Red Snappers and Red Herrings: Pelvic Tuberculosis Causing Elevated CA 125 and Mimicking Advanced Ovarian Cancer. A Case Report and Literature Review.

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Abstract

Female genital tuberculosis (FGTB) is a form of extra-pulmonary tuberculosis that has been primarily described in developing countries, where it is an important cause of infertility, ectopic pregnancy, and miscarriage. FGTB is rare in the United States and because its clinical presentation is non-specific and often insidious, FGTB may be misdiagnosed as a gynecologic malignancy or endometriosis. The tendency of tuberculosis to dramatically increase serum CA 125 levels contributes to the potential for FGTB to be mistaken for ovarian cancer in particular. We describe the case of a young woman who presented with what was initially thought to be advanced ovarian cancer but who had tuberculosis of the peritoneum, uterus, and ovaries discovered at laparotomy. This case emphasizes the importance of considering tuberculosis in the differential of any patient presenting with an abdomino-pelvic mass and an elevated CA 125 level.

Introduction

Approximately one-third of the world's population is infected with tuberculosis (TB) and TB remains one of the top five causes of death among adult women worldwide.[1] Extra-pulmonary TB is common in the developing world and may involve virtually any organ. The prevalence of female genital tract tuberculosis (FGTB) is difficult to estimate, due in part to significant variability in both the reporting and classification of the various forms of extra-pulmonary TB.[2] It is clear, however, that tuberculous involvement of the female genital tract remains a common cause of morbidity and infertility among women in countries with a high prevalence of TB.[2,3]

Though TB in Hawai'i is much less common than in developing nations, the State of Hawai'i has one of the highest annual TB case rates in the United States. Hawai'i reported 127 new cases of active TB in 2015, a rate of 8.9 new TB cases per 100,000 people—roughly three times the national tuberculosis case rate of 3.0 per 100,000.[4] The incidence of FGTB in Hawai'i is not known, but is likely very low: of the 127 new Hawai'i TB cases in 2015, only three involved the urogenital tract (patient gender not reported).[4]

Because FGTB is uncommonly encountered in developed countries, awareness of its various clinical presentations is limited. FGTB can be difficult to distinguish clinically from malignancy, and from ovarian cancer in particular. The propensity of FGTB to markedly increase serum CA 125 levels is an additional confounder that is not widely appreciated in the United States, where many clinicians' experience with TB is limited to pulmonary disease.

CA 125 is a large transmembrane protein initially described in 1981 by Robert Bast and colleagues while studying an ovarian cancer cell line, and which subsequently became a useful and widely used tumor marker.[5] CA 125 is elevated in some 75%-90% of patients with advanced ovarian cancer,[6] though abnormally high levels may also occur in a variety of non-malignant conditions, including endometriosis, cirrhosis, and pancreatitis.

We present the case of a woman with FGTB whose clinical picture initially suggested advanced ovarian cancer, including a markedly elevated CA 125.

Case Presentation

A 36-year-old Filipino woman was admitted to Kaiser Moanalua Medical Center in September of 2016 for exploratory laparotomy, for staging and de-bulking a presumed large ovarian cancer. The patient immigrated from the Philippines to Hilo, Hawai'i in August of 2015. Her screening purified protein derivative (PPD) and chest X-ray (CXR) on entry to the United States were negative. She returned to visit family in the Philippines for several weeks in early 2016.

In May of 2016 she noted the onset of a dry cough, lower abdominal pain, intermittent emesis, and fevers. Her clinical evaluation by her primary care team was felt consistent with a viral syndrome: a complete blood count, metabolic panel, and urinalysis were unrevealing save for new anemia. In the context of a continued cough and intermittent fevers, a CXR was ordered in June and showed modest bilateral pleural effusions, prompting a CT scan of her chest, abdomen, and pelvis in August. Her CT (Figure 1) showed a 14 cm complex cystic/solid pelvic mass suggesting ovarian cancer. Enlarged epicardial and parasternal lymph nodes were also noted; no parenchymal lung lesions were present. A serum CA 125 level was markedly elevated (408.3 U/ml; upper limit of normal 35 U/ml), supporting a suspicion of ovarian CA.

