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Case Report

Clinical usefulness of very high serum soluble interleukin-2 receptor levels for the detection of tuberculous peritonitis in a patient with chronic myelogenous leukemia

Running title: Very high serum soluble interleukin-2 receptor levels to detect tuberculous peritonitis

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Abstract

Tuberculous peritonitis is difficult to diagnose due to the disadvantages of ascitic culture and peritoneal biopsy. Although previous reports suggested that very high serum soluble interleukin-2 receptor (sIL-2R) levels may reflect the clinical activity of tuberculosis, little is known about the diagnostic utility of serum sIL-2R for tuberculous peritonitis. We describe a case of tuberculous peritonitis with chronic myelogenous leukemia. The abnormally high serum sIL-2R value and negative findings for other possible causes including lymphoma suggested tuberculous peritonitis and we administered anti-tuberculosis treatment before definitive diagnosis. Abnormally high serum sIL-2R levels may contribute to earlier diagnosis of tuberculous peritonitis, along with ruling out other potential differential diagnoses.

Key Words

soluble interleukin-2 receptor; chronic myelogenous leukemia; tuberculous peritonitis; tuberculosis; ascites

Introduction

Tuberculous peritonitis is difficult to diagnose because culture from ascitic fluid has low sensitivity and takes approximately 4-8 weeks to yield results [1,2]; furthermore, peritoneal biopsy is invasive and may lead to a delay in starting treatment and definitive diagnosis [1]. A high level of ascitic fluid adenosine deaminase (ADA) is a useful marker for the detection of tuberculous peritonitis [1]. However, false-positive results can occur in patients with activated lymphocytes such as those with hematologic malignancy [3,4]. Such cases require an alternative diagnostic marker. Although serum soluble interleukin-2 receptor (sIL-2R) is often used as a biomarker in the clinical management of malignant lymphoma [5,6] and hemophagocytic syndrome [7], its levels also increase non-specifically in a variety of diseases [8,9]. However, other than hematologic malignancies, very high sIL-2R levels (e.g., more than 5,000 U/mL) occur in several conditions; namely, specific infections, several autoimmune diseases, and during organ transplant rejection [10-24].

A case study reported that high serum sIL-2R levels were useful to monitor the response to anti-tuberculosis treatment for tuberculous peritonitis in a hemodialysis patient without malignancy [17]. However, it is unknown what cut-off values of serum sIL-2R are helpful in the diagnosis of tuberculous peritonitis in patients with active hematologic malignancies, since serum sIL-2R levels are often highly elevated in

hematologic malignancies. We herein show that extremely high serum sIL-2R levels were useful in suggesting tuberculous peritonitis and allowed the early initiation of anti-tuberculosis drugs, likely contributing to the successful outcome in a patient with active chronic myelogenous leukemia (CML).

Case report

A 59-year-old woman with leukocytosis and thrombocytosis was referred to our hospital. Two months prior to her admission, she had developed abdominal distension that had been gradually worsening. She also presented with dyspnea on exertion, loss of appetite, and weight loss. Her medical history included cervical cancer. Her husband and daughter had a history of tuberculosis.

On the first day of hospitalization (HD1), her blood pressure was 102/69 mmHg, pulse rate was 117 /min, and temperature was 38.4°C. The complete blood count showed a hemoglobin of 8.0 g/dL, platelet count of 175.4×10^4 / μ L, and white blood cell (WBC) count of 31,800 / μ L (87% neutrophils, 2% lymphocytes, 2% monocytes, 5% basophils, and 1% others). Biochemistry examinations showed a lactate dehydrogenase (LDH) level of 541 U/L (normal, 124–222 U/L), C-reactive protein (CRP) level of 12.8 mg/dL (normal, 0.0–0.4 mg/dL), aspartate aminotransferase (AST) level of 113 U/L (normal, 13–30 U/L), alanine aminotransferase (ALT) level of

52 U/L (normal, 6–27 U/L), and albumin level of 2.0 g/dL (normal, 3.5–5.0 g/dL). A renal function test was normal. The patient tested negative for tuberculosis by interferon-gamma release assay (IGRA), T-SPOT.*TB* test (enzyme-linked immunospot assay) on HD4. A bone marrow biopsy revealed granulocytic and megakaryocytic hyperplasia with significant fibrosis. Philadelphia translocations were detected by fluorescence in situ hybridization. Contrast-enhanced computed tomography (CT) showed massive ascites and hepatosplenomegaly (Figure 1). There were no findings suggestive of lung tuberculosis. From HD1, hydroxyurea treatment was initiated for cytoreduction (Figure 1). On HD9, the patient was diagnosed with chronic myelogenous leukemia based on positive findings of major BCR/ABL mRNA IS in the blood and was treated with dasatinib. After treatment, her leukocyte count decreased rapidly. However, the patient had a sustained high fever despite broad-spectrum antibiotics and antifungal treatment and also developed renal function impairment and decreased blood pressure (74/43 mmHg). Abdominal paracentesis performed on HD22 showed translucent and yellow fluid with an adenosine deaminase (ADA) level of 83.5 U/L, above the >30 U/L cutoff for the diagnosis of tuberculosis [1]. Laboratory examination of the ascitic fluid also showed albumin level of 1.3 g/dL, LDH level of 731 U/L. Cytologic examination of the fluid showed WBC count of 1,189 / μ L (59% neutrophils, 39% lymphocytes, and 2%

