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Multifocal tuberculosis in Southern Tunisia: What is specific with?

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Abstract

Objective: Tuberculosis (TB) is a public health concern worldwide. Multifocal Tuberculosis (MFT) is a severe disease and relatively an unusual form of TB. We aimed to identify the epidemiological and evolutionary characteristics of MFT in Southern Tunisia and to analyse its chronological trends between 1995 and 2016.

Methods: We conducted a retrospective study from January 1995 to December 2016 in South of Tunisia including all new TB cases. MFT was defined as concurrent tubercular involvement of two or more non-contiguous organs.

Results: We included 2771 new cases of TB. Totally, 74 new cases of MFT were enrolled, representing 4.5% of extra-pulmonary TB and 2.7% of overall TB cases. The sex ratio (Male/Female) was 1.24. The median age of MFT patients was 45 years (IQR= [28-63 years]). The main sites were lungs in 40 cases (54.1%), pleura in 30 cases (40.5%), lymph nodes in 21 cases (28.4%) and abdomen in 19 cases (25.7%). The median duration of anti-TB treatment was 9 months (IQR= [6-13 months]). The case-fatality rate was 5.4%. The mean age of MFT patients was significantly higher (45.7±20.3 vs 40.5±19.4 years; p=0.022) than unifocal TB. The average duration of treatment was significantly higher in MFT (10.9±5.8 vs 8.7±4.1 months; p=0.005). The number of MFT has declined from 1995 to 2016 without a significant change (Rho=-0.4; p=0.861).

Conclusion: MFT is a severe and an uncommon disease which was relatively high in our region. It should always be suspected in TB patients especially in countries where TB is endemic.

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Introduction

Tuberculosis (TB) is a public health concern worldwide [1]. It remains a principal cause of morbidity and mortality in developing countries that have fragile healthcare infrastructures. TB is an infectious disease due to the bacillus *Mycobacterium tuberculosis* (MT) [2]. Lungs are the main affected site but other extra-pulmonary sites may be affected [3].

In Tunisia, TB is endemic and pulmonary TB is the most frequently involved site [4]. Multifocal Tuberculosis (MFT) is a severe disease and relatively an unusual form of TB that occurs mainly in immune-compromised individuals but may rarely affect immune-competent individuals [5,6]. The study of MFT epidemiology is not a common practice and there are some isolated cases in literature. MFT diagnosis remains challenging and may delay treatment, which can cause a high risk of complications and mortality [5,7]. In fact, there is no clear and standardized diagnostic approach to this form of TB [8]. Given that, clinical presentations are polymorphous and many differential diagnoses are available. A high level of suspicion is required particularly in countries with high TB prevalence if there are non-specific symptoms that indicate the presence of multiple TB sites [5].

In light of the lack of reliable data of MFT in our country, we aimed to identify the epidemiological and evolutionary characteristics of MFT and to analyze its chronological trends between 1995 and 2016.

Patients and methods

Study design

We conducted a retrospective study over a period of 22 years, from January 1995 to December 2016 in South of Tunisia.

Data collection and case definition

We collected data from the center of TB control of Southern Tunisia, as an effective component of the National TB Program. We included all new TB cases of any age. Patients who were lost to follow-up were excluded from the study.

We collected socio-demographic characteristics such as age, gender and residency on a pre-established fact sheet and we collected clinical and evolutionary data such as anatomical sites, duration of anti-TB treatment and the disease evolution. Cure rates depend on clinical course and radiological data.

MFT was defined as concurrent tubercular involvement of two or more non-contiguous organs [9,10].

An area was defined as rural if it is located more than 11 kilometers away from the city center.

Statistical analysis

We performed statistical analysis using SPSS 20 software. The description of the qualitative variables was carried out by the determination of the absolute and relative frequencies. Quantitative variables were driven by means and standard deviations when they were normally distributed. If not, we used medians and Inter Quartile Range (IQRs).

In order to analyze chronological trends of MFT over time, we calculated the correlation coefficient of Spearman (Rho).

We used Chi square and Fisher exact test to compare two frequencies when applicable.

