

Tuberculous spondylitis: Epidemiologic and clinical study in non-HIV patients from Northwest Spain

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Abstract

Objectives

To study the epidemiology, clinical features, and outcome of non-human immunodeficiency virus (HIV) patients diagnosed with tuberculous spondylitis (TS) in a well-defined region of northwestern Spain.

Methods

Retrospective chart review of patients older than 14 years of age diagnosed with TS at two contiguous areas between 1986 and 1999.

Results

Thirty-seven patients (19 men; mean age 60.3 years) were diagnosed with TS. The average annual incidence rate of TS was 0.55/100,000 population 15 years of age and older. The thoracic and lumbar regions were affected in most cases. The mean duration of symptoms before diagnosis was 28 weeks (range 3-129). Active or healed pulmonary tuberculosis was observed in only 30%. The tuberculin skin test was negative in 24%. The most common findings at the time of diagnosis were back pain and elevated ESR (either 89%). Of note, only 19% had fever. On admission plain radiographs disclosed the presence of spondylitis in 84% of the patients. Computed tomography scan and magnetic resonance imaging yielded conclusive diagnostic data in the cases with normal radiographs, and were very useful in the visualization of abscesses and intraspinal compression. Cultures of material from percutaneous needle aspiration and open bone biopsy were positive for *Mycobacterium tuberculosis* in 79% and 77% of the cases, respectively. Antituberculous therapy was given to all patients (mean duration of treatment 44 weeks). Surgical procedures were performed in 12 cases, in 7 of them to remove paraspinal and/or epidural abscesses, and in 5 because of neurological complications. Local pain and neurological deficits were the most frequent sequelae (16 and 8 cases, respectively). One patient died during the course of treatment due to a co-morbid disease. None of the patients had relapses of tuberculosis.

Conclusion

TS is a major cause of morbidity. There is a long delay to the diagnosis in most patients. Awareness of its clinical features and early therapy are required to reduce severe complications.

Key words

Tuberculosis, spondylitis, epidemiology, Spain.

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Introduction

Tuberculous spondylitis (TS) is defined as an infection by *Mycobacterium tuberculosis* (MT) of one or more components of the spine, namely the vertebrae, intervertebral disks, paraspinal soft tissues or epidural space. It is an uncommon form of infection, occurring in fewer than 1% of patients with tuberculosis, and accounts for 25-60% of all bone and joint manifestations of this disease (1, 2).

Although potentially curable, this disease may cause serious functional sequelae, even death, especially in cases where diagnosis is delayed (3). The need for continued awareness of this uncommon, but potentially curable form of spinal infection prompted us to describe our experience with patients seen over a 14-year period in two contiguous areas of Northwestern Spain, where tuberculosis is somewhat more frequent than in other neighboring regions. To reduce the risk of overestimating the frequency of this complication, patients with human immunodeficiency virus (HIV) infection were excluded.

Patients and methods

Data collection and inclusion criteria

The charts of all patients older than 14 years of age diagnosed with TS at the Departments of Medicine of Complejo Hospitalario de Ourense (Ourense, Spain) and Hospital Xeral-Calde (Lugo, Spain) between January 1986 and December 1999 were reviewed. These hospitals are the referral centers for two well-defined contiguous areas of Northwestern Spain, with a mixed rural and urban population (40% and 60%, respectively) of approximately 483,000 people older than 14 years. Inclusion criteria required the patients to have been a resident in one these areas for at least 12 months before the diagnosis. Patients were either sent to the hospitals by general practitioners or were self-referred to the emergency units. Partial information about the patients from Lugo has previously been reported (4).

The human immunodeficiency virus (HIV) has frequently been implicated in the development of tuberculosis (5).

However, the present study was designed to assess the incidence, clinical features and outcome of patients without this debilitating disease, as the inclusion of HIV patients could bias the actual spectrum and incidence of this complication. Thus, patients with HIV infection were excluded. The absence of HIV infection was established by a negative enzyme immunoassay, which is routinely performed in patients diagnosed with TS in the last 7 years, or by the absence of both clinical features and high risk behavior for immunodeficiency, as assessed by chart review, in the remaining patients.

