

Short Communication

Mycobacterium Tuberculosis and Hepatitis Co-Infection in Dialysis Patients: Synergic Immune Dysregulation Leading to Disease Progression

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Abstract

Patients with end stage renal disease (ESRD) ongoing hemodialysis treatment (HD) have more than 10 [6-16] fold increased risk for development of tuberculosis (TB). The tuberculin reaction is sometimes negative; this may be due to an overwhelming infection impairing the immune response. Tuberculous cervical lymphadenitis is the commonest form of nonrespiratory TB. We report herein three dialysis patients; two of them had extrapulmonary TB, such as tuberculous lymphadenitis and had hepatitis C virus (HCV) or hepatitis B virus (HBV) infection together. Finally, it was considered that ESRD, dialysis and HCV or HBV infection might reduce the effectiveness of the body's immune system, which can allow dormant bacteria to become reactivated.

Keywords: tuberculosis, dialysis, hepatitis C, hepatitis B, immune dysregulation

Introduction

Chronic infections contribute significantly to morbidity and mortality in dialysis patients. These infections are acquired either before or after initiation of dialysis, and the later may be via nosocomial modes of transmission. Consequently, policies that deal with infection control in dialysis units have assumed increasing importance. The incidence and prevalence of hepatitis B virus (HBV) infection is steadily declining; however, both hepatitis C virus (HCV) and tuberculosis (TB) remain important diseases among dialysis patients [1-3].

People have been contracting tuberculosis (TB) since ancient times. These are the developing countries that show the highest incidence, as most of them are in Africa, Latin America and Asia. An estimated 1 billion people are infected with *Mycobacterium tuberculosis* (*Mtb*) worldwide; 8 million new cases of TB and 3 million deaths occur each year. One-year mortality from all causes has been reported to be from 1.6% to as high as

28% for patients with tuberculosis. It is estimated that 2 billion people worldwide have latent TB infection (LTBI), and 10 to 15 million of those live in the United States [4-7].

TB generally occurs earlier in the course of immunodeficiency than other opportunistic infections. The lungs also are the main sites of expression of clinical tuberculosis: 82 percent of patients manifest pulmonary disease. Tuberculous cervical lymphadenitis is the commonest form of nonrespiratory TB, and the majority of patients are Asian, or black, and there is a 2-to-1 female-male predilection. Skeletal TB tends to involve weight-bearing joints; vertebral column (50%), hip (15%), and knee (15%) joints are affected most often. The organism may be seen in the joint fluid in cases of arthritis, but if this is unsuccessful, synovial biopsy can be diagnostic. Treatment is with standard antituberculous chemotherapy, and surgical intervention is rarely required [1-4]. Patients with end stage renal disease (ESRD) ongoing hemodialysis therapy (HD) are at increased risk of developing TB. That's why routine TB screening is recommended for this population. But accuracy of the tuberculin skin test (TST) is decreased since ESRD is also a known risk factor for skin test anergy [8,9].

We report herein three patients treated by conventional bicarbonate hemodialysis thrice a week using low flux polysulfone membrane (Fresenius Medical Care, Bad Homburg, Germany) with different localizations of TB and association of HCV or HBV infection. Medical records were kept constantly for all patients, and these records included data such as symptoms of hepatitis, history of liver enzyme abnormalities, medication history, past medical history, history of transfusions, dialysis schedule, bleeding episodes, and demographic and risk factors. Screening of anti-HCV antibodies and HbsAg and monitoring of alanine aminotransferase (ALT) were part of HD centre routine.

Case 1**Correspondence to:**

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A 47-year-old man treated with HD because of ESRD caused by chronic glomerulonephritis for 3.5 years, developed sputum production, hemoptysis, progressive dyspnea, fever, anorexia and weight loss. According to his medical history, he had been treated 20 years previously for pulmonary TB. The chest radiograph was deemed suggestive of TB and the patient was hospitalised. The patient had a 20 cigarettes/day smoking history (for approximately 18 years, until seven years ago) and also had chronic HCV infection since two years.