For the comparison of two means, we used Student's T test for independent samples.

The difference between two groups was considered to be significant when $p<0.05$.

Results

Patients' characteristics

During a 22-year study period, we included 2771 new cases of TB among whom 1651 patients (59.6%) had extra-pulmonary TB. Totally, 74 new cases of MFT were enrolled, representing 4.5% of extra-pulmonary TB and 2.7% of overall TB cases. We found 41 males (55.4%) with a sex ratio (Male / Female) of 1.24. The median age of MFT patients was 45 years (IQR= [28 - 63 years]). We found that 32 cases (43.2%) were living in rural areas (Table 1).

Table 1: Socio-demographic, clinical and evolutionary characteristics of patients with multifocal tuberculosis

Variables		Number	Percentage (%)
Men		41	55.4
Age groups (years)	<15	3	4.1
	[15-39]	29	39.2
	[40-59]	19	25.7
	≥60 years	23	31
Rural areas		32	43.2
Number of involved sites	Two sites	71	95.9
	Three sites	3	4.1
Anatomical involved sites	Lungs	40	54.1
	Pleura	30	40.5
	Lymphnode	21	28.4
	Abdomen	19	25.7
	Urogenital tract	12	16.2
	Bone and joints	11	14.9
	Larynx	6	8.1
	Brain	65	6.8
	Skin	4	5.4
	Blood	2	2.7
	Mediastinum	1	1.4
Miliary tuberculosis		6	8.1

We noted that 71 cases (95.9%) had simultaneously two sites of TB. The main sites were lungs in 40 cases (54.1%), followed by pleura in 30 cases (40.5%), lymph nodes in 21 cases (28.4%) and abdomen in 19 cases (25.7%). We found that 6 patients had miliary TB (8.1%) (Table 1). These latter were exclusively present in urban areas.

The median duration of anti-TB treatment was 9 months (IQR= [6-13 months]). We noted 4 deaths, with a case-fatality rate of 5.4%. According to the number of involved sites, all deaths were exclusively observed among men and patients with

two sites of TB. We did not notice a significant difference in the case-fatality rate by residency (p= 0.31).

Specificities of multifocal tuberculosis

The mean age of MFT's patients was significantly higher than unifocal TB (45.7 ± 20.3 vs 40.5 ± 19.4 years; p = 0.022). Patients aged 60 years and above were significantly the most affected by MFT (31.1% vs 19%; p=0.01). We did not find a significant difference according to gender (p = 0.863) and to urbanity of residence (p = 0.789) between MFT and unifocal TB. We noted that the average duration of treatment was significantly higher in MFT(10.9 ± 5.8 vs 8.7 ± 4.1 months; p = 0.005) (Table 2).

Table 2: Comparison of the epidemiological and evolutionary characteristics between multifocal and unifocal tuberculosis

Variables	MFT	UFT	OR (95% CI)	p
Age ≥ 60 years (%)	31.1%	19%	1.9 [1-2-3.2]	0.01
Men	55.4%	54.4%	1.04 [0.6-1.6]	0.863
Rural areas	43.2%	41.7%	0.9 [0.6-1.5]	0.789
Mean duration of treatment (months)	10.9 ± 5.8	8.7 ± 4.1	-	0.005
Case-fatality rate (%)	5.4	2.8	2 [0.7-5.6]	0.158

UFT: Unifocal tuberculosis; MFT: Multifocal tuberculosis; OR: Odds ratio; CI: Confidence interval

Chronological trends of multifocal tuberculosis between 1995 and 2016

Chronological trends analysis showed that the number of MFT has declined from 1995 to 2016, but no significant change was observed over time (Rho= -0.4; p = 0.861) (Figure 1).