Diagnosis of tuberculous spondylitis

The diagnosis of TS was made on the basis of: (a) compatible clinical presentation, including inflammatory back pain, stiffness, fever, constitutional symptoms and neurologic involvement; (b) radiograph and/or computed tomographic (CT) scan and/or magnetic resonance imaging (MRI) evidence of a focal destructive vertebral lesion, with or without paravertebral soft tissue mass; and (c) positive culture for MT and/or histologic findings of caseating granulomas in biopsied tissue; we also accepted as a positive result the isolation of MT from other tissues coupled with a positive response of spondylitis after antituberculous therapy.

Clinical definitions

Fever was recorded if the temperature at the time of admission was $\geq 37.7^{\circ}\text{C}$. A constitutional syndrome was considered to be present if the patient had asthenia, anorexia, and a weight loss of at least 4 kg. Anemia was defined as hemoglobin < 12 gm/dl and leukocytosis as a peripheral white blood cell count $> 10,000/\text{mm}^3$. The erythrocyte sedimentation rate (ESR) (Westergren) was considered to be elevated if it was ≥ 20 mm/1st hour. A positive response to treatment was considered to be the improvement of symptoms, while a relapse was the occurrence of a new episode of tuberculous vertebral disease after the treatment was completed.

Therapeutical schedule

Patients from Ourense received treat-

Table I. Epidemiological and predisposing factors in 37 patients with tuberculous spondylitis.

		%	Range
Age (mean $\pm$ SD)	60.3 $\pm$ 14.4		24-82
Age > 60 years	23	62	
Men/Women (% males)	19/18	51	
Delay in diagnosis (weeks)	28 $\pm$ 27		3-129
Incidence (Cases/100,000 people older than 14 years)	0.55		
Predisposing factors			
None	17	46	
Pulmonary tuberculosis			
Previous (Radiograph sequelae)	8	22	
Active	3	8	
Alcoholism	4	11	
Chronic hepatic disease	2	5	
Previous tuberculous spondylitis	1	3	
Previous aneural tuberculosis	1	3	
Multiple myeloma	1	3	
Connective tissue disease (corticosteroid treated)	1	3	

ment with isoniazid (INH), rifampin (RIF) plus either pirazinamide (PZA) or ethambutol (EMB), or both, at standard doses for 2 months, followed by INH and RIF for at least 7 additional months. In Lugo the therapeutic schedule changed over the period of study. Until 1991 patients were given treatment with INH, RIF and EMB and the complete length of treatment was 12 months. Afterwards, between 1992 and 1994 patients with TS were treated with INH, RIF, EMB and PZA for 2 months followed by INH and RIF for another 4 months. As of 1995, because of the uncommon resistance to INH in Lugo (fewer than 3% of strains), EMB has been removed from the latter regi-

men. In patients with large soft tissue masses, cord or radicular compression or highly destructive lesions producing spinal bone instability, percutaneous drainage of the accessible abscesses or open surgical procedures were performed.

Statistical analysis

The Instituto Nacional de Estadística and the government of Galicia provided the population distribution. The target population was census-based and referred to the entire population 15 years and older who receive medical attention in the hospitals of Ourense and Lugo in the year 1992, as the prevalence of AIDS in Ourense and Lugo is lower than 1%. As the pediatric population is not seen in our departments, we computed the incidence rates for the 1986-1999 period using the number of new cases 15 years and older observed as the numerator and the estimated number of residents in our areas who were 15 years of age and older as the denominator. The average annual incidence rate was calculated as the incidence for the 14-year period divided by 14. Rates are reported as the number of cases per 100,000 population of residents 15 years or older. Means and standard deviations (SD) were provided for continuous data, and the number of cases with their proportions was provided for qualitative data.

Results

Thirty-seven patients were diagnosed with TS and had no history of HIV infection.

Epidemiological data

The mean age of the patients at the time of diagnosis was 60.3 $\pm$ 14.4 years (range 24-82). Most of them (62%) were older than 60 years. The sex distribution (male/female) was similar (Table I). The diagnostic delay from the beginning of the clinical picture attributable to the tuberculous infection was considerable (28 $\pm$ 27 weeks; range: 3 - 129 weeks). The average annual incidence rate of the disease in the entire population 15 years and older was 0.55 cases/100,000. No increased tendency in the number of cases diagnosed over the 14-year study period was observed. Three patients had concomitant pulmonary tuberculous disease, and 10 had had a previous history of tuberculosis (8 pulmonary, 1 spinal at some other level, and another aneural). Other predisposing factors were alcoholism (4 patients), multiple myeloma and connective tissue disease treated with corticosteroids (one each). However in the remaining patients (n=17; 46%) no evidence of tuberculous infection or underlying disease was found.

