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Spinal tuberculosis: proposed spinal infection multidisciplinary management project (SIMP) flow chart revision

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Abstract. – OBJECTIVE: We propose a revised flow chart of spinal infection multidisciplinary management project (SIMP) aimed to standardize the diagnostic process and management of spinal tuberculosis (TB).

MATERIALS AND METHODS: We reviewed data from all TB cases with osteoarticular involvement treated at a large tertiary teaching hospital in Bologna, Northern Italy, from January 2013 to December 2017. We cross-linked notified osteoarticular TB cases with SIMP database and we analysed clinical, diagnostic, and treatment data of all cases managed by SIMP.

RESULTS: Osteoarticular TB accounted for the 7.8% (n=40) of all TB cases notified between 2013 and 2017 (N=513). Among the identified cases, 52% (n=21/40) had spine involvement: all were enrolled and evaluated by SIMP multidisciplinary group. Females accounted for 57% (12/21) of patients, the median age was 52 years (range 24-82). In the 67% (n=14/21) of cases, the major clinical symptom of spinal TB was back pain reported for a median of 4.5 months (range 1-12 months) before hospital admission. The interferon gamma release assay was positive in 75% (n=16/21) of patients. All patients performed MRI with gadolinium, which indicated spondylodiscitis in 90%. 18F-FDG-PET/CT revealed average maximum standardized uptake value (SUV max) of 12.54 (range 5.3-22) in 17/19 (89.5%). Bacteriological confirmation of TB was obtained in 86% of cases (n=18/21). One-third of patients (7/21) underwent surgery and 95% successfully completed the anti-TB treatment.

CONCLUSIONS: Our data reveal that a multidisciplinary approach to spine tuberculosis facilitates early and accurate diagnosis and can improve medical and surgical management of this disease.

Key Words:
Spondylodiscitis, Spine tuberculosis, Multidisciplinary management.

Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases, with an estimated 10 million new cases and a mortality of 1.3 million people in 2017[1]. In the European Union, the incidence of extra-pulmonary TB (EPTB) has increased from 16.4% in 2002 to 22.6% in 2017[2]. Osteoarticular TB is one of the most common EPTB localizations, often affecting the spine (3.9% of call cases) and other bones/joints (5.1%)[2].

In Bologna urban-area, Northern Italy, a multidisciplinary approach was established for spine infections (SIMP, Spine Infection Multidisciplinary Management Project) in 2009, which included spine surgeons, infectious diseases specialists, and nuclear and interventional radiologists. In 2011, SIMP group developed a standardized treatment algorithm to guide physicians in the diagnosis and treatment of spondylodiscitis, with special focus on bacterial infections[3]. In this paper we conducted a retrospective analysis of all spine TB cases managed by SIMP from January 2013 to December 2017 and we propose a revised algorithm adapted to the diagnosis and management of osteoarticular TB.

Background

Spinal TB is one of the most severe forms of EPTB and treatment outcome is strictly dependent on the stage of disease at presentation: a timely and accurate diagnosis, therefore, is mandatory to promptly start an effective treatment and to avoid neurological complications and irreversible disabilities.

Clinical manifestations of osteoarticular TB vary from systemic symptoms, like low-grade fe-

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vers, night sweats, weight loss, anorexia, to local manifestations, which can vary depending on the infectious process localization. Typical findings in patients with spinal disease are persistent back pain and limitation of movements of the affected area sometimes associated with soft tissue effusion and/or systemic manifestations. Although less than 50% of patients with osteoarticular TB have also pulmonary TB at the time of diagnosis, chest imaging is mandatory from a public health perspective to reduce the risk of transmission[4].