Physical examination revealed a thin, ill-appearing man with difficulty speaking due to increased respiratory effort. The temperature was 38.6°C orally, with a respiratory rate of 32/min. The examination was remarkable for loud rhonchi over all lung fields. There was no lymphadenopathy or rash. Heart sounds and abdominal examination were unremarkable. Laboratory studies revealed a hematocrit (hct) of 42% (without treatment by erythropoietin) with a leukocyte count of 12800/mm³ with left shift and a high erythrocytes sedimentation rate (ESR) as 84 mm/h; the serum albumin, BUN and creatinine were 4 g/dL (normal, 3.4 to 4.2), 129 mg/dL (normal, 20 to 48) and 9.5 mg/dL (normal, 0.7 to 1.4), respectively. Testing for HBsAg, HBeAg and human immunodeficiency virus (HIV) yielded negative results. Meanwhile, anti-HCV (ELISA) and HCV-RNA-polymerase chain reaction (PCR) (5.77x10³ IU/ml), anti-HBs (1000 IU/mL) and anti-HBc IgG were positive together with pre-treatment high titres of alanine aminotransferase (ALT: 75, normal, 0-41 IU/L) and aspartate aminotransferase (AST: 42, normal, 0-38 IU/L). We determined the levels of IL-1 β (5 pg/ml; normal, 0 to 5), IL-6 (14 pg/ml; normal, 0 to 5.4), TNF- α (27 pg/ml; normal, 4 to 8.1), and sIL-2R (4799 U/ml; normal, 223 to 710). Serum IL-1 β , IL-6, IL-8, TNF- α and sIL-2R levels were determined with quantitative ELISA and IMMULITE diagnostic kits.

A chest radiograph and computed tomography (CT) showed bilateral reticular and nodular opacities settled in superior and middle lobes of lungs and cavity (14x12 mm) in upper lobe posterior segment of the right lung (Figure 1 and 2). Although TST was negative, the case was accepted as an endogenous reactivation of the latent infection. Sputum yielded acid-fast bacilli and therapy was begun with isoniazid (INH) 300 mg daily for 9 months, rifampin (RIF) 600 mg for 9 months, and pyrazinamide (PZA) 1.5 g daily for 2 months. Sputum cultures yielded pansensitive *Mtb*. While at the 3rd month of treatment, liver function worsened and ALT increased to >300 IU/L, INH-RIF treatment was discontinued. After three weeks, liver functions recovered and patient again received INH-RIF. At the 9th month of treatment, patient well responded to therapy, he had only dyspnea, and other symptoms were resolved. Patient did not receive any treatment for hepatitis C. However, illness was gradually grave and he died from cardiovascular arrest after an attack of hemoptysis and acute respiratory distress on the 13th month of treatment.

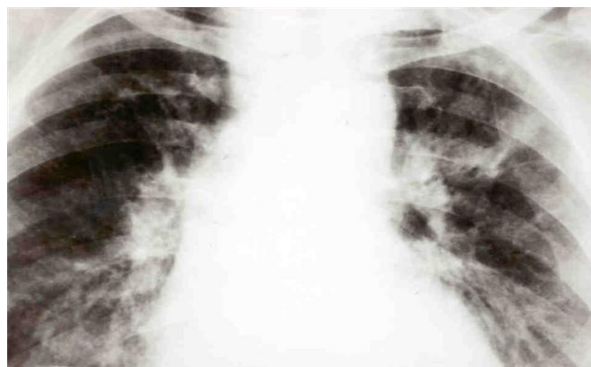


Fig. 1. A chest radiograph showed bilateral reticular and nodular opacities settled superior and middle lobes of lungs and cavity (14x12 mm) in upper lobe posterior segment of right lung.

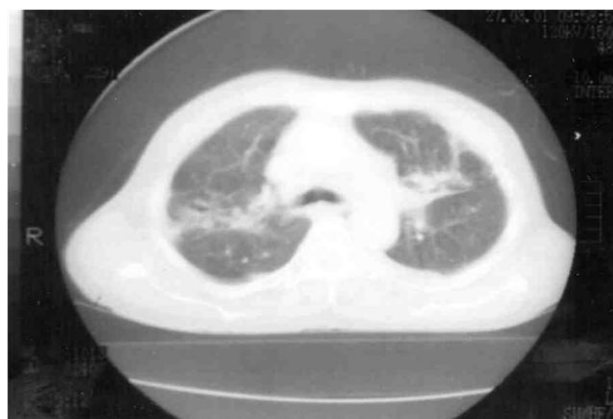


Fig. 2. A computed tomography showed bilateral reticular and nodular opacities settled superior and middle lobes of lungs and cavity (14x12 mm) in upper lobe posterior segment of right lung.

