Markedly-Elevated Serum CA125 in a Woman with Cervical Tuberculosis

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Abstract

Cervical tuberculosis (TB) is an uncommon disease and accounts for 5-24% of female genital tract TB. Since it is not suspected clinically, the diagnosis of tuberculous cervicitis is often a histological surprise, even in endemic areas. Patients with chronic kidney disease (CKD) are susceptible to TB infection. The risk is 32 times higher than that in the general population. CA125, a tumor marker for ovarian cancer, may show elevation in both pulmonary and extra-pulmonary TB. Elevation of CA125 is not related to renal insufficiency. It is necessary to rule out TB infection in patients with CKD, unexplained ascites, pleural effusion, and elevated CA125. We described a dyspneic patient with CKD, pleural and pericardial effusion, in whom elevated CA125 was noted after initial survey. The patient was later diagnosed with cervical TB after cervical biopsy. Hence, it is important to pay more attention to elevated serum CA125 as it might be a biomarker in the evaluation of TB infection. (Acta Nephrologica 2011; 25: 81-85)

KEY WORDS: CA125, cervical tuberculosis, chronic kidney disease

Introduction

CA125, a mucin-like glycoprotein with a molecular weight of 110 KD, has been used primarily as a marker of epithelial ovarian cancer (1). CA125 is also expressed in the coelomic epithelium, such as the pleura, peritoneum and pericardium (2-4). Benign causes of elevated CA125, which include Mycobacterium tuberculosis (TB), liver cirrhosis, endometriosis, pelvic infection, and others, should be differentiated from ovarian cancer (5, 6).

Patients with chronic kidney disease (CKD) are susceptible to TB infection. The incidence is 32 times higher than that in the general population and it is inversely associated with renal function (7). Genitourinary TB occurs in 2-10% of pulmonary TB cases in developed countries, and 15-20% in developing countries (8). Female genital TB usually affects women below 40 years of age (9, 10). Endometrium and fallopian tube are the two most common infected sites. Cervical TB accounts for 0.1-0.65% of all cases of TB infection and 2-24% of genital tract TB (11). The infection route of cervical TB is usually via hematogenous spread from pulmonary TB, or lymphatic spread and direct extension from the genital tract. Treatment for genital TB is standard anti-TB therapy for six months (12).

We presented a patient with CKD and elevated serum CA125, who was finally diagnosed with biopsy-proven cervical TB.

Case Report

A 58-year-old woman presented to our hospital
on August 13, 2009 with complaint of general weakness and bilateral leg edema for several days. She had the history of type 2 diabetes mellitus (DM) and hypertension under irregular medication control in a local medical department. During the past three months, she had episodic diarrhea without abdominal pain, nausea, vomiting nor loss of body weight. Laboratory data revealed blood urea nitrogen (BUN) 24 mg/dL, creatinine (Cr) 2.1 mg/dL, estimated GFR 25.7 mL/min calculated by Modification of Diet in Renal Disease formula, cholesterol 464 mg/dL, triglyceride 478 mg/dL and glucose (AC) 170 mg/dL.

Upon admission on August 18, 2009, chest X-ray revealed bilateral pleural effusion and cardiomegaly. Blood chemistry showed BUN 34 mg/dL, Cr 3.1 mg/dL, sodium 135 mmol/L, and potassium 2.95 mmol/L. The complete cell count showed white cell count (WBC) 9540/µL, hemoglobin 7.6 g/dL, hematocrit 22.8% and platelet 161,000/µL. Urinalysis showed proteinuria with daily urinary protein 2093 mg. There were no occult blood nor growth of salmonella or shigella in stool. Panendoscopy disclosed gastro-esophageal reflux disease and gastritis. The anemia was attributed to CKD, DM and chronic illness. Diagnostic thoracocentesis revealed clear effusion, with lactate dehydrogenase (LDH) 71 U/L, total protein (TP) 1.0 g/dL and glucose 113 mg/dL. The serum LDH was 344 U/L, TP 6.6 g/dL, albumin 2.9 g/dL, glucose 100 mg/dL. The cell count of effusion showed WBC 126/µL, polymorphic neutrophils (PMN) 3%, lymphocyte 30%, monocyte 67%, and methothelial cell 3%. The culture of pleural effusion grew no bacteria, fungus or TB. Further survey of pleurisy was not performed because of relatively low lymphocyte count and transudative effusion. The transudative effusion was attributed to CKD and volume overload initially. Duretic therapy was given to her empirically.

