

CASE REPORT

Peritoneal Tuberculosis Mimics Ovarian Cancer: A Case Report

Jesús Solier Insuasty Enríquez¹, Adrián Bolívar², Lauren Sofía Calvo^{2*}, Sandra Liliana Roberto²

¹Internista Oncólogo Clínico, Unidad de Oncología Hospital Universitario de Santander, Profesor Departamento de Medicina Interna Universidad Industrial de Santander-UIS, Grupo Germina, Bucaramanga, Colombia

²Médicos Universidad Industrial de Santander, Bucaramanga, Colombia

Abstract: Peritoneal tuberculosis is a form of abdominal and/or pelvic tuberculosis. This entity can sometimes imitate ovarian cancer clinically, and is accompanied by an increase of serum cancer antigen 125 (CA-125) level, which may make the differential diagnosis between the two diseases a challenge for clinicians. We report herein a case of a 49-year-old woman whose symptoms, signs, imaging and laboratory findings suggested ovarian cancer, and document the risk factors for the development of tuberculosis. Finally, the diagnosis of peritoneal tuberculosis can be obtained through further research and appropriate data analysis. The purpose of this case is to improve the medical community's understanding of the importance of distinguishing peritoneal tuberculosis in patients with suspected ovarian cancer, so as to make accurate differential diagnosis and avoid subjecting patients to unnecessary surgery.

Keywords: Rheumatoid arthritis, Ovarian tumor, Tuberculosis, Risk factors, Tuberculous peritonitis, CA-125 anesthetics, Solid tumors, Apoptosis

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*CORRESPONDING AUTHOR

Lauren Sofía Calvo
E-mail: laurensofiac@hotmail.com

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1. Introduction

The Out of all gynecological cancers, ovarian cancer is the leading cause of death in the United States. It has estimated that about 22,240 new cases would be diagnosed in the United States in 2013, and the estimated death toll would be 14,030^[1]. In the United States, less than 2% women are likely to develop ovarian cancer^[1]. Globally, ovarian cancer was the seventh most common cancer in women in 2008, with the highest incidence in developed countries^[2]. In Colombia, the incidence of ovarian cancer ranks seventh among the general population (men and women) and seventh among women. The age-standardized rate is close to 8 per 100,000 residents, with an annual incidence of 4.7%, which is much higher than the global incidence (1.8%) and the incidence in the Americas (1.6%). In 2008, 1,457 new cases and 730 deaths were reported^[3].

In the West, the incidence of tuberculosis and extrapulmonary tuberculosis is rising at the cost of increased human immunodeficiency virus (HIV) infection^[4] and at the cost of immunosuppressive therapy, which plays an increasingly important role in promoting this increase.

The determination of serum glycoprotein cancer antigen 125 (CA-125) level is the most widely used biochemical method to detect ovarian cancer. About 50% of women with early disease and more than 80% of women with advanced ovarian cancer have elevated serum CA-125 levels^[5]. However, the specificity of CA-125 is limited. About 1% of healthy women have elevated CA-125 levels,

which fluctuate during the menstrual cycle^[6]. The level of CA-125 also increases under various benign and malignant conditions.

Tuberculosis caused by *Mycobacterium tuberculosis* is a global health problem, especially for developing countries^[6-8]. In 1993, it was declared a global emergency by the World Health Organization (WHO). In 2010, the global estimated incidence was 128 cases per 100,000 people, of which Asia and Africa had the highest incidence (2–5 cases per 100,000 people). It is estimated that between 2000 and 2020, nearly 1 billion people would be infected, 200 million people would become ill, and 35 million people would die of tuberculosis^[6,8-10].

In Colombia, the estimated incidence of tuberculosis was 24.5 per 100,000 inhabitants in 2011. Although new tuberculosis cases have decreased in the past decade, the proportion of extrapulmonary tuberculosis has increased from 14% to 20%, indicating that despite the progress made in the prevention, diagnosis and treatment of tuberculosis, the spread of extrapulmonary tuberculosis still cannot be controlled^[6,11].