Case 2

A 24-year-old man was undergoing HD because of ESRD caused by vesicourethral reflux for 30 months. He developed left supraclavicular lymphadenitis, anorexia, weight loss, night sweating, weakness, and fever (38.5°C orally). The patient had no smoking and risk factors for HIV infection. Physical examination revealed a thin uremic and ill-appearing man.

Pre-treatment laboratory studies revealed the serum albumin 2.7 g/dl, BUN 125 mg/dl, creatinine 11.6 mg/dl, ALT 115 IU/L and AST: 54 IU/L, respectively. Blood cell counts showed leukocytosis (15.100/mm³), and HCT was 34% (with 50 iu/kg/week erythropoietin treatment). Results were negative for serum HBSAG, HBEAG and HIV; however anti-HBS (200 iu/ml) was positive. Meanwhile, anti-HCV (ELISA) and HCV-RNA-PCR (5.12x10⁴ IU/ML) were positive. serum levels of IL-1 β , IL-6, TNF- α and sIL-2r were 5 pg/ml; 8.2 pg/ml; 22.8 pg/ml and 3122 U/mL, respectively.

The chest radiograph was normal. Weekly acid-fast bacilli (AFB) smears and cultures of specimens remained negative throughout the hospitalization. TST was also negative. However, lymph node biopsy revealed granulomatous lesions that complex of Langhans giant cells, caseous necrosis, epithelial histiocytes and fibroblasts covered by lymphocytes (Figure 3).

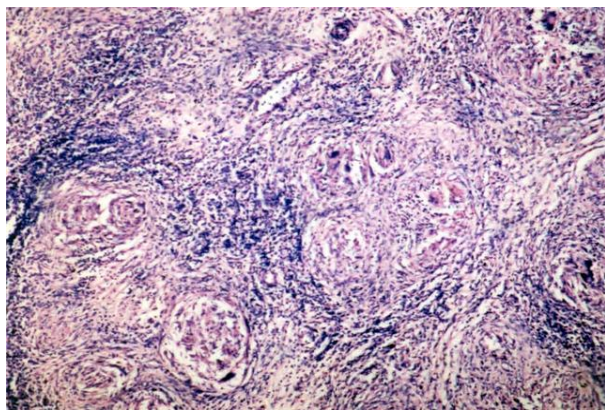


Fig. 3. Histopathologic findings of the lymph node biopsy.

Therefore, therapy was begun with INH, RIF, and PZA. At the 2nd month of treatment, this patient also had increased ALT levels >200 IU/L such as case 1, and approximately 20 days, INH-RIF treatment was discontinued. After 8 Months of treatment, patient responded well to therapy and presently remains asymptomatic. Thereafter, therapy was stopped, and the patient was referred to hepatology for treatment of hepatitis C.

Case 3

A 33-year-old man was treated with HD because of ESRD caused by rapidly progressive glomerulonephritis for 11 years. He also developed left supraclavicular lymphadenitis, anorexia, weight loss, night sweating, weakness, and fever (39.1 °C orally). The patient smoked 25 cigarettes per day for ten years and discontinued with this habit two years ago. He had no risk factors for HIV infection. This case also worked as a prison employee. Physical examination revealed a thin uremic and ill-appearing man. The examination was remarkable for loud rhonchi in bibasal lung fields.

Pre-treatment laboratory studies revealed the serum albumin 3.2 g/dL, BUN 88 mg/dL, creatinine 7.9 mg/dL, ALT 82 IU/L and AST: 31 IU/L, respectively. Blood cell counts showed Hct of 27.3% (with treatment of erythropoietin, 100 IU/kg/week) with leukocytosis (13.800 /mm³) and a high ESR as 90 mm/h. Results were negative for serum anti-HCV (ELISA), HbeAg and HIV; however, both HBs Ag and HBV-DNA-PCR (3.5x10⁴ IU/ml) were positive.

