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Diagnosis and management of tuberculosis in peritoneal dialysis

(Diagnostic et prise en charge de la tuberculose en dialyse péritonéale)

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Summary

Infectious complications represent the second cause of death in chronic renal failure, in particular tuberculosis (Tb), which remains more frequent in dialysis patients.

The aim of our work is to determine the prevalence of Tb in our patients on peritoneal dialysis (PD) and to analyze the clinical, paraclinical and evolutionary profile of this infection.

This is a retrospective cross-sectional study, including PD patients diagnosed with Tb. We analyzed their clinical and paraclinical profile, the diagnosis and localization of Tb, as well as the evolution under treatment.

We retained 12 cases of Tb among the 228 patients followed in PD (5.26%) from 2006 to 2022, with an M/F sex ratio of 0.7 and an average age of 52.7 ± 10 years. The median time between the start of PD and the diagnosis of Tb was 21 months [5 - 37].

The diagnosis of Tb was retained with certainty in 7 cases, based on bacteriological and/or histological evidence. The diagnosis was presumptive in 5 cases on a bundle of clinical and paraclinical arguments. The localization of Tb is pulmonary in 4 cases and extra-pulmonary in 8 cases including 3 cases of tuberculous peritonitis.

Anti-bacillary treatment is started after a median delay of 20 days [9-37] after the onset of symptoms. This treatment was complicated by 2 cases of drug-induced hepatitis and 1 case of polyneuritis.

The evolution is marked by healing in 11 patients. Regarding tuberculous peritonitis, the catheter was removed in one patient and maintained in the other two cases with favorable outcome.

In PD, the diagnosis of Tb is often difficult and extra-pulmonary involvement is more frequent.

Key words : Anti-bacillary, Peritoneal dialysis, Peritonitis, Tuberculosis

Résumé

Les complications infectieuses représentent la deuxième cause de mortalité chez l'insuffisant rénal chronique notamment la tuberculose (Tb) qui reste plus fréquente chez les dialysés.

Le but de notre travail est de déterminer la prévalence de la Tb chez nos patients en dialyse péritonéale (DP) et d'analyser le profil clinique, paraclinique et évolutif de cette infection.

Il s'agit d'une étude transversale rétrospective, incluant les patients en DP avec diagnostic de la Tb. Nous avons analysé leur profil clinique et paraclinique, le diagnostic et la localisation de Tb, ainsi que l'évolution sous traitement. Nous avons retenu 12 cas de Tb parmi les 228 patients suivis en DP (5.26%) de 2006 à 2022, avec un sex-ratio H/F à 0.7 et un âge moyen de 52.7 ± 10 ans. Le délai médian entre le début de la DP et le diagnostic de la Tb était à 21 mois.

Le diagnostic de Tb était retenu avec certitude dans 7 cas, en se basant sur des preuves bactériologiques et/ou histologiques. Le diagnostic était présomptif dans 5 cas sur un faisceau d'arguments cliniques et paracliniques. La localisation de Tb est pulmonaire dans 4 cas et extra-pulmonaire dans 8 cas dont 3 cas de péritonite tuberculeuse. Le traitement anti-bacillaire est débuté après un délai médian de 20 jours après le début des symptômes. Ce traitement s'est compliqué de 2 cas d'hépatite médicamenteuse et 1 cas de polynévrite.

L'évolution est marquée par la guérison chez 11 patients. Concernant la péritonite tuberculeuse, le cathéter a été retiré chez un patient et maintenu dans les deux autres cas avec évolution favorable.

En DP, le diagnostic de Tb est souvent difficile et les atteintes extra-pulmonaires sont plus fréquentes.

Mots clés : Anti-bacillaire, Dialyse péritonéale, Péritonite, Tuberculose

INTRODUCTION

Peritoneal dialysis (PD) is an extrarenal purification method that can be offered as a first-line treatment for the management of stage 4-5 chronic kidney disease (CKD).