In case of clinical suspicion of spinal TB, it is crucial to collect detailed information about patient's country of origin or long term residence, in high endemic countries, past family, and personal history of latent or active TB, known contacts with active pulmonary TB cases, and other risk factors that can lead to a deficiency in one or more components of the immune system (e.g., HIV infection, chronic steroid therapy, anti-TNF drugs). The priority is then to confirm/rule-out TB diagnosis through bacteriological tests as microscopic examination, molecular tests, and culture on specimens collected from affected area. Although inexpensive, microscopic examination for Acid-Fast Bacilli (AFB) is not a sensitive test, it does not provide any information about drug susceptibility and it cannot distinguish between Mycobacterium tuberculosis complex and non-tuberculous mycobacteria. In 2010 the World Health Organization (WHO) published the first policy guidance on Xpert MTB/RIF test, a new molecular test that allows both the rapid confirmation of TB and the identification of rifampicin-resistant strains. The first policy guidance recommended to use the test only for respiratory specimens, but in 2013 Xpert MTB/RIF was approved also for selected specimens for the diagnosis of extra-pulmonary TB (EPTB)[1]. However, there were insufficient data concerning test performance for musculoskeletal TB. As reported by Held et al[5] in 2014, the sensitivity of Xpert MTB/RIF on spine samples was 95.6% and the specificity 96.2%, with positive predictive value of 97.7% and negative predictive value of 92.6%.

Currently, the diagnostic gold standard for the diagnosis of active TB and EPTB remains the detection of *Mycobacterium tuberculosis* by culture. However, the cultures require prolonged incubation, adequate laboratory infrastructure, and trained staff, but they allow to perform full drug-susceptibility test (DST) to determine resistance to first-line and second-line anti-TB drugs.

Presumptive TB can be further investigated using immunological tests, like the traditional tuberculin skin test (TST) and the Interferon Gamma Release Assays (IGRA) performed on blood samples. The skin test may be scored false positive due to Bacillus Calmette Guerin (BGC) vaccination, which may be relevant mainly for people coming from endemic countries where TB immunization campaigns are still active. On the other hand, IGRA tests are not influenced by BCG vaccination and therefore, if positive, can identify people with latent TB infection with a specificity of 100% in settings with a low TB incidence. The interpretation of the results of these tests depends on the clinical context, and that these tests cannot distinguish between latent and active infection[6].

In patients with spinal TB who do not have risk factors for multidrug-resistant TB, the first line recommended therapy is a combination regimen of rifampicin, isoniazid, ethambutol, and pyrazinamide for the first two months, followed by a continuation phase with rifampicin and isoniazid. This therapy needs to be managed by an infectious diseases/TB specialist and eventually modified on the basis of drug susceptibility testing. The recommended duration of the treatment for spinal TB is not well defined, mainly due to the difficulties in assessing the treatment response. Some experts recommend 9-12 months, others 12-14 or until the complete resolution of clinical and radiological signs of disease[7].

The general principles for the management of spinal TB are mostly conservative, consisting of orthopaedic corset/plaster cast wearing, bed rest, and specific antibiotic therapy[8,9]. The role of surgery is mainly during the diagnostic process and to treat the complications of the disease.

Although anti-TB drugs and non-surgical measures play a critical role in the treatment of spinal TB, kyphosis deformity, abscess formation, and spinal cord compression are common[10]. Therefore, some patients may still require surgery in addition to anti-TB treatment. Neurological impairment, especially if it is incipient or worsening, is an absolute indication to surgical debridement and stabilization[9-11]. Presence or progression of neurological signs may result from abscess or vertebral collapse, with higher risk in old age and in cervical localization. Abscesses occurrence is an indication for surgery also because antibiotics do not penetrate enough, and drainage is usually necessary[12].

Classically, an anterior approach was performed to reach a complete decompression of the neurological structures since TB infection usually involves the

anterior structures of the spine; this approach allows a wide debridement of infected material but involves a major morbidity and destabilization of the vertebral column. Therefore, it was always followed by a posterior instrumentation and, whenever possible, by a reconstruction of the anterior body with autologous bone graft or synthetic prosthesis[13]. It is clear that a double, anterior and posterior, approach is highly demanding for the patient; resulting in high volume blood loss, prolonged surgical times, and wide surgical exposure. Currently, a wide circumferential decompression of the neurological structures throughout an only posterior approach is preferred, as it offers the possibility to restore the stability and correct the deformity during the same procedure[14]. A drainage of the vertebral abscess is possible through a transpedicular posterior approach, in the lumbar spine, or a costotransversectomy, in the dorsal spine with minimal surgical invasiveness.

