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The clinical-morphological profile of bone and joints tuberculosis – our experience in relation to literature data

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Abstract

Aim: The authors made a morphological assessment of musculoskeletal 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 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 54 cases coming out of 841 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 despite the tissue involved (either bones or joints or both structures). Bone tissue, lower limb and right side of the body have been more frequently touched by the TB lesions. Axial bones (spine, ribs and hip bone) and knee joint have been the favorite sites. From morphological point of view, the inflammatory cellular population has been dominated by the epithelioid and giant Langhans cells that surrounded areas less or more extended of classical acidophilic fine granular necrosis. The fibrosis was observed more frequently around bone lesions, usually in an incipient phase. Overall, the granulomatous reaction was of reactive type but one should notice hyporeactive or areactive, disorganized reaction encountered quite often in bone or associated bone and joints lesions. *Conclusions*: Osteoarticular tuberculosis (OATB) has a complex and dynamic clinical morphological picture, which is still partly known, described and understood especially in the field of morphological changes. Further detailed and integrative analysis of both clinical and morphological aspects is required so the suspicion of diagnosis at the admission becomes as soon as possible certitude.

Keywords: extrapulmonary tuberculosis, skeletal tuberculosis, bones, joints.

Introduction

Tuberculosis (TB) endemic in animals from the Paleolithic, long before affecting humans, still remains a major universal concern and health problem worldwide at the beginning of the XXIst century, being the second most frequent infectious disease after malaria and the most common cause of death due to an infectious disease worldwide, despite the remarkable progresses realized in the last decades concerning the screening, monitoring and therapeutic strategies [1–6].

There were identified some major factors that are contributing to maintaining this unwanted status of TB of still global problem characterized by the resurgence in developed countries, especially among ethnic minorities [5, 7]:

- Immigration from areas where TB is endemic, having high prevalence;
- Increasing number of elderly either debilitated with other diseases (diabetes mellitus, chronic renal failure, chronic obstructive disease, liver cirrhosis, lymphoproliferative disorders, etc.) or with immunity deterioration due to aging;
- Growing number of immunocompromised patients;
- Emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (Mt);
- Wide range of socioeconomic factors (alcohol and drug abuse, poverty, unemployment, poor nutrition, poor living facilities, homelessness, etc.);
- The HIV epidemic, TB being often the first manifestation of HIV infection.

Extrapulmonary TB (EPTB), defined as any bacteriologically confirmed or clinically diagnosed case of TB involving organs or anatomical sites other than the lungs (pleura, lymph nodes, gastrointestinal tract, genitourinary tract, skin, osteoarticular system, or meninges), and more common in Asian and African countries, follows the same trend as TB in general, with a "revival" in the last decades in developed countries like western European countries and USA, from 7.6% of all TB cases in the 1960s to 20–40% in recent studies and especially also among ethnic minorities, women, blacks, and HIV-positive TB patients [8–13].

Osteoarticular tuberculosis (OATB), known also as bone and joint TB or musculoskeletal TB, even identified in the spine of Egyptian mummies dating back to around 9000 years ago, is considered a rare form of TB, accounting for 1–5% of all TB cases [2, 7, 14–17]. However, the osteoarticular involvement is considered the third most common type of EPTB, after pleural and lymph node TB, accounting for between 10% and 18% of all EPTB cases [15, 18, 19].

Any bone or joint can be the target of mycobacterial infection. Therefore, medical practice identified several entities within the TB osteoarticular involvement, namely [16, 20]:

(*a*) *Spinal TB or spondylitis* – the most common form of OATB, one of the oldest reported diseases in humans and a common manifestation of EPTB representing alone 50% of all cases of osteoarticular involvement [7, 21, 22];

(*b*) *Extraspinal manifestations* – less common [7, 16, 23]:

- Peripheral arthritis – 60%;
- Osteomyelitis – 38% the least common musculoskeletal manifestation of TB [21, 24];
- Tenosynovitis and bursitis – 2%;
- Soft tissue/skeletal muscle involvement – extremely rare.

