Extrapulmonary tuberculosis in ten hemodialysis patients: a single center experience

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Abstract
Tuberculosis (TB) infection is increasing all over the world especially among immunocompromised patients including end stage renal disease (ESRD) patients. Symptoms and signs are non-specific and involvement is generally extra-pulmonary in ESRD patients. We presented ten ESRD patients with TB. Six of our cases presented with TB lymphadenitis, two with Pott’s disease, one with breast TB and one with lung TB and Wegener’s granulomatosis. The diagnosis of TB is based on the finding of an acid fast bacilli-positive smear, positive culture of Mycobacterium tuberculosis, and typical histopathologic findings. Anti-TB therapy with isoniazid, rifampin, pyrazinamide and ethambutol combinations are generally successful. Non-specific constitutional symptoms and unexplained deterioration of general health in ESRD patients should attract attention of clinicians about TB infections.

Keywords: End stage renal disease, tuberculosis, extrapulmonary.

Introduction
Tuberculosis (TB) is an old disease that in ancient tissue specimens mycobacterial DNAs were detected. TB infection rate is increasing all over the world and patients with HIV, malignancy, diabetes mellitus, renal failure, transplantation, substance abuse, and members of the underdeveloped countries are especially under risk of TB [1]. Patients with end stage renal disease (ESRD) are more susceptible to TB infection because of the failure of cellular immunity. Clinical symptoms of TB may be nonspecific and insidious in uremic patients such as, fatigue, appetite loss, low grade fever, night sweating, general malaise. Additionally, the nonspecific presenting symptoms together with the frequent extrapulmonary localization can cause delay in diagnosis of TB. The most common forms of extrapulmonary TB are lymphadenitis, gastrointestinal, bone, genitourinary, peritoneal, pleural, pericardial and miliary TB [2].

Between 2010-2015 years we have identified ten cases with various organ involvements because of the fact that TB usually has atypical presentation and diagnosis may be delayed in patients maintained by hemodialysis (HD).

Case presentations
Case 1: A 65 year old woman with ESRD was on HD for 2 years. She was hospitalized in physisiatry clinic with suspicion of manic disorder in an ajitated state. Because of known renal disease she was transferred to nephrology clinic with cavitory lesions in chest graphy and erytrocyte casts in urine. She complained for hemoptysis, fever, night sweating, dyspnea and productive cough. Proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) was strongly positive (16.8 IU/ml). Although five times repeated sputum ARB analysis was negative, as PCR. She was not cooperated, willing to sleep on the ground instead of her bed and medical records demonstrated that she had the diagnosis of uveitis six months ago and examined for nodulary lung lesions three months before the admission. Central nervous system (CNS) involvement was not confirmed with MRI although clinically apparent because of uncooperation. We diagnosed her as Wegener’s granulomatosis. Plasmapheresis and intravenous cyclophosphamide was started. At the end of the first month CNS symptoms and cavitory lung lesions were revealed. However, meantime sputum culture was reported positive for TB. Besides HD and control of TB with anti-TB therapy, 3 cycles cyclophosphamide therapy was administered. All of her complaints subsided, PR3-ANCA levels decreased, cavitory lesions were healed with these therapies. Anti-TB therapy was continued for 12 months. She is now under routine follow up more than 3 years with HD therapy without any complaints that may be related with Wegener’s granulomatosis and/ or TB.

Case 2: A 84 year old man with ESRD due to polycystic kidney disease and was on HD for 3 years. An abscess on the left mammarian area was detected during routine follow up. This abscess was a fluctuating mass with a fistula draining its content. According to the

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histopathologic evaluation of the surgically removed material, it was necrotising granulomatous inflammation. TB was suspected but he had no parenchymal lung lesion or lymphadenopathy, however pleural effusion determined in the left lung. He was diagnosed as pleural TB and anti-TB therapy has been started because of his complaints of weakness, night sweating, fever and productive cough and high adenosine deaminase (ADA) levels (85.2 IU/l) in pleural effusion aspiration material. Anti-TB therapy was continued for 12 months after the diagnosis of breast TB. He is now under our control for nearly 3 years without any major problems on regular HD sessions and with normal clinical and laboratory conditions.

**Case 3:** A 60 year old man with ESRD was on HD for 3 years. He has been suffering from weakness and back pain for the last twelve months. He had night sweating and sense of fever but he did not measured his body temperature before. His laboratory findings were as follows; erythrocyte sedimentation rate (ESR): 77 mm/h, C-reactive protein: 16.3 mg/dl. Tuberculin skin test was anergic. The chest X-ray revealed pleural effusion and calcifications. Findings on spinal MR imaging were degeneration and edema of lumbar vertebrates, erosion of intervertebral joints, abscess of epidural space and multiple abscess between paravertebral space and psoas muscle. Aspiration of the psoas abscess was a cheese-like material and TB-PCR was positive both in this material and sputum. Depending on diagnosis of spinal and probably lung TB, we started anti-TB therapy. During follow-up period, his complaints were regressed and we planned to administer anti-TB therapy for one year.

