

Clinical-Morphological Aspects in Spinal Tuberculosis

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ABSTRACT: Osteoarticular tuberculosis (OATB) Aim: The authors made a clinical morphological assessment of tissue samples from patients admitted in Surgical Departments of the Emergency County Hospital of Craiova, Romania, between 1990 and 2015, proved as presenting tuberculous lesions of the spine in the Department of Pathology of the same Hospital. Materials and Methods: The studied material consisted of bone, joint and sometimes muscle tissue fragments resulted from biopsies or surgical excisions from 7 cases coming out of 54 patients investigated in the above-mentioned period of time, where the established histological diagnosis was tuberculosis (TB). For diagnostic confirmation, Ziehl-Neelsen staining has been used as a rule but, in some cases, immunohistochemistry was also used. Results: TB lesions have prevailed in men and around the age of 50 years. Thoracic segment of the spine was the most involved. Epithelioid and giant Langhans cells dominated the inflammatory cellular population. Necrosis was always present, usually in its classical acidophilic form. Fibrosis was almost always absent. On the whole, the granulomatous reaction was in almost half of the cases hyporeactive and disorganized. Conclusions: The clinical morphological profile of our series is fitting with data described in the literature. Because of its life threatening potential, spinal TB should be investigated thoroughly especially in its morphological features in order to obtain as quickly as possible an etiological diagnosis.

KEYWORDS: Extrapulmonary tuberculosis, Spine tuberculosis, Bones, Joints

Introduction

Spinal tuberculosis (STB) or spondylitis or spondylodiscitis refers to an infection by *Mycobacterium tuberculosis* (Mt) affecting the intervertebral disk, the vertebral body itself or the posterior vertebral arch, with or without involvement of the spinal canal [1-3].

It is one of the oldest reported diseases in humans. Although discovered and described by Pott in 1776, skeletal changes, such as collapse of the vertebrae (Pott's disease), have been reported in pre-dynastic Egypt (3500-2650 BC), and Neolithic Sweden culturally associated with the earliest cattle breeders (3200-2300 BC) but molecular proofs of Mt presence were detected in 9,000-year-old human fossils and non-specific morphological changes consistent with tuberculosis were found in a fossil *Homo erectus* dated from the middle Pleistocene (490-510,000 years BP) [2,4-8].

Tuberculous spondylitis is the most common form of osteoarticular TB (OATB), representing

alone 50% of all cases of OATB involvement. Osseous involvement by TB is, in its turn, reported as the most common site of extrapulmonary tuberculosis (EPTB) in Taiwan (with 24.5% of cases) to the third most common site in the United States (with 11.3% of cases, after pleural and lymph node involvement) [2,9-14].

Tuberculosis of the spine is a potentially life-threatening infection because it can produce neurological complications and, the most important, it is one of the most common worldwide causes of a kyphotic spinal deformity [15-17].

Moreover, there is a small number of cases of atypical spinal TB, not resembling with tuberculous spondylitis that often make diagnostic delays and even errors [18-19].

The aim of this study is to report some main clinical and especially morphological aspects of TB lesions of the spine admitted in Surgical Clinics and especially Orthopedic Clinic of the Emergency County Hospital of Craiova,

Romania, and diagnosed in in the Departments of Clinical Laboratory and Pathology between 1990 and 2015.

Material and Methods

The study group consisted of 7 cases admitted and diagnosed in the above-mentioned period and medical unit with TB inflammatory lesions of the spine. The group was part of a larger series of 54 patients proved as presenting tuberculous lesions involving structures of the osteoarticular system which, in turn, were part of a series of 841 patients proved as presenting tuberculous lesions in extrapulmonary sites in the Department of Pathology in the studied period of time.

The studied material consisted of: (a) accompanying notes of tissue specimens coming from surgery rooms; (b) histological records, paraffin blocks and Hematoxylin-Eosin (HE) stained slides of each case from the Department of Pathology’s archives.

The study was of retrospective type and the assessed parameters were grouped in:

[I] Clinical parameters: general involvement of the spine; temporal distribution of cases; gender; age; suspicion of the etiological diagnosis at admission.

[II] Morphological parameters:

(I) Lesions’ site in the spine.

(b) Assessment of: granuloma cellularity; presence and type of necrosis; presence of fibrosis; the granulomatous lesions degree of differentiation.

(c) Clarification of atypical lesions or caseous necrosis as dominating aspect of the lesion but with a non-specific granulomatous reaction around.

Serial sections were cut from paraffin block and stained as follows:

- First section-Haematoxilin-Eosin (for first diagnosis)

- Second section-Ziehl-Neelsen staining (for identification of acid-fast bacilli)

- Immunohistochemical staining for Mt (for etiological confirmation). The antibody used is presented in Table 1. Positive external control was made on sections from cases with pulmonary TB known as positive for Mt on Ziehl-Neelsen stained slides.

Table 1. Antibody used to identify Mt

Antibody	Source	Dilution	Pretreatment
Mo a Hu Mt clone BGN-3875	Novus Biologicals	1:500	20 minutes Citrate buffer, pH 6

Mt: *Mycobacterium tuberculosis*

Histopathology was assessed and areas of interest selected utilizing a CX31 Olympus microscope using the ×4 magnification objective. For final image acquisition, optical planapochromate corrected objectives with magnifications of ×4, ×10, ×20 and ×40 were used in order to capture high quality micrographs.