Patients and Methods

We reviewed data on all pulmonary (PTB) and EPTB cases with involvement of musculoskeletal system notified in S. Orsola-Malpighi tertiary teaching hospital, located in Bologna, Italy, from January 2013 to December 2017. We cross-linked notified musculoskeletal TB cases with database of SIMP and we collected clinical, diagnostic, and treatment data of all cases managed by SIMP, according with the inclusion and exclusion criteria defined by the study protocol of SIMP algorithm[3]. Of these cases, we analysed demographic details, clinical manifestations, duration of symptoms, delays in diagnosis, microbiological results, treatment regimen and duration, surgical approach, and treatment outcomes. Bacteriological tests (i.e., microscopic examination for AFB, Xpert MTB/RIF, and *M. tuberculosis* culture) were performed on material collected from involved area, depending on TB localization. For positive cultures, DST for first line drugs (and second line drugs, if needed) was performed. Case classifications and treatment outcomes were categorized according to WHO definitions[15]. Surgery was reserved to patients affected by instability and/or severe deformity of the spine, compression of the neurological structures or uncontrolled pain. During treatment, all patients were jointly evaluated by infectious diseases and spine surgeons on monthly basis.

Categorical variables were analyzed as absolute numbers and their relative frequencies. Continuous variables were analyzed as mean and standard deviation if normally distributed or as median and interquartile range (IQR) if non normally distributed. All descriptive analyses were performed using Stata IC 13.1 (Stata Corp, College Station, TX, USA).

Results

From January 2013 to December 2017, 513 TB cases were diagnosed in our center. Of these, 73% (n= 374) were pulmonary TB, of which 29% (n=109) had also extrapulmonary involvement, and 27% (n=139) were exclusively EPTB. Osteoarticular TB accounted for the 7.8% (n=40) of all TB cases and 16% of TB cases with extrapulmonary involvement. Of the 40 patients with osteoarticular involvement, 52% (n=21) had TB of the spine (4% of total TB cases), 22% (n=9) of the hip, 15% (n=6) of the knee, 2 patients had skull bone involvement, 1 of the shoulder and 1 of the metatarsus. All patients with spine TB were enrolled and evaluated by SIMP multidisciplinary group.

Social-demographics characteristics and clinical presentations are presented in Table I. Out of 21 cases, 12 (57%) were females, the median age was 52 years (range 24- 82), 4 (19%) patients were Italian, 5 (24%) were from Pakistan while the others were from Bangladesh (n=2), Morocco (n=2), Mali (n=2), Ukraine (n=1), India (n=1), Eritrea (n=1), Philippines (n=1), Cameroon (n=1), Nigeria (n=1), respectively. Overall, 6/21 (29%) patients had also pulmonary TB, 2 had also a pleural localization and 7 also lymph nodes localization. All patients were HIV negative, with 20/21 (95%) representing newly-diagnosed TB cases and 1 previously-treated case.

In 62% of cases (n=13/21), infection affected the dorsal tract of the spine (2 of them had also lumbar tract involvement and 1 with cervical-dorsal-lumbar tract involvement), while in 6 cases infection was localized in the lumbar tract and in 2 cases cervical-lumbar localization occurred.

