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Tuberculosis among Chronic Hemodialysis Patients: A Senegalese Single Center Experience

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Abstract

Summary: Tuberculosis is a common infectious disease in chronic hemodialysis due to alteration of the immune system associated with chronic kidney disease. The objectives of this study are to determine the prevalence of tuberculosis in chronic hemodialysis patients and to identify its diagnostic and therapeutic difficulties. Methods and patients: This was a descriptive retrospective study over a period of 20 years (1994-2014). It includes the records of periodic hemodialysis patients in the Nephrology Department of the Aristide Le Dantec University Teaching Hospital in Dakar which clinical symptoms and laboratory favor tuberculosis. Results: Of 258 chronic hemodialysis patients treated in Hospital Aristide Le Dantec hemodialysis center, 29 cases (11.4%) of tuberculosis disease are diagnosed. The mean age is 43.21 ± 12.48 years, and the sex-ratio is 0.8. The median time to onset of tuberculosis after initiation of hemodialysis is 22.86 ± 28.86 months. The diagnosis of tuberculosis is sure only in 17% of cases. Extra-pulmonary sites are found in 79% of cases. The average duration of treatment is 9.39 ± 1.64 months (6 - 13 months). Various treatment protocols are adopted. Mortality is 21%, 50% due to disseminated tuberculosis. Conclusion: The diagnosis of tuberculosis in the chronic hemodialysis patients is often difficult due to the atypical symptoms, the frequency of extra-pulmonary location and the lack of evidence of sure diagnosis.

Keywords

Tuberculosis, Hemodialysis, Dakar

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1. Introduction

Tuberculosis (TB) is one of the most frequent infectious complications in chronic hemodialysis patients (CHD) due to dysfunction of cell-mediated immunity (CMI), which occurs in chronic kidney disease (CKD) and increases during dialysis [1] [2]. It has several features. First, the symptoms are often atypical; extra pulmonary locations are more frequent [3] and furthermore toxicity of drugs is more pronounced [3] [4]. The objectives of this study are to determine the patterns of tuberculosis in chronic hemodialysis, tolerance of treatment and outcomes.

2. Patients and Methods

This was a descriptive retrospective study over a period of 20 years (1994-2014) on the records of 258 patients treated with regular periodic hemodialysis. The eligible patients must have been on dialysis for at least three months. They were dialyzed 2 to 3 times a week with duration of 4 to 6 hours in Hospital Aristide Le Dantec hemodialysis center. Our local ethics committee based on the hospital approved this study. The diagnosis of TB was retained:

- A number of presumptive arguments. Clinical (unexplained persistent fever for more than two weeks, asthenia, anorexia, dry weight loss associated with respiratory symptoms, digestive, osteo-articular), paraclinical: laboratory findings (inflammatory syndrome, hypercalcemia, tuberculin skin test (TST) positive for interferon gamma detection assays (IGRAs) and cyto-chemical analysis of effusion fluid of serosa ± assay of adenosine deaminase (ADA)); and morphological (standard X-ray, ultrasound, computed tomography, bronchoscopy). The TST is performed by intradermal injection of 0.1 ml of tuberculin purified protein derivative into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The skin test reaction was read 72 hours after administration. Inflammatory syndrome is defined by the elevation of the white blood cells and CRP.
- Sure arguments (bacteriological and/or histological).

First-line antituberculosis drugs were used at doses adapted to renal function: Rifampicin (R) (10 mg/kg/day), isoniazid (H) (5 mg/kg/day), pyrazinamide (Z) (30 mg/kg/48 h), ethambutol (E) (20 mg/kg/48 h) and streptomycin (S) (500 mg, twice a week).

