

Original Article**Tuberculosis in Peritoneal Dialysis patients: A Diagnostic challenge.**El Bardai G^{1,2}, Er rami R¹, Chouhani B A^{1,2}, Kabbali N^{1,2}, Sqalli Houssaini T^{1,2}¹Nephrology, dialysis, and transplantation department. Hassan II university hospital, Fez. Morocco.²Laboratory of Epidemiology and Health Science Research (ERESS), Faculty of Medicine-Fez, Sidi Mohammed Ben Abdelah University, Fez, Morocco**Abstract**

Introduction: Tuberculosis (TB) is a common infectious illness in people with chronic kidney disease (CKD). Peritoneal localization, which is generally uncommon, has become a significant form in peritoneal dialysis patients. Positive diagnosis is challenging in this population due to the non-specific clinical presentation.

Material and Methods: From 2014 to 2021, we included all patients on peritoneal dialysis who had been treated for TB in the nephrology department of the HASSAN II university hospital of Fez. The goal of our investigation is to describe clinical and paraclinical presenting patterns, methods used to maintain the diagnosis, and treatment outcomes in order to raise the diagnostic challenge of tuberculosis in this group.

Results: We found five cases out of 125 incident patients. One patient had lymph node involvement, while four others had peritoneal involvement. The patients' average age was 31.9 ± 11.9 years (20-50 years), including two females. Clinically, four individuals experienced a change in their overall condition as well as stomach discomfort. Three patients had a protracted fever, and one patient had extensive joint discomfort. All of the patients suffered from lymphopenia and a biological inflammatory condition. A CT scan of the abdomen revealed a compartmentalized effusion in two individuals, one of whom had deep adenopathies and the other had calcified adenopathies. The involvement was kept due to the rapid detection of MYCOBACTERIUM TUBERCULOSIS DNA by molecular biology test (GeneXpert®) in the peritoneal fluid of three patients, on lymph node biopsy, which revealed tuberculous adenitis in one patient and a positive adenosine desaminase assay in the fifth patient. Four patients were diagnosed with TB within one year of starting peritoneal dialysis, while the fifth patient was diagnosed three years later. According to the RHZE/RH regimen, all patients received antituberculosis medication for 6 to 9 months (R: Rifampicin, H: Isoniazid, Z: Pyrazinamide, and E: Ethambutol). All patients had remission with the removal of the catheter and the conversion to hemodialysis.

Conclusion: Tuberculosis is a disease that is frequently misdiagnosed in peritoneal dialysis patients because of pauci symptomatic images that mirror a peritoneal fluid infection with common microorganisms. The introduction of new diagnostic procedures has enhanced patient treatment.

Key words: Tuberculosis, diagnosis, peritoneal disease.

Introduction

Mycobacterium tuberculosis is a contagious infectious illness caused by a tuberculosis complex mycobacterium, primarily Mycobacterium tuberculosis or Koch's bacillus (KB) [1]. It is still a huge public health issue across the world, particularly in underdeveloped nations [2]. It is commonly seen in people with CKD. Peritoneal localization, which is generally uncommon, has become a significant type in peritoneal dialysis patients [3]. Positive diagnosis is challenging in this population due to the non-specific clinical presentation [4]. The purpose of this study is to characterize the demographic, clinico-biological, and therapeutic aspects of peritoneal dialysis patients with TB who have been diagnosed, in order to increase the diagnostic challenge of tuberculosis in this group and to assess its prognosis.

Materials and Methods

This is a retrospective, descriptive study, including cases of tuberculosis diagnosed according to the criteria of the National Tuberculosis Control Program [4], in peritoneal dialysis patients within the nephrology department at the HASSAN II university hospital of Fez during an 8-year period between 2014 and 2021.

Definition of tuberculosis cases: according to the criteria of the National Tuberculosis Control Program [4]

-A bacteriologically confirmed case was confirmed by rapid detection of MYCOBACTERIUM TUBERCULOSIS DNA by molecular biology test (GeneXpert®), direct examination of smears, and culture of pathological products.

- A clinically diagnosed case (diagnosis without bacteriological evidence) based on: clinical signs (altered general condition, unexplained fever, cough...) that persist for more than two weeks; radiological abnormalities; tuberculin and interferon gamma release test positivity;

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histological presence of specific lesions (epithelioid and giant-cellular granulomas with caseous necrosis); and predisposition (notion of tuberculosis contact, immunosuppressed subjects).

The definition of peritoneal fluid infection: [5]

The diagnosis is made if at least two of the following three criteria are met: abdominal pain or cloudy peritoneal fluid; leukocyte count greater than 100 per mm³ in the drainage fluid with a neutrophil count greater than 50%; bacteriological culture and/or positive microscopic examination.

Definition of deadlines:

The definition of deadlines

- Tuberculosis healthcare delay: the time between the onset of symptoms and the start of anti-tuberculosis treatment.
- Delay in care if the time between diagnosis and treatment exceeds the 21-day limit set by the world health organization (WHO) [3, 6].