On August 28, 2009, she complained of chest discomfort, accompanied by dyspnea. Echocardiography was performed under suspicion of ischemic heart disease, and showed mild pericardial effusion without tamponade sign and proper left ventricular function. As for survey on pericardial effusion, antinuclear antibody was negative, and tumor markers showed carcinoembryonic antigen (CEA) 0.55 ng/mL (reference range 0-7), CA125 421 U/mL (reference range 0-35) and CA199 less than 2 U/mL (reference range 0-37). Genitourinary tract malignancy should be ruled out because of high CA125 level. Her medical history showed that she was menopausal and had urinary incontinence. She had no childbirth, abnormal vaginal bleeding, low abdominal pain, or postcoital bleeding. Pelvic examination revealed irregular nodular surface of cervix. The gynecologic echography showed mild ascites and normal adnexa. The cell count of ascites showed WBC 23/µL, PMN 1%, lymphocyte 53%, and monocyte 46%. The culture of effusion grew no bacteria, fungus or TB. There was no malignant cell in the ascites. Cervical biopsy showed small focus of caseous necrosis surrounded by abundant epithelioid cells, granulomas, Langhans’s giant cell, lymphocyte and fibrostic tissue (Fig. 1). Acid fast stain disclosed an acid fast bacillus in the granuloma (Fig. 2). Anti-TB therapy, consisting of isoniazid (INH) (300 mg/day), rifampin (RIF) (600 mg/day), and pyrazinamide (PZA) (1500 mg three times per week, with renal dosage adjustment), was prescribed to her. Ethambutol (EMB) was not given for fear of ocular toxicity due to her poor compliance. After discharge, she received directly observed therapy (DOT). However, she was admitted in January 2010 for spontaneous intracranial hemorrhage and died 10 days later. Decrease in amount of pleural effusion was noted by chest plain film, which might be related to diuretic therapy or anti-TB therapy. There were no follow-up of serum CA125 level or amount of pericardial effusion.

**Discussion**

Patients with CKD are susceptible to tuberculosis infection. Yuan et al. found inverse association between renal function and TB. They identified 71 cases of TB from 1498 Chinese patients with CKD.
from 1997 to 2002. The incidence was 31 times higher than that in the general population during the same period (7). Retrospective studies of patient on maintenance hemodialysis have led to estimates of a 10-25-fold risk of TB infection (13). The increase in susceptibility may be related to impaired cellular immunity in patients with CKD.

Genitourinary TB occurs in 2-10% of pulmonary TB cases in developed countries, and the percentage rises up to 15-20% in developing countries. However, the actual frequency of female genital TB is underestimated because it is often under diagnosed in asymptomatic patients (8, 10, 14). More than 90% of patients having female genital TB are under the age of 40, which implies possible hormonal effect. In postmenopausal women, genital TB is rare and accounts for 1% of patients with postmenopausal bleeding. The exact cause of low incidence of the disease in this age group is not known (15, 16). Most authors believe that an atrophic endometrium is a poor milieu for the growth of mycobacterium tuberculosis. Genital TB usually has an indolent course and it takes years to come into clinical notice after initial seeding (10).

Patients with genital TB present with infertility (44%), pelvic pain (25%), abnormal vaginal bleeding (18%), amenorrhea and vaginal discharge (5%), and post-menopausal bleeding (2%) (9). Saracoglu et al. found no anomalies (43%), adnexal mass (23.6%), myomalike lesion (23.6%), adnexal tenderness (4.2%), irregular uterus (1.4%), and cervical polyp (1.4%) on pelvic examination (17). Mondal and Dutta found that the endometrium is involved in 56% of cases, fallopian tubes in 24%, ovaries in 15%, and cervix in 6% (10).

For laboratory study of genital TB, a high erythrocyte sedimentation rate is non-specific but only indicates inflammation. Mantoux test or purified protein derivative (PPD) test showed a sensitivity of 55% for genital TB in populations with a low TB prevalence (18). The PPD test might be falsely negative in immunocompromised or malnourished patient. The validity of PPD test is often falsely positive in population living in endemic region and receiving regular bacille Calmette-Guérin (BCG) vaccine. Body fluid study may show dominance of lymphocyte, elevated adenosine deaminase (> 30 U), and low methothelial cell count (< 5%). Polymerase chain reaction is a rapid, sensitive, and extensively applicable method for detecting TB. The gold standard remains the proof of acidfast bacilli in biological specimens or culture. The Pap smear of our patient was negative as Gupta et al. reported that direct smears were uncommonly positive (19). Culture of menstrual fluid or blood has a good yield for positive culture (20). Microscopic examination of acid-fast bacilli requires at least 10,000 organisms per milliliter in the specimen. Culture is more sensitive, requiring only 100 organisms per milliliter. It may take as long as 8 weeks to grow on Lowenstein-Jensen medium. Hysterosalpingogram shows coronal or fimbrial block, beaded tube, or hydrosalpinx in more than 70% of patients. Ultrasonographic finding includes adnexal mass, thickened omentum, and ascites. Laparoscopic examination in patients with genital TB showed that 59% of them had abnormal fallopian tubes and consented to have direct biopsy performed (11). It is mandatory to perform direct biopsy of the affected site for establishing the diagnosis.