The new TB cases were treated with a four RHZE or SRHE during the attack phase of two-months, followed by a maintenance phase involving HR for a variable period. The retreatment protocol for relapsing cases comprised an initial phase lasting three months involving five antibacillary agents SRHZE for two months, then RHZE for the 3rd month and a maintenance phase involving RHE for five months. Monitoring of treatment included the verification of compliance, efficiency and seeking treatment side effects. Non-compliance was assessed by both a self-reported survey and an inspection of remaining tablets. For each record, we collected epidemiological (age, gender, history of TB, initial nephropathy, date of first hemodialysis, immunization against TB), clinical (weight, fever, anorexia, clinical exam etc.), paraclinical, therapeutic and outcome data. The collected data were entered and analyzed statistically using the SPSS 20.0.

3. Results

Of 258 regular hemodialysis patients treated in Hospital Aristide Le Dantec hemodialysis center, 29 (11.4%) cases of TB disease were collected. The mean age was 43.21 ± 12.48 years (18 - 73) and the sex ratio (M/F) was 0.8. The history of treated TB before initiation of hemodialysis was found in 7% of cases. Vascular nephropathy (38%), glomerular (28%) and polycystic kidney disease (10%) were the most common causes of CKD. The average time between the initiation of hemodialysis and diagnosis of TB was 22.86 ± 28.86 months (0-108 months). Seventeen patients (59%) developed TB during the first year of dialysis. The main general signs found were unexplained prolonged fever (90%), anorexia (76%) and decreasing dry weight (62%). Respiratory symptoms were the most noted. These were cough (62%), chest pain (45%), and dyspnea (45%). On physical examination, the pleural effusion was found in 40% of cases, as cites in 14% of cases, cervical lymphadenopathy in 7% and pericardial effusion in 3% of cases.

The biological inflammatory syndrome was noted in all patients. The CRP average was 155.62 ± 152.37 mg/l. Anemia was observed in 42% of patients, the mean hemoglobin was 8.56 ± 1.5 g/dl. Lymphopenia was observed in 34% of cases. Mean serum calcium was 93.86 ± 8.72 mg/l; it was high in 7% of cases. The mean serum albumin was 33 ± 5.13 g/l; it was low in 21% of cases. The tuberculin skin test was negative in 76% of cases.

Tests interferon release assays Ɣ (IGRAs) were performed in six patients, they were positive in 100% of those cases. Twenty-one of the serous effusions were studied, cytochemical analysis showed a high exudate cells. The mean albumin level in serous effusion was 41.78 ± 7.65 g/l. The average rate of lymphocytes was 74.13 ± 11.82%. Adenosine deaminase (ADA) was measured in three patients, it was positive in two cases. The chest radiograph was systematic; it showed a pathological appearance in 75% of cases. CT scan done in five patients was pathological in all cases. The diagnosis of tuberculosis was sure in 17% of cases; 7% to the bacteriology, 7% at histology and 3% at autopsy. Extra-pulmonary tuberculosis was noted in 79% of cases. The tuberculosis locations are summarized in **Table 1**.

According to the therapeutic patterns, the average duration of treatment was 9.39 ± 1.64 months, with a range of 6 to 13 months (6 months for first cases and more for relapses).

Side effects (SE) were reported in 48% of patients. They were linked to H in 60% of cases, Z in 20% of cases, S in 13% of cases and E in 7% of cases. No SE was reported with R. The noted side effects are reported in **Table 2**.

These SE regressed after therapeutic adjustment. Non-compliance with treatment was reported in 13% of cases. The treatment was extended with education for good adherence. The outcome was positive in 72% of cases. Relapse of tuberculosis was reported in 9.5% of cases. The outcome was positive after new treatment in all cases. Treatment is ongoing in 7% of cases. The mortality rate was 21%. It was attributed to disseminated TB in 50% of cases, cardiovascular comorbidity in 33% of cases and sudden death in 17% of cases.

