

Peritoneal tuberculosis and peritoneal carcinomatosis: differential diagnosis

Tuberculose peritoneal e carcinomatose peritoneal: diagnóstico diferencial

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ABSTRACT Peritoneal tuberculosis accounts for 1-2% of all tuberculosis cases and invariably imposes a difficult diagnosis. The disease presents with a wide spectrum of clinical manifestations of which fever and abdominal pain are the most frequent. Here, we report the clinical case of a 48-year-old woman who had ascites, fever, and weight loss and was initially diagnosed with ovarian cancer and peritoneal carcinomatosis. Further investigation, including laboratorial exams and omental biopsy resulted in the diagnosis of peritoneal tuberculosis without lung tuberculosis. The patient presented favorable response to the standard treatment. The objective of this report is to emphasize that, among the myriad of diseases that can affect the peritoneum, tuberculosis peritonitis should be considered as a differential diagnosis, particularly when the patient presents ascites and an unspecific abdominal condition. In addition, we present an in-depth discussion of the main findings and investigative approach for peritoneal tuberculosis.

Keywords: Peritoneal tuberculosis; Ascites; Abdominal pain.

RESUMO: Tuberculose peritoneal é uma doença de difícil diagnóstico e representa cerca de 1-2% das formas desta infecção. Sua apresentação clínica é variada e inespecífica, sendo dor abdominal e febre os achados mais frequentes. Relata-se caso de paciente do sexo feminino, de 48 anos, com ascite, febre e perda ponderal, cujo diagnóstico inicial era câncer de ovário com carcinomatose peritoneal. A investigação adicional com exames laboratoriais e biópsia de omento estabeleceram o diagnóstico de tuberculose peritoneal. Não havia tuberculose pulmonar. Foi feito tratamento específico com resposta satisfatória. O presente trabalho objetiva ressaltar que, dentre as diferentes patologias que acometem o peritônio, a peritonite tuberculosa deve ser um diagnóstico considerado, principalmente na presença de ascite e quadro abdominal inespecífico e discutir os principais achados e a abordagem investigativa.

Palavras-chave: Tuberculose peritoneal; Ascite; Dor abdominal.

INTRODUCTION

Peritoneal tuberculosis is a disease that often leads to a difficult diagnosis. Because of its unspecific clinical presentation, physicians tend to underestimate its existence. In fact, the peritoneum represents the sixth most common anatomical site of extrapulmonary tuberculosis corresponding to 1-2% of all forms of this infection^{1,2}.

Peritoneal tuberculosis affects predominantly young adults in the 3rd and 4th decades of life; however, it can occur at any moment during the lifetime³. Greatest incidence occurs in patients with severe comorbidities, particularly AIDS⁴ patients; in general, this particular group of patients present disseminated tuberculosis associated with the severe immunodeficiency condition.

In this report, we present the case of a 48-year-old woman with ascites, abdominal pain and fever, initially

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diagnosed as ovarian cancer with peritoneal carcinomatosis, with a final diagnosis of tuberculous peritonitis. We present clinical and laboratorial features that key to establish the differential diagnoses; moreover, we discuss the main caveats that should be considered in the investigation of this medical condition.

CASE REPORT

We report the case of a 48-years-old, woman, born in in the town of Almenara in the northeast region of the State of Minas Gerais and currently residing in the town of and Cosmópolis in the central region of the State of Sao Paulo. She was previously healthy, with a report of a left ovarian neoplastic cyst under follow-up for 5 years. In addition, she was a former smoker (4 pack-years) and social drinker. She sought medical attention for an increase in abdominal volume three weeks prior to consultation. The abdominal volume increased mostly in the afternoons and also presented with postprandial worsening. The patient also complained of unmeasured weight loss and episodes of fever of about 38°C at no preferential time. Moreover, she reported daily contact, for a year before the onset of symptoms, with a patient diagnosed with pulmonary tuberculosis. On physical examination, the only changes found were cutaneous-mucous pallor and massive ascites. Serological tests for HIV, syphilis and hepatitis C virus were negative, rheumatoid factor and antinuclear factor (ANA) were not reactive. There was immunological memory to the hepatitis B virus. On admission, the patient presented with 13.2 g/dL hemoglobin, C-reactive protein (CRP) 273 mg/L, 0.64 mg/dL creatinine, glycated hemoglobin 6.4%, total bilirubin 0.61 mg/dL, international standardized ratio (INR) 1.02 and albumin 3.7 g/dL.