Data Collection:

Data were collected using a data collection form that was filled out using the patient's chart. The data collected were: demographic data (sex, age, socio-economic level...); history (diabetes, hypertension, length of time on dialysis, tuberculosis infection...); clinical signs (altered general condition, weight loss, unexplained prolonged fever, chills, night sweats, respiratory manifestations, ascites, adenopathies), time of onset of tuberculosis in relation to the beginning of dialysis; biological data [cytobacteriological study of the peritoneal fluid; direct examination and culture for *Bacillus KOCH*, molecular biology test (GeneXpert®), interferon gamma release test (Quanti-Interferon®), adenosine desaminase assay], radiological data (X-ray and/or thoracic CT scan, ultrasound and/or abdominal CT scan), the histological results of the biopsies performed; the anti-thoracic CT scan, ultrasound and/or abdominal CT scan), the histological results of the anti-tuberculosis treatment; the molecules used with dosage modifications done in accordance with ICAR [7], and the associated side effects were collected. The evolution of the patients concerning cure, relapse, resistance, and death were also collected.

Results

We identified five cases of tuberculosis in 125 incident peritoneal dialysis patients over the period from 2014 to 2021 in the nephrology department at HASSAN II university hospital of Fez. These included two women and three men, with a sex ratio of 1.5. The patients had a mean age of 31 ±11.9 years (20–50 years). Most of the patients were of low (4 patients) and medium (1 patient) socioeconomic level. One patient had a history of tuberculosis infection, three patients had hypertension, and one patient had type 2 diabetes mellitus. The causes of end-stage renal failure were undetermined in two patients; glomerular in two patients; and of lithiasis origin in one patient. (Table 1)

The delay between the start of dialysis and the onset of the clinicobiological picture was less than one year in four patients and three years in one patient. The most frequent clinical signs were altered general condition and abdominal pain, which were present in all patients; prolonged fever in three patients; and inflammatory joint pain in one patient. Physical examination revealed pleural effusion syndrome in one patient and peripheral cervical adenopathy in one patient. Biologically, an inflammatory syndrome was reported in all five patients

with an elevation of protein reactive C which averaged 110 mg/l ± 55.6 (52-171 mg/l) and ferritin at 625ug/l ±255 (300-871µg/l) as well as an inflammatory anemia at 6.9 g/dl ±1.46 (5.3 - 9.2 g/dl) and a lymphopenia averaging 546/µl ± 104 (390-650/µl).

Peritoneal sampling was done with a cytobacteriological study in four patients and came back positive with high white blood cells (WBC) on average at 1820/mm³± 104.1(1400-2300/mm³). In all four patients, the diagnosis of peritoneal fluid infection was retained, and the patients were treated with empirical antibiotic therapy targeting both gram-positive and gram-negative germs. We administered a third-generation cephalosporin (1 g per day intraperitoneally).

Other supplementary evaluations were carried out in light of the unfavorable progression. A search for KB in the peritoneal fluid yielded no results. In two patients, an abdominal CT scan revealed a compartmentalized effusion associated with deep adenopathies in one and calcified adenopathies in the other. (Table 1)

All patients had a chest X-ray, which came out normal in four patients and revealed a pleural effusion in one.

Tuberculosis involvement was eventually retained because to the quick identification of MYCOBACTERIUM TUBERCULOSIS DNA by (GeneXpert®) in peritoneal fluid in three patients, lymph node biopsy, which revealed tuberculous adenitis in one patient, and a positive adenosine desaminase assay in the fifth patient. The average diagnostic delay was 39 days ±29.2 (15-90 days) between the beginning of symptoms and the diagnosis. Four of the five patients had peritoneal involvement, while one had lymph node involvement.

All patients were given an anti-bacillary therapy regimen based on Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol (RHZE (attack phase) / RH (maintenance phase)) for 6 to 9 months. Side effects associated with anti-tuberculosis treatment were observed in one patient, who suffered from digestive disorders such as vomiting and diarrhea without neurological signs, which did not require discontinuation of treatment.

The progression was marked by catheter removal in all patients with hemodialysis switch, and all patients were declared cured without death. (Table 1)

Discussion

Infections continue to be a major source of morbidity and death in dialysis patients, particularly those receiving peritoneal dialysis [8]. The most feared complication of this technique is the development of peritoneal fluid infections, which necessitate emergency antibiotic therapy and can be caused by contamination during handling, orifice infection by continuity, bacterial translocation through the digestive wall, or perforation of a hollow organ.

Complicated peritoneal fluid infections such as recurrent infections, mycotic infections, and those related to gastro intestinal perforation or orifice infection require catheter removal with temporary or permanent transfer to hemodialysis [9,10,11]. In most cases, uncomplicated peritonitis is treated on an outpatient basis with good evolution [11]. Tuberculosis is a common infectious disease in long-term dialysis patients. The frequency of latent tuberculosis infection in this group is unknown, particularly among individuals on peritoneal dialysis [12].