4. Discussion

The prevalence of TB in the CHD in our series was 11.4%. In the literature it is variously appreciated. It is similar to that reported in a previous study in Senegal [3]. It corroborates those found in Tunisia, Brazil and India, where it was respectively 10%, 10.3% and 10.5% [5]-[7]. A higher prevalence (15.5%) was reported in Mali [8]. However, low prevalence was reported in Turkey, Ivory Coast and Morocco with respectively 5.2%, 5.9% and 6% [9]-[11]. In developed countries, low prevalence was noted in the US and Japan; it was respectively 1.6% and 4.93% [12] [13], however, in Belgium it was high in the range of 15% and it was attached to an immigration factor [14].

Table 1. TB sites in our study.

Localisation of TB	Numbers	Percentage %
Pulmonary	**6**	**21**
Extra-Pulmonary	**23**	**79**
Pleural	10	34
Peritonal	5	17
Lymphnodes	3	10
Spondylodiscitis	1	4
Genito-urinary system	1	4
Multifocal	3	10

Table 2. Reported side effects (SE).

SE	Number of patients	Suspected anti TB	Management
LL paresthesia	5	H	Vitamin B
Acute delirium	3	H	Decrease dose of Vitamin B
Drug-induced hepatitis	1	H	Decrease the dose
Hyperuricemia	3	Z	Stop Z
Hypoacousia	2	S	Stop S
Decreased visual acuity	1	E	Decrease the dose

In our series, the prevalence of TB was 56.2 times higher than in the Senegalese general population where it is estimated to be 200/100,000. The high prevalence of TB in the CHD patients compared to the general population was confirmed by other authors [3] [7] [10] [11] [15]. A literature review reported that the incidence is 6.9 to 52.5 times higher in dialysis patients [16]. It is explained by the CMI deficiency related to CKD. TB occurs most often during the first year of the start of hemodialysis. During this phase there is a decrease in CMI, promoting the reactivation of an old or a new TB infection [3] [7] [12]. In our study, the period average was 22.86 ± 28.86 months, 59% of TB diagnosis was made during the first year after the start of hemodialysis.

TB of dialysis is characterized by its insidious development and nonspecific clinical signs [3] [6] [7] [15]. As in our series, unexplained prolonged fever, anorexia and dry weight loss are the most marked signs. The main respiratory symptoms found were cough in 62% of cases, chest pain and dyspnea. They are often wrongly attributed to the dialysis constraints [3] [6] [9] [11] [15].

As in our study, the presence of a biological inflammatory syndrome is common [3] [5] [9] [11]. Some authors reported hypercalcemia, it would be an early indicator of TB in hemodialysis patients [17] [18], and it was reported in 7% of our patients.

In our series TST was negative in 76% of cases, this result corroborates those found by several authors, its negativity reflects the state of anergy secondary to lower CMI [3] [5] [9] [11] [15]. The authors agree on the low diagnostic value of this review in the context of dialysis [3] [6] [11] [15]. To increase the sensitivity of the test, some authors recommend the TST double stages with a 7 to 15 day intervals for patients not responding to the initial test [12] [14], others have proposed that the TST positivity threshold 5 mm instead of 10 mm as in HIV positive patients [19] [20].

The use of IGRAs tests in hemodialysis patients is controversial. Savaj [21] found 23.4% of positive IGRAs tests against 43.5% positive TST. Maden [22] did not find a significant difference between the two tests. However, other authors have demonstrated the superiority of IGRAs tests compared to the TST in sensitivity and specificity [13] [23].

In our series, 21 serous effusions were analyzed, they found a rich exudate cells in all cases. This result is similar to those reported by some authors [3] [10]. The dosage of the ADA was positive in two of the three patients examined. According to Gobert [24] there is a strong correlation between the positivity of this assay and the existence of TB; it would be more reliable in the ascites than in the pleural effusions. Nevertheless, a positive determination of ADA is not definitive evidence of TB.

Searching Koch Bacilli in biological fluids is rarely contributive; cultures are long, and not cost effective [5] [7] [8] [10]. The GeneXpert is a sensitive tool that allows a rapid detection of bacilli within hours, but a negative result does not exclude TB [25]. In our study the KB was isolated in 7% of cases.