Clinical and laboratory features

In Table II the main clinical and laboratory features of the patients at the time of admission are shown. Pain at the affected spinal area was the most common symptom (89%), followed by constitutional syndrome in 49%. Surprisingly, only 19% had fever. In 11 patients (30%) there were some nerve root symptoms with radicular pain, distesthesia, sensory deficit, muscle weakness and/or loss of reflexes. Six patients (16%) showed signs of spinal cord involvement (extensor plantar response and hyperactive tendinous reflexes or clonus in knees or ankles). Nevertheless, no patient suffered complete paraplegia. The spinal lesion always affected at least one discal space and the two contiguous vertebral bodies. Although all spinal levels were involved, there was a predilection for the lower thoracic and lumbar vertebrae (Fig. 1). In 13 cases more than one

Table II. Clinical features and laboratory findings on admission in 37 patients with tuberculous spondylitis.

	No. cases	%
Back pain	33	89
Constitutional syndrome	18	49
Fever	7	19
Radicular sequelae	11	30
Spinal cord involvement	6	16
Diffuse thoracic or abdominal pain	6	16
Peripheral tuberculous arthritis	1	3
Elevated ESR	33	89
Anemia (Hemoglobin <12 g/l)	13	35
Leukocytosis (>10,000/mm ³)	4	11
Tuberculin skin test positive	28	76

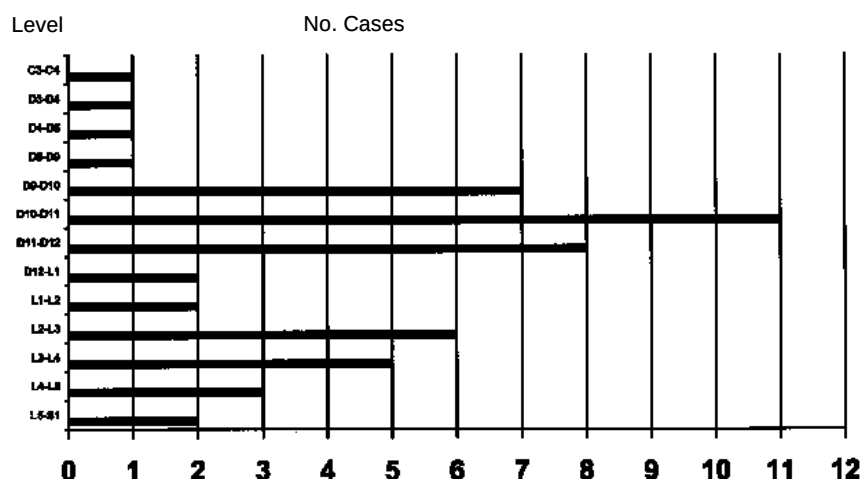


Fig. 1. Location of the spinal damage in 37 patients with tuberculous spondylitis. In this figure all the spine levels involved are shown. The most common site of infection was D10 - D11 (n = 11 patients) followed by D11 - D12 (n = 8 patients) and D9 - D10 (n = 7 patients), respectively.

Table III. Diagnostic yield of patients surveyed in the present study.

	No. cases	Positivity	Key in diagnosis
Culture in needle-aspirated material from disk or abscess	24	19	19
Culture after surgery from disk or abscess material	13	10	10
Extra-spinal culture	1	1	1
Histology	16	12*	7

*Histologic finding of caseating granuloma.

Table IV. Main features at the time of the diagnosis on plain radiograph, CT-scan, MRI and ^{99}Tc bone scan.

	Normal	Abnormal	Disk or bone alterations	Paravertebral or psoas abscess	Epidural abscess
Plain radiograph	6	31	31	10	0
CT-scan	0	19	19	14	6
MRI	0	18	18	14	12
^{99}Tc bone scan	0	8	-	-	-

Table V. Treatment and sequelae in 37 patients with tuberculous spondylitis. The duration of treatment was 44 ± 15 weeks (range 26-77).

