Research Article

Cutaneous tuberculosis in Southern Tunisia: clinical and therapeutic particularities

F Hammami, M Koubaa, K Rekik, F Smaoui, C Marrakchi, M Ben Jemaa

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Abstract

Introduction: Tuberculosis remains a global health burden. Among all sites, cutaneous tuberculosis represents an uncommon manifestation with myriad presentations which explains the high rate of misdiagnosis. We aimed to study the epidemiological, clinical, and therapeutic features of cutaneous tuberculosis in southern Tunisia.

Methods: A retrospective study including all patients diagnosed with extrapulmonary tuberculosis was conducted in the south of Tunisia between 1998 and 2019. This study specified the particularities of cutaneous tuberculosis cases over a 22-year period.

Results: We encountered 1663 cases of extrapulmonary tuberculosis, among whom 56 cases were cutaneous tuberculosis (3.3%). Thirty eight (38) were women (67.9%). The mean age was 43±20 years. Multifocal tuberculosis was noted in 12 cases (21.4%). Systemic symptoms of tuberculosis represented by asthenia (55.3%), fever (42.8%) and weight loss (37.5%) were noted. Elevated C-reactive protein levels (50%) and accelerated erythrocyte sedimentation rates (42.8%) were also noted. The diagnosis was confirmed histologically (80.4%) and microbiologically (12.5%) . The median duration of antitubercular therapy was 11(9-14) months for multifocal tuberculosis cases (12 cases) and 8(6-12) months for cutaneous tuberculosis cases without any other sites of tuberculosis (44 cases). Adverse effects were noted in 14 cases (25%). The disease evolution was favorable in 54 cases (96.4%). Two patients had a relapse (3.6%).

Conclusions: Cutaneous tuberculosis remains a common disease in south Tunisia. Patients should be screened for cutaneous tuberculosis starting with a general skin examination. Skin biopsy, the cornerstone of the diagnosis should be performed on any suspected cutaneous lesion.

Keywords: Cutaneous tuberculosis, Tunisia, Mycobacterium, Antitubercular

Infectious Diseases Department, Hedi Chaker University Hospital, University of Sfax, Tunisia Lanka

Address for correspondence: Dr. Fatma Hammami, Infectious Diseases Department, Hedi Chaker University Hospital, University of Sfax, Tunisia Telephone: +216-20-755-665 E-mail: *fatma.hammami@medecinesfax.org*

https://orcid.org/0000-0001-5254-2176

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Introduction

Although its incidence has been declining, tuberculosis (TB) remains a global health burden, with a cumulative reduction of 9% from 2015 until 2019.[1]. Extrapulmonary TB represented 16% of the notified cases in 2019.[1] Among all sites, cutaneous TB (CTB) represents an uncommon manifestation with a rate of less than 2% of all extra-pulmonary TB.[2] An increase in its incidence was related to an increase in multi-drug resistant TB.[3] CTB is not a well-defined entity due to its various clinical manifestations. A recent classification has been developed based on three criteria including pathogenesis, clinical presentation, and histologic evaluation.[4] The diagnosis requires a high index of suspicion based on clinical features, which guides the clinician to perform a skin biopsy and look for signs suggesting CTB. Mycobacterial culture remains the gold standard for the diagnosis of CTB.[2] The infrequent identification of the bacillus by common testing tools and the myriad presentations of the lesions explains the high rate of the misdiagnosis ranging from 33% to 50%.[5] Treatment of CTB, based on antitubercular therapy follows the standard regimen for treatment of pulmonary TB, associated occasionally with surgical procedures.[2]

Tunisia is an intermediate endemicity country for TB with an incidence rate of 35 per 100 000 population in 2019.[6] Despite the adoption of a national control programme, an increase of TB was reported due to inadequate preventive measures.[7] Previous studies reported an estimated prevalence of four cases of CTB per year.[8] The aim of this study was to determine the epidemiological, clinical, and therapeutic features of CTB in southern Tunisia over a 22 year period from 1998 to 2019.

Methods

Study design

We conducted a retrospective study, including all patients diagnosed with extrapulmonary tuberculosis in the south of Tunisia between 1998 and 2019. We specified the particularities of CTB cases over a 22-year period.