Peritoneal tuberculosis is an abdominal and/or pelvic tuberculosis that can involve the liver, spleen, omentum and gastrointestinal tract^[6-8,12]. This clinical entity can be manifested in three different forms: wet ascites, dry adhesion or fibrosis, greater omentum thickening and ventricular ascites. However, in most cases, it is a combination of abdominal pain/pelvic pain, weight loss, fever, abdominal distension, infertility, irregular menstruation, adnexal mass, and/or ascites^[5,6,13]. These symptoms and signs are nonspecific and could be reminiscent of symptoms and signs caused by ovarian cancer, so it is difficult to distinguish the two clinical entities. The following is a case of peritoneal tuberculosis imitating ovarian cancer. It is speculated that the drug treatment of rheumatoid arthritis (RA) might be involved in the origin of the disease.

2. Case presentation

The current report presents a case of 49-year-old woman from Santander, Colombia, with intermittent fever, chills, and fatigue. The patient was accompanied by extensive uremic abdominal pain, mainly manifested in lower abdomen, abdominal distension, nausea and vomiting. Her medical history showed that they were used to diagnose and treat rheumatoid arthritis with flutamide and meloxicam 7 years ago and adalimumab 4 years ago. The contact history of patients who underwent hysterectomy four years ago and diagnosed with pulmonary tuberculosis five years ago was successfully obtained. Physical examination revealed decreased floor ventilation of the right lung

and vocal cords. Slight abdominal distension, palpation pain, positive ascites wave, and no mass or visceral enlargement were reported.

The patient's chest X-ray showed right pleural effusion, and abdominal ultrasound showed mixed content masses, including pelvic cavity, diaphragm and excreta, as well as a large amount of cell fluid. The laboratory findings are as follows: lactate dehydrogenase 570 U/L, hemoglobin 10.9 g/dl, leukocyte 3,000 /L and C-reactive protein 192 mg/dl. Pulmonary ultrasonography showed that the effusion in the right pleural septum was about 430 C, without further change. Abdominal puncture was performed to extract 500 ml of the light yellow and turbid liquid. Ziehl-Neelsen staining was negative, and acid-resistant bacilli (BAAR) was detected. Gram-negative flora and cytology results were negative. Adenosine deaminase (ADA) and ascites culture were negative. Chest computed tomography (CT) axial scan showed small calcified granuloma in the lung field and a low-density area in the right hilar, which may correspond to some adenomas. For suspected pneumonia, clarithromycin and ampicillin were used for treatment, and thoracoscopy was performed. The results showed that the liquid was yellow, turbid and dominated by lymphoblasts, Ziehl-Neelsen staining and Gram-negative flora were negative. ADA level was 100 U/L (normal 0–45 U/L). Potassium hydroxide (KOH) examination and culture were negative. Cytological examination showed a moderately active chronic inflammatory process. The standard of light is negative exudate. Similarly, bacterial examination and sputum culture were negative. The level of CA-125 was 187 U/ml (normal 0–35 U/ml), and HIV-1 and HIV-2 antibodies were negative.

A new abdominal ultrasound examination ruled out pelvic cystic and solid masses, and abdominal double contrast CT showed the process of peritoneal infiltration. With this in mind, in the previous contact with patients with pulmonary tuberculosis, lymphocyte exudation in pleural effusion and cytological examination showed chronic inflammatory process, elevated ADA level, bilateral pleural and peritoneal thickening. In the imaging study, class 1 phase 1 anti-tuberculosis treatment was started.

Finally, thoracoscopy showed that there were multiple micro-adjustments on the white pleura, and the pleural fluid was clear. We took biopsies of parietal pleura and pulmonary wedge. Histological Ziehl-Neelsen staining showed that the amount of BAAR was low. In addition, no malignant tumor was found, and chronic granulomatous inflammation was observed. It was composed of granuloma, accompanied by central caseous necrosis and obvious mononuclear inflammatory infiltration. Therefore, we confirmed and

decided to continue anti-nucleation treatment on the patient, who was discharged after the rheumatism was under control.

3. Discussion

The usefulness of diagnostic studies that can be used to detect peritoneal tuberculosis is limited because this entity can mimic ovarian cancer both in radiological studies and at the laboratory level. The usefulness of imaging-based methods, such as ultrasound, CT and MRI, in the detection of peritoneal tuberculosis is limited due to the narrow size and distribution of peritoneal implants. In addition, peritoneal tuberculosis can also imitate pelvic masses and lead to peritoneal thickening, similar to peritoneal thickening caused by cancer. Since the results of ultrasound examination are highly operator-dependent, we cannot be rule out that the final interpretation may be a false positive^[8,12].