Although OATB and especially skeletal TB is an important debilitating disease, it still represents a diagnostic and treatment challenge, the condition being often missed. One argument could be the low amount of bacilli in bone and joint lesions, colony counts being 1000 times lower than in pulmonary disease. Another argument would be the lack of information about the disease, statistical data in the literature regarding the incidence and prevalence of OATB being very scarce [25–29].

Taking into consideration these arguments that are still standing for more than two decades, our research group initiated in the 2000s a project focused on all cases with EPTB discovered in our Hospital starting from 1990 in general and on each extrapulmonary location in particular. Partial results concerning osteoarticular involvement were published in 2005 [30] and 2014 [31], this paper being the final report on some main clinical and especially morphological aspects of bone and joint TB lesions admitted in our Hospital and diagnosed in our Department of Pathology between 1990 and 2015.

Materials and Methods

The study group consisted of 54 cases admitted in Surgical Clinics and especially Orthopedic Clinic of the Emergency County Hospital of Craiova, Romania, between 1990 and 2015 and diagnosed in the Departments of Clinical Laboratory and Pathology with TB inflammatory lesions of the osteoarticular system (OAS) structures. The group was part of a larger series of 841 patients proved as presenting tuberculous lesions in the Department of Pathology in the studied period of time.

The studied materials were from the following data sources: (*a*) accompanying notes of tissue specimens coming from operation theaters; (*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 two studies:

[I] Clinical study including: general involvement of OAS; temporal distribution of cases; clinic of origin; gender; age; suspicion of the etiological diagnosis at admission.

[II] Morphological study, focused on:

(*a*) Lesions' location in OAS.

(*b*) Assessment, on routine stained samples, of: granuloma cellularity; presence and type of necrosis; presence of fibrosis; the degree of differentiation of the granulomatous lesions.

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

Besides the original HE slides of each case, serial sections were cut from paraffin blocks and either stained with Ziehl–Neelsen staining for acid-fast bacilli or immunomarked for Mt, in order to confirm the etiology. 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*.

Histopathological aspects were selected with a CX31 Olympus microscope using the ×4 magnification eyepiece. For image acquisition, we used optical planapocromate corrected objectives with magnification of ×4, ×10, ×20 and ×40. The most significant images were acquired using a LiveViewPro II digital camera, saved directly on the computer and processed using the specialized image analysis software 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 temporal evolution, the studied time interval was divided into five-year periods since 1990. For age evaluation, the scales are presented in Table 2.

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 [32] (Table 3).

Table 2 – ***Stratification scale for age***

Age group		Age period	
G1	0–14 years	*P1*	Child (Ch)
G2	15–24 years	*P2*	Adolescent (Ad)
G3	25–34 years	*P3*	Young adult (YA)
G4	35–44 years		
G5	45–54 years	*P4*	Mature adult (MA)
G6	55–64 years		
G7	65–74 years	*P5*	Elderly (Eld)
G8	>75 years		

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 + LGC		
R	G2	II		m EC M L and P	EN 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; EN: Eosinophilic necrosis; IN: Incipient necrosis; i: Immature; LGC: Langhans giant cell; L: lymphocyte; Ma: Macrogranulary; M: Macrophage; m: Mature; Mi: Micro-granulary; NCN: Noncaseous necrosis; P: Plasma cell.

For numerical parameters, the following statistical indicators were calculated: lowest value (VMIN); highest value (VMAX); mean value (AV); standard deviation (STDEV). For graphical representation, VMAX, VMIN, AV + STDEV and AV – STDEV were used. χ^2 (Chi-square) correlation test was used to compare distribution of parameters divided into classes using stratification scales.

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

Results

General involvement of OAS

The first approach of the OAS involvement by TB infection was the separation of cases in groups depending on the type of tissue affected. Thus, the first observation was that in our series the joints alone were slightly more affected than bones, gathering more than one-third of the cases. It is also interesting to point out that almost 30% included patients with lesions involving both bony and articular structures (Figure 1a). This separation depending on the type of tissue involved was used further to compare the behavior of the other studied parameters.

