

Can D-dimer levels predict the treatment outcome in a patient with tuberculosis?

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Abstract

Tuberculous peritonitis is a leading cause of mortality and morbidity particularly in the developing world. Delay in initiation of treatment distinctively increases mortality. Treatment response to anti-tuberculosis drugs is usually observed by regression of symptoms and clearance of ascites. With initiation of treatment, laboratory values including CA-125 levels generally return to normal levels in 3 months. However, there is still no consensus about treatment response during the follow-up period. Serum D-dimer level is used as an inflammation marker in some cases. A case with Tuberculous peritonitis successfully monitored by serum D-dimer levels is presented.

Keywords: Tuberculous peritonitis, D-dimer.

Introduction

Tuberculous peritonitis (TP) is the gastrointestinal manifestation of tuberculosis, and TP is associated with an increased risk of mortality.¹

The D-dimer antigen is a product of fibrin degradation that is formed by the sequential action of enzymes of coagulation cascade.²

In the current practice, evidence of elevated D-dimer level is used as a marker both of VTE and DIC.^{3,4} Recent evidence also suggests a key role for D-dimer level in the diagnosis of infectious diseases.⁵

In spite of the fact that D-dimer levels are important in the diagnosis both of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC), there is still no study reporting their role in TP's diagnosis and treatment. A TP case successfully treated with anti-tuberculous drugs and appropriately monitored by serum D-dimer levels is presented.

Case Report

An 18-year-old girl was admitted to our hospital due to

abdominal dullness, nocturnal fever, malaise and nausea. Her medical history revealed no important features. At the time of admission, her vital signs showed the following: temperature; 38.1°C, blood pressure; 110/65mmHg, and heart rate; 96 beats/min. On physical examination, there was moderate tenderness on the entire abdomen with tense ascites. Obtained laboratory test results were as follows: white blood cell count, 3,410/μL; stab cell ratio, 84.5%; erythrocyte sedimentation rate (ESR), 68mm/h, C-reactive protein (CRP), 165 U/L (normal:0-25) and serum D-dimer, 9.4μg/dl (normal: 0-0,5). Serum albumin level was 3.2g/dl and serum globulin level was 4.1g/dl. Liver and renal function tests were in normal ranges. Diagnostic paracentesis showed; WBC: 1400/mm³: lymphocyte: 800/mm³, albumin 2.5 mg/dl, Ca-125:532U/L and glucose 80mg/dl. The ascitic adenosine deaminase (ADA) level was 48 U/L (normal 0-18). Serum ascites-albumin gradient was calculated as 0.7 mg/dl, which was compatible with low-gradient (exudative) ascites. Furthermore, the polymerase chain reaction (PCR) test for Mycobacterium tuberculosis (M. tuberculosis) was also positive. Computed axial tomography (CT) of the chest and doppler ultrasonography of the venous system showed no pathologic finding. CT of abdomen showed tense ascites with peritoneal thickening and a dirty omentum (Figure-1). Histopathologic examination of laparoscopic biopsy materials revealed caseous necrosis of the peritoneal lymph nodes. Taken together, a diagnosis of Tuberculous Peritonitis (TP) was made. Therefore, treatment was initiated with isoniazid (INH) 300mg/day, rifampicin (RMP) 600mg/day, pyrazinamide (PZA) 15 mg/kg/day and ethambutol (EMB) 15-25 mg/kg/day for the current case. In the first 2 months of treatment, quadruple antituberculosis treatment was administered and 6 month treatment schedule was completed by administration of INH+RMP for four months. During hospital stay and follow-up stage in outpatient clinic, the patient was weekly evaluated by laboratory parameters including levels of CA-125, CRP and D-dimer (Figure-2).

The pre-treatment serum CRP level was 88 U/L, CA-125 value of the patient was 279U/l and the CA-125 level in ascites was 532U/l. Following 6-month administration of combined anti-TBC treatment, her ascites was completely