In the 67% (n=14/21) of cases, the clinical presentation of spinal TB was represented by back pain for a median duration of 4.5 months (range 1-12 months) before the first access to the hospital. For 67% of patients (14/21), the first presentation to a health facility was an admission in the emergency department, while for 4 patients was a visit to orthopaedic surgeon and 3 patients were referred to the general practitioner. The 28% (n=6/21) of patients presented neurological manifestation at admission: all of them had cauda equina syndrome,

and one patient had paraparesis. At presentation, all patients had an increased value of Erythrocyte Sedimentation Rate (ESR) with a mean value of 65 mm/h (range 25-120), and 90% (n=19/21) had also an increased value of C-reactive protein (CRP, normal value <0.5 mg/dL) with a mean value of 5.2 mg/dL (range 0.9-12.86 mg/dL).

All patients had an IGRA test performed that was positive in 75% (n=16/21).

All patients underwent MRI study of the spine with contrast (gadolinium), and in all cases it was consistent with spondylodiscitis. As recommended by the SIMP flow chart, 90% (n=19/21) of patients also performed [18F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) in the initial phase and in 17/19 (89.5%) it showed pathological uptake with an average Maximum Standardized Uptake value (SUVmax) of 12.54 (range 5.3÷22). In two patients there was a diffuse non-specific bone 18F-FDG uptake (an increased SUVmax was documented in lymph nodes with a value of 21.7 in one case and 14.1 in the other) but the MRI with gadolinium was suggestive of spine infectious process. Two patients did not perform 18F-FDG-PET/CT because they came to our attention after diagnosis of spinal TB.

Bacteriological confirmation was obtained in 86% of patients (n=18/21). The diagnosis was achieved in 7 patients by vertebral biopsy, in 6 patients through lymph node biopsy, in 3 cases through material drained from ilio-psoas abscess, 1 patient through a bronchoalveolar lavage, and in 1 patient through a pleural biopsy (Table II). Ninety-five percent of specimens (n=17/18) were positive to culture examination, while one was positive only to Xpert MTB/RIF test. The Xpert MTB/RIF test identifies one rifampicin-resistant strain that was confirmed to be a multi-drug resistant TB case at the first line DST. There were also 3 cases mono-resistant to pyrazinamide and 1 case mono-resistant to isoniazid at the full DST. All bacteriologically confirmed cases had granulomatous lesions at histology, 82% of them (n=9) with caseating granuloma; only one specimen was positive to Ziehl-Neelsen stain. The 3 not microbiological confirmed cases had histological patterns suggestive for TB on vertebral biopsy.

All patients were treated according to WHO guidelines and based on DST profile[16,17]. Levofloxacin was used only in the MDR-TB patient, in the 4 mono-resistant cases, in 1 case who did not tolerate the first line regimen, and in the paraparetic patient. The MDR-TB patient was treated for 22 months (8 months with amikacin, cycloserine, levofloxacin, ethambutol, and pyrazinamide and 14 months of the same drugs without amikacin). Ninety-five percent (n=20/21) of patients completed the treatment, while one patient died at 5th month of therapy for reasons not related to TB. The mean treatment duration, not considering the MDR patients, was 12 months (range 9-15). All cases showed a progressive improvement of the radiological aspects at the MRI with gadolinium during and at the end of treatment. The 68% of patients (n=13/19) repeated also 18F-FDG-PET/

Table I. Social-demographics characteristics and clinical presentation of the studied population.

		No.=21
Sex	M (%)	43% (9/21)
	F (%)	57% (12/21)
Median Age		52 (range 24÷82)
Nationality	European	Italy 4
		Ukraine 1
	Asian	Pakistan 5
		Bangladesh 2
		Philippines 1
		India 1
	African	Morocco 2
		Mali 2
		Eritrea 1
		Cameroon 1
		Nigeria 1
Symptoms	Back pain	67% (14/21)
	Neurological manifestation	28% (6/21)
Spinal localization	Dorsal tract	62% (13/21)
	Lumbar tract	29% (6/21)
	Cervical-lumbar tract	9% (2/21)

Table II. Microbiological confirmation.