The chest radiograph was showed bilateral basal minimal pleural effusion. Cultures of specimens were negative for AFB and also TST was negative. However, lymph node biopsy revealed granulomatous lesions similarly case 2. Therefore, therapy was begun with INH, RIF, and PZA. On the 9th Month of treatment, we observed that patient well responded to therapy; so we decided that antib therapy was stopped. Patient did not receive any treatment against hepatitis during this time such as previous ones.

Discussion

The data suggests an increase greater than 10 (6-16) fold in incidence of TB among patients with ESRD compared to the total population. The majority of patients were

over 40 years of age; race and economic status appeared to be risk factors, and TST in the main were unhelpful diagnostically. The tuberculin reaction is sometimes negative; this may be due to an overwhelming infection impairing the immune response, alternatively there may be an initial immunological deficiency that predisposes to a non-reactive state [10-12].

However, all of the cases were under 40 years of age, and TST was negative in all cases. HD centers in the United States were surveyed in 1995 regarding a number of HD associated diseases and practices. A total of 2,647 centers, representing 224,954 patients, responded. Acute infection with the HBV occurred in 0.06% of patients, and the prevalence of antibody to HCV was 10.4% among patients and 2.0% among staff. The percentage of centers reporting patients with other pathogens was 7.9% for active TB [13,14].

Cytokines are important in the host defense against viral infections, specifically the role of cytokines in the host defense against the two major forms of human hepatitis virus, HBV and HCV. Antigen presenting cells (APCs), such as macrophages and Kupffer cells produce IL-12 after viral infection, which leads to the activation of natural killer (NK) cells and promotes the differentiation of Th1 CD4+ cells; it is a critical factor in viral immunity. Limited studies suggest that NK cells are functionally impaired in both chronic HBV and HCV infection [20-24]. These results could be suggested why host defense functionally impaired against viral infections in dialysis patients with HCV.

In a recent study, we reported that especially TNF- α is hyper expressed in CRF patients with HCV suggests a mechanism of inflammation in the liver. In contrast of past studies performed by Cuprophane (CU) and Haemophan (HE) dialysers, our study was showed that Polysulphone (PS) dialyser does not specifically influence levels of TNF- α , IL-1 β , IL-6 and IL-8, except sIL-2R after single HD [25].

Depressed cell-mediated immunity may be explained by shortened lymphocyte survival, lymphopenia, inhibition of lymphocyte transformation, and suppressor T-cell activity. This is manifested by cutaneous anergy, prolonged graft survival, and abnormal responses to HBV and TB [26].

Incidence of TB was reported previously as 23.6% (26 patients, 6 females and 20 males) of HD patients in a HD center from Turkey. It was reported that infection was characterized clinically by a very insidious onset, the main symptoms being anorexia, loss of weight and low-grade fever, a very high sedimentation rate and lymphocytes predominant in the peripheral circulation, pleural and peritoneal fluids. Pulmonary TB was seen in 70% patients. There were extrapulmonary presentations in 8 of the 26 (30%) patients [29]. However, we reported herein the incidence of TB was 3.0 % (three of total 97 dialysis patients) among our dialysis population, and two out of three cases with extrapulmonary TB, and two of them had tuberculous lymphadenitis.

Some authors reported the difficulties of the diagnosis of TB in HD patients. Some time *Mtb* was not isolated in spite of multiple localizations [30]. In general, there

are no specific symptoms or signs that form the hallmark of TB in dialysis patients [1]. Signs suggesting TB such as weight loss, persistent fever, pulmonary infiltrates and pleural effusion, may also be considered as complications of CRF [1].

The high incidence of extrapulmonary disease may be a significant factor in the delay in diagnosis of TB in these patients [1]. Therefore, HD centers should administer tuberculin and anergy test their patients. This suggestion is especially important for our region where TB prevalence is 2 times higher than that of whole Turkey (31). Timely identification and treatment of high-risk population such as dialysis patients is essential to successfully combat the spread of TB. INH preventive therapy should be considered in HD patients especially in anergic ones (32).

Our dialysis patients had *Mtb* and hepatitis co-infection, two them had HCV and other one case had HBV infection. We did not see any serious complications except elevated liver enzymes in two patients with HCV. Finally, it was considered that ESRD, dialysis and HCV or HBV infection might reduce the effectiveness of the body's immune system, which can allow dormant bacteria to become reactivated.

Conflict of interest statement. None declared.

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