The most significant images were acquired using a LiveViewPro II color CCD digital camera, saved directly on the computer and processed using the specialized image analysis software package analySIS Pro.

For some parameters, be they clinical or morphological, the need for an accurate assessment of the tuberculous inflammatory process required the development of allocation criteria of cases that generated stratification scales of cases according to each criterion.

Thus, for age evaluation, the scales are presented in Table 2.

Table 2. Stratification scale for age

Age period		Age
P1	Child (Ch)	0-14 years
P2	Adolescent (Ad)	15-24 years
P3	Young adult (YA)	25-44 years
P4	Mature adult (MA)	45-64 years
P5	Elderly (Eld)	>65 years

In order to determine the degree of effectiveness of inflammatory complex intervention, we applied a modified granulomatous lesions classification system according to their organization, system proposed but only for lymph node lesions by Ramanathan *et al.*, in 1999 [20] (Table 3).

Table 3. Granulomas classification according to their degree of organization [modified after Ramanathan *et al.* (1999)]

Type	Code*	Code**	Grade	Cells	Necrosis	
Hyp	G1	Ia	Well diff	EC	Scarce	Absent/IN
		Ib		EC+GLC		
R	G2	II	Well diff	m EC M L and P	AN Mi	
Hypo	G3	III		Poor diff	M i EC L and P	BN Ma
A	G4	IV	Dis	M L, P PMN	NCN	

Hyp: Hyperplastic; R: Reactive; Hypo: Hyporeactive; A: Areactive; BN: Basophilic necrosis; diff: Differentiated; Dis: Disorganized; EC: Epithelioid cell; AN: Acidophilic necrosis; IN: Incipient necrosis; i: Immature; LGC: Langhans giant cell; L: lymphocyte; Ma: Macrogranular; M: Macrophage; m: Mature; Mi: Micro-granular; NCN: Non-caseating necrosis; P: Plasma cell; PMN: Neutrophils.

The data was processed and the graphs were drawn using the Microsoft Excel module of the Microsoft Office 2010 Professional software package.

Results

Clinical data

Cases with STB represented only a small part from the larger series with OATB (almost 15%) and even a smaller part from the entire review series of EPTB, meaning 1% of all investigated cases (Fig.1).

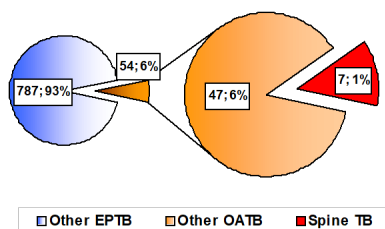


Fig.1. Spine involvement

Temporal evolution

As the Figure 2 shows, all STB cases were admitted in our hospital after 2010, representing the last five years period of our 26 years period of study of OATB.

If we compare the evolution trend with that of the larger series of OATB cases, we could observe that the OATB case on the whole had a descending trend during the studied period of time while the spine TB cases “exploded” in the last five years.

However, in this time, the number of cases varied from year to year (2 cases in 2010, one case in 2011, one case in 2013 and, finally, 2 cases in 2014), with a general decreasing trend.

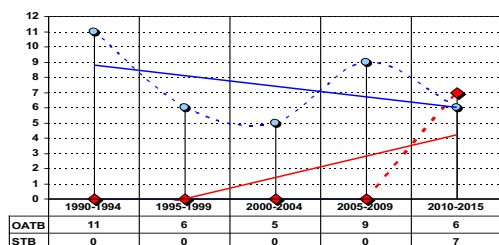


Fig.2. Temporal evolution of cases

Gender and Age

Most of our cases were males (Fig.3) but the lesions did not “avoid” the females.

The mean age was of 53,5 years. The youngest patient was a male of 33 years old and the oldest one was a female of 72 year old.

Females were both over 44 years old, belonging to the “Mature Adult” and “Elderly” categories while the Males were generally around 50 years old.

However, the youngest male patient was 33 year old, as mentioned before, and therefore included in the category “Young Adult”, and the oldest male patient was 65 years old (Fig.4).

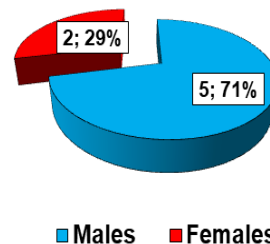


Fig.3. Gender distribution

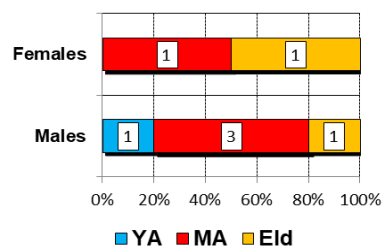


Fig.4. Age distribution

Clinical suspicion

The diagnosis of TB was suspected in all cases excepting one (Fig.5).

Due to the improvements in imagistic examination offered by the new techniques of investigation such as computed tomography (CT) and magnetic resonance imaging (MRI), one could better reveal characteristic aspects like destructive lesions in one of the anterior margins of the body of a vertebra, multiple levels of involvement, with “mirror” vertebral caries aspect, increasing loss of disc height (Fig.6) or larger sized paravertebral soft-tissue abscesses, often with calcifications and rim enhancement around (Fig.6b).

