RESEARCH ARTICLE

TUBERCULOSIS RELAPSE; RETROSPECTIVE ALGERIAN STUDY

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ABSTRACT

Introduction: Tuberculosis relapse is defined by the reappearance of active tuberculosis one year or more after the first episode of tuberculosis is treated and declared cured.

The objective is to establish the epidemiological, clinical, radiological, and evolving profile of patients with tuberculosis relapse.

Methods: This is a retrospective study covering cases of tuberculosis relapses, collected in the pulmonology department of the Sidi Bel Abbes University Hospital for 11 years (2008–2019).

Results: Our series is made up of 17 men and 4 women. The average age was 43 years old. Active smoking was found in 66%, alcoholism in 28%, diabetes in 38%, and a low socioeconomic level in 83%. The average time between the first episode and relapse is 2 ± 1 years. A direct examination of the sputum confirmed the diagnosis of tuberculosis. Radiologically, tuberculosis manifested itself as extensive excavated lung lesions in 45% of cases. The evolution was favorable in the majority of cases; however, there was resistance to anti-tuberculosis drugs in one case and one death following bilateral pneumothorax.

Conclusion: Tuberculous relapses are the prerogative of young smokers with poor social conditions. The seriousness lies above all in the risk of the emergence of resistance to anti-tuberculosis drugs.

KEYWORDS: Mycobacterium Tuberculosis, Relapse, Reinfection, Resistance to Anti-Tuberculosis Drugs.

INTRODUCTION

Tuberculosis represents a major health problem worldwide. According to the WHO, tuberculosis is ranked the second infectious disease after COVID-19, with more than 10 million new cases of tuberculosis recorded in 2021(1).

Control of this scourge relies on the identification of cases and successful treatment. Despite the significant advancements in recent decades, co-infection-related challenges make it difficult to control this infection. The human immunodeficiency virus (HIV) increases the risk of resistance and infection among socially vulnerable subjects, notably drug addicts, alcoholics, and prisoners.

According to the National Tuberculosis Control Program, a tuberculosis relapse is a resumption of confirmed active tuberculosis that occurs one year or more after the first episode is treated and declared cured.

Through this work, we describe the epidemiological, clinical, radiological, and evolutionary profiles of patients with tuberculosis relapse at the

pulmonology department of the Sidi Bel Abbes University Hospital.

PATIENTS AND METHODS

This retrospective study examined patient records from the Sidi Bel Abbes University Hospital's pulmonology department for the period of 11 years (2008–2019) that had at least one tuberculosis relapse confirmed by positive smears.

Inclusion criteria

All files of patients with confirmed pulmonary tuberculosis treated with the first-line regimen and declared cured with negative control smears at the end of treatment

The data collected are age, sex, level of education, socio-economic status (profession, number of people in the family, type of housing), sexual habits, drug addiction, smoking, alcoholism, comorbidities, clinical examination data, body mass index, HIV status, and radiological images, as well as the types and extent of lesions according to the classification of Falk et al(2). Information concerning the first and other episodes of tuberculosis (year, site, bacteriological status, prescribed diet, compliance with treatment and control smears, antibiogram, and resistance to treatment).

Exclusion criteria

Incomplete files

- Case of therapeutic failure

- Case of progressive resumption, which is characterized by the reappearance of positive smears in a patient following an untimely two-month break from first-line therapy after the patient had taken the medication for at least one month.

RESULTS

During the study period, out of 677 tuberculosis patients hospitalized in the pulmonology department of the Sidi Bel Abbes University Hospital, we identified 21 patients with a tuberculosis relapse confirmed by bascilloscopies, or 3.1% of all tuberculosis cases.

Our cohort is made up of 17 men and 4 women, with a sex ratio of 4.25. The average age of our patients is 43 ± 1 years, with extremes ranging from 27 to 70 years but the peak frequency concerns the age group 38 to 48 years old. Sixty-six percent are active smokers and alcoholics in 28% of cases, including 3 patients with occasional consumption. The notion of drug addiction to the type of cannabis is found in 3 patients. The level of education is low, and the majority of subjects are illiterate (81%). The socio-economic level is low at 52%, including nine cases of unemployment and three cases with a history of incarceration. The number of comorbidities recorded is 65%, with diabetes (38%), COPD (28.5%), and one case of HIV infection following. The epidemiological characteristics of the population studied are summarized in Table 1