Infectious complications represent the second cause of mortality in dialysis patients, mainly Tb in our endemic context. This infection is often latent and can reactivate in dialysis patients. In Morocco, the annual incidence of Tb in the general population is 87 cases/100,000 inhabitants, and the isolated pulmonary form represents more than half of the cases [1]. In a Moroccan study, Bardai et al. noted 5 cases of Tb among 53 PD patients, i.e., a prevalence of 9.43% [2].

The clinical picture of Tb is often atypical, and bacteriological confirmation is difficult, making its diagnosis late.

The aim of our work is to determine the prevalence and location of Tb in our PD patients and to analyze the clinical, paraclinical, and evolutionary profile of this infection.

MATERIALS AND METHODS

This was a retrospective descriptive study, carried out in the PD unit of the Ibn Sina University Hospital in Rabat, Morocco, and covering a period from 2006 to 2022.

We identified 228 patients managed in the PD unit, and we retained only those patients who presented with a diagnosis of Tb.

From the medical records of the dialysis patients, we collected their personal history, the notion of Tb infection, and the functional signs reported by the patients, as well as the complete clinical examination.

We performed the biological and physiological workup in the patients and the search for Koch's bacilli (BK) in biological fluids by direct examination in culture and by the polymerase chain reaction (PCR) of mycobacterial DNA (GeneXpert).

We specified the results of the radiological workup and the anatomopathological study of the biopsies performed for each patient.

The treatment protocol used included a quadruple combination for the first 2 months: rifampicin, isoniazid, ethambutol, and pyrazinamide, followed by a maintenance phase of 4 to 10 months, depending on the location of the Tb, based on a combination of rifampicin and isoniazid.

The dosage of antibacterial drugs was adapted to the weight of the patients and their dialysis status [3]. Residual rifampicin and isoniazid levels were routinely measured after the start of treatment. Adverse events were noted. Pyridoxine supplementation was systematic.

We described the short- and long-term evolution of our patients, based on clinical (fever, appetite, general condition, weight, dialysate fluid, etc.) and paraclinical (C-reactive protein, blood count, calcium levels, imaging, etc.) signs, as well as the side effects of antituberculosis drugs.

RESULTS

Of the 228 patients followed in the PD unit, 12 patients presented with Tb, a prevalence of 5.26%. The mean age of our patients was 52.7 ± 10 years with a male-to-female ratio of 0.7. The initial nephropathy was diabetic, vascular, indeterminate, tubulointerstitial, and glomerular nephropathy in 4, 3, 2, 2, and 1 case, respectively.

A history of relapsed pulmonary Tb was found in 1 patient, and the notion of Tb infection was reported in another patient in the family.

The median interval between the initiation of PD and the onset of clinical signs of Tb was 21 months (range [5-37]), with extremes ranging from 1 month to 5 years. In 4 patients, Tb was diagnosed during the first year of PD, representing 33.3% of patients.

Clinically, alteration in the general condition with fever and signs of Tb impregnation was present in almost all patients (92%). Signs of bacterial impregnation were evident in the majority of cases in the form of asthenia, night sweats, and weight loss of between 3 and 6 kg (83%). Patients reported dyspnea in 4 cases, cough in 3 cases, chest pain in 2 cases, and hemoptysis in 1 case.

Clinical examination revealed a unilateral pleural effusion syndrome in 4 patients with peripheral adenopathies. On PD, the peritoneal dialysate fluid was cloudy in 3 cases.

Biologically, we observed an inflammatory syndrome in all patients with an elevated C-reactive protein level, hyperleukocytosis with lymphopenia, and hypoalbuminemia.

Radiologically, chest radiography was systematic in all patients, supplemented by a computed tomography (CT) scan in 7 cases, showing necrotic mediastinal adenopathies in 6 patients and excavated pulmonary nodules in 4 cases, including 1 case of miliary tuberculosis. At the serosal level, we noted unilateral pleurisy in 4 cases, pericarditis in 1 patient, and thickening of the peritoneal fat in 2 cases.

The abdominal CT scan showed necrotic abdominal adenopathy in 1 case.

Mycobacterium tuberculosis was tested in a total of 19 targeted samples. The analysis was positive in the sputum of 2 patients, in the dialysate fluid of 3 patients, and in the pleural fluid of 1 patient.