The seventh case was a 72 year old woman, who presented on the imagistic examination an area of osteolysis of the T12 vertebral body that had no suggestive features for TB.

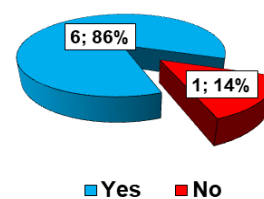


Fig.5. Clinical suspicion

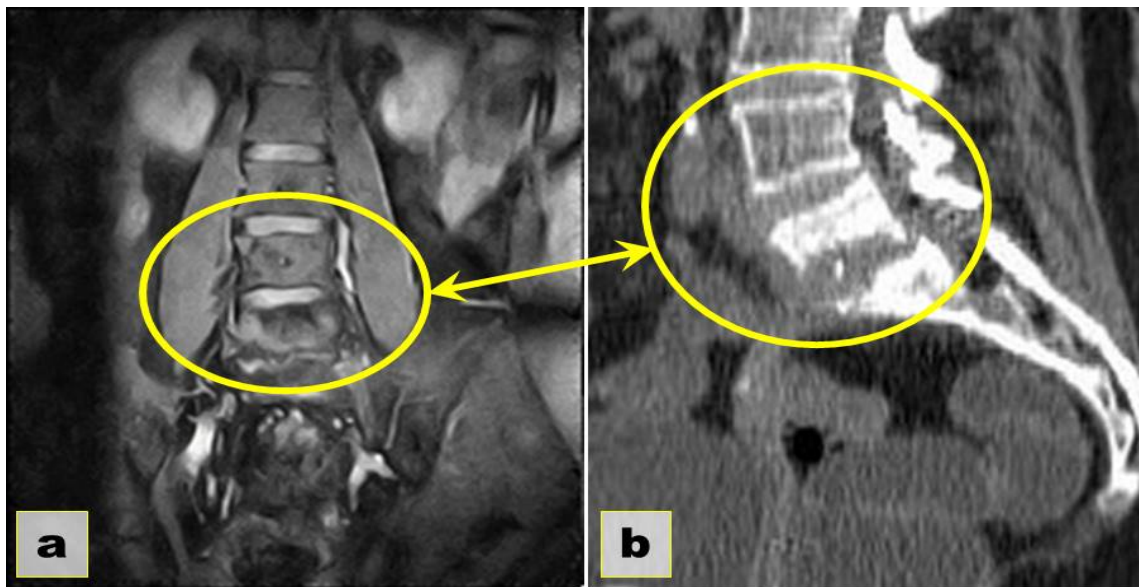


Fig.6. Spinal tuberculosis - L4-L5-S1 level
 (a) MRI coronal plane STIR 1: "mirror" vertebral caries; (b) CT: Extensive erosive changes involving the inferior aspect of L5 and superior part of S1 with widened intervertebral space (yellow circles)

Morphological data

Lesion site

As mentioned above, spinal involvement from all OATB studied cases was reduced in comparison with the "50%" reported in the literature [11,12,14,21].

However, the distribution on spine segments was somehow similar with the one reported in the literature, the main involved segment being the thoracic one, followed by the lumbar region (Fig.7).

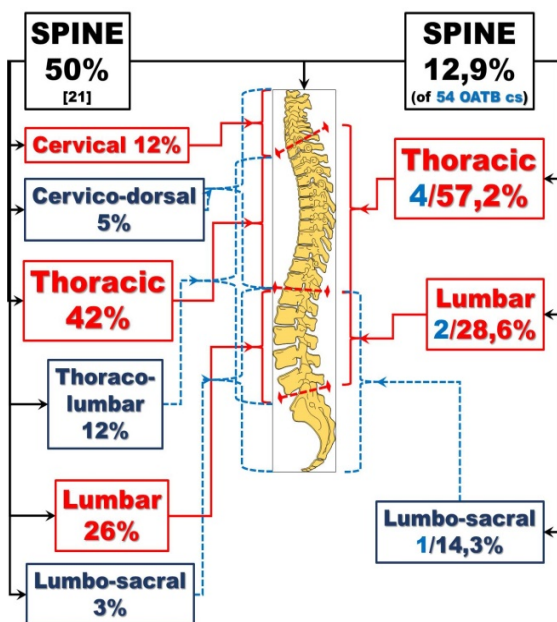


Fig.7. Site distribution

Second observation concerning the site concerned the type of spine tissue involved.

In more than half of the cases (4 cases) TB lesions involved both the vertebral bones and the intervertebral joint structures. In other two cases only the articular structures were involved, and in only one case only the vertebral bone harbored the TB lesion.

The third observation referred to the number of vertebrae affected by the tuberculous process.

Thus, there was only on case with only one vertebral body involved. In more than half of the cases (4 cases) two vertebrae were involved. In the remaining two cases three vertebrae were affected, in both case in the thoracic region.

Granuloma cellularity

The inflammatory population of cells was dominated by the couple of macrophage cells: epithelioid cells and giant Langhans cells (Fig.8a and Fig.9a-b).