Six of our other seven cases were TB lymphadenitis and one was spinal TB. One of TB lymphadenitis patients died during anti-TB therapy due to other comorbidities, one had resistant infection with recurrent spontaneously draining neck and axillary lymph nodes and multiple abscess in psoas muscle and other patients healed. Patient with spinal TB also responded anti-TB therapy successfully and healed.

**Discussion**

TB is a common, life-threatening granulomatous disease commonly manifesting as cavitated lung nodules. Patients with ESRD are under risk of TB, because of impaired cellular immunity. Particularly HD patients are 6-25 times more likely to develop TB and mortality rate of HD patients with TB is high (17-75%) compared with the general population [3]. These situations may be explained with depletion of useful proteins, trace metals and vitamins by dialysis and also induces an immune response through biocompatibility of membrane and fluid or entry of microorganisms [4]. During primary infection, bacteria go to different tissues by blood circulation and after years, with cellular immune response failure in dialysis patients latent infection reactivates.

Previous studies reported a high frequency of cases of TB discovered in the first year of HD. Poor general health status of some patients at the beginning of HD, when the host immunity might be most profoundly depressed was the underlying reason. However, the pathogenesis of TB patients with a longer duration of HD (HD>1 year) differs from uremic patients with TB. Although the uremic states improves with maintenance HD, the progression of comorbidities (poorly controlled diabetes, smoking, low serum albumin, anemia, ischemic heart disease, the progression malignancy and the use of immunosuppressive agents) increases the risk of active TB [5-7].

The rate of extrapulmonary TB (either isolated or associated with pulmonary TB) is 60-80% in this population. Additionally, involvement of lymph nodes (especially cervical) is the most common feature in dialysis patients [3,7]. For the diagnosis of TB lymphadenitis histopathologic evaluation, acid-fast bacteria smear and culture of the lymph node material are essential. Excisional biopsy have the highest success to diagnose TB.

Although spinal TB (Pott’s Disease) is the most common cause of skeletal TB, the incidence of skeletal TB is reported rarely in HD patients. It commonly affects thoracic and upper lumbar vertebrates. Paravertebral abscess (cold abscess) is common and aspiration of abscess supports the diagnosis of TB [8]. Back pain, muscle spasm, rigidity and constitutional symptoms may also be seen. In HD patients, the clinical picture is often confused with uremia and mineral bone disease. Because of this, diagnosis of Pott’s disease is commonly delayed and serious complications such as spinal cord compression are not rare [9]. Radiography, computed tomography and magnetic resonance imaging may be useful to diagnose both TB lymphadenitis and Pott’s disease.

Wegener’s granulomatosis is a vasculitis of small and medium sized vessels (especially in the upper and lower respiratory tracts, as well as in the kidneys) associated with anti-neutrophil cytoplasm antibodies (ANCA). It is rare and primarily affects adults between 40-65 years old but can affect people of all ages. Clinical presentation is often obscure with nonspecific symptoms (weight loss, fever, fatigue, arthralgia, myalgia). Also WG is the most common cause of pulmonary-renal syndrome presenting with renal dysfunction and pulmonary hemorrhage. Alveolar hemorrhage occurs in approximately 20% of patients and necrotizing and crescentic glomerulonephritis occurring in 75% of patients at some point in their disease [10,11]. Renal replacement therapy is required in 20%-30% of patients. High dose pulse cyclophosphamide forms the mainstay of treatment. TB and WG share many features including constitutional symptoms and respiratory tract involvement. Therefore, discrimination between TB and WG can be difficult at disease onset. Although previous studies have shown the presence of ANCA in TB patients [12,13], a recent study show did not [14]. PR3-ANCA is strongly associated with WG, and over 90 % of patients have been reported
to demonstrate ANCA positivity during active disease associated with relevant clinical and histopathological data. We determined co-existence of TB and WG in a female patient who was on HD for two years. Although this entity has a poor prognosis she did well with plasmapheresis and anti-tb treatment until now.

The diagnosis of TB may be complicated and difficult in patients with dialysis because of impaired immune functions, atypical clinical presentation, nonspecific symptoms and signs that may be attributable to uremia, and a higher occurrence of extrapulmonary TB. The prevalence of anergy to tuberculin skin test in the ESRD patients is significantly higher than in the general population (44% versus 16%) and exhibits poor sensitivity in ESRD patients [15]. The diagnosis of TB is based on the finding of an acid fast bacilli-positive smear, positive culture of Mycobacterium tuberculosis, and typical histopathologic findings.

Anti-TB therapy generally comprises classical as isoniazid (INH), rifampin (RFP), pyrazinamide (PRZ) and ethambutol (EMB) combination. Although drug dose and duration of therapy are not definite, some authors followed the same treatment guidelines as in patients not on dialysis. RFP 300-600 mg/day, INH 300 mg/day on dialysis days after HD, EMB and PRZ 15–25 and 25–30 mg/kg after each thrice-weekly HD, respectively. Extrapulmonary TB should be managed for 9–12 months (with RIF and INH), with EMB and PZA added for the first 2 months [16].

In conclusion, constitutional symptoms such as fever, sweeming, fatigue, weight loss and unexplained deterioration of general health status in dialysis patients must suspect clinicians about TB infections. As well as clinical considerations, laboratory and imaging modalities are useful to diagnose TB. Because of its morbidity and mortal consequences, treatment should be started promptly.

References