Data collection and case definitions

Data were collected from the regional registries of TB of Southern Tunisia, which received notified cases from public and private health care institutions. The Centre of Tuberculosis Control notified all TB cases as an integrate of the National Tuberculosis Surveillance programme. All cases coming from both rural and urban areas were included. We specified socio-demographic characteristics, including age, gender, and urbanity of residence. Previous medical history, systemic symptoms, and laboratory investigations were recorded. Tuberculin skin test (TST) results, diagnostic methods and the associated sites of TB were specified. The treatment received, its durations and the disease evolution were noted.

The diagnosis was based on histopathological proof, represented by the presence of epithelioid cell granulomas associated with caseous necrosis isolated from skin biopsy samples or from another associated site elsewhere in the body. Microbiological proof, based on the isolation of *Mycobacterium tuberculosis* from skin biopsy or another associated site, also confirmed the diagnosis. In default, it was clinically confirmed, based on strong clinical evidence associated with positive TST and followed by an adequate response to antitubercular therapy.

Statistical analysis

Statistical analysis was performed using the SPSS 20 software. Categorical variables were presented as numbers and percentages. Continuous variables were expressed as means and standard deviations (SD), if they were normally distributed. For non-normally distributed data, we used median and interquartile ranges.

Results

During the study period, we encountered 1663 cases of extrapulmonary TB, among whom 56 cases were CTB (3.3%); Thirty eight (38) were women (67.9%). The mean (SD) age was 43 (±20) years. Patients aged between 15 and 39 years were the most affected age group (19 cases; 33.9%) followed by patients aged between 40 and 59 years (17 cases; 30.4%). Previous medical history included diabetes mellitus in 10 patients (17.8%) and renal failure in 3 patients (5.3%). All patients tested negative for human immunodeficiency virus. Thirty-two patients had an urban origin (57.1%).

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

		Number	Percentage (%)
Total		**56**	**100**
Gender	Females	38	67.9
	Males	18	32.1
Age groups (years)	< 15	4	7.1
	15-39	19	33.9
	40-59	17	30.4
	≥ 60	16	28.6
Systemic symptoms of tuberculosis	Asthenia	31	55.3
	Fever	24	42.8
	Weight loss	21	37.5
	Loss of appetite	21	37.5
	Night sweats	10	17.8
Associated sites	Multifocal (≥ 2 sites)	12	21.4
	Pulmonary	8	14.3
	Lymph node	7	12.5
	Osteoarticular	5	8.9
	Urogenital	2	3.6
	Tuberculous meningitis	2	3.6
	Abdominal	1	1.8
Adverse effects of ATT	Total	14	25
	Increase in hepatic enzyme levels	7	12.5
	Skin reactions	3	5.3
	Optic neuropathy	3	5.3
	Leukopenia	1	1.8
Disease evolution	Recovery	54	96.4
	Relapse	2	3.6

Scrofuloderma was the most frequent clinical presentation (46.4%), followed by tuberculous gumma in 25% of the cases. Lupus vulgaris was noted in 16% of the cases. Multifocal TB was noted in 12 cases (21.4%). There were 8 cases of pulmonary TB (14.3%), 7 cases of lymph node TB (12.5%) and 5 cases of osteoarticular TB (8.9%) associated with CTB. Systemic symptoms of TB represented by asthenia (55.3%), fever (42.8%) and weight loss (37.5%) were noted (Table 1).

Table 2. Laboratory investigations among cutaneous tuberculosis cases

	Number	%
Total	56	100
Elevated CRP	28	50
Accelerated ESR	24	42.8
Lymphopenia	24	42.8
Leukocytosis	17	30.4
Anemia	17	30.4
Hyponatremia	14	25

CRP: C-reactive protein,
ESR: erythrocyte sedimentation rate

Elevated C-reactive protein levels were noted in 28 cases (50%) with a mean level of 33±13 mg/L. Accelerated erythrocyte sedimentation rates were noted in 24 cases (42.8%) with a median of 65 (28-72) mm/h. Leukocytosis was noted in 17 cases (30.4%) (Table 2).

The diagnosis was histologically confirmed in 45 cases (80.4%) and microbiologically confirmed in 7 cases (12.5%). Polymerase chain reaction from pus samples were positive for *Mycobacterium tuberculosis* in 3 cases (5.3%). Sputum (2 cases; 3.6%), lymph node (1 case; 1.8%) and cerebrospinal fluid (1 case; 1.8%) cultures were positive for *Mycobacterium tuberculosis.* Culture results revealed no resistance to rifampicin or isoniazid. Four cases were clinically confirmed (7.1%). TST was positive in 34 cases (60.7%).