However, in two cases neutrophils added to the inflammatory cellular population, signaling a superinfection of the TB inflammatory focus (Fig.8a).

Presence and type of necrosis

Necrosis was present in all cases and exhibited all its morphological variants. The most frequent variant observed was the classic acidophilic fine granular necrosis (Fig.8b and Fig.9c).

However, in one case the necrosis was incipient in the center of the granulomatous lesions (Fig.8b and 9b) and in another case the aspect was basophilic macrogranular.

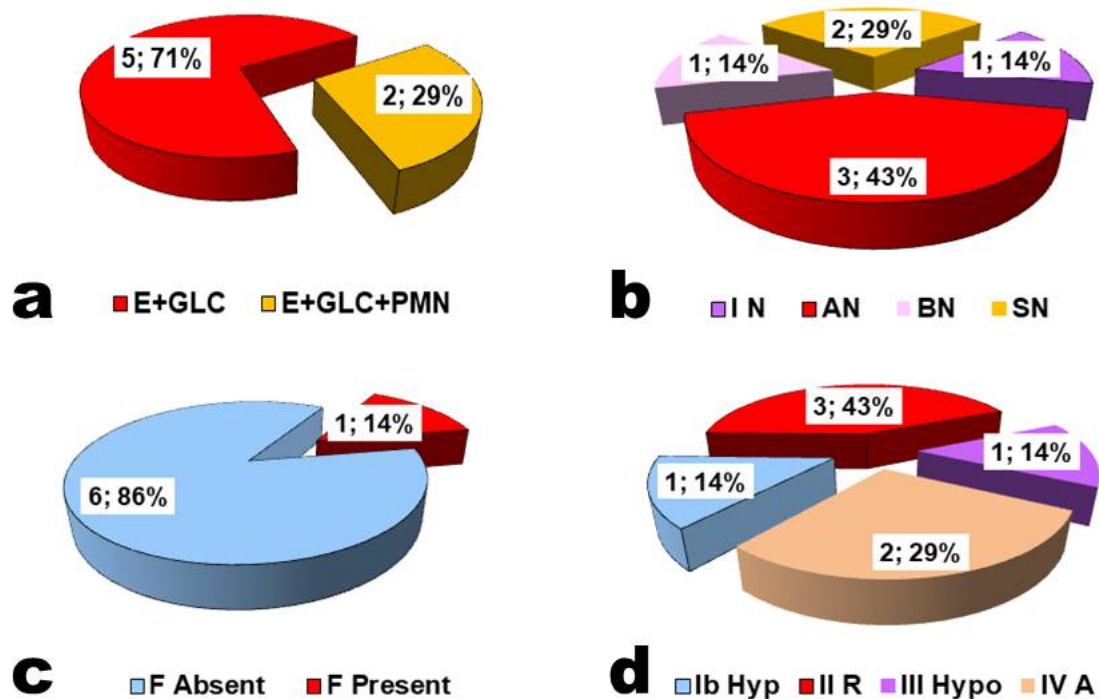


Fig.8. Granuloma morphology
 (a) Cell distribution; (b) Types of Necrosis; (c) Presence of Fibrosis; (d) Types of Granulomas