	No. cases	%
Surgical treatment	12	32
Paravertebral/psoas abscess drainage	6	16
Spinal cord decompression	4	11
Epidural abscess drainage	1	3
Radicular decompression	1	3
Percutaneous drainage of psoas abscesses	2	5
Sequelae	24	65
Back pain	16	43
Neurological deficit	8	22
Visible spinal deformity	4	11
Death	1	3

discal space and the adjacent vertebrae were affected.

In this series the mean ESR was 55 ± 37 mm/1st hour (range 3-155). Thus, elevation of the ESR at the time of diagnosis was observed in most cases (89%). Anemia was detected in only 35% of patients, and leukocytosis in 11%. Of note, only 28 patients had a positive tuberculin skin test.

In 29 cases the diagnosis of spondylitis was confirmed by culturing MT from material obtained from either involved discal area or paravertebral abscess (Table III). Noteworthy was the high percentage of positive cultures in material obtained from percutaneous needle aspiration and biopsy under radiographic guidance (79%). Cultures from surgical biopsy were also positive in a high number of cases (77%). However, acid-fast stain positivity, which was carried out on the pathologic specimens was only positive in 14% of the samples. In 7 cases a diagnosis was performed on the basis of the histologic finding of caseating granulomas.

In Table IV the imaging findings of the 37 cases at admission are shown. Plain radiographs disclosed abnormalities in the majority of cases. However, 6 of them were normal. Both CT scan and MRI showed high sensitivity and disclosed abnormalities such as vertebral body erosions and narrowing of the disc space in all patients; thus they were very useful in detecting early involvement in patients with normal plain radiographs. They were also useful in identifying paraspinal or psoas muscle abscesses. MRI was especially precise in the location of epidural abscesses. Figure 2a shows typical radiographic changes in a patient with TS. In Figure 2b MRI changes found in the same patient are shown. In 8 cases in which ^{99}Tc gammagraphy was performed, hypercaptation at the affected vertebral area was also identified. Finally, no skip-like lesions were identified in our series.

Management and outcome

All patients completed the therapeutic regimen described in the Methods section (Table V). The duration of medical treatment was 44 ± 15 weeks (range 26-