The analysis of pleural, pericardial, and bronchoalveolar fluids was found to be exudative and lymphocytic in nature in 5 cases, and the bacteriological investigation was negative.

The anatomopathological study of the 8 biopsies taken from the pleural, peritoneal, pericardial, and lymph node levels was in favor of Tb in only 2 cases (lymph node and peritoneal) after the demonstration of tuberculoid granuloma with caseous necrosis.

At the end of the clinical and paraclinical examinations, the diagnosis of Tb was retained with certainty in 7 cases based on bacteriological and/or histological evidence (*Table I*).

In the other patients, the diagnosis was presumptive, based on a range of arguments (clinical, biological, radiological, and evolutionary) (*Table II*).

↓ Table 1. Presentation of patients with a confirmed diagnosis of tuberculosis

Case	Sex/ Age	Duration in PD (months)	Functional/ clinical signs	Imaging	Search for BK (site/ result)	Histology (site/result)	Location	Time to symptoms/ treatment	Evolution
1	H/43	42	AEG Cloudy dialysate fluid	- Mediastinal PDAs - Peritoneal thickening	Dialysate (+)	Peritoneum / Tuberculoid granuloma	Peritoneal	20 days	Good removal of Kt of PD /switch in HD
2	F/50	36	AEG Dyspnea Axillary ADP	-Interstitial lung infiltrate - Mediastinal and axillary PDAs	Spit (+)	ADP / non- specific adenitis	Pulmonary	9 days	Hepatocellular sufficiency / INH discontinuation (a cirrhosis liver)
3	H/55	20	AEG Cough, hemoptysis	Lung nodules	Spit (+)	NR	Pulmonary	20 days	Good
4	H/63	1	AEG Febrile pleural effusion	Unilateral pleurisy	Spit (-) Pleural fluid (+)	Pleura / Inflammatory remodeling	Pleural	8 days	Good
5	F/63	4	AEG/fever Cloudy dialysate fluid	-Mediastinal PDAs -Abdominal necrotic PDAs	Spit (-) Dialysate (+)	NR	Peritoneal	8 days	Good Polyneuritis/INH overdose Kt of PD in place
6	H/64	22	AEG Cloudy dialysate fluid	-Lung micronodules -Mediastinal PDAs - Peritoneal thickening	Dialysate (+)	NR	Peritoneal and pulmonary	5 days	Good Kt of PD in place
7	F/68	16	AEG Peripheral ADP	Normal lung imaging	Spit (-)	ADP / Tuberculoid granuloma	Ganglionic	4 months	Good

M: male; F: female; PD: peritoneal dialysis; AEG: altered general condition; Kt: catheter; HD: hemodialysis; NR: not performed; ADP: adenopathy

The location of Tb was pulmonary in 4 cases and extrapulmonary in 7 cases, and in 1 case the involvement was pulmonary and peritoneal.

Concerning the extrapulmonary localizations, isolated peritoneal localization was retained in 2 cases. In 3 cases, the Tb was located at the pleural level, in 1 case at the pericardial level, and in 1 case at the lymph node level (Figure 1).

We noted 3 cases of tuberculous peritonitis, confirmed by the search for Mycobacterium tuberculosis in the dialysate. In 1 case, this peritonitis was associated with pulmonary asymptomatic Tb miliaria. Removal of the PD catheter was indicated in 1 case in which the peritoneal biopsy confirmed the diagnosis of Tb by the presence of a tuberculoid granuloma with caseous necrosis (Figure 2).