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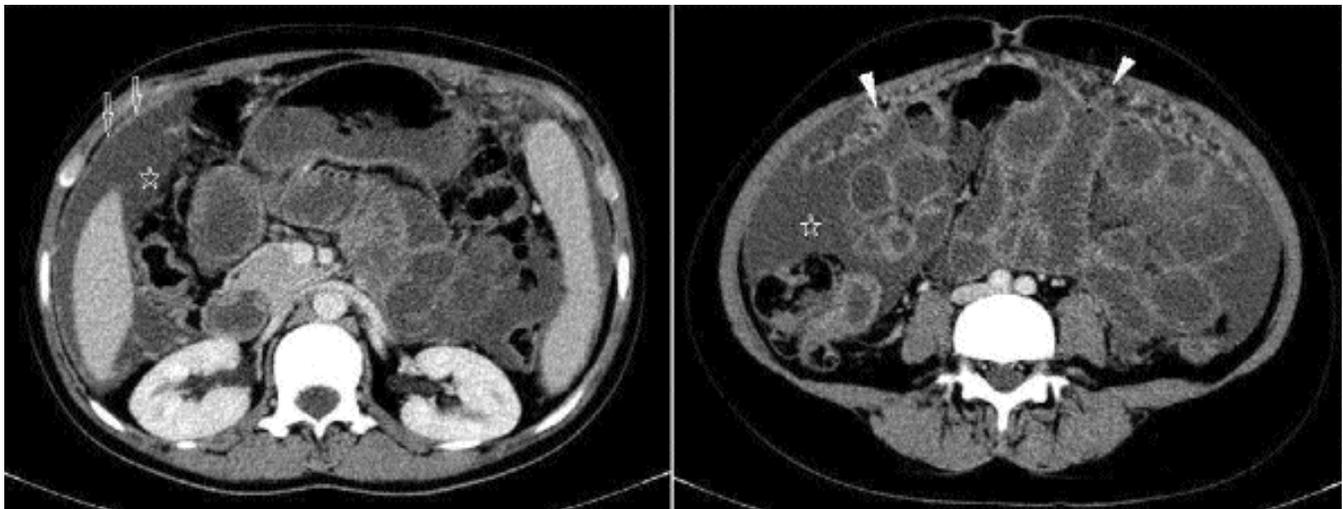


Figure-1: Axial contrast enhanced CT images; (A) moderate volume ascites (star), smoothly thickened, enhancing parietal peritoneum (arrow) and (B) omental thickening (arrowhead).

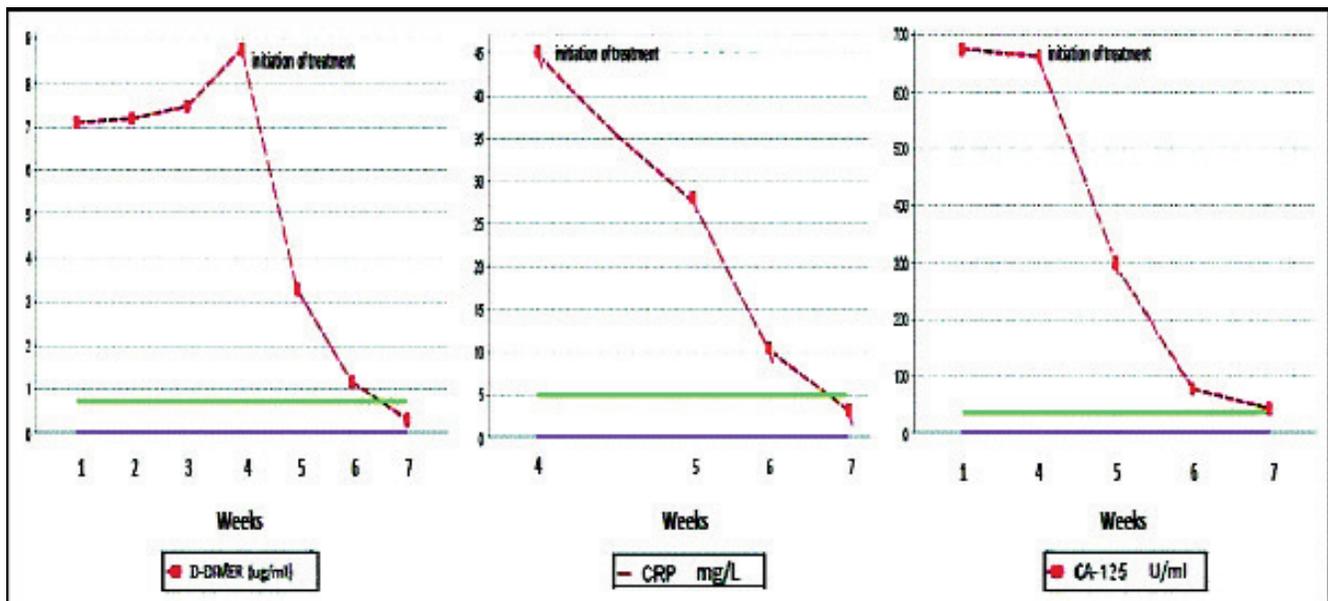


Figure-2: Laboratory parameters including levels of CA-125, CRP and D-dimer.

resolved and the levels both of serum CA-125 and CRP were in normal ranges. Furthermore, one week after starting anti-tuberculosis drugs, her D-Dimer level gradually reduced. Finally, at the third week of the treatment her D-dimer level returned to normal ranges (0.3µg/dl).