The histological study was done in five of our patients; it had confirmed the diagnosis in two lymph node biopsies and autopsies. Some authors suggest the use of invasive procedures with tissue biopsy, because it helps to confirm the diagnosis, to start early treatment, and to have a good outcome [11] [15] [18]. In addition to the poor specificity of symptoms, also the site of TB is often extra-pulmonary. In the literature, this frequency varies from 47% to 100%; the lymph node and peritoneal tuberculosis are the most common sites [3] [5] [9] [11] [15]. In our study, the extrapulmonary location was predominant (79%). All the authors reported the difficulty in the diagnosis of TB in the CHD; it is due to non-specific symptoms and the frequency of extrapulmonary location [3] [5] [7] [9] [11] [15]. In our series sure diagnosis was only achieved in 17% of patients, 7% bacteriology, 7% on tissue biopsy histology and 3% at autopsy.

Some authors recommend starting a probabilistic TB treatment without formal proof of TB in CHD based on strong presumptive arguments. The favorable response to treatment will later confirm the diagnosis [3] [5] [8] [9]. The treatment of TB in the CHD is not codified. The protocols and duration of antituberculosis treatment vary according to the authors. Some associate RHZ [11] [15], others RHZE [5] [10] [11] for the first two months, and HR during the maintenance phase. Dosages of R and H should not be changed, while the Z and E are respectively administered at the dose of 30 mg/kg and 20 mg/kg every 48 hours. Streptomycin is given at a dose of 750 mg every 72 hours, six hours before each dialysis with close monitoring of serum. [3] In the Senegalese TB program, this drug is reserved for retreatment protocols.

Because of their inability to excrete chemicals, side effects of TB drugs are commonly observed in the CHD [4]. Isoniazid was the most offending drug, it was responsible for 53% of neuropsychiatric effects in our series, against 100% in Niang studies [3], 54% in Yao studies [10] 43% in studies of Sen [9] and Quantrill. [4] These effects can be avoided by administering pyridoxine to 100 mg daily [3]. The retrobulbar optic neuritis was re-

ported in Sen [9] and Yao [10] studies with respectively 43% and 46% of cases. Visual acuity and color vision before and regularly during treatment and control serum level are also recommended [26]. The incidence of drug-induced hepatitis is very low in our serie. Compared with Turkish serie, N Sen found 3 cases of hepatotoxicity among 18 patients [9]. Only early detection and adequate treatment can guarantee a good prognosis. The combination of immune deficiency, malnutrition and tuberculosis infection increases the risk of tuberculosis and mortality [3] [9] [11]. The death rate ranges from 0% - 75% according to studies [8]-[11] [15]. It is often attributed to delayed diagnosis and treatment. In our study, the outcome was favorable in 72% of cases. We noted the death of 6 patients (21%). Mortality was attributed to disseminated tuberculosis in 50% of cases. This result is superimposed on that found in Mali (70% of favorable evolution) [8], and better than that reported in Ivory Coast 57% [10]. However a better evolution was reported in Turkey [9] and Brazil [15] with respective recovery rates of 94.5% and 97%.

Some authors recommend early treatment of latent tuberculosis infection in chronic hemodialysis patients to prevent progression to disease state [6] [9]. Anti LAM (Antilipoarabinomannan Antibody) antibody is sometimes useful to diagnose latent tuberculosis which can help to start treatment earlier [27]. The drug of choice is H which can be administered 2 to 3 times a week under the supervision of the dialysis team, at a dose of 15mg / kg/dose for a period of 6 to 9 months, associated with pyridoxine 100 mg/j [4]. Chemotherapy is not devoid of SE; it requires close monitoring [4]. In our series no cases of latent tuberculosis infection was sought.

5. Conclusion

TB among chronic hemodialysis is more common compared to the general population because of immune dysfunction associated with chronic kidney disease. Early diagnosis and treatment are the guarantee of a good outcome.

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