Thoracentesis was arranged in an effort to establish a diagnosis and for possible cancer staging. Serous, non-bloody pleural fluid was aspirated, with negative cytology and acid fast bacilli (AFB) staining; AFB culture of the pleural fluid was subsequently sterile.

A CT-guided needle biopsy of a thoracic lymph node was performed; the pathology specimen showed focal necrosis and no clear evidence of malignancy. Several granulomas were noted, with negative AFB and fungal staining.

Preparations were made for hospital admission with a plan to establish a definitive diagnosis via laparotomy and to begin

chemotherapy if a malignancy was confirmed. In the interim, the patient's weight loss became severe—over 23 pounds lost from a baseline of 114 pounds. Periodic fevers continued, and her fatigue progressed to the point of prostration. She became increasingly concerned about terminal malignancy.

Upon hospital admission in September of 2016, the patient's physical exam revealed a very thin, weak woman who was afebrile. Her lungs were clear and a fixed, midline abdominal mass of about 15 cm was easily palpable. She had no ascites or lymphadenopathy. Admission labwork showed mild anemia with a hemoglobin of 11.3 gm/dl and a normal white blood cell count of 6.3 K/ul.

The patient was taken to the operating room for an exploratory laparotomy. On entering the patient's abdomen, multiple pale nodules studding the peritoneum and mesentery were immediately evident, along with a vigorous inflammatory exudate and dense adhesions (Figure 2).

Intraoperative frozen sections were sent from the peritoneum and showed granulomas without clear evidence of malignancy. A large pelvic mass was found, containing copious purulence; the abscess was drained and specimens were sent for culture. The mass encased the patient's uterus and ovaries, was tenaciously adherent to the anterior abdominal wall and surrounding structures, and could not be resected. She underwent lysis of adhesions, drain placement, multiple peritoneal biopsies, and abdomen closure. Several intra-operative specimens sent for formal pathology confirmed the presence of many granulomas and scattered acid-fast bacilli (Figure 3).

The Kaiser Permanente Infectious Diseases service was consulted and the patient was promptly started on four-drug treatment for presumed extra-pulmonary tuberculosis. Her HIV antibody test was negative. Her PPD, negative a year earlier, was repeated and was markedly positive at 30 mm. Fluid from within the patient's pelvic mass was sent for *Mycobacterium tuberculosis* (MTB) PCR which was positive. MTB grew in culture four weeks later from her operating room specimens (Figure 4).

The patient returned to Hilo seven days after her laparotomy, afebrile, and slowly gaining strength. Her CA 125 level decreased dramatically during the first two months of TB therapy (Figure 5). At least six months of tuberculosis treatment is planned.

Discussion

The patient's combination of vague abdominal pain, striking CT findings, and a relatively recent negative PPD led clinicians to suspect a diagnosis of advanced ovarian cancer. Her markedly elevated CA 125 level appeared to support a presumptive diagnosis of malignancy.

It is not widely known that tuberculosis involving the abdominal/ pelvic cavities is a cause of dramatic serum CA 125 elevations.[7-9] Markedly high CA 125 levels have played a "red herring" role in cases similar to this case outside of the US, leading clinicians to suspect ovarian cancer when tuberculosis of the genital tract/ peritoneum was in fact the culprit.[7-8,10] Our case demonstrates the importance of considering FGTB in the differential of ovarian/ uterine masses with an increased CA 125