Therapeutically, the median time from the initiation of antibacterial therapy to the onset of symptoms was 20 days (range [8-52]), reflecting the diagnostic difficulty. This delay was shorter in the group of patients with diagnostic evidence (median delay of 9 days, with a range of [8-20])

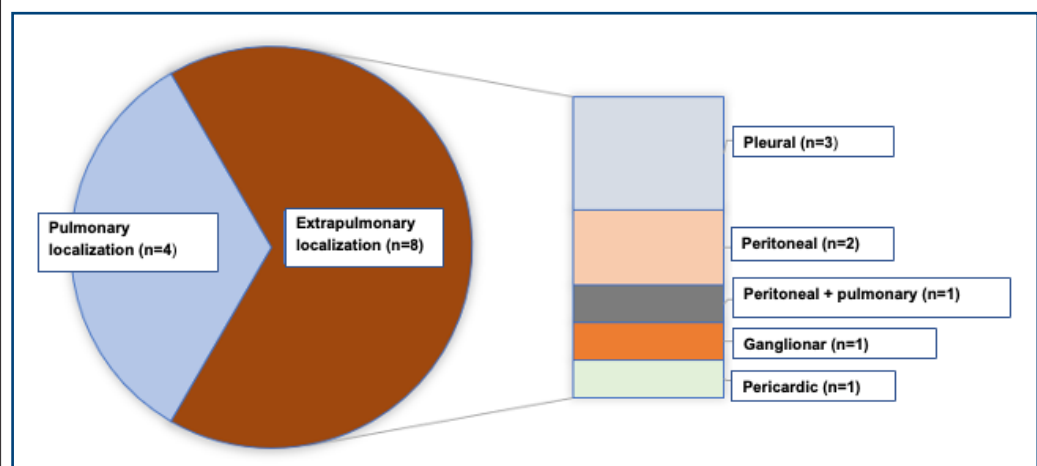
than in the group of patients with a presumptive diagnosis (median delay of 30 days, with a range of [20-60]).

All patients received the standardized protocol of antibacterial treatment according to our national protocol, with the exception of 1 patient, who was contraindicated to isoniazid treatment due to liver toxicity. This patient was put on a combination of rifampicin, ethambutol, and levofloxacin for the first 2 months, and then maintenance treatment was based on a combination of rifampicin and ethambutol for 10 months.

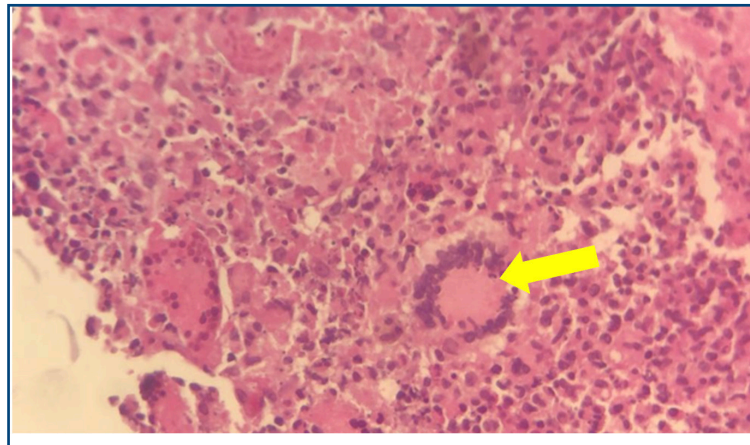
↓ Table II. Presentation of patients with a presumptive tuberculosis diagnosis

Case	Gender/ Age	Duration in PD (months)	Functional/ clinical signs	Imaging	Search for BK (site/result)	Histology (site/result)	Location	Time to symptoms/ treatment	Evolution
8	H/34	5	AEG Dyspnea	Unilateral pleurisy	Spit (-) Pleural fluid (-)	Pleura / Inflammatory remodeling	Pleural	20 days	Good
9	F/43	60	AEG/fever Cough/Dyspnea	-Pulmonary micronodules -Mediastinal PDAs -Unilateral pleurisy	Spit (-) Pleural fluid (-)	Pleura / Inflammatory remodeling	Pleuro- pulmonary	2 months	Good
10	F/48	24	AEG Thoracic pain	Pericarditis	Spit (-) Pericardial fluid (-)	Pericardium / Inflammatory remodeling	Pericardial	21 days	Good
11	F/51	1	AEG Dyspnea	-Pulmonary micronodules -Mediastinal PDAs	Spit (-) Bronchoalveolar fluid (-)	NR	Pulmonary	2 months	Good Cholestasis / Rifampicin overdose
12	H/52	48	AEG Febrile cough	Unilateral pleurisy	Spit (-) Pleural fluid (-)	Pleura / Inflammatory remodeling	Pleural	1 month	Death/ Superinfection of pleural fluid