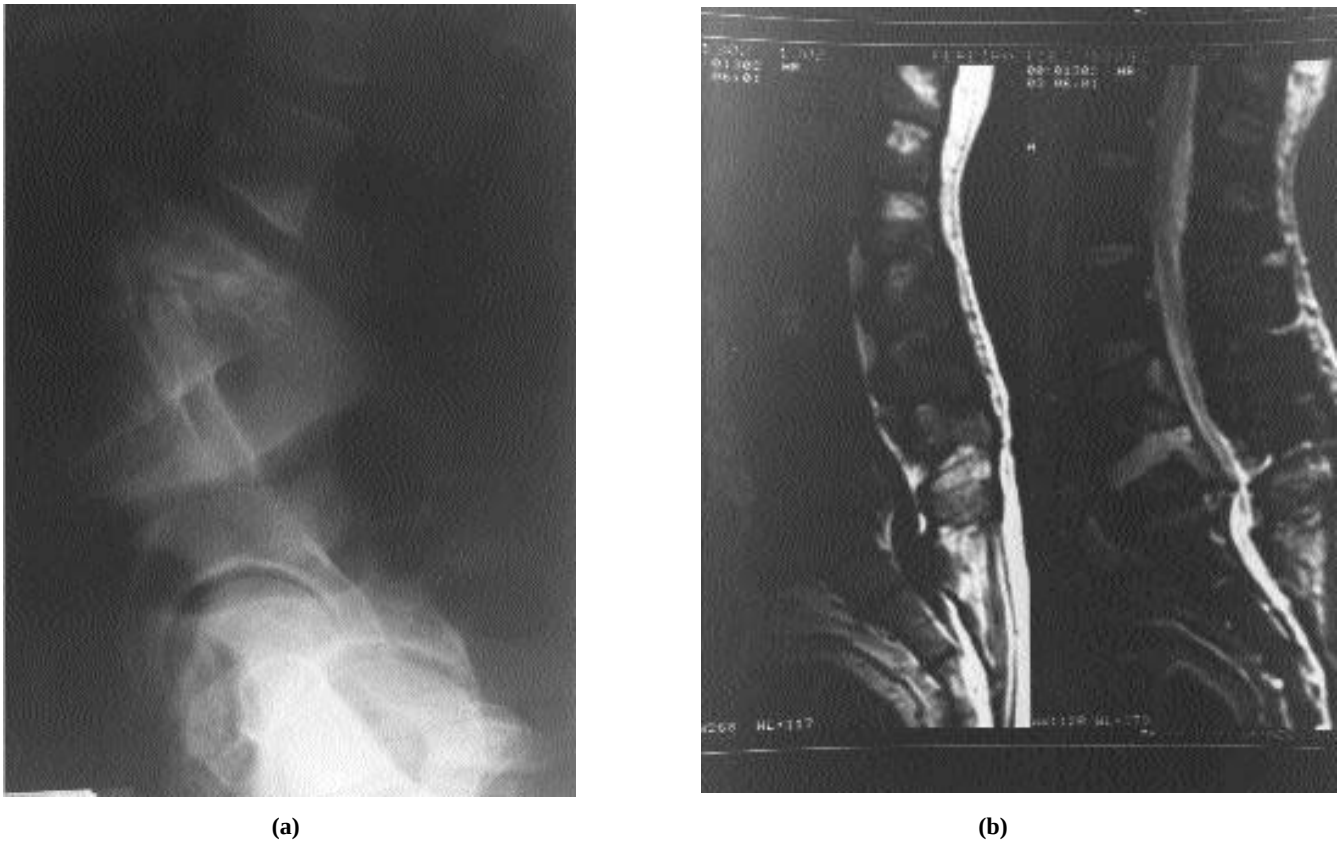


Fig. 2. (a) Plain radiograph of a patient with tuberculous spondylitis. Collapse of the L5 vertebral body was observed. Severe narrowing of the space between L5 and S1 was also detected. (b) Magnetic resonance T1 weighted image of the same patient showing collapse of the L5 vertebral body, an abnormal signal at the L4 vertebral body, and severe destruction of the L5-S1 disc. In a T2 weighted image a hyperintense collection is also observed.

77). Percutaneous drainage of the psoas abscesses was carried out in 2 patients. Twelve patients underwent surgery. The most frequent reasons for surgery were either paravertebral or psoas abscess drainage. In 4 patients spinal cord decompression was performed. In one patient evacuation of an epidural abscess was needed and in another patient decompression of a root nerve was required.

Different degrees of sequelae were observed in 65% of patients. Residual pain in the affected area was the most frequent complication. Kyphoscoliosis was also observed. Neurologic deficits, in particular radicular or spinal cord complications, were detected in 8 patients. One patient died due to a comorbid disease. No relapses were documented after a mean follow-up period of 7.1 ± 4.2 years.

Discussion

The present study describes the clinical spectrum of TS in central Galicia. It constitutes an extension of a former

epidemiologic study on osteoarticular complications in Northwestern Spain (4). However, unlike the former report, the present study specifically focuses on the analysis of the spinal manifestations of tuberculosis in that part of Spain. Of note, in Galicia tuberculosis has an incidence of 72.7 cases per 100,000 inhabitants per year (6). This frequency is higher than the average annual incidence for Spain, which is already a country with a high incidence of TB (7-9), and even higher than in other countries with lower levels of economic and social development (10). This high rate is not due to other factors such as acquired immunodeficiency syndrome (AIDS), intravenous drug use, alcoholism, immigration from areas with a high prevalence of tuberculosis or poverty but is related to a long-standing historic deficit of measures towards the prevention of the disease (6, 11).

The mean age of the patients in the present study was 60.3 years, and 62% of them were older than 60 years. These

figures contrast with those recorded globally for tuberculosis, where the mean age is 40.5 years and most patients are between 15 and 44 years. With regard to the sex distribution, we observed a similar proportion between males and females, which is in accordance with the distribution registered in our area for extrapulmonary TB. In contrast, in pulmonary tuberculosis the incidence in Galicia is twice as high in males (6, 11).

Osteoarticular tuberculous infection in Galicia accounts for 1.45% of all cases of tuberculosis. Based on earlier epidemiological studies (4, 6) and the data reported in the present study, TS would represent a 53% of the cases of osteoarticular tuberculosis and 0.75% of the total number of cases of tuberculosis. Thus, although more frequent in our area, it remains a rare disease. This fact, along with the high incidence of back pain in the general population and the paucity of systemic manifestations, may explain the inappropriately long delay in the diagnosis of most cases.