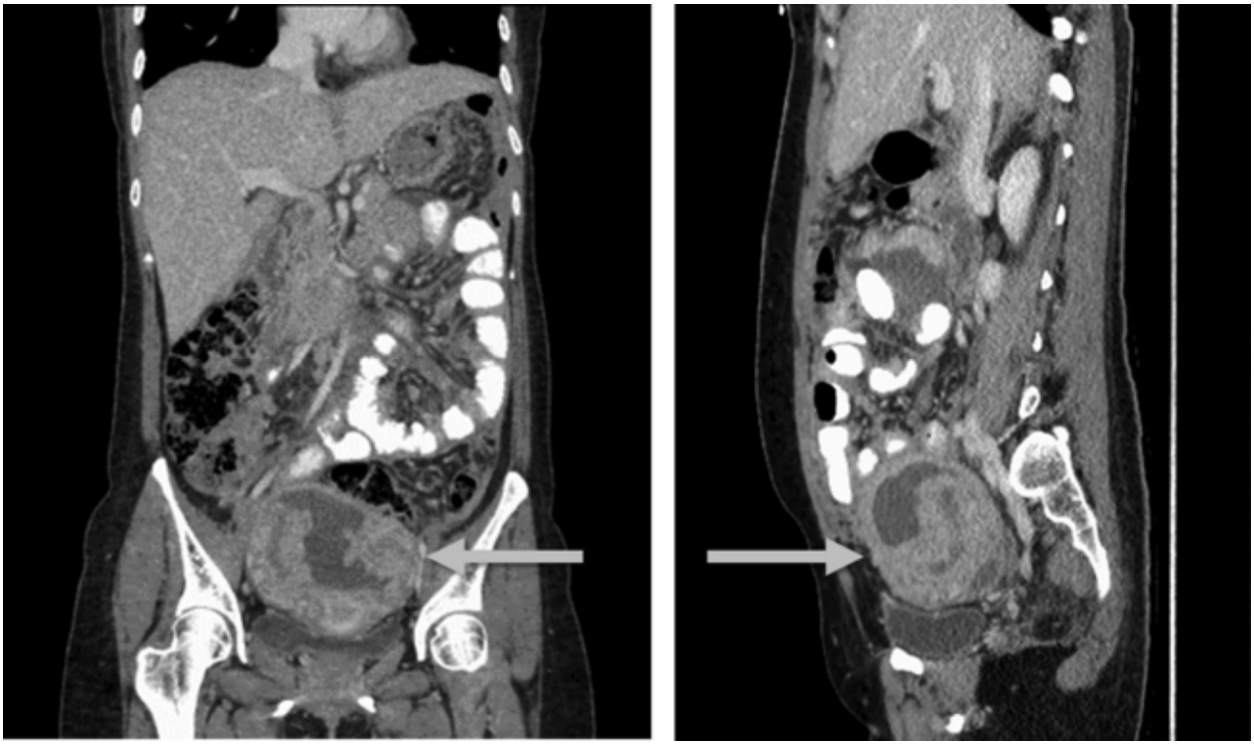

Figure 1. On CT scan, a 14 cm complex cystic/solid pelvic mass (as indicated by arrow) concerning for ovarian cancer was seen. Enlarged epicardial and parasternal lymph nodes were also noted; no parenchymal lung lesions were present. The findings were suspicious for advanced ovarian cancer.