Both transabdominal ultrasound and transvaginal ultrasound can be used for detecting ovarian cancer. Transvaginal ultrasound has better and easier access to the ovary (regardless of the patient's abdominal wall fat). The upper limit of normal ovary in premenopausal women is 20 ml and that in postmenopausal women is 10 ml. Ultrasound interpretation should consider the presence of capsule wall spacing or irregularity^[14]. In this regard, it is worth noting that in studies involving women with clinically detectable ovarian cancer and other prospective screening studies, the sensitivity of ultrasound as an observation-dependent result ranges from 80% to 100%^[15]. In screening studies, the specificity ranges from 94% to 99%, including two studies on women with a history of familial ovarian cancer^[16-18]. However, it must be emphasized that even in high-risk patients, transvaginal ultrasound cannot effectively detect early ovarian cancer. This may be more effective when used with determination of CA-125 level for screening, but the predicted values of ultrasound and CA-125 are still low^[18].

At the laboratory level, the level of CA-125 increases. This serum marker is usually used in the diagnosis of ovarian cancer. High levels are found in 80% of patients with ovarian malignancies, but it is usually not specific when interpreted alone, because high levels of serum markers are found in healthy people and other diseases (hysteromyoma, endometrial cancer, breast cancer, lung cancer and pancreatic cancer), Pelvic inflammation, acute pancreatitis, endometriosis, cirrhosis with or without ascites, pleural or peritoneal effusion of any cause, and peritoneal tuberculosis^[19]. According to a research report, about 90.1% to 100% of patients had elevated tumor marker levels, with an average of 565 U/ml^[20]. Therefore, considering nonspecific symptoms, uncertain radiological and laboratory studies, and the low

incidence of peritoneal tuberculosis and ovarian cancer (136 cases reported in the United States in 1999 and 26,800 cases reported in 1997 (5)), peritoneal tuberculosis is often mistaken for ovarian cancer. The studies by Ulusoy *et al.* and Uzunkoy *et al.* showed that the proportion of patients with peritoneal tuberculosis diagnosed with ovarian cancer ranged from 1.2% to 1.4%^[12,22].

In this case, the patient's symptoms and initial ultrasound findings of pelvic mass, coupled with high levels of CA-125, could be mistaken for a diagnosis of ovarian cancer. However, subsequent studies and appropriate analysis of the data obtained enable timely and accurate diagnosis of peritoneal tuberculosis, avoiding unnecessary surgery. In a retrospective study of 11 patients finally diagnosed with abdominal tuberculosis, 9 patients underwent highly invasive surgery (laparotomy or laparoscopy) due to the initial clinical suspicion of intraperitoneal tumors, making them unnecessarily exposed to the risks involved in these operations^[11].

Therefore, it is important to consider peritoneal tuberculosis in the differential diagnosis of patients with adnexal masses and ascites, especially those from countries with high tuberculosis prevalence, because misdiagnosis will not only delay the correct treatment of the disease, but also lead to chemotherapy (and its corresponding complications), unnecessary surgical procedures, and even death.

Abdominal tuberculosis is a relatively rare but emerging disease in Western countries. Its pathophysiology includes lymph or blood diffusion of primary lung lesions, and may involve different abdominal structures, such as gastrointestinal tract, peritoneum, solid organs or lymph nodes^[4]. Overall, it accounts for 12% of extrapulmonary tuberculosis cases and 1%–3% of total nuclear disease cases^[21,22].

Many cases have been shown to be associated with an increased risk of developing tuberculosis, among which the status of immunosuppression is prominent, such as in HIV-infected patients, and the high prevalence of pulmonary and extrapulmonary tuberculosis has been widely documented. Although rheumatoid arthritis is associated with a threefold increase in the risk of tuberculosis in the general population, the risk of tuberculosis has doubled due to the use of some modified anti-rheumatic drugs^[23]. Therefore, many tuberculosis cases have been reported in the treatment of rheumatoid arthritis with corticosteroids, parathyroid hormone, tumor necrosis factor alpha (TNF- α) inhibitor and leflunomide^[24].