The uterine cervix is infected by hematogenous spread, by lymphatic spread, or by direct extension. In rare cases, cervical TB may be a primary infection, introduced by a partner with tuberculous epididymitis or other genital disease. Gross finding of TB cervicitis includes extensive ulceration, and reactive atypical hyperplasia of the cryptal epithelium with friable papilla formation. Microscopically, TB cervicitis is characterized by the presence of multiple granulomas or tubercles, accompanied by caseous necrosis surrounded by epitheloid histiocytes and multinucleated giant cells of Langhans. The features can resemble carcinoma both macroscopically and microscopically (16, 21). If specimens reveal granulomas without proof of acid fast bacilli by TB culture or PCR, the cause of granulomatous cervicitis should be differentiated. The differential diagnosis of granulomatous cervicitis includes amoebiasis, schistosomiasis, bru-
cellosis, tularaemia, sarcoidosis, and foreign body reaction (22). We reviewed four case reports of TB cervicitis and summarized the clinical presentation, pelvic finding, and biopsy result in Table 1 (12, 22-24).

Most authors suggest standard anti-TB therapy for patient with cervical TB, which consisted of INH 5 mg/kg/day, RIF 10 mg/kg/day, EMB 15 mg/kg/day, and PZA 25 mg/kg/day for two months, followed by INH and RIF for another four months. Serial biopsy usually confirms a therapeutic response (12, 24). For first-line anti-TB therapy, INH and RIF are metabolized by liver and require no renal dosage adjustment. About 80% of EMB is excreted unchanged by kidney and renal dosage adjustment is indicated to prevent irreversible ocular toxicity. The dosage of EMB is 15 mg/kg/day in patient with CKD stages 1-3 and 15 mg/kg three times per week in patient with CKD stages 4-5. Although PZA is metabolized largely by the liver, one study of its elimination found much higher level detectable for up to 48 hours after administration. The dose of PZA is adjusted to 25 mg/kg three times per week in patients with CKD stages 4-5 (13).

CA125 is a glycoprotein of high molecular weight, which is detected by the monoclonal antibody OC 125, first described by Bast et al. in 1981 (25). CA125 is elevated in a variety of malignant and benign conditions, including ovarian cancer, lung cancer, Mycobacterium tuberculosis, liver cirrhosis, endometriosis, pelvic infection and others (5, 6). CA125 is expressed by cells of coelomic epithelium. It is determined in normal mesothelial lining cells by immunohistochemical methods and in normal bronchial epithelial cells by immunoperoxidase staining technique (4). If these cells are activated by physiological or pathological reactions such as menstruation, inflammation or tumorigenesis, they secret CA125. Therefore, the concentrations of CA125 increase in serum and other body fluids (2, 3). Renal disease may cause elevation of tumor marker concentration, especially CEA and cytokeratins. CA125 might be elevated in TB and in TB peritonitis, which was not due to renal insufficiency (26). Andrew et al. demonstrated that even marked renal insufficiency was not itself associated with significant elevation of CA125 (27). Tzitzikos et al. found that CA125 was slightly increased in one out of 30 patients on maintenance hemodialysis, and the cause of CA125 elevation was attributed to active hepatitis C (28).

In cases with elevated CA125, the patient’s history and presenting complaints must be properly evaluated for the differential diagnosis. Initial investigations like pelvic ultrasonography should be performed to exclude ovarian pathology. A secondary survey for pericardium, peritoneum, and pleura should be obtained in the absence of ovarian pathology (29).

There are emerging case reports and small-scale studies demonstrating the relationship between activity of TB and elevation of CA125. Kanagarajan et al. reported elevated CA125 in both pulmonary and extra pulmonary TB, except TB lymphadenopathy (30). Yilmaz et al. found CA125 level to be a marker of 97.5% sensitivity and 100% specificity for estimation of pulmonary TB activity. Their study suggested that it was reasonable to use CA125 for monitoring rather than screening the disease (31). However, Kalantri et al. observed that CA125 was not elevated in 9 of the 10 cases of pulmonary TB without pleural effusion. The observation pointed out that pulmonary TB without involvement of mesothelium might not
evoke elevation of CA125 (32). The evidence of the association between TB and CA125 is strongest in the cases of TB peritonitis, which exhibit highly elevated CA125 level (33).

Patients with genital TB present with a symptom complex similar to that of ovarian cancer, i.e., abdominal distension, pelvic tumor, and ascites. CA125 is very often ordered in the diagnostic work-up. Its elevation can be attributed to any peritoneal infectious process. Genital TB without peritoneal involvement is less likely to evoke an elevated CA125 level. Therefore, in our case, the serosal involvement should be ruled in by elevated CA125 level and ascites. Negative bacteriological studies of the pleural effusion and ascites could not exclude peritoneal or pleural TB (31).

In conclusion, we emphasized the need to investigate the possibility of genital TB, including detailed history taking, pelvic examination, ultrasonography, endometrial fluid sampling for TB AFS, culture, and PCR, and direct biopsy for microscopic diagnosis, if patients noted to have ascites, abdominal discomfort, and elevated CA125 level. Anti-TB chemotherapy should be prescribed for at least six months according to patient’s renal function.

References