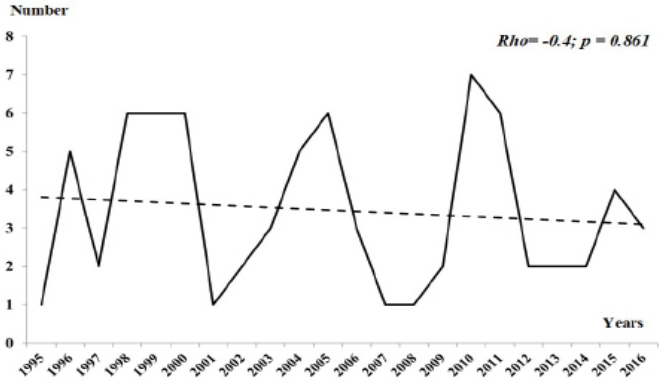

Figure 1: Chronological trends of multifocal tuberculosis new cases between 1995 and 2016.

Discussion

TB continues to be endemic and MFT remains relatively high in our region. It represented an extreme form of tubercular infection which requires early and prolonged treatment to reduce its morbidity.

In our study, we noted that different organs of the body were affected and that lungs were the most frequently involved site. Several studies have shown that MFT can affect any type of viscera or organ in the body [5–7,9,11]. Similar to our results, it has been reported that lungs were usually the most affected site in literature [7,9,12]. In fact, the airway is the main route of transmission of *Mycobacterium tuberculosis* which, once inhaled, leads to a primary pulmonary focus usually contained by cell-mediated immunity. From this pulmonary focus, the infection can spread through blood to distant organs or via lymphatics to contiguous structures [9,13]. Possible explanation for that is that there was an association between smoking and the development of pulmonary TB [14,15]. Indeed, the steady increase in the frequency of smoking in the world may explain in part the high frequency of pulmonary TB [14,16].

Among extra-pulmonary sites, pleura was the most common site in our study. Pleural involvement may be secondary not only to hematogenous dissemination, but also to rupture in the pleural cavity of a caseous pulmonary site or lymphadenopathy [17]. This might be due to the fact that pleura are accessible organs and represent a form with easy diagnosis [17].

Similar to our findings, lymph nodes were among the most frequently affected sites in patients with MFT in literature [6,11]. The disease is often cervical and therefore accessible for anatomo-pathological examination, which allows early diagnosis [6,18,19].

In our study, abdomen was the third site of TB among extra-pulmonary sites. Likewise, abdominal TB was one of the most frequent sites of extra-pulmonary TB in previous studies [20]. MT may involve any organ in the abdomen which leads to non-specific clinical symptoms, thus to delayed diagnosis and treatment [20]. Abdominal involvement is mainly secondary to hematogenous dissemination and may rarely occur by swallowing expectorates containing MT or ingestion of contaminated milk products [20].

In literature, osteoarticular, uro-genital or cutaneous lesions were rare and uncommon sites of TB, which was consistent with our study. They most often result from the haematogenic dissemination of MT [4,12,21,22].

Meningeal TB is not only the most severe form of extra-pulmonary TB, but it is a form whose diagnosis is difficult, and then may delay treatment [23]. In our study it represented only 6.8% of all TB cases.

According to our results, the mean age was significantly higher in MFT. This can be explained by the fact that some patients with pulmonary TB were more susceptible to develop MFT, such as intense transmission, malnutrition, low innate immunity, or impaired acquired immunity [6,7]. Otherwise, in our study we had no information concerning the immune and nutritional status of the patients.

According to our results, the anti-TB treatment was longer in MFT than in unifocal TB and the disease evolution was favorable for these two forms of TB in most cases. The prognosis of MFT depends on the site affected by TB, the early onset of anti-TB drugs and good adherence to treatment [6,17]. Indeed, patients with nervous system involvement required prolonged treatment of 9 to 12 months and corticosteroids were recommended for pericarditis and meningeal TB [6,11,17,24].

Conclusion

MFT is a severe and an uncommon disease which was relatively high in our region. It has declined from 1995 to 2016 without a significant change. MFT may affect any organ or viscera

and lungs were the most affected site.

However, MFT is often misdiagnosed and it takes time to determine the appropriate treatment. Thus, it should be always suspected in TB patients and screening for MFT would be recommended in any patient with pulmonary or extra-pulmonary TB, especially in countries where TB is endemic.

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