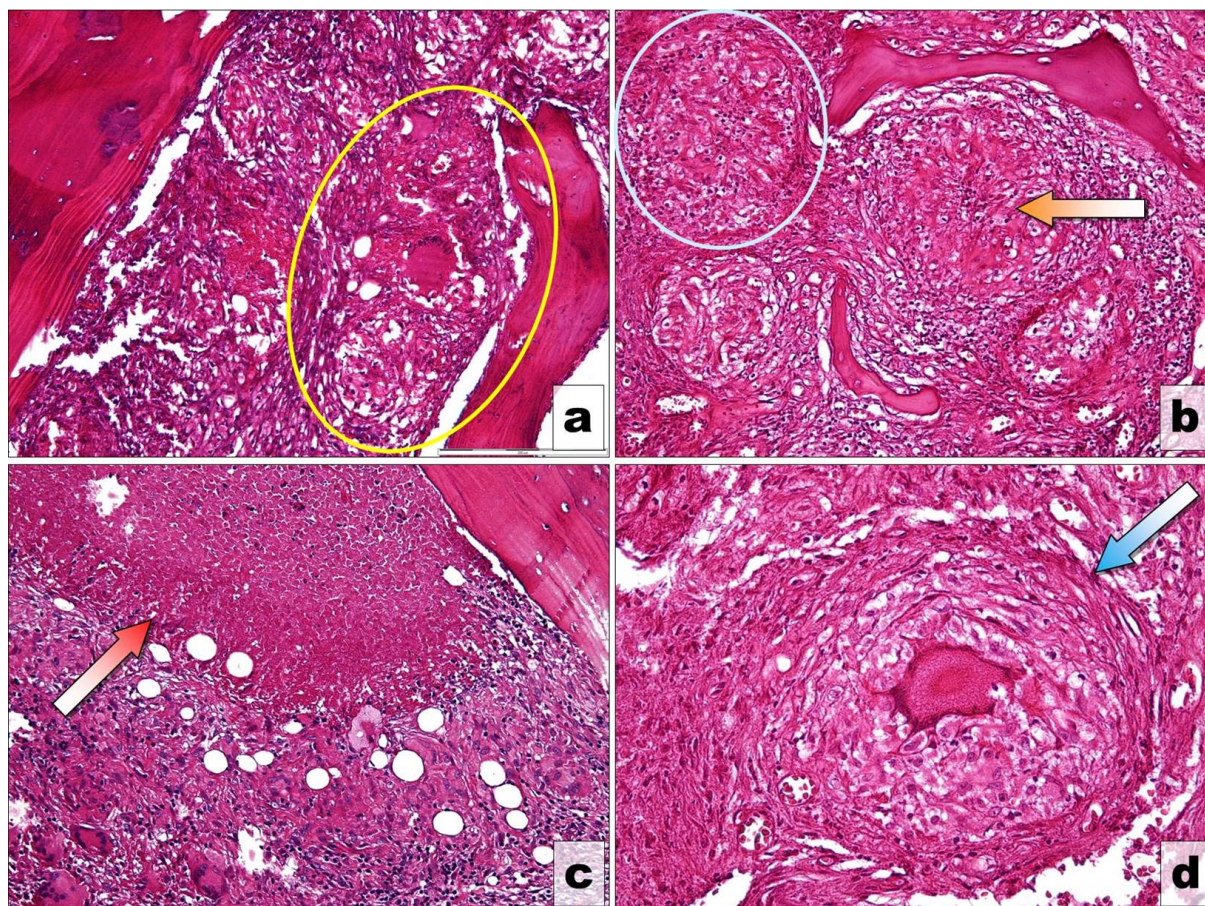


Fig.9. Granuloma morphology
 (a) Giant Langhans cell granuloma producing bone erosion (yellow circle) H-E stain, X100;
 (b) Epithelioid granuloma (blue circle) and Incipient necrosis (orange arrow)
 (c) Acidophilic fine granular necrosis (red arrow); (d) Fibrosis around LGC granuloma (blue arrow)

In the remaining two cases, the classical, caseous aspect of the necrotic material was transformed by the superadded infection in purulent aspect.

Presence of fibrosis

The process of perilesional fibrosis was observed in only one of the seven cases, where the collagen fibers isolated the necrotic area inside the vertebral body of the T12 vertebra creating a cystic appearance on the imagistic investigations.

Granuloma differentiation

Putting together all morphological aspects of the granulomatous reaction, its general aspect had significant variations. On one hand, three of

the cases presented type II, reactive granulomas, with both epithelioid and giant Langhans cells and classical acidophilic, fine granular necrosis. Other three cases, in turn, expressed hyporeactive and even areactive granulomas, the latter with the purulent transformation of the necrotic areas.

Lesions extension

Another characteristic of our series was the extension of the lesion from the initial site, by contiguity, in the paraspinal spaces (Fig.10a and c) and, moreover, generating cold abscesses (Fig.10b and d) found in sites far from the infectious focus, particularly in the sheaths of the psoas muscles.