M: male; F: female; PD: peritoneal dialysis; AEG: altered general condition; Kt: catheter; HD: hemodialysis; NR: not performed; ADP: adenopathy



↑ Figure 1. Distribution of tuberculosis cases by location



↑ Figure 2. Peritoneal biopsy showing a giant cell granuloma with caseous necrosis (tuberculous peritonitis)

The adverse effects of antibacterial drugs in 3 patients were the following:

- Cholestasis in 1 case, secondary to a rifampin overdose
- Polyneuritis in another case, secondary to an isoniazid overdose.

The effects were reversible after a dosage adjustment of the antibacterial drugs.

- In the 3rd case, it was hepatocellular insufficiency on a cirrhosis liver, having required the definitive stop of isoniazid.

The evolution of these patients is marked by the curing of 11 patients without relapse after a mean follow-up of 65 ± 37 months. One patient died of severe sepsis following superinfection of the pleural fluid despite the start of antibacterial treatment.

Concerning tuberculous peritonitis, in 2 cases, the PD catheter was maintained in view of the good clinical improvement and the clearing of the dialysate fluid after the beginning of the treatment, without relapse of the peritonitis of nearly 10 years in one of the cases.

In the 3rd patient, in view of the absence of clinic-biological improvement and the delay in the dialysate culture, the diagnosis of tuberculous peritonitis was retained on the peritoneal biopsy after removal of the PD catheter and placement on hemodialysis.

DISCUSSION

Tb is an infectious disease that complicates many immunocompromised conditions, such as chronic end-stage renal disease and dialysis. These complications are more frequent in Tuberculosis-endemic countries, with an incidence reaching 4200/10000 dialysis patients, than in endemic regions, with fewer than 100/100000 dialysis patients [2,4,5,6].

The literature reports a prevalence of Tb in PD ranging from 5% to 25%, with a higher relative risk than in the general population [4,7,8]. In our study, the prevalence was 5.26%.

The dialysis population is a group at risk of Tb infection, mainly due to a deficit in cell- and humoral-mediated immunity [9].

Immune disturbances are favored by advanced age and certain comorbidities, such as diabetes and immunosuppressive treatment, by reduced protein intake and vitamin D deficiency, and by iron overload disrupting phagocytic activity [10,11].

The notion of a history of Tb is very important because it allows targeting patients at risk. In our series, only 1 patient had a personal history of Tb, and another patient had the notion of a Tb infection.

Several studies report a high frequency of Tb cases discovered during the first year of dialysis [4,12]. Immune system disturbances start as early as stage 3 of CKD and worsen in later stages. This alteration persists at the initiation of dialysis, making patients more vulnerable to infectious complications as soon as they are put on dialysis [4,9,12]. In our series, one-third of Tb cases were diagnosed during their first year of PD.

The clinical presentation of Tb in dialysis patients is often insidious and atypical. Patients frequently present with systemic symptoms, such as fever, anorexia, and weight loss. These symptoms may mimic the signs of uremia, delay the diagnosis, and may be absent [13,14]. In our series, the clinical manifestations were dominated by an altered general condition.

Pulmonary manifestations range from a simple cough to hemoptysis, chest pain, or dyspnea without any real respiratory distress. Other manifestations are attributed to extrapulmonary involvement, such as chest pain, peripheral adenopathies, and uni- or bilateral pleural effusion syndrome. In our series, 7 patients presented respiratory signs, related to thoracic Tb involvement (pleural, pulmonary, or pericardial).

Patients may present with an extrapulmonary location in 60% to 80% of cases, with a possible disseminated form of the disease [14].

Given the potential for unusual presentation and location of Tb in PD patients, the diagnosis of Tb should be evoked in patients with nonspecific systemic symptoms [15].

Chest radiography is routinely performed in all patients with suspected Tb even in the absence of chest symptoms. Radiological signs are not specific and may be missed in up to 30% of cases [16]. In our series, imaging was performed in all patients, having revealed at least 1 abnormality in 11 cases.