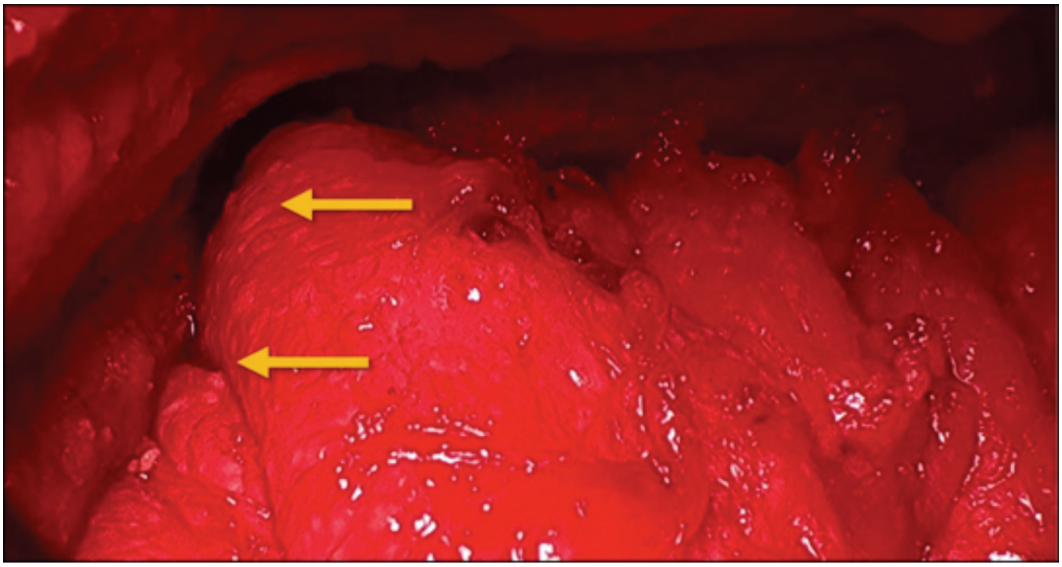

Figure 2. Innumerable pale, miliary nodules (arrows) were seen over the serosa of the small intestine and mesentery, with inflammatory, densely fibrinous adhesions throughout the pelvis. An amorphous pelvic mass encased the uterus and both ovaries.

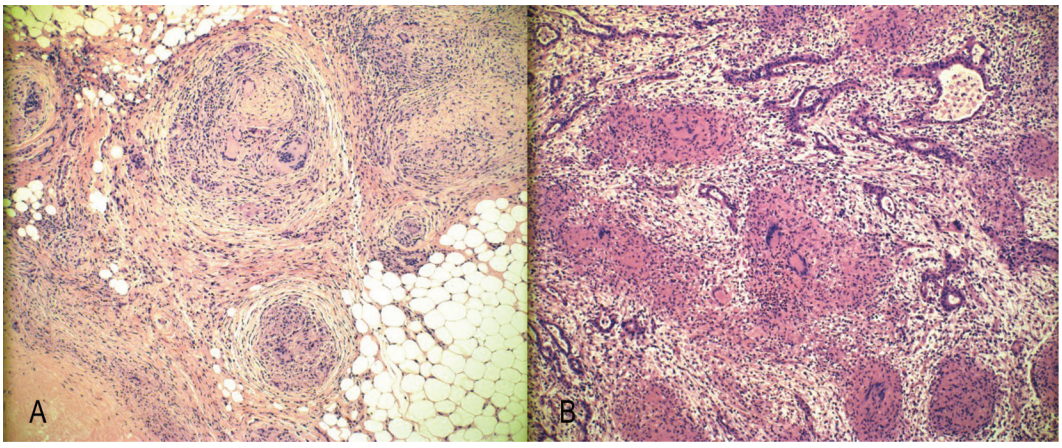

Figure 3. Multiple caseating granulomas and Langhans giant cells were seen in biopsy specimens of the peritoneum (A) and the pelvic mass (B). Rare AFB ("red snappers") were visible on Fite stain.

level, even in countries with low TB prevalence, if a patient's social or travel history is suggestive of possible TB exposure. This is particularly true for younger women, as ovarian cancer usually occurs after menopause while FGTB most commonly affects women younger than forty years old.[8,11] In our patient's case it appears likely that she contracted tuberculosis during a visit to the Philippines several months prior to the onset of her abdominal symptoms. The Philippines, which has made significant strides in controlling tuberculosis over the last decade,[12-13] remains a country with a high burden of TB with an estimated TB incidence of 324,000 cases in 2015.[13]

The mechanism by which TB increases serum CA 125 is not well understood. CA 125 has been localized by immunohistochemistry to mesothelial proliferation around tuberculous granulomas,[14] and CA 125 production by mesothelial cells is dramatically increased in the presence of various cytokines associated with tuberculosis, including IL-1 beta and TNF-alpha.[15] CA 125 levels appear to be generally higher in patients with abdominal, pelvic, or peritoneal forms of tuberculosis than with pulmonary/pleural space infections.[7,9,16-17] Because serum CA 125 levels normalize with successful TB treatment, some authors have suggested its potential utility as a biomarker to track the effectiveness of tuberculosis therapy.[9,17-19] Our patient's early, dramatic fall in CA 125 after initiating TB treatment would appear to support this approach.