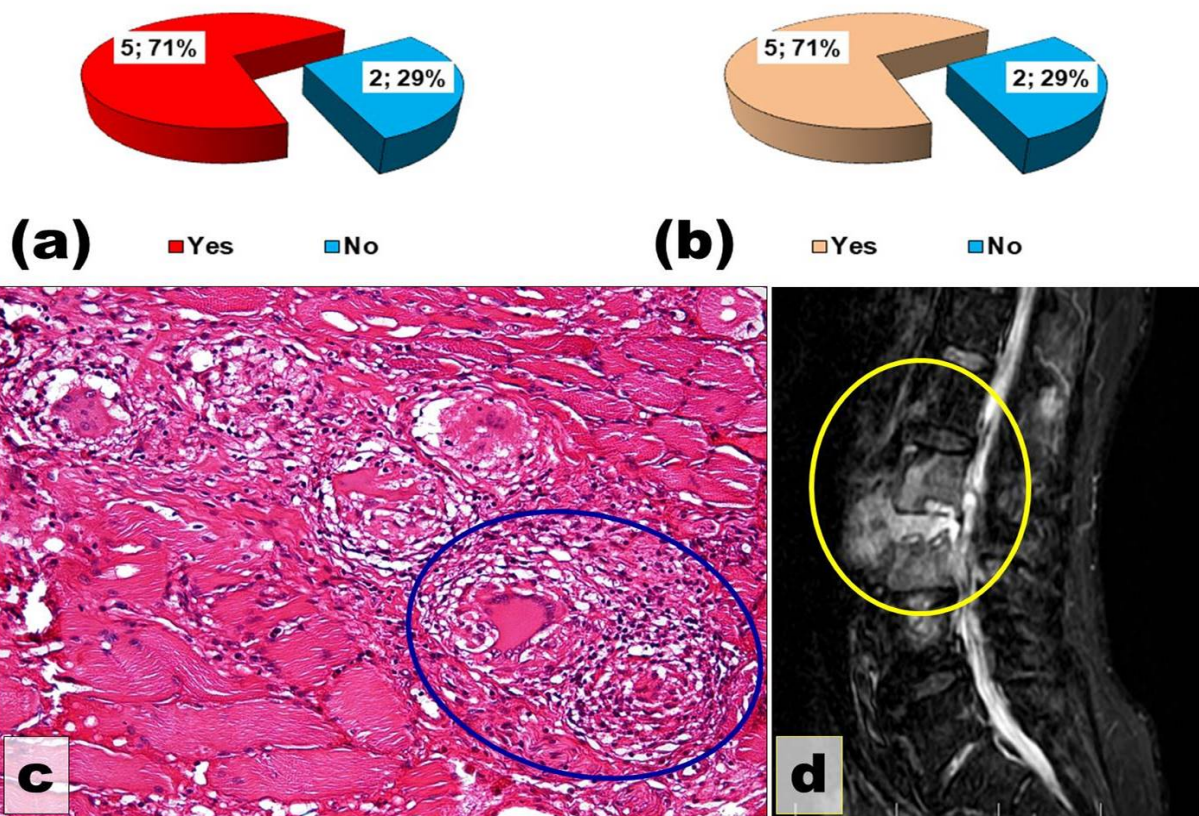


Fig.10. Extraplural extension (a) Muscle involvement. (b) Presence of cold abscesses (c) Giant Langhans cell granuloma in the muscle (darck blue circle) H-E stain, X100; (d) IRM sagittal STIR 1: Anterior cold abscess and L4-L5-S1 arthritis (yellow circle)

Discussions

Clinical data

It is generally accepted, as we mentioned before, that spine involvement represents the largest part, around half of OATB cases [3,11,12,14]. But, as Figure 11 illustrates, the percentage varies in a wide range, depending on series reported [22-32], from more than 80% [22] to less than 40% [31,32].

In this context, our study, with such a reduced number of cases with STB in such a long period of time, is a particular one for two reasons. The first is that, even if the studied period is very large (more than 25 years), the hospital is a general hospital where the Orthopedics and Pediatric Surgery departments are two of the sixteen surgical departments that provided EPTB cases. The second is a particularity of Romanian health care system

that we mentioned in our previous studies on OATB [2,33,34], namely OATB lesions and especially STB lesions are still directed for treatment, including surgical procedures in dedicated hospitals.

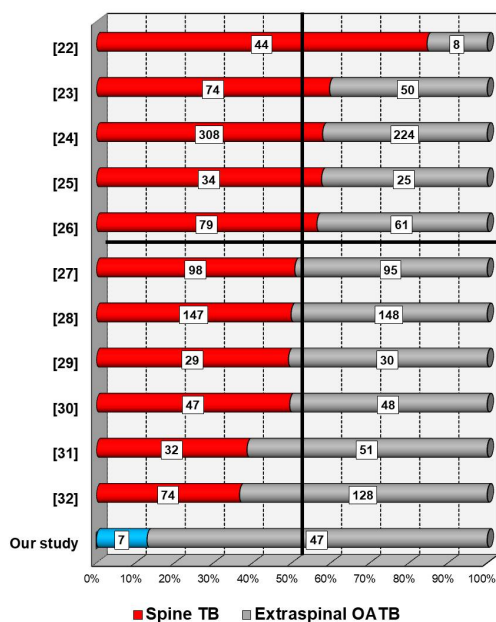


Fig.11. Comparison with other studies of STB presence

Temporal evolution

The evolution of STB cases presence during the large period of time taken into consideration could be explained for the period with lack of cases by the above mentioned particularity of our national health care system, and then by the fact that patients had no history of tuberculosis and, therefore they addressed firstly following their complains to the specialist in bone and joint diseases.

Gender and Age

In our series the males prevailed with TB lesions of the spine.

But if we consider different reports from the literature (Fig.12) we could see that in some studies males prevailed [35-37] in other there was no significant predilection for one of the genders [38,39] and, surprisingly, there are studies where women are more significantly affected by TB in different regions of the spine [40,41].

And these are only few of the numerous reports available. Therefore, we could not allege that in spine involvement, TB has a clear predilection for one of the genders.

We could say the same thing about the patients' age.

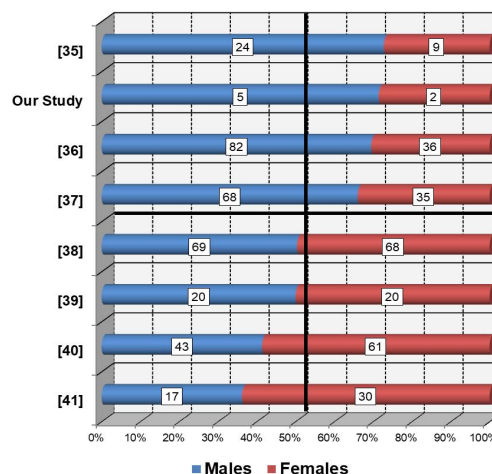


Fig.12. Comparison with other studies of Gender distribution

Figure 13 illustrates clearly that TB infection can involve the spine at any age. From the enormous amount of data we picked again only few reports [39,42-47] where we can see, for instance that the youngest patient was two years old [42,43] and the oldest patient was 92 year old [47]. Also, we can observe that there are series of patients with the mean age placed in the "young adult" period of life [42-44], other series with the age placed in the "mature adult" period of life [39,45,46], and surprisingly, there are series of patients where the mean age is higher than 70 years, in other words, an entire series of old patients [47].