TNF is a proinflammatory cytokine, which plays an important role in the pathogenesis of androgen (AR)^[25]. In addition, it plays an important role in the immune response to various bacterial infections of

tuberculosis infection^[26]. It has been observed that the use of TNF antagonists (anti-TNF) such as infliximab, etanercept and adalimumab has been found to be associated with an increased risk of developing TB and to a lesser extent other infections such as candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, leprosy and nocardiosis^[25,27,28]. However, the mechanism involved in this phenomenon is not limited to the reduction of TNF-mediated immune response; studies have shown that anti-TNF changes the inherent and adaptive response of different cell lines to *Mycobacterium tuberculosis*, partly due to the changes of phagocytic activity and apoptosis mechanism. Changes in interferon and T cell secretion and other mechanisms lead to increased susceptibility to infection and bacterial reactivation through different pathways^[26]. As reported in the literature, anti-TNF monoclonal antibody adalimumab has been used for treating pulmonary and extrapulmonary tuberculosis. Azevedo *et al.* reported a case of splenic tuberculosis in a patient with ankylosing spondylitis who began taking adalimumab after a clinical tuberculosis test and normal chest X-ray one year ago^[29]. Similarly, Blanco *et al.* recorded cases of two patients with rheumatoid arthritis and one patient with ankylosing spondylitis who developed tuberculosis during adalimumab treatment, although some scientific associations issued recommendations on preventing the recurrence of latent tuberculosis in patients treated with anti-TNF^[27-30]. These findings not only confirm the relationship between the use of these drugs and the risk of tuberculosis, but also draw attention to the continuous evaluation of screening and preventive measures to prevent this complication.

Due to the side effects described in the literature using anti-TNF, some preventive measures must be considered before anti-TNF is included in the treatment regimen^[30,31]. These drugs are banned in pregnant or lactating women, patients with grade III and IV functional heart failure according to the New York Heart Association, high-risk patients with active infection or development of active infection, recurrent pulmonary infection, multiple sclerosis, and patients with current diagnosis or a history of cancer in the past five years^[31]. With regard to the specific risk of tuberculosis, isoniazid is recommended for any patients who receives anti-TNF treatment and has the following characteristics: (i) a history of untreated or partially treated tuberculosis; (ii) a history of exposure to active tuberculosis cases; (iii) chest X-ray showing residual changes of primary pulmonary tuberculosis; and (iv) final hardening with diameter greater than or equal to 5mm in tuberculin test^[30].

Leflunomide is an anti-rheumatic drugs with immunomodulatory, immunosuppressive and

antiproliferative properties. Through de novo inhibition of pyrimidine synthesis, it can significantly improve the symptoms and signs of rheumatoid arthritis, even if it shows a slight advantage in improving all aspects of the disease, such as quality of life and patients' perception of improvement, compared with other anti-rheumatic drugs^[32]. Its use is also associated with an increased risk of tuberculosis, which is related not only to its immunosuppressive properties, but also to its anti-TNF activity^[20,32]. Therefore, various studies have reported the development of pulmonary and extrapulmonary tuberculosis in patients during leflunomide monotherapy and in combination with other anti-rheumatic drugs^[20,24,28]. Hocevar *et al.* reported the development of 5 cases of pulmonary tuberculosis, of which 4 patients with rheumatoid arthritis received leflunomide monotherapy and 1 patient with adolescent chronic arthritis received leflunomide and methotrexate^[24]. On the other hand, Grover *et al.* recorded a patient with rheumatoid arthritis who was diagnosed with Pott disease after the treatment with methotrexate and leflunomide^[20]. Therefore, it is worth noting that this drug not only increases the risk of tuberculosis, but also is related to other manifestations. The location of these manifestations may hinder early diagnosis. Therefore, these patients, especially those living in areas with high incidence of tuberculosis, need to be carefully evaluated.

Although peritoneal tuberculosis is a rare disease, peritoneal tuberculosis should be considered in the differential diagnosis of patients with adnexal masses and ascites, especially those from countries with high tuberculosis prevalence, as well as patients receiving immunosuppressive therapy, because, as mentioned above, the latter implies an increased risk of the development and/or reactivation of pulmonary and extrapulmonary tuberculosis infection.

Conflict of interest

The authors declared no conflict of interest.

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