The second approach was to count the lesions encountered in our cases. Thus, we observed that there were patients with multiple lesions of the OAS in the same patient and in the same OAS structure. The distribution of the existing individual lesions revealed a slight predominance of the bony structures involvement either alone or in association with joint involvement (Figure 1b). The explanation is that, in some cases, the TB inflammatory process involved the joint and both bones forming the joint.

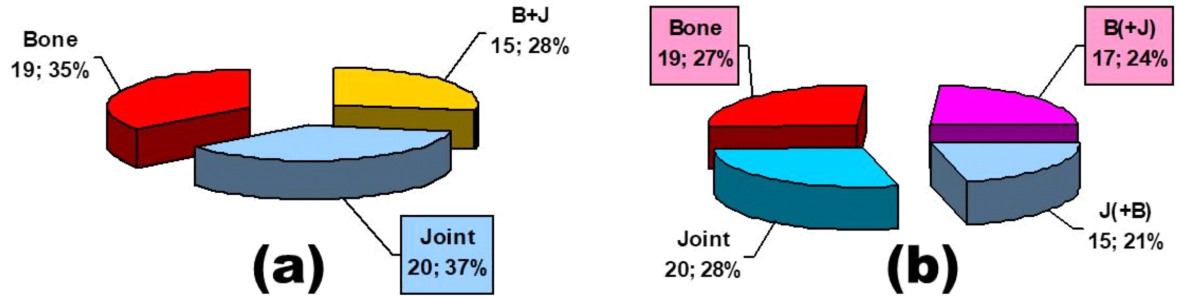

Figure 1 – ***Tissue involvement: (a) Number of cases; (b) Number of individual lesions. B: Bone; J: Joint.***

Clinical data

Temporal evolution

Following in time the evolution of the total number of hospitalized cases, we observed that the incidence decreased in the 2000s until almost half of the values registered at the beginning of or study (the '90s) and then "exploded", showing a doubling as compared with the beginning at the end of the study (Figure 2, black line). However, this spectacular increasing was determined by the rise of the number of patients belonging to the groups of joint lesions and of bone and joint lesions (Figure 2, blue and orange lines).

It is interesting to observe that the number of cases with only bone involvement had a smooth but steady decreasing trend (Figure 2, red line). The different trends of the temporal evolution of cases was validated also statistically (χ^2 correlation test p-value = 0.02 <0.05).

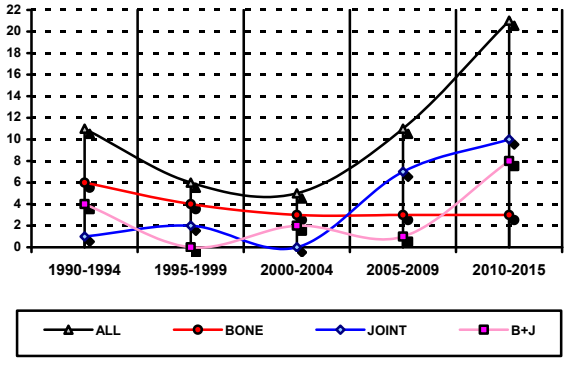

Figure 2 – ***Temporal distribution of cases.***

Gender

TB lesions of OAS were encountered usually in men regardless of whether they were located in the bones or

joints or at both levels (Figure 3). There was, however, a slight difference between the simultaneous involvement of bone and joint and the involvement of joint alone, meaning that the latter was more frequently observed in women but with no statistical significance (χ^2 correlation test p-value = 0.844 >0.05).