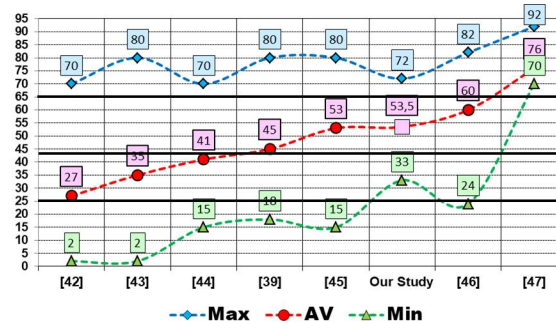


Fig.13. Comparison with other studies of Gender distribution

So, for the age too, we couldn't allege that in spine involvement, TB has a clear predilection for one of the age groups or periods of life.

Morphological data

Lesion site

In the literature it is stated that thoracic and lumbar segments are the most affected spine regions by the Mt infection. Moreover, there is no consensus in defining spine regions.

Some studies use the classical anatomical description of spine regions. Other studies take

into consideration the extension of the lesions to two neighboring anatomical regions and, therefore, introduce in the classification sub regions comprising two neighbor anatomical regions. We have chosen for exemplification the clinical extended classification (Fig. 14).

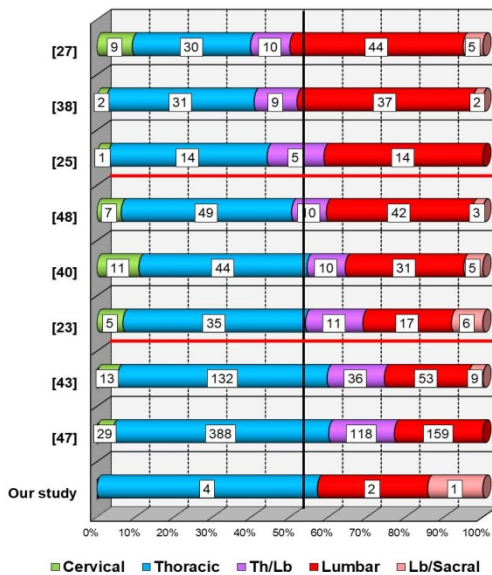


Fig.14. Comparison with other studies of spine segment involvement

Thus, there are studies where lesions placed in the inferior regions of the spine, including here also the border thoracic-lumbar sub region, are prevailing [25,27,38]. At the opposite side,

there are studies where lesions placed in the upper part of the spine are prevailing [43,47]. Our study is included in this last category. Finally, there are studies where there is a balance between the involvement of upper and lower parts of the spine [23,40,48].

So, even in the different spine segments we couldn't talk about a certain tropism of TB infection.

Morphology of the lesions

Except for the paper of Ramanathan et al [20], we didn't find studies in the literature that focused on the analysis of microscopic morphological aspects of TB infection. Therefore, we used for comparison some previous studies of ours focused on other body systems affected by TB like lymph node system, oral cavity structures and, finally the osteoarticular system as a whole [2,33,34,49,50].

Thus, concerning the granuloma cellularity, in all sites, inflammatory cellular population was dominated by epithelioid and giant Langhans cells. Neutrophils were significantly present, in terms of percentage, only in spine lesions (Fig.15a).

In only few cases of other parts of osteoarticular system necrosis was absent. Otherwise, necrosis was a constant presence in TB lesions of the studied body systems.