Type of material	No. of patients	No. of patients	Smear microscopy	Xpert MTB/RIF	M. tuberculosis culture
Vertebral biopsy	7	1	+	+	+
		3	–	+	+
		3	–	–	+
Lymph node biopsy	6	3	–	+	+
		2	–	–	+
		1	–	+	–
Ilio-psoas abscess' drainage	3	3	–	+	+
Bronchoalveolar lavage	1	1	–	+	+
Pleural biopsy	1	1	–	+	+

No.: number, +: positive, -: negative

Table III. Surgical intervention.

Segment	Indication	Surgery
D3-D5	T4 fracture+uncontrolled pain+neurological compression	D3-D6 laminectomy+ posterior stabilization D2-D8
L5-S1	Cauda equina syndrome	Laminectomy +Discectomy+debridement
D12-L2	Uncontrolled pain+neurological compression	Laminectomy D10-L4+ posterior stabilization D10-L4
L3-L4	Neurological compression	L5-S1 laminectomy+posterior stabilization
D10-D11	Uncontrolled pain	Laminectomy+debridment
D11-L2	Cauda equina syndrome	Laminectomy D10-L4+ posterior stabilization D10-L4
L4-L5-S1	Paraparesis	Laminectomy L4-L5+ posterior stabilization

CT at the end of treatment that revealed the normalization of FDG uptake in the 70% (n=9/13) of them and a SUVmax reduction for the remaining 4 patients.

One-third of patients (7/21) underwent a surgical intervention (Table III). All were treated through a posterior approach, that allows a complete decompression of the neurological structures, a stabilization of the spine through trans-pedicle screws, and rods positioning; with a posterior approach it was also possible to correct the spine deformity.

Discussion

The main finding of this study is that in a low TB prevalence setting, such as Italy, we identified an unexpected high proportion of spinal TB (7.8%) compared to previous case series in literature[18]. We hypothesize that the multidisciplinary approach of SIMP allowed to increase the diagnostic sensitivity of all the specialists involved, who were guided by a comprehensive diagnostic flow-chart to promptly reach the diagnosis. This management was essential also because patients did not initially present specific symptoms of TB, but typically reported only back pain and that's why they were referred to the emergency department or to an orthopedic specialist and not to an infectious disease specialist. Our results also confirmed that the inflammatory blood markers' elevation at presentation can guide clinicians to diagnose/exclude an infectious process.

In our cohort of patients affected by spinal TB, however, 25% of cases had a negative IGRA test consistent with previous reports in the literature. A negative test does not rule out a TB diagnosis[6]. Therefore, a thorough clinical and radiological workup with appropriate invasive diagnostic and bacteriological tests are essential to reach a correct diagnosis.

There are no systematic data in literature about the use of 18F-FDG-PET/CT in osteoarticular TB[19]. Our data showed that patients affected by spine TB presented a higher average SUVmax than the aver-

age value (7.3) reported elsewhere[3]. Data on a larger cohort of patients would be needed, however, to establish if the SUVmax value can help to discern mycobacterial infections from bacterial ones. The execution of 18F-FDG-PET/CT at presentation also guides the interventional radiologist to select the area with the highest SUVmax for the targeted spine biopsy, increasing its sensitivity.

In most cases we did not repeat the 18F-FDG-PET/CT after 2-4 weeks of medical therapy or after 6-12 weeks from surgery because we preferred monitoring treatment efficacy based on the MRI imaging and on clinical response. Instead, we used 18F-FDG-PET/CT to assess treatment response at the end of therapy in patients who presented an improvement of the MRI images, but not a complete resolution, and in the 3 patients with a clinical diagnosis of spinal TB, in order to establish the most appropriate treatment duration. The complete normalization of FDG uptake provided an additional element to guide the treatment interruption. The routine use of 18F-FDG-PET/CT is limited by its costs and availability only in high resource settings, so its use should be limited to selected cases.

In our cohort, we obtained a high bacteriological confirmation through biopsy; suggesting that if biopsy targets the correct lesion place there are high chances to obtain microbiological confirmation.