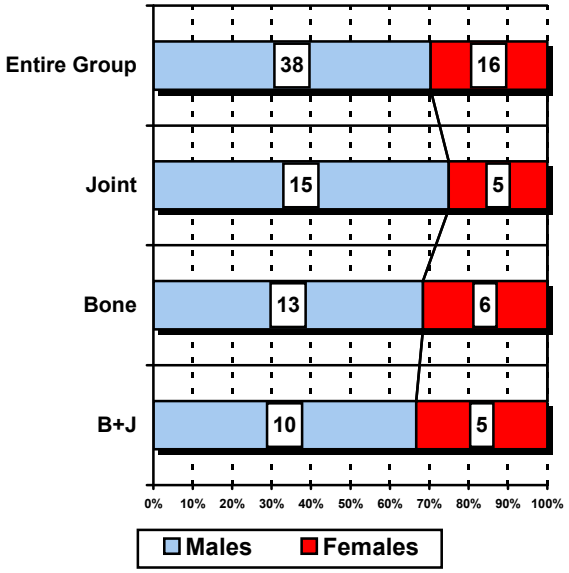

Figure 3 – ***Gender distribution.***

Age

In general, TB lesions of the OAS predominated in adulthood. However, there were some differences of the age distribution between the three groups. Thus, in the group with only bony lesions there was a bimodal distribution: just over 40% of patients were younger than 44 years and just over 30% were elderly (Figure 4).

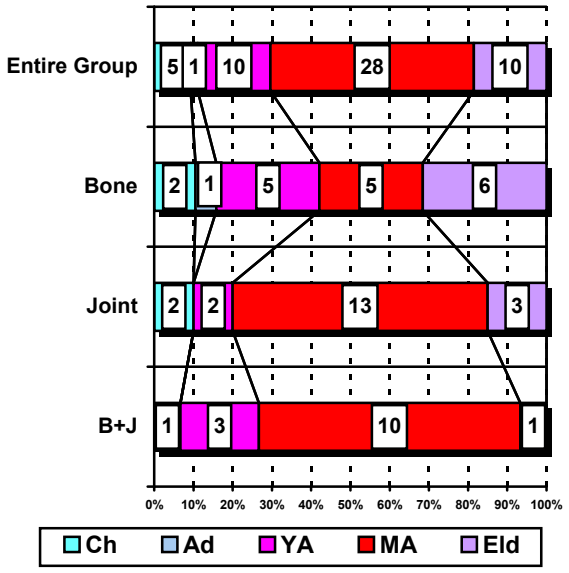

Figure 4 – ***Age distribution depending on patients' periods of life. B: Bone; J: Joint; Ch: Children; Ad: Adolescent; YA: Young adult; MA: Mature adult; Eld: Elderly.***

On the other hand, in the "Bone+Joint" group the majority of patients (more than 70%) were over 44 years of age. Even these differences seem to be evident in the graphic representation (Figure 4), they were not validated from the statistical point of view (χ^2 correlation test p-value = 0.256 >0.05). This could be explained if we look to the mean ages of the three subgroups of patients and to the range of the majority of cases (Figure 5). Thus, patients with joint lesions have the "highest" mean age – 50.5 years – with a relatively large range of the majority of cases (32–70 years) whereas patients with bone lesions are "younger", with a mean age of 47 years and a larger range of the majority of cases (26–69 years).

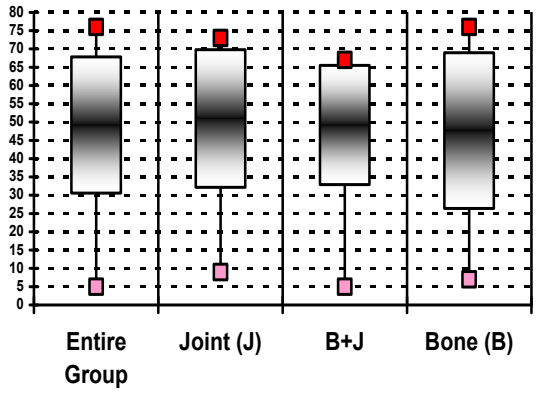

Figure 5 – ***Statistical distribution of ages.***

Clinical suspicion

The clinical suspicion of TB infection at the admission was significant for the entire group, almost reaching 50% (Figure 6a). Although the suspicion was higher in patients with involvement of an articular structure and its neighboring bones than in patients with either bone or joint lesions, this difference had no statistical significance (χ^2 correlation test p-value = 0.548 >0.05). In cases where TB infection was not suspected, the diagnosis ranged from inflammatory process to proliferative process. Here, the difference between different groups was obvious (Figure 6b). Thus, whereas in patients with bony lesions the predominant suspicion was of tumor process, in patients with both bony and articular involvement the suspicion was of an inflammatory process, difference that was validated from statistical point of view (χ^2 correlation test p-value = **0.004** <0.05).