A transvaginal ultrasound was performed, which

revealed a complex left-side ovarian tumor, with a high risk of malignancy, in addition to a diffusely thickened epiploon and implants in the paramesocolic wall on the left. Abdominal tomography showed a nodule in the parietal peritoneum, with densification of omental adipose planes (omental cake), suggestive of peritoneal carcinomatosis.



Figure 1. Abdominal computed tomography scan showing the omental thickening (omental cake).

The initial diagnostic hypothesis was advanced ovarian cancer with secondary implant and neoplastic ascites. During hospitalization, the patient had fever of about 38 °C, especially in the afternoon, without improvement with broad-spectrum antibiotic therapy. Blood cultures for mycobacteria, fungi and bacteria were negative.

Two diagnostic paracenteses were performed, which revealed a predominance of lymphomononuclear cells (77% and 100%, in each paracentesis, respectively), normal glucose, absence of bacterial structures and epithelial cells on bacterioscopy, absence of neoplastic cells, negative oncotic cytology, negative rapid molecular test for tuberculosis, and increased adenosine deaminase (ADA) 47.6 (reference value up to 33.0 U/L) (Table 1).

Table 1: Ascitic fluid analyzes performed during hospital stay.

Ascitic fluid	28/05/2020	04/06/2020
Lactate dehydrogenase	299 U/L	323 U/L
Glucose	84 mg/dL	82 mg/dL (serum: 91mg/dL)
Protein	4.6 mg/dL	NR
Albumin	2.6 g/dL	2 g/dL (serum: 3.7g/dL)
White blood cells	380/mm3 (77% lymphomononuclear cells)	145/mm3 (100% lymphomononuclear cells)
Mesothelial cells	Rare	Rare
Adenosine Deaminase	47.6 U/dL	46.2 U/dL
Bacterial culture	Negative	Negative
Gram stain	Rare white blood cells	Rare white blood cells
<i>M. tuberculosis</i> culture	Negative	NR*
Direct fungal test	Negative	Negative
Rapid molecular test for <i>M. tuberculosis</i>	NR	Negative
Oncotic citology	Negative	Negative

Source: UNICAMP Clinical Pathology Laboratory

NR not realized

An omental biopsy was performed, which resulted in the identification of a chronic granulomatous inflammatory process, with focal caseous necrosis, which was not compatible with the main diagnostic hypothesis up to that time.

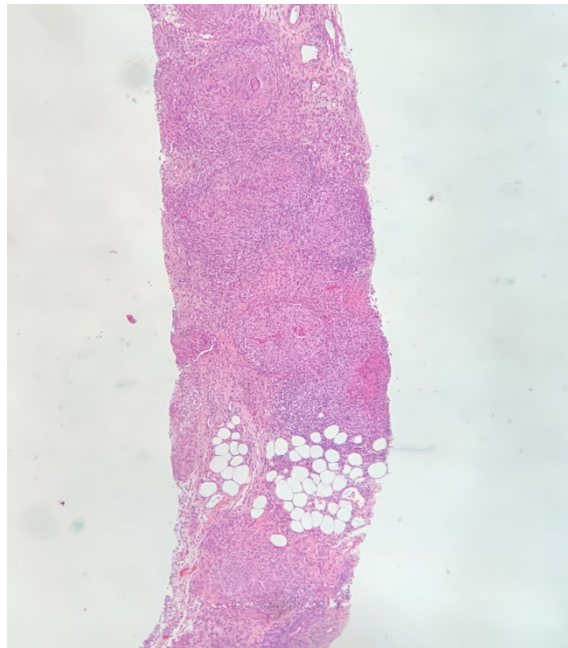


Figure 2. Omental biopsy stained with Hematoxylin-Eosin (HE) showing multiple granulomas.

Taken together, the clinical presentation of the disease, the result of the biopsy, and the presence of increased ADA in the peritoneal fluid corroborated the hypothesis of peritoneal tuberculosis. Thereafter, the treatment with rifampicin, isoniazid, pyrazinamide and ethambutol (RIPE scheme) was then instituted and scheduled for 6 months. Pulmonary tuberculosis was investigated through culture for mycobacteria and rapid molecular test for tuberculosis in tracheal aspirate, and both resulted negative. After approximately 15 days of hospitalization, the patient developed acute respiratory failure, and the diagnosis of SARS-COV-2 pneumonia was made, from which she recovered without sequelae. During her stay in the intensive care unit, the RIPE regimen was maintained, and the patient presented an improvement in the ascites, and no recurrence of fever.