The capacity of tuberculosis and other non-malignant conditions to increase serum CA 125 levels has encouraged the search for more specific cancer markers. Human epididymis protein 4 (HE4) is expressed at high levels in ovarian, endometrial, and lung cancers, and may have an important role in helping discriminate between benign and malignant causes of CA 125 elevation[20-21]—of relevance, recent reports suggest that HE4 does not appear to be increased in patients with tuberculosis.[22-24]

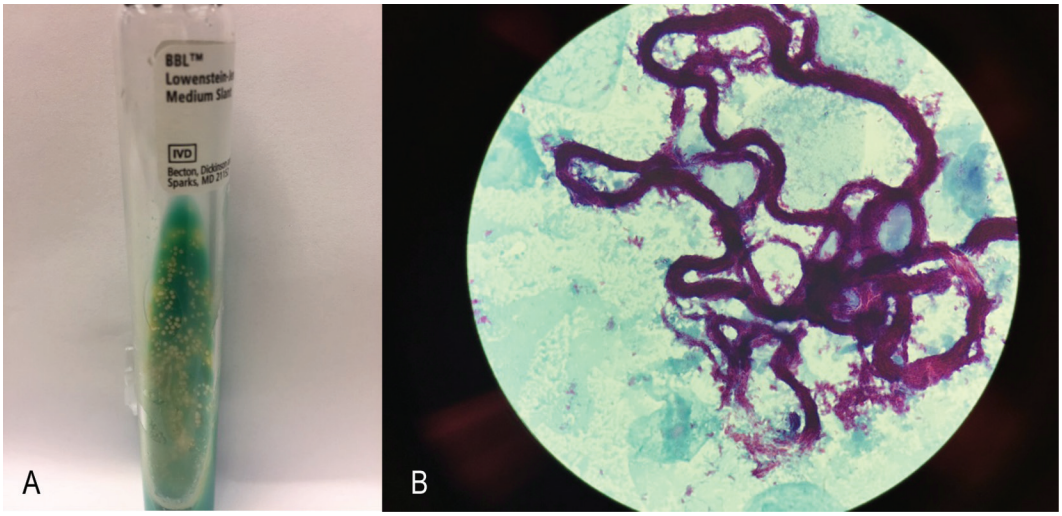

Figure 4. A culture of the patient's pelvic mass biopsy grew M. tuberculosis (MTB), shown here growing on Lowenstein-Jensen agar (A). In liquid media, "serpentine cords" of acid-fast bacilli were seen, typical of MTB (B).

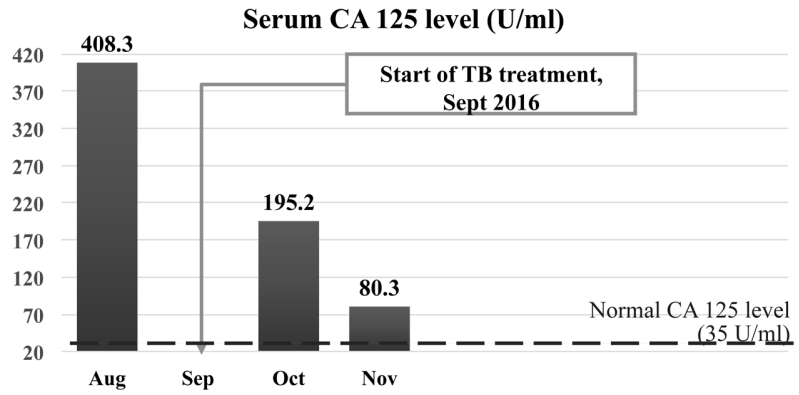

Figure 5. The patient's serum CA 125 was markedly elevated shortly prior to her diagnosis of TB, and was dramatically lower after two months of treatment.

Conclusion

Tuberculosis, like syphilis, has been termed "the great imitator." We hope that this case heightens awareness of the capacity of TB to mimic ovarian cancer in particular—mirroring not only its symptoms and radiologic findings but also raising CA 125, the tumor marker widely associated with this malignancy.

Conflict of Interest

None of the authors identify any conflicts of interest.

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