Discussion

Despite improvements in the treatment of infectious diseases, mortality rates remain very high in TP mostly

due to late diagnosis. Worldwide incidence of TP for all forms of Tuberculosis (TBC) is reported as 0.1 - and 0.7%.⁶ On the other hand, TP and TBC of gastrointestinal system is less frequently seen in developed countries, as compared to less developed regions.⁷ In Turkey, no trial investigating the incidence of TP was conducted up to this date.

The most common clinical features are; abdominal distention (82%), clinical ascites (79%), abdominal

tenderness (76%), fever (74%), weight loss (62%), abdominal pain (58%) and diarrhoea (16%)⁷ as was seen in our case.

In a trial conducted in UK on 36 patients; the most common laboratory findings were determined as low haemoglobin and high CRP levels.⁸ The presented case had laboratory features of inflammation including higher levels of CRP and higher sedimentation rate.

Haematological and biochemical studies are indicators for malnutrition and infection. Hyperglobulinaemia and hypoalbuminaemia are also common symptoms observed in abdominal tuberculosis.⁹ Hyperglobulinaemia was also a striking finding in our case.

In TP cases, ascitic fluid content is mainly composed of high protein and low glucose with low serum-ascites albumin gradient. Leucocyte levels are high in ascites and proportion of lymphomonocytes is increased. Ascites with low albumin gradient is observed in all TP cases, though specificity is low. Besides, provided that TP develops on a chronic liver disease, sensitivity is also decreased.¹⁰ Ascitic fluid analysis also revealed low gradient ascites which was compatible with TP.

CA-125 is a carbohydrate antigen with high molecular weight. In TP cases, increased CA-125 levels were documented in literature. Limited national and international publications indicate that high serum CA-125 levels return to normal values following treatment in TP cases.^{11,12} In our case, the level of CA-125 was 336U/ml in the ascitic fluid which was consistent with peritoneal tuberculosis.

ADA is an aminohydrolase which inverts adenosine to inosine and its activity is high in T lymphocytes. In TP cases, ADA levels in ascitic fluid increases, due to stimulation of mycobacterial antigens.¹³

Ongoing difficulties in TP diagnosis, relatively long durations required for culture examination and less widespread use of rapid diagnostics methods like PCR with high cost lead to investigations for a rapid and alternative non-invasive test for diagnosis. Provided that limit value is selected as 33 U/L or 35 U/L, sensitivity and specificity was determined as 100% and 97%, respectively.¹⁴ Additionally, the current case had a positive ADA result.

TP ascitic fluid has high attenuation values, due to high protein content. In one trial, fine septae and debris in ascitic fluid were reported as characteristic features.¹⁵

In addition, mesenteric involvement leading to patchy or

widespread increase in density and presence of stellate appearance is indicated in CT. In the same trial; presence of disperse lymph nodes, omental thickening leading to omental cake appearance and presence of fibrotic layer surrounding omental line were detected.¹⁶ In the current case, ascites with septation was determined by radiologic examination. Furthermore, her CT findings of mesenteric thickening were also consistent with this diagnosis.

TP may be diagnosed by evaluating peritoneal biopsy samples obtained by laparotomy, laparoscopy and percutaneous biopsy via histological diagnostic methods. In various publications, laparoscopy is reported to be superior to laparotomy and unguided percutaneous peritoneal biopsy and provided that it's used in combination with targeted biopsy of peritoneal cavity through laparoscopic appearance, TP is indicated to be diagnosed with a rate of 80-95% with this method.¹⁷ Our patient did have some specific histopathologic features of tuberculosis on laparoscopic peritoneal biopsy samples.

D-dimer testing plays a key role to rule-out venous thromboembolism in clinical practice.² Additionally, elevated levels of D-dimer have also been determined in advanced age, during pregnancy, malignancy, postoperative period, trauma, inflammatory states and infections.¹⁸

Previous studies have also linked higher D-dimer levels to infectious diseases.¹⁹ Therefore, we measured the initial D-dimer level and thereafter checked its level weekly to monitor the regression of the disease in the current case.

Finally, in addition to conventional laboratory parameters such as CRP or CA-125, serum D-dimer level was used to observe the efficacy of treatment in the presented case. Further studies should be conducted to have an adequate understanding of this phenomenon.

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