Table 1: Clinical features, diagnostic, therapeutic, and evolutionary elements of tuberculosis in peritoneal dialysis patients. DT2: diabetes mellitus, HBP: high blood pressure, AGC: altered general condition.

Cases	Sexe	Age	Medical history	Causal nephropathy	Seniority on dialysis	Clinical signs	Chest x ray	CT scan	GeneXpert	Location	Treatment	Evolution
1	M	36	DT2	Diabetic nephropathy	2014	AGC	Normal	Not done	Not done	Ganglionic	2RHEZ 4RH	Complete remission
2	M	26	HBP	Undetermined	2016	AGC Abdominal pain	Normal	Not done	+	Peritoneal	2RHEZ 4RH	Complete remission
3	F	25	RAS	undetermined	2021	AGC Fever Abdominal pain	Normal	Effusion partitioned+ Deep adenopathies	+	Peritoneal	2RHEZ 4RH	Complete remission
4	F	20	HBP	Glomerular	2015	AGC Abdominal pain	Normal	Not done	Not done	Peritoneal	2RHEZ 4RH	Complete remission
5	M	50	HBP	Lithiasis nephropathy	2020	AGC Fever Abdominal pain	Pleur- sis	Effusion en- cysted+ Cystic fibrosis	+	Peritoneal	2RHZE 7RH	Complete remission

Peritoneal tuberculosis (PTB) was found in 4% of the 125 peritoneal dialysis patients in our study during an 8-year period (2014–2021). In comparison to the overall population, it is rather high. In 2016, the number of TB incident cases in Morocco was 36,000, suggesting an incidence of 103 new cases per 100,000 inhabitants. In the same year, 3300 people died as a result of this disease, with a mortality rate of 9.3 per 100,000 people [13]. After cardiovascular disorders, it is the world's fifth greatest cause of mortality [14].

Tuberculosis infection usually occurs within one year of the initiation of dialysis [15], and this delay has been explained by reactivation of latent tuberculosis [16]. The causes of the increased risk of tuberculosis in dialysis patients have been attributed to impaired cellular immunity, malnutrition, zinc and pyridoxine deficiency [17, 18]. In peritoneal dialysis patients, local disturbances of intraperitoneal immune defense most likely predispose to reactivation of peritoneal tuberculosis. Alterations in pH, osmolality, and volume dilution of peritoneal fluid may locally impair phagocytic and lymphocytic activity and lead to infection [19]. In our study, the diagnosis of tuberculosis was made within one year after the start of dialysis in four of our patients. This delay was prolonged in the 5th patient, reaching 3 years.

The most frequent tuberculosis attack in patients undergoing peritoneal dialysis is peritoneal attack [16], manifested by abdominal pain and fever, which may mimic an infection of the peritoneal fluid by the usual germs, even if the cytology of the bacteriological fluid is positive, with a predominance of polynuclear neutrophils (PNN) [20, 21], which leads to a high level of suspicion of tuberculosis, and hence the need to carry out additional examinations if there is any doubt [20, 21]. Prolonged fever, weight loss, and anorexia are the most common indicators of call-in hemodialysis patients [22,23]. The most common indicators in our investigation were altered, overall condition and stomach discomfort in all patients, persistent fever in three patients, and arthralgia in one. Peritoneal samples were taken in all patients and were positive in 4 patients, with a predominance of PNN in 3 patients and a predominance of lymphocytes in only 1 patient. Three of our patients received initial antibiotic coverage for bacterial peritonitis. They were switched to antitubercular treatment when the diagnosis was established or when their condition was clearly refractory to the

usual treatment of peritonitis.

The diagnostic delay between the onset of symptoms and the diagnosis was on average 39 days ± 29.2 (15-90 days). This delay exceeds the recommendations of the WHO, which suggests a management delay of 21 days in the general population [3, 24]. In the Tunisian study, the average management delay for dialysis patients with tuberculosis was 113 days [25]. Our delay also exceeds the delays reported in the literature for the general population; a median health-care delay of 24 days (IQR10 - 45) was found in a recent American study [3].

The removal of the catheter during PTB is controversial. Some authors advocate its removal, while others prefer to keep it in place after the initiation of anti-tuberculosis treatment [26, 27,28]. In our series, all our patients benefited from the removal of the catheter. We estimate that this procedure contributed to the healing and survival of all our patients, with a zero mortality rate compared to an average of 30% in the same category of patients who kept the catheter [29].

Conclusion

Despite the development of novel TB diagnostic procedures that have improved patient care via early identification, tuberculosis is frequently misdiagnosed in peritoneal dialysis patients because of pauci symptomatic presentations, that mirror a peritoneal fluid infection with common pathogens. Because of the increased risk of activation of latent TB due to the compromised immune system, there is an urgent need to implement a comprehensive screening program in peritoneal dialysis patients.

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