Morphological data

Lesion site

The body segment involvement was practically similar either we took into consideration the number of cases or the number of individual lesions. Thus, the most affected segment of the body was the lower limb, followed by the trunk and the upper limb. There was a single patient (woman, 58 years of age) with a lesion in the head and neck region, *i.e.*, festered chronic TB inflammation of the left mastoid process (Figures 7 and 10).

If we refer to the mediosagittal plane of the body, in both bone individual involvement and joint individual involvement left side of the body was slightly more affected either we took into consideration the number of cases or the number of individual lesions.

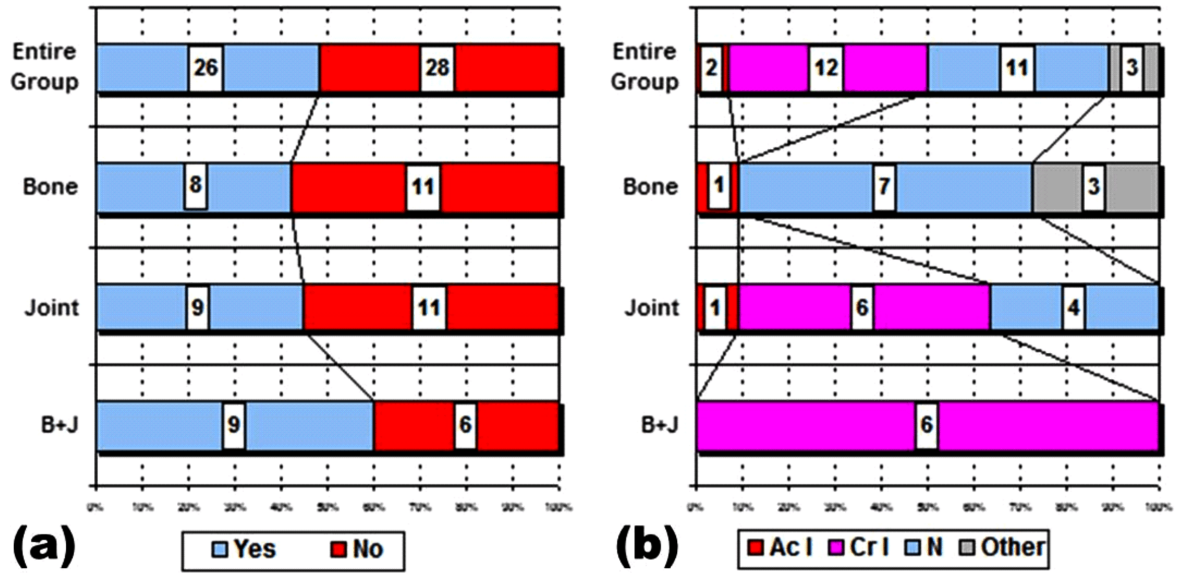

Figure 6 – ***The suspicion of diagnosis: (a) Suspicion of TB; (b) The suspected diagnosis. TB: Tuberculosis; B: Bone; J: Joint; Ac I: Acute inflammation; Cr I: Chronic inflammation; N: Neoplasia.***