TABLE 1- The Epidemiological Characteristics of The Cohort

Epidemiological Characteristics	Numberfrequency15 Cases
Average age (years) [27-37 years] [38-48 years] [49-59 Years] [60-70 years]	43±1 02(9.5%) 15(71.4%) 03(14%) 01(4.7%)
Gender Male Women	 17(81%) 4(19%)
Risk Factors Tobacco Alcoholism Diabetes COPD HIV Substance addiction	 14(66%) 6(28.5%) 8(38%) 06(28.5%) 01(4.7%) 3(14%)
Level of Studies Illiteracy Primary level	 17(81%) 04(19%)
Socio-Economic Condition Weak unemployment	 15 (52.3%) 10 (47.6%)

HIV: human immunodepression Virus, COPD: Chronic obstructive pulmonary disease.

The average time to onset of tuberculosis recurrence is 3±1.2 years with 80% late onset beyond 2 years. The majority presented a single episode of relapse, 3 cases having two recurrences and one case with 3 recurrences. Poor compliance is observed in 12% (side effects, discontinuous treatment)

TABLE 2- Radiological and Biological Clinical Signs of The Cohort

The time of occurrence	
the 1st year	Number 1(4.8%)
the 2nd year	2(9.5%)
>2 year	18(85.7%)
Symptoms	
Hemoptysis	12(57%)
Purulent sputum	7(33%)
Chest pain	3(14.2%)
DGC	15(71.4%)
X-ray images	
cavitations	13(62%)
infiltrate	8(38%)
bilateral extensive lesions	7(33%)
pneumothorax	3(14.2%)
Biology	
Anemia	6(28.5%)
Hypo albuminemia	7(33%)
ARF	2(9.5%)
Glycated HB	6(28.5%)

DGC: deterioration of general condition, ARF: acute renal failure, HB: hemoglobin

Malnutrition is dominant in our patients (85%) with a BMI <19 kg/m2. Non-specific symptoms, hemoptysis (57%), and deterioration of general condition (71.4%). On the biological level, 5 cases presented anemia, 2 cases had acute renal failure secondary to dehydration, and 6 cases had an increase in glycated hemoglobin of 9±1%. Fourteen percent had pneumothorax associated with lung involvement. The radiological lesions were caves (62%), infiltrates (38%) on retractile images, and recesses related to sequelae of pulmonary tuberculosis. They were extensive and bilateral in 33% (table 2). Bacilloscopies confirmed the accurate diagnosis. We noted two cases with multiple relapses that these patients presented during our study period, with three recurrences spaced 2.1 years apart on average, always in the same location as the first episode. These cases present a great management challenge due to the high risk of multi-resistance to treatment, as identified in one of the patients following the results of the antibiogram. Furthermore, the majority of patients had a single relapse. The 2nd-line regimen is introduced to 24 SRHZE/RHZE/RHZ patients. The evolution was favorable in the majority of cases, apart from one death occurring following respiratory distress in bilateral pneumothorax. The 3rd line regimen was prescribed for one patient.

DISCUSSION

According to the WHO global estimate(3), 6.8% relapse cases were reported in 2019. Episodes of recurrent tuberculosis have been reported not only in countries with high tuberculosis prevalence but also in countries with low prevalence. prevalence(4, 5).

In the Eastern Mediterranean region the relapse rate is 3.5% according to the WHO report(6). It is close to the rate recorded in our study (3.1%) as well as that found by Mjid et al in Tunisia (3.5%)(7) but lower than that of Morocco (5.1%)(8).

Tuberculosis relapse is due to either exogenous reinfection or endogenous reactivation by reactivation and multiplication of the same strain of mycobacteria as that involved in previous tuberculosis. These are mycobacteria that persisted after stopping previous treatment. Exogenous reinfection is a new contamination by a new strain of mycobacteria different from that involved in the first episode(9-11). Is it an exogenous reinfection or an endogenous reactivation? This question has been the subject of numerous debates(12, 13). These two modes of infection produce identical clinical pictures, only molecular techniques can distinguish them. This involves molecular genotyping of mycobacterium strains. tuberculosis, applied since the 1990s with two methods:

restriction fragment length polymorphism (RFLP) and the MIRU-VNTR (Mycobacterial interspersed repetitive - unit-variable- number tandem-repeat). It is based on the Polymerase chain amplification (PCR) of repetitive sequences found at specific loci of the genome(14, 15). In Algeria, these techniques are not available in a hospital environment. It is important to distinguish reactivation from reinfection because of the implications that can follow. So, a high rate of relapse due to endogenous reactivation means that treatment needs to be improved, while a high rate of reinfection means that Mycobacterium tuberculosis is being spread less. According to Vega et al(16), Sonnenberg et al (17) relapse is generally due to endogenous reactivation in areas with low prevalence of tuberculosis whereas, areas with high incidence recurrence is attributed to exogenous reinfection in 75% of cases.