Prior to hospital discharge, a new transvaginal ultrasound showed regression of the cyst in the topography of the left ovary, corroborating the hypothesis that it was a tuberculous rather than neoplastic abnormality. After four months using the RIPE regimen, the patient underwent a new computed tomography scan of the total abdomen, which demonstrated resolution of the ascites and signs of peritonitis, as well as a marked reduction in the nodular peritoneal thickening in the topography of the greater omentum; small amount of loculated fluid in the topography of the left ovary, with a smaller volume compared to the

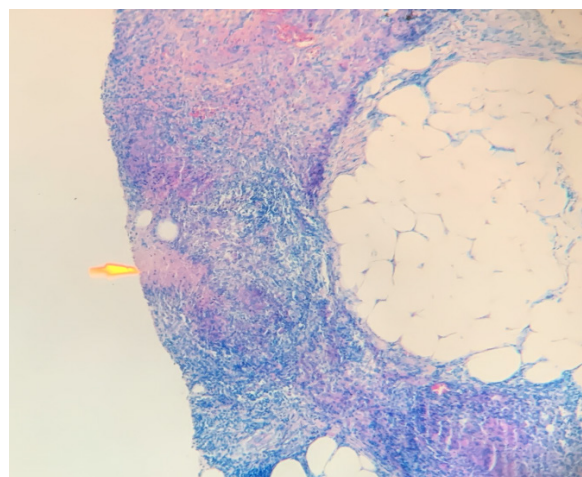


Figure 3. Omental biopsy stained with Ziehl-Neelsen highlighting area of caseous necrosis (yellow arrow).

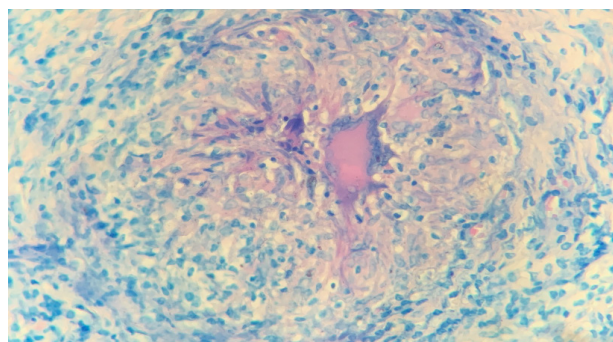


Figure 4. High-magnification image of a granuloma with giant cell without the presence of bacillus, stained with Ziehl-Neelsen.

previous study. This finding was regarded as below the detection limit of the method; therefore, it was raised the possibility of a diagnosis of a cyst in the ovary or parametrium.

DISCUSSION

Tuberculosis is a major public health problem in the world, and Brazil is one of the countries with the largest number of reported cases. It is estimated that one third of the world population is infected with the *Mycobacterium tuberculosis* bacillus, the etiologic agent of this disease, which is responsible for a chronic granulomatous inflammatory process⁵. The peritoneal form corresponds to a small percentage of the total cases, but upon evaluating the diseases that can affect the peritoneum, tuberculosis should be regarded as a potential diagnosis in patients with nonspecific abdominal abnormalities, especially in the presence of ascites³.

Peritoneal tuberculosis usually occurs after the reactivation of latent tuberculosis foci in the peritoneum (following hematogenous spread of primary pulmonary

or miliary foci), but it can also occur by hematogenous spread of active pulmonary tuberculosis or by contiguity after tuberculosis salpingitis. In patients with HIV infection, approximately 50% develop extrapulmonary forms of tuberculosis, while this percentage drops to 10-15% in uninfected patients. Other factors that may be associated with the development of peritoneal tuberculosis are alcoholism, diabetes mellitus, underlying malignancy, and the use of immunosuppressants^{4,6,7}. In the case herein reported, the patient had been exposed for a long time to the tuberculosis bacillus, but she did not present any factor that could predispose to the development of the extrapulmonary form of the disease.