The diagnosis of certainty is based on the isolation of bacillus of Koch (BK) in biological fluids (sputum, peritoneal fluid, pleurisy, etc.) or the demonstration of a typical caseous granuloma on biopsy [10].

Molecular diagnostic techniques, such as PCR-based tuberculosis DNA testing (GeneXpert), have improved the diagnosis of Tb. The combined sensitivity and specificity of PCR were 88% and 95%, respectively, when used as an initial test for the diagnosis of Tb. [17]. The WHO recommends its use as a first-line test, especially in cases of a suspected extrapulmonary form [18]. With the dialysate, it allows a rapid diagnosis with a sensitivity of 81% and a specificity of 99% [19].

In our series, BK testing in biological fluids was positive in 31% of the specimens taken, and the biopsy was conclusive in 25% of the biopsies taken.

The absence of bacteriological or histological confirmation should not exclude the diagnosis of Tb. In our patients, the median interval between the onset of symptoms and the diagnosis of Tb

was approximately 20 days, and the diagnosis of Tb was made on presumptive criteria in 42% of cases. Jebali et al. made the diagnosis of Tb in PD after a mean delay of 113 days, with a presumptive diagnosis in 31% of cases [15]. Vikrant et al. had a presumptive diagnosis in 54% of cases [10].

Interferon-gamma release assays show promise in the diagnosis of Tb (Quantiferon Gold), with evidence of increased sensitivity and specificity in many populations with suspected latent Tb [5,20].

Tuberculous peritonitis usually manifests with fever, abdominal pain, and cloudy dialysis [21].

Laboratory findings in tuberculous peritonitis are also nonspecific, and tuberculous peritonitis may be associated with a predominance of polymorphonuclear lymphocytes or neutrophils on cytologic testing of PD fluid. These factors, combined with the sometimes insidious onset of tuberculous peritonitis, frequently result in a significant delay in diagnosis [12, 21].

Tuberculous peritonitis should be suspected in any culture-negative peritonitis or culture-positive peritonitis refractory to appropriate antibiotic treatment, even in the absence of other clinical symptoms or signs suggestive of Tb [21]. In our series, 3 cases of tuberculous peritonitis were confirmed.

Therapeutically, the initial quadruple therapy was effective with a treatment duration that varied between 6 and 12 months depending on the location of the Tb. The dosage should be adapted to the weight and status of the dialysis patient, with monitoring of residual serum levels of rifampicin and isoniazid in order to adapt the dosage and avoid toxicity [3].

This toxicity is essentially hepatic, gastrointestinal, and neuropsychiatric. The incidence of these adverse effects varies from 10% to 50% according to the series [10,15]. In our series, the incidence of adverse effects of antituberculosis treatment was 25%, which resolved after adaptation of the treatment.

The management must also include the nutritional aspect, with adequate protein intake and correction of vitamin deficiencies.

For tuberculous peritonitis, evolution under treatment is judged on the clearing of the dialysate fluid, the disappearance of clinical signs, and the normalization of the biological balance. There is no consensus on the removal of the PD catheter. In fact, several series have demonstrated satisfactory results with the maintenance of the catheter, as in 2 of our patients [8,22,23]. If the catheter is withdrawn, reinsertion of the catheter can be carried out between 2 and 3 weeks after the clearing of the dialysate fluid [24].

CONCLUSION

Tuberculosis is a frequent infectious pathology in dialysis patients, especially in PD. The diagnosis is often delayed due to the atypical clinical presentation and the delay in bacteriological results. The diagnosis can be based only on presumptive arguments in order to start an adapted treatment as soon as possible.

In the case of tuberculous peritonitis, removal of the PD catheter is not systematic. This catheter must be maintained in the event of a good clinicobiological evolution of the peritonitis with a good functioning of the catheter.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this article.

-Authorship :

- LD proposed the work, conducted the case census, wrote the article and edited the manuscript.
- SB proofread and participated in the corrections
- OA participated in the identification of cases and corrections
- RB proposed corrections
- NO suggested corrections
- LB checked the methodology, proofread and corrected the article

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