All patients had a histological picture suggestive of TB, even if Ziehl-Neelsen stain was positive in one case only. This data underlines the importance to collect specific samples for histological examination, while confirms the low sensitivity of Ziehl-Neelsen stain, as previously reported[1].

Of all microbiological confirmed cases, the 72% (13/18) were positive to Xpert MTB/RIF test confirming the high sensitivity and specificity of this test for non-respiratory specimens[1-7]. Despite the low number of patients, a considerable proportion presented a mono-resistant drug TB, and this re-emphasizes the importance to conduct full DST to guide the treatment regimen choice.

The surgical treatment of the Pott's disease is challenging and should always be performed in high volume spine centers by experienced surgeon[9-14]. As confirmed by our data, surgery is a support to diagnostic phase and to medical treatment.

Revision of the Flow-Chart

As previously reported, the key points of the flow chart followed by the multidisciplinary group of SIMP are the following: 1) MRI with gadolinium as the diagnostic gold standard; 2) 18F-FDG-PET/CT at the presentation and after 2-4 weeks of medical therapy or after 6-12 weeks from surgery in order to evaluate the treatment efficacy; 3) CT-guided 8G caliber-Trocar Biopsy performed by interventional radiology before the beginning medical therapy if the patient has no critical clinical problems; 4) specific antibiotic therapy; 5) surgical treatment[3].

Based on our results we would like to propose a flow chart revision specifically for spinal TB:

1) MRI with gadolinium remains the diagnostic gold standard also for the diagnosis of spinal TB.
2) Role of 18F-FDG-PET/CT. While it remains one of the paramount diagnostic exams at the presentation, to be performed in the diagnostic path and/or in order to identify the best site where to perform a biopsy, the repetition of 18F-FDG-PET/CT in the evaluation of spinal TB treatment response should be reserved to the following circumstances: a) if bacteriological confirmation of TB is not obtained; b) poor clinical/MRI response, mainly in clinically diagnosed TB; c) in MDR-TB cases. In these situations, follow-up 18F-FDG-PET/CT should be performed during treatment.
3) An IGRA test should be performed in all patients with suspected spondylodiscitis, to guide the diagnostic and treatment decisions and to avoid the use of antibiotics with anti-tubercular activity that may influence the clinical picture and decrease the sensitivity of microbiological tests; however, it should be considered that negative IGRA tests cannot rule out active TB.
4) On the specimens collected by CT-guided 8G calibre-Trocar biopsy is essential to always perform: a) histologic exam and Ziehl-Neelsen stain if there is the presence of granulomatous lesion (it is important also to exclude *Brucella* spp. infection); b) smear microscopy for AFB, Xpert MTB/RIF molecular test and mycobacterial culture in addition to traditional aerobic and anaerobic culture.
5) Anti-TB treatment: the use of levofloxacin should be restricted to the mono/multidrug resistant TB cases and/or in case of intolerance to one of the first line drugs[14]. Treatment duration depends on clinical and radiological response: according to our experience it should last at least 12 months for drug susceptible or mono-resistant cases.
6) Surgical treatment may be needed, if there are indications by surgeons.

If points 1-4 do not allow clinicians to reach a timely bacteriological TB confirmation (positivity of microscopic examination and/or Xpert MTB/RIF) and suspicion for TB remains high (i.e., epidemiological history and/or clinical manifestations, positivity of IGRA test, presence of granulomatous lesion at histologic exams) we recommended to repeat the biopsy and/or search for other possible sites of TB localization to obtain new specimens before starting anti-TB treatment.

Conclusions

Despite being a relatively uncommon localization of TB, our data reveal that a multidisciplinary approach to spinal tuberculosis can improve the diagnostic accuracy and management of the disease. The SIMP approach enhances effective collaboration between different specialists to improve the timely diagnosis and treatment of both non-tubercular and TB spondylodiscitis.

Conflicts of interest

The authors declare that they have no conflicts of interests.

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