In TS the vertebral infection is generally due to reactivation of latent foci that were formed during the primary disease, after a latent period of variable duration. It can also be secondary to blood or lymphatic dissemination from reactivated pulmonary or extrapulmonary foci. The absence of well-established risk factors has been considered to play an additional role in the long delay to the diagnosis (12-14). In this regard, it is interesting to note that in Northwest Spain only 13 of the 37 patients with TS had evidence of previous tuberculous infection. Presumably a remote, unrecognized pulmonary infection might have been the source of the infection in the remaining patients.

Tuberculosis of the spine has a predilection for the subchondral bone of the vertebral bodies and spreads slowly from there to the entire vertebral body and intervertebral disc. As observed in the present study, extension of the infection into the adjacent paraspinal soft tissues with the formation of abscesses is common.

The symptoms and signs of TS vary considerably. The usual presentation consists of localized back pain increasing over a period of several months, local tenderness and spinal motion loss (15). As described in this series, it is not always accompanied by general symptoms. Conversely, these general symptoms are more frequent in spinal infections by either brucella or pyogenic bacteria, and this fact can help determine the etiology of the spondylitis process at its outset (3,14).

In keeping with other series, we found different degrees of nervous involvement in a significant proportion of patients (14, 16, 17).

Hematologic and biochemical alterations are usually variable and non-specific. In the present study an elevated ESR was the most frequent finding. As in other series, the tuberculin skin test was not positive in all patients (18-20). In general, most of the false negative reactions to this test occur in elderly or severely ill patients, HIV-positive patients, or those who are on immunosuppressive treatment (1, 20), but it is not exceptional to see false negative tuberculin reactions in young, non-HIV pa-

tients (21).

Regarding the location of the lesions, image visualization is essential. Plain radiographs of the spine constitute the first procedure. Rarefaction and loss of definition in the subchondral bone of two or more adjacent vertebral bodies and increase of paravertebral soft tissue are frequently seen. At a later stage subchondral destruction and collapse of the anterior part of vertebral bodies, disk space narrowing, and paravertebral abscesses may be observed (11, 22, 23). Nevertheless, abnormalities visible on plain radiographs are not generally apparent until 8 or more weeks after the initial inoculation (24). Thus, in early stages of the disease data provided by CT scan or MRI are especially useful (12, 25). Due to the high contrast resolution and the ability to detect spinal cord infiltration, MRI has proved to yield a higher diagnostic accuracy than CT scan in incipient TS lesions (2, 26-29). Of note, in Northwest Spain ⁹⁹Tc gammaigraphy yielded positive results in all cases on whom it was performed. Thus, it may be considered as a good screening test in the diagnosis of TS.

As observed in the present study, the lower dorsal and lumbar spine are the most frequently affected sites (14). In all our cases at least 2 adjacent vertebrae were infected. Nevertheless, in 13 cases 3 or more contiguous vertebrae were injured. This was due to the local spreading of the disease through anterior and posterior longitudinal ligamentous planes.

Fine-needle aspiration or open biopsy of the vertebral lesions or paravertebral abscesses is required for the diagnosis of TS (1, 30). However, negative cultures may be the result of small number of viable bacilli in the samples, which makes difficult the bacterial growth. Due to this, samples must be incubated for at least 8 weeks (31). Nevertheless, as in 7 patients from our series, a diagnosis can be made on the basis of caseating granuloma seen on biopsy. In the near future the incorporation to the clinical practice of mycobacterium DNA amplification techniques by means of polymerase chain reaction will allow to identify mycobacteria in

difficult cases (32, 33).

A routine practice in both areas of central Galicia was to treat the patients with only antituberculous medication, and keep surgical treatment for patients in whom complications had occurred. Although a 6-month course of chemotherapy has proved to be effective in the treatment of pulmonary tuberculosis, some reports have suggested that this regimen may be a little less effective in treating TS, especially those with pronounced osseous destruction or abscesses (34, 35). Of note, despite having no resistance to medical treatment 12 of our 37 patients required adjuvant surgical procedures and sequelae were observed in 65% of patients.

In conclusion, our study provides evidence that TS is still a major infectious disease, capable of producing osteoarticular and neurological complications in Southern Europe. Low physician awareness can explain the long delay in the diagnosis. Therefore, a greater degree of suspicion of this condition is required.

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