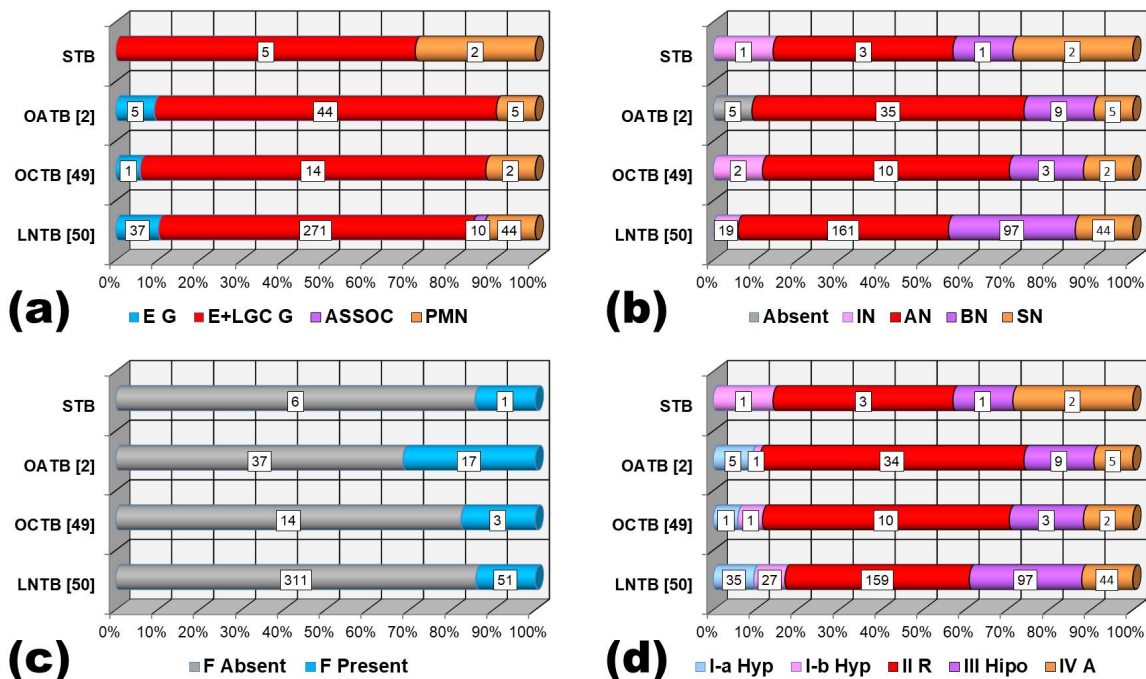


Fig.15. STB lesion morphology-comparison with other studies (a) Specific granuloma cells distribution; (b) Presence and types of necrosis; (c) Presence of Fibrosis; (d) Granuloma types of differentiation

The main aspect of necrotic material was that of acidophilic, fine granular necrosis. However, in lymph node lesions and spine lesions almost half of the cases presented basophilic and purulent necrosis, aspects, suggesting a worse evolution of the inflammatory process (Fig.15b).

The fibrosis, as a sign of repair and healing, was usually absent in all the studied locations, except for the lesions in other parts of the osteoarticular system, where the healing process was present in almost one third of the cases (Fig.15c).

Finally, lymph node lesions and spine lesions presented a significant number of cases, over 40%, with poorly differentiated (grade III) granulomas and disorganized (grade IV) granulomas, suggesting a conflict with worse prognosis (Fig.15d).

Lesions extension

Extension of the lesions in the neighboring tissues and migration of the infection distantly from the initial lesion are events frequently observed in spine lesions, indicating a more severe and late disease stage. From this point of view too, data picked from the literature revealed a wide range of situations. In this respect, we have chosen some studies that were mentioning the presence of cold abscesses (Fig.16).

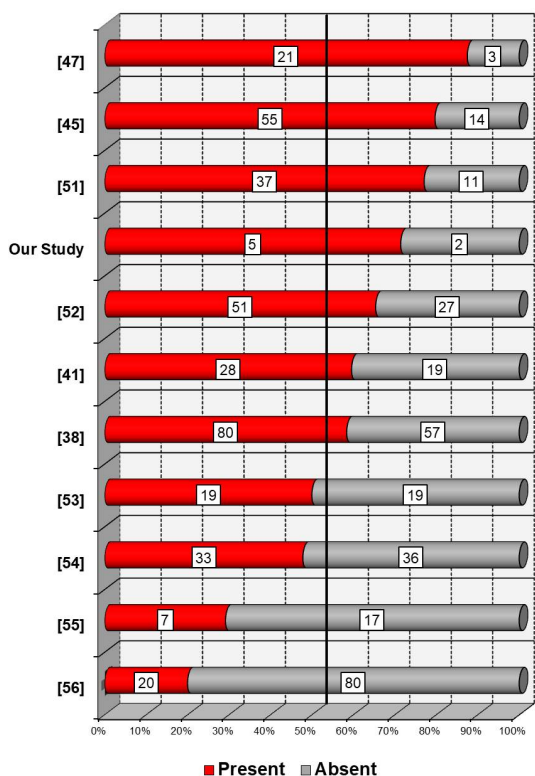


Fig.16. Comparison with other studies of abscess presence

Cold abscesses are considered a frequent complication, but its true incidence is unknown. Many of these studies reported the significant presence of this type of migration of the TB infection, from more than 50% up to more than 80% of the cases [38,41,45,47,51,52].

Other studies found this complication in less than 50% of the cases, going to even less than 20% of the cases [53-56].

In our study, cold abscesses were a significant presence, meaning that our small series gathered together cases in late stages of the disease.

Another sign of severity is the number of vertebrae involved.

In the reports picked from the literature the average number of vertebrae involved varied between “2” and “5” [38,45,51-53,57-59], with an extreme number of 15 vertebrae involved described by Alothman et al [45] (Fig.17).

In our study, the highest number of vertebrae involved was “3” and the average number was “2”.

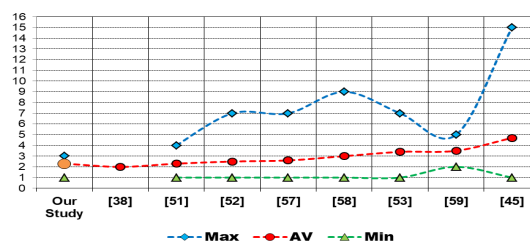


Fig.17. Comparison with other studies of number of vertebrae involved

Conclusions

The “profile” of our small series could be defined as follows: TB spine lesions appeared mainly in adult males, more often in the thoracic region, almost always with the involvement of more than one vertebral body and distant extension. The morphology of granulomatous reactions revealed in the majority of cases active, extending and destructive inflammatory with tendency towards worse evolution and superinfection.

The clinical morphological profile of our series is fitting with data described in the literature. Because of its life threatening potential, spinal TB should be investigated thoroughly especially in its morphological features in order to obtain as quickly as possible an etiological diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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