monocytes). The polymerase chain reaction test for *Mycobacterium tuberculosis* in the ascitic fluid was negative. We considered that the high ascitic ADA levels might have been a false-positive result for tuberculous peritonitis since ADA activity often increases in patients with CML blastic crisis [25]. In the present case, high serum sIL-2R (4,251 U/mL; normal, 122–496 U/mL) levels were also observed on HD18, which increased to 7,369 U/mL on HD29, despite the improvement of leukocytosis and thrombocytosis. Although none of the results were suggestive of tuberculosis, since tuberculous peritonitis can cause extremely high serum of sIL-2R levels [17] and her family had a history of tuberculosis, we suspected tuberculous peritonitis or malignant lymphoma with CML. Due to her cardiopulmonary deterioration, methylprednisolone pulse therapy was started on HD29 since we could not rule out lymphoma completely despite the lack of lymphoma cells in the ascitic fluid. Furthermore, continuous renal replacement therapy was started on HD30 with a vasopressor agent. Since concomitant use of rifampicin and a tyrosine kinase inhibitor was not recommended by the potential CYP3A4-mediated drug interaction problem [26] and the patient was unable to take medication orally, intravenous levofloxacin, isoniazid, and streptomycin were also added as an alternative anti-tuberculosis treatment option on HD32 [27]. Seven days after administering the anti-tuberculosis drugs, the patient was eventually diagnosed with tuberculous

peritonitis based on *M. tuberculosis* positivity in ascitic fluid culture on HD39. In response to the anti-tuberculosis therapy, the serum sIL-2R levels markedly decreased to 1,810 U/mL on HD 67 and 1,225 U/mL on HD93, and the patient's body weight also decreased with the improvement of ascites volume (Figure 1). Although the exact cause of the cardiopulmonary deterioration on HD29 remained unclear, progression of tuberculous peritonitis may have affected it from the entire clinical course. She was discharged with no symptoms and signs on HD98. One year after discharge, she achieved a major molecular response with anti-CML therapy.

Discussion

We described a case of tuberculous peritonitis associated with CML. In this case, very high serum sIL-2R levels led us to suspect tuberculous peritonitis and we were able to administer anti-tuberculosis drugs before the definitive diagnosis. The early treatment intervention may have enabled us to improve the patient's conditions including ascites, along with decreased serum sIL-2R levels.

Tuberculous peritonitis occurs rarely and more often in immunosuppressed patients, such as those with HIV/AIDS [1]. In general, it is difficult to diagnose because of the lack of specific clinical features. Definitive diagnosis requires culture from ascitic fluid and/or peritoneal biopsy [1]. However, these have disadvantages:

the former has low sensitivity and takes approximately 4-8 weeks to obtain results [1,2] and the latter is invasive. These factors often lead to a delay in diagnosis and initiation of anti-tuberculosis therapy, possibly affecting patient prognosis. Therefore, a blood biomarker with high accuracy for the diagnosis of tuberculous peritonitis is needed.

Although IGRAs cannot distinguish between latent and active tuberculosis, IGRAs are highly specific tests for detection of tuberculosis. [27,28]. However, low lymphocyte count (especially, $<500/\mu\text{L}$) and immunosuppression may lead to a negative result of IGRA [27,28]. In the present case, although the exact reason was unclear, the negative result of IGRA can be false-negative possibly due to low lymphocyte count ($314/\mu\text{L}$ on HD4) [28] and immune dysfunction by CML itself [29]. The sensitivities of mycobacterial smear and acid-fast bacterium culture are only 3% and 21–35%, respectively [1]. ADA values in ascitic fluid above 30 U/L are a useful marker for the diagnosis of tuberculous peritonitis, with sensitivity and specificity over 90% [1]. ADA is an aminohydrolase involved in purine metabolism, which modulates T cell differentiation [1]. ADA levels increase proportionally to the differentiation of T cells in response to tuberculosis antigen [1]. In general, T cell activity increases in patients with active CML [30] and ascitic ADA levels might increase, reflecting purine metabolism in activated T cells in ascitic fluid, in addition to blood ADA elevated [25].