However , Shen et al (18) suggest that the time between the first episode of tuberculosis and recurrence determines the type of infection, whether by an endogenous or exogenous strain. Thus, Marx et al(19) reported that relapses occurred mainly during the first year after the end of treatment, while late recurrences were more often secondary to reinfections therefore the risk of exogenous reinfection increased with time. On the other hand, the study carried out by Shao et al(20), based on the sequencing of the mycobacterium genome in order to identify reinfection and endogenous reactivation, did not demonstrate any significant difference in terms of interval separating the first episode and recurrences of endogenous reactivation or exogenous reinfection.

According to the results of our study, patients with tuberculosis relapse are young male subjects, malnourished, smokers with a low socioeconomic level. The characteristics of this particular profile determine the risk factors for tuberculosis relapse. The latter occurs in men more than women(21, 22). This may be due to men's bad habits related to smoking and alcohol abuse. According to the literature, tuberculosis recurrence is linked to age. For Kim et al (23), in the United States it is very widespread among those over 65 and rarer among young people. Whereas in Catalonia(24), it is common among the youngest. 71% of patients were under 49 years of age. Smoking has been identified as a risk factor for tuberculosis relapse (25). Tobacco intoxication promotes infections, particularly infection

tuberculosis. It leads to histological modifications of the bronchial mucosa and a dysfunction of the muco-ciliary escalator. Likewise, anti-infectious immunity is altered (reduction in the bactericidal phagocytic activity of alveolar macrophages and reduction in the secretion of TTNF by lymphocytes(26, 27). Alcoholism and drug addiction are also predictive factors for relapse demonstrated by Millet et al (4) and Thomas et al(25).

They risk altering the subject's immunity and thus contributing to tuberculosis infection. A particular socio-economic situation (unemployment, incarceration) common to both new cases and recurrences(21) found by Brugueras et al (24). Among the comorbidities, undernutrition although it is "is a classic, frequent and well-described sign in tuberculosis. Benator et al(28) identified it as a risk factor for relapse. Diabetes and mainly glycemic imbalance is recognized as a factor increasing the risk of treatment abandonment, relapse and treatment failure of tuberculosis(29, 30). Likewise, post-smoking COPD is a risk factor for relapse(31) probably due to the use of corticosteroids and the immune deficiency linked to smoking. It is well established that HIV co-infection is a predictive factor for tuberculosis relapse knowing that tuberculosis is the most common opportunistic infection associated with AIDS with a higher mortality rate(17). In our series, one seropositive case was recorded. The advantage of this longitudinal study was the long and sufficient duration to have a reflective image of the anti-tuberculosis program. However, we must recognize several limitations, first, the cases of relapse were only hospitalized, sparing those treated on an outpatient basis by the UCTMR centers; and second, the absence of molecular tests, in particular the Xpert-MTB/RIF test. It is a rapid diagnostic molecular test that simultaneously detects Mycobacterium complex tuberculosis and resistance to rifampin and is recommended for retreatment cases.

CONCLUSION

The relapse rate recorded is low compared to a fairly long period. Despite the small sample of this study, we were able to identify the predictive factors of tuberculosis relapse which are age, male sex , smoking, malnutrition and the existence of residual cavitary image. However, the most significant threat to the TB control program is the occurrence of resistance to TB treatment.

Subjects with risk factors correctly treated and declared cured run a risk of recurrence of the disease, so we propose that they be considered in screening strategies.

Availability of Data and Material

Data is available upon request from the corresponding author.

Competing Interests

The authors declare that they have no conflicts of interest concerning this article.

Authors' Contributions

NF Conceived the study, participated in its design, performed statistical analysis, helped draft the manuscript, and coordinated and validated the study.

MC Participated in its design, performed statistical analysis, helped to draft the manuscript and validated the study.

AK Participated in its design, performed statistical analysis, helped to draft the manuscript and validated the study.

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