Antitubercular therapy was based on separate formulations in 49 cases (87.5%) and fixed-dose combinations in 7 cases (12.5%). The median duration of antitubercular therapy was 11(9-14) months for multifocal TB cases (12 cases) and 8(6-12) months for CTB cases without any other sites of TB (44 cases). Adverse effects were noted in 14 cases (25%), represented by an increase in hepatic enzyme levels in 7 cases (12.5%) and skin reactions in 3 cases (5.3%). The disease evolution was favorable in 54 cases (96.4%). Two patients had a relapse (3.6%), which occurred 8 months (one case) and 2 years (one case) after discontinuation of antitubercular therapy (Table1). No death was reported. The follow-up period was 17 months (12-35) months.

Discussion

Although it was a rare disease, with a rate of 3.3% among extrapulmonary TB cases in our study, CTB represented a diagnostic challenge. A high index of suspicion is required, which is usually followed by the appropriate investigations, based mainly on skin biopsy providing histopathological and/or microbiological proof of TB.

Studying socio-demographic characteristics, a predominance of younger patients and females were noted, both of which were considered as risk factors for extrapulmonary TB.[9] A study in India reported the predominance of a younger age group among CTB cases. This was explained by contact with active TB cases, as well as an increase of physical activity causing skin trauma during an early age.[10] In fact, in endemic countries, primary inoculation of TB occurs in children, which is secondary to even minor trauma.[2] As for female predominance, studies conducted in China,[11] and in Tunisia,[8] found similar results. However, males outnumbered females in other studies,[12,13] which might be related to the imbalance gender distribution between countries and the frequent outdoors exposure noted with males.

Once the diagnosis of CTB is suspected, a skin biopsy is performed and sent for histopathology examination as well as for acid-fast bacilli stain and culture.[4] Polymerase chain reaction provides a rapid and sensitive means to detect *Mycobacterium tuberculosis*.[14] Other investigations might help the clinicians during the diagnosis process including chest x-

ray and sputum examination.[15] The diagnosis of CTB might be facilitated by the presence of TB elsewhere in the body. Multifocal TB was noted in 27.6% of the cases of CTB in a previous study,[16] which was similar to our results. Young age, poorly controlled diabetes mellitus, human immunodeficiency virus infection, renal failure and solid organ transplantation increase the risk of CTB and systemic TB.[17] However, another study reported that visceral TB including pulmonary and extrapulmonary TB were rarely associated with concomitant cutaneous involvement, which was noted in 3.5% of patients with visceral TB.[18] The real incidence of CTB might be underestimated, especially when patients consult for systemic symptoms or signs at another associated site. Thus, patients who are suspected or diagnosed with TB should be screened for CTB, starting with a general skin examination, and followed by cutaneous biopsy if needed.

Treatment of CTB follows the same regimen as TB of other organs, starting with an initial bactericidal or intensive phase based on daily isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin for 8 weeks, and followed by continuation or sterilizing phase, which is based on isoniazid and rifampicin for 9 to 12 months.[15,19] Most CTB cases are sensitive to oral antitubercular therapy.[3] Recovery can be achieved with only chemotherapy as long as the strict adherence to treatment is respected. However, in some forms of CTB, surgery including excisional biopsy and debridement is required along with medical treatment.[4] Many factors can negatively influence results of treatment, such as the patient's immunity, the stage of the disease, the type of cutaneous lesion, the patient's compliance and the treatment duration.[15] The prognosis of CTB remains good. A previous study reported a rate of 93% of recovery with antitubercular therapy and relapse in 0.9% of the cases,[20] while another study reported healing of all patients with clinical response observed between 2 and 6 weeks of initiation of antitubercular therapy.[10]

Conclusion

In the south of Tunisia, CTB remains a common disease. Patients should be screened for CTB starting with a general skin examination. In the presence of any suspected cutaneous lesion, skin biopsy, the cornerstone of the diagnosis should be performed, which provides histopathological evidence of TB. Recovery is achieved with antitubercular therapy as long as a strict adherence to treatment is respected.

Declarations

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- Author contributions
  (I) Conception and design: FH, MK, CM, MBJ;
  (II) Administrative support: FH, MK, KR, FS, MBJ;
  (III) Provision of study materials or patients: FH, MK, KR, CM, MBJ;
  (IV) Collection and assembly of data: FH, MK, FS, MBJ;
  (V) Data analysis and interpretation: FH, MK, KR, CM, MBJ;
  (VI) Manuscript writing: FH, MK; (VII) Final approval of manuscript: All authors.

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