The main clinical findings are nonspecific, especially abdominal pain and fever with insidious evolution, as the most common symptoms. Other common findings are ascites, fatigue, anorexia, normocytic and normochromic anemia, and increased inflammatory markers. Our patient had a significant increase in CRP (273 mg/L), and about 15-25% of patients have concomitant pulmonary involvement, which was not identified in this patient^{8,9,10}. Ascites is found in approximately 73% of patients on physical examination¹⁵. Its presence characterizes the “wet” form of peritoneal tuberculosis, the most common; the “dry” form is characterized by caseous nodules and peritoneal fibrosis, while the “fibrotic” form is characterized by involvement of the omentum and mesentery, with a cluster of intestinal loops and loculated ascites, which may form abdominal tumors^{11,12}.

Based on clinical suspicion, the initial investigation consists of the analysis of the ascitic fluid and imaging exams; nevertheless, the microbiological or histological confirmation are also required^{10,14}. The ascitic fluid is typically constituted of lymphocytic exudate, with a serum-ascites albumin (GASA) gradient <1.1, and protein levels greater than 2.5-3g/dl^{5,11,13}. In this case, however, the GASA value was 1.42, while the protein levels remained high (4.6 mg/dL).

The microbiological analysis of the ascitic fluid has a low sensitivity of about 3% for detection of acid-alcohol resistant bacillus (BAAR) and 35% positivity for culture¹⁴.

However, a meta-analysis published by Riquelme et al.¹⁴ revealed a major non-invasive strategy to aid the diagnosis: the presence of adenosine deaminase in the ascitic fluid, with sensitivity and specificity of 100% and 97%, respectively.

Imaging exams are very important to explore the differential diagnosis. Despite the non-specific findings, the ultrasound of the total abdomen, can provide information of the presence of peritoneal thickening, echogenic debris and thin fibrin beams, in addition to ascitis¹⁵. Computed tomography, on the other hand, is more sensitive for identifying mesenteric nodules, adenomegaly with a hypodense center, splenic lesions and calcifications thus providing an interesting means to differentiate tuberculosis

and peritoneal carcinomatosis, its main differential diagnosis^{15,16,17}. Changes in the omentum may be present in up to 80% of the cases, with the omental cake pattern being less frequent in tuberculosis as compared to peritoneal carcinomatosis¹⁸. In the case herein reported, we determined the presence of the omental cake pattern on the abdominal computed tomography (Figure 1).

The gold standard method for investigating omental cake pattern is laparoscopy with biopsy of the peritoneum, which confirms the diagnosis in 85-90% of cases; moreover, using this approach it is possible to rule out carcinomatosis, as previously reported¹³. The finding of a granulomatous inflammatory process is not pathognomonic of tuberculosis, and may be found in diseases such as peritoneal sarcoidosis and peritonitis caused by atypical mycobacteria¹⁹. The presence of caseous granuloma and acid-alcohol resistant bacillus (BAAR) is determined in less than 33% of cases²⁰. The histopathological analysis of the case herein reported revealed granulomas (Figure 2) and focal caseous necrosis (Figure 3), in addition to the absence of the *Mycobacterium tuberculosis* inside the giant cells, even in Ziehl-Neelsen staining (Figure 4).

Once the diagnosis is confirmed, the response to treatment is usually positive, based on the standard six months “RIPE” scheme, as recommended for the treatment of pulmonary tuberculosis and extrapulmonary forms. The lack of clinical suspicion, resulting in late diagnosis and treatment, is responsible for clinical deterioration in approximately 80% of cases and a mortality rate of 35%, as described elsewhere^{14,21}.

This case report highlights the diagnostic challenge of peritoneal tuberculosis. The initial diagnosis was peritoneal carcinomatosis and the initiation of specific treatment for tuberculosis occurred after histopathological diagnosis, four weeks after the beginning of symptoms.

After resolution of the pulmonary infectious condition due to COVID-19, the patient presented a decrease in ascites and the episodes of fever ceased. She was discharged from the hospital with a prescription of rifampicin and isoniazid after having completed 2 months on the RIPE regimen.

CONCLUSION

Peritoneal tuberculosis is a rare form of disease that requires systematic clinical suspicion and histopathological confirmation for diagnosis; in countries with high incidence of tuberculosis, such as Brazil, the diagnosis should be always considered in face of atypical peritoneal disease. It has high morbidity and mortality if unidentified, but otherwise, good response to the specific treatment, with recovery time in a few weeks and low mortality rate of approximately 5%. Therefore, it should be considered as an important differential diagnosis of peritoneal carcinomatosis.

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