to detect extrapulmonary infections. In most immunocompetent people, the host defenses are able to initially contain *M. tuberculosis*, so that infections remain hidden for years prior to activation and contagion [16]. According to the Hawaii State Department of Health, individuals diagnosed with tuberculosis are strongly advised to seek treatment when admitted to the United States, but many are lost to follow-up [17]. An improved system for the detection and treatment of tuberculosis is needed.

Differentiating between abdominal TB and metastatic ovarian cancer presents a diagnostic dilemma due to similarities in clinical presentation; both may present with vague symptoms and abdominal pain. Ovarian cancer is usually high aggressive and disseminates throughout the peritoneal cavity, producing ascites. Cancer cells travel through peritoneal fluid and preferentially latch onto the omentum. Ovarian cancer can also metastasize through direct extension to nearby organs, such as the uterus, cervix, bladder, and colon. The rapid tumor growth may result in gastrointestinal obstruction, gastrointestinal bleeding, and tumor cachexia [18].

A few clinical considerations could potentially assist in differentiating between abdominal TB and ovarian cancer. In the United States, ovarian cancer is more common than abdominal TB and affects 12.1 per 100,000 new women per year [14]. Abdominal TB can affect people at any age, but most cases occur in predominantly young adults with a mean age from 30 to 40 years [10, 20]. In contrast, ovarian cancer typically occurs in postmenopausal women with a mean age of 63 years [19]. The women in these cases were 55 and 75 years-old.

An elevated CA-125 with an abdomino-pelvic mass, as seen in case 1, is highly suspicious for ovarian cancer. However, an elevated CA-125 does not rule out other conditions given its poor specificity, ranging from 75 to 90% in advanced ovarian cancers [21]. When activated by tumor inflammation, colonic and bronchial epithelial cells also produce CA-125. Multiple malignant and nonmalignant conditions can also increase the serum level of CA-125. Examples include endometrial cancer, cervical cancer, breast cancer, colon cancer, lung cancer, endometriosis, menstruation, pregnancy, liver cirrhosis, congestive heart failure, diabetes mellitus, and tuberculosis [7].

The use of imaging to diagnose abdominal TB remains controversial. Some studies argue that ultrasonography and CT can help provide definitive diagnosis, others claim nonspecific patterns of peritoneal thickening, and some find no abnormalities [22-28]. Image-guided biopsy is not traditionally employed in the diagnosis of abdominal TB or ovarian cancer. Ultrasound-guided biopsy yields a 25% accuracy in the diagnosis of abdominal tuberculosis and 87% accuracy for ovarian cancer [29]. While biopsy poses the theoretical risk of seeding ovarian tumor cells, it is rarely observed [29, 30].

Case 2 was highly suspicious for a uterine malignancy given the patient's advanced age, pyometra, and 4.4 cm endometrial mass on pelvic ultrasound. When pyometra is present in a postmenopausal

woman, gynecologic malignancy should be highly considered [31]. This case is a rare presentation of FGTB. Unlike uterine cancer, FGTB almost exclusively affects premenopausal women because atrophic endometrium does not support the growth of *M. tuberculosis* [32]. In the few reported cases of postmenopausal FGTB, the presenting symptom was postmenopausal bleeding secondary to tubercular endometritis [33,34]. Although the patient's endometrial biopsy revealed acute and chronic endometritis, she denied any history of postmenopausal bleeding.

Since 79% of FGTB involves the endometrium, many studies have examined the efficacy of endometrial biopsy in the diagnosis of FGTB [12]. Microscopy of endometrial specimens for acid fast bacilli provides a quick diagnosis with low sensitivity, and histological findings of caseous granulomatous lesions with giant epithelioid cells are highly suggestive of TB but not diagnostic since they can also appear in syphilis and certain fungal infections [35, 36]. Polymerase chain reaction has been attempted, but only 53% of endometrial biopsies were found to have detectable levels of *M. tuberculosis* DNA [37]. Culture remains the golden standard for diagnosis of *M. tuberculosis*, however, the length of time required for culture may result in a delay in diagnosis of a gynecologic malignancy [38].

An inexpensive tuberculin purified protein derivative (PPD) skin test can quickly screen for both active and latent TB infections. Interferon-based blood tests like QuantiFERON®-TB Gold are preferred over PPDs for patients with a history of Bacille Calmette-Guerin vaccination, a vaccine commonly administered in developing countries [39, 40]. These tests are informative in suggesting a history of TB exposure, but they do not rule out the possibility of a coexisting gynecologic cancer. For example, Saygili et al. reported a case of primary endometrioid adenocarcinoma with coexisting endometrial tuberculosis [41]. In general, clinical suspicion is key, and TB should be included in the differential diagnosis of select patients who present with signs and symptoms of gynecologic cancer.

The inability to identify TB infection also poses a public health risk. Numerous extrapulmonary TB cases are discovered unknowingly in the operating room, which exposes healthcare workers, including the surgical and pathological teams, to lethal bacteria. Preoperative diagnosis is ideal but requires a high index of suspicion. In the event of accidental exposure to *M. tuberculosis*, the patient's pulmonary status should be thoroughly investigated since extrapulmonary tuberculosis is generally considered not contagious in the absence of pulmonary tuberculosis, [42] and proper post-exposure measures should be taken. Moreover, if preoperative diagnosis remains inconclusive, surgery should be performed by a gynecologic oncologist to treat and stage possible cancer.

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