Therefore, in patients with active CML and ascites, use of ascitic ADA levels may test positive regardless of the causes of the ascites. In the present case with CML, we considered the possibility of a false-positive tuberculous peritonitis result based on the high ADA value. Both CML and tuberculous peritonitis could have contributed to the elevated ascitic ADA levels.

In tuberculosis, serum IL-2R is expressed on the surface of T cells activated by the *M. tuberculosis* antigen, and its levels are thought to increase by migration of the soluble receptor [31]. Serum sIL-2R values are reportedly associated with tuberculosis activity [17,32,33]. In addition, Porcel et al. demonstrated the excellent diagnostic performance of pleural sIL-2R, which has a sensitivity of 91% and a specificity of 94%, for tuberculous pleuritis [34]. On the basis of these observations, extremely high serum sIL-2R levels may serve as a useful diagnostic marker for tuberculous peritonitis. To our knowledge, abnormally high serum sIL-2R levels (over 5,000 U/mL) occur in the following limited conditions: malignant lymphoma [35]; leukemia [36]; Kawasaki disease [10]; systemic lupus erythematosus [11]; adult-onset Still's disease [12]; hemophagocytic syndrome [7,13]; infectious mononucleosis [14]; dengue hemorrhagic fever [15]; acute hepatitis B infection [16]; tuberculosis [17]; leprosy [18]; visceral leishmaniasis [19]; malaria [20]; lung, liver, and kidney transplant rejection [21-23]; and burn injury [24]. Abnormally high serum sIL2R levels

are also observed in CML blastic crisis, but not in the chronic and accelerated phases [37]. In addition, in the present case, while the leukocytosis nearly resolved after tyrosine kinase inhibitor (TKI) therapy, serum sIL2R levels increased, which suggested that it resulted from other causes. Based on these observations, as well as her medical history and clinical symptoms and signs, we considered tuberculosis or malignant lymphoma as the differential diagnosis in the present case. Because of the patient's family history of tuberculosis and negative findings for malignancy by ascitic cytology and flow cytometry, we strongly suspected tuberculous peritonitis. In addition to these considerations, due to her cardiopulmonary deterioration, we administered anti-tuberculous drugs. As a result, we were able to start the anti-tuberculous therapy seven days before the positive tuberculosis ascitic culture.

Hence, on based on these observations, very high sIL2R levels may be useful to suspect or diagnosis tuberculous peritonitis in patients with evident ascites after ruling out other conditions that may lead to abnormally-elevated sIL2R levels [7,10-24,35-37]. Moreover, sIL2R levels can be measured noninvasively and repeatedly. Ascitic ADA levels and very high serum sIL-2R levels combined could help to effectively diagnose tuberculous peritonitis. However, further validation studies are required.

Previous studies reported that the development of tuberculous peritonitis was

associated with comorbidities including liver cirrhosis, HIV infection, diabetes mellitus, use of steroids and immunosuppressants, and continuous ambulatory peritoneal dialysis [1]. To our knowledge, only seven cases of chronic myelogenous leukemia with tuberculosis have been reported [38-42], including two cases of tuberculous peritonitis [38,41]. In these two cases, tuberculosis developed after TKI treatment for CML. Immunosuppression via T cells caused by TKIs [43] may have contributed to the onset of tuberculous peritonitis. Our case had massive ascites on admission; thus, it was unclear that the administration of dasatinib affected the tuberculous peritonitis development or progression.

In conclusion, the present case suggested that tuberculous peritonitis should be considered in patients with abnormally high serum sIL2R levels and ascites as one of the potential differential diagnoses. Abnormally high serum sIL-2R levels might be one of the indicators for anti-tuberculosis treatment initiation when the possibility of tuberculosis is not excluded and the possibility of other diseases including lymphoma is meticulously excluded. The clinical usefulness of very high serum sIL-2R levels in combination with ascitic ADA in the management of tuberculous peritonitis warrants further exploration.

Conflict of interest

None.

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Figure Legends

Fig 1. Clinical course after admission

Findings of abdominal computed tomography (CT) examination at the level of the 12th thoracic vertebra. (A) Hepatosplenomegaly and moderate ascites observed before the administration of dasatinib on HD1. (B) Massive ascites observed before anti-tuberculosis treatment on HD28. (C) Improved hepatosplenomegaly and reduced ascites on HD38.

Bosu, bosutinib; CPFG, caspofungin; Dasa, dasatinib; DRPM, doripenem; EB, ethambutol; HD, hospital day; HU, hydroxyurea; Ima, imatinib; INH, isoniazid; LVFX: levofloxacin; MCFG, micafungin; MEPM, meropenem; PIPC/TAZ, piperacillin/tazobactam; SM, streptomycin.

Figure