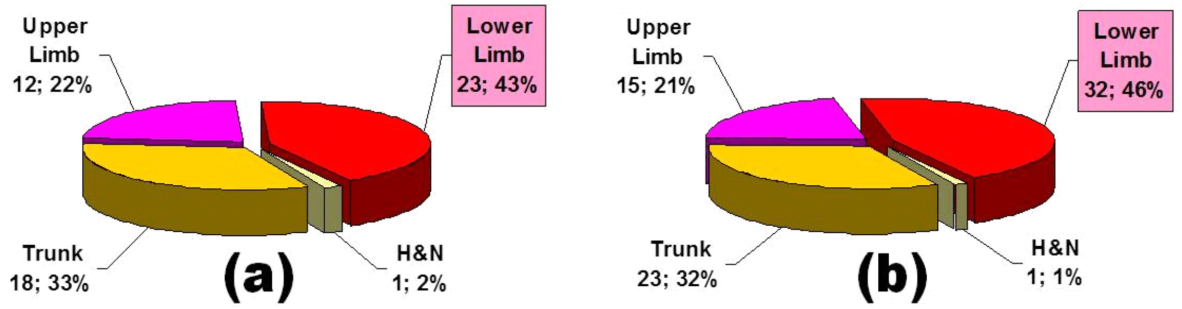

Figure 7 – ***Body segments involvement: (a) Number of cases; (b) Number of individual lesions. H & N: Head and neck.***

The distribution of TB lesions in each segment of the body depending on the mediosagittal revealed some differences. Thus, whereas almost two-thirds of the lesions belonging to the lower limb were found on the left side, more than one-half of the lesions of the upper limb were found on the right side plane (Figures 8b and 10).

The analysis of tissue involvement showed that, especially when we take into consideration the individual lesions, each of the two main tissues were affected in more than 70% of the encountered lesions. Bones and joints were simultaneously involved in 45% of the lesions.

The analysis of tissue involvement depending on the body segments revealed some differences between the body segments, more obvious when we took into consideration the individual lesions (Figures 9a, 9b and 10) and validated statistically (χ^2 correlation test p-value <**0.0001** in both situations).

Thus, in the trunk, clearly predominated the bony lesions, more frequently alone but also associated with lesions of the articular structures joining the affected osseous structures. In turn, in the upper limb, especially if we take into consideration the individual lesions and not the cases, the joint involvement was present in almost three quarters of the studied lesions, more frequently alone than associated with bony lesions. In all cases, the bones affected were those neighboring to the involved joint (Figures 9 and 10). In the lower limb, the distribution was more obvious than in the upper limb. Thus, the joint involvement at the level of individual lesions represented slightly over 90%. This time, joint lesions were more frequently associated with lesions extended to or coming from the neighboring bones (Figures 9 and 10).

The analysis of individual bone involvement revealed that the most affected bones were the ribs. In all cases, the lesions were limited to the osseous structures, without extension to the neighboring joins (Figures 10 and 11a).

The next most affected bone was the body of the spinal vertebrae. In contrast to the ribs, the TB process involved in the majority of cases the intervertebral space and articular structures. TB process affected then, in the same number of cases, the bone of the pelvic belt and the main long bones of the lower limb (femoral and tibial bones). There was, however a difference, meaning that whereas the coxal bone was usually involved alone, the lower limb bones were most often affected in association with at least one of their neighboring joints.

From the upper limb, the radius was the most involved bone, usually without concomitant involvement of the neighboring joints. Other bones, like ulnar bone, fibular bone or tarsal bones had TB lesions only in rare, individual cases (Figure 10).

The analysis of individual joint involvement revealed

that the most affected joint was by far the knee joint (Figures 10 and 11b). In half of the cases, the lesions were limited only to the articular structures, without extension to the neighboring bones. The next joints in order of frequency were the intervertebral joints that presented more often extension of the lesion to the neighboring vertebral bodies.

The following joint, as frequency, was the hip, the second main weight-bearing joint. It was usually involved alone, without extension to the neighboring bones. Finally, the joints with at least two cases involved were the wrist joint and the foot joint both having lesions restricted to the articular structures.

Other joints, like pubic symphysis, elbow joint, radial-ulnar joint or tibial-fibular joint had TB lesions only in rare, individual cases and always extended to/from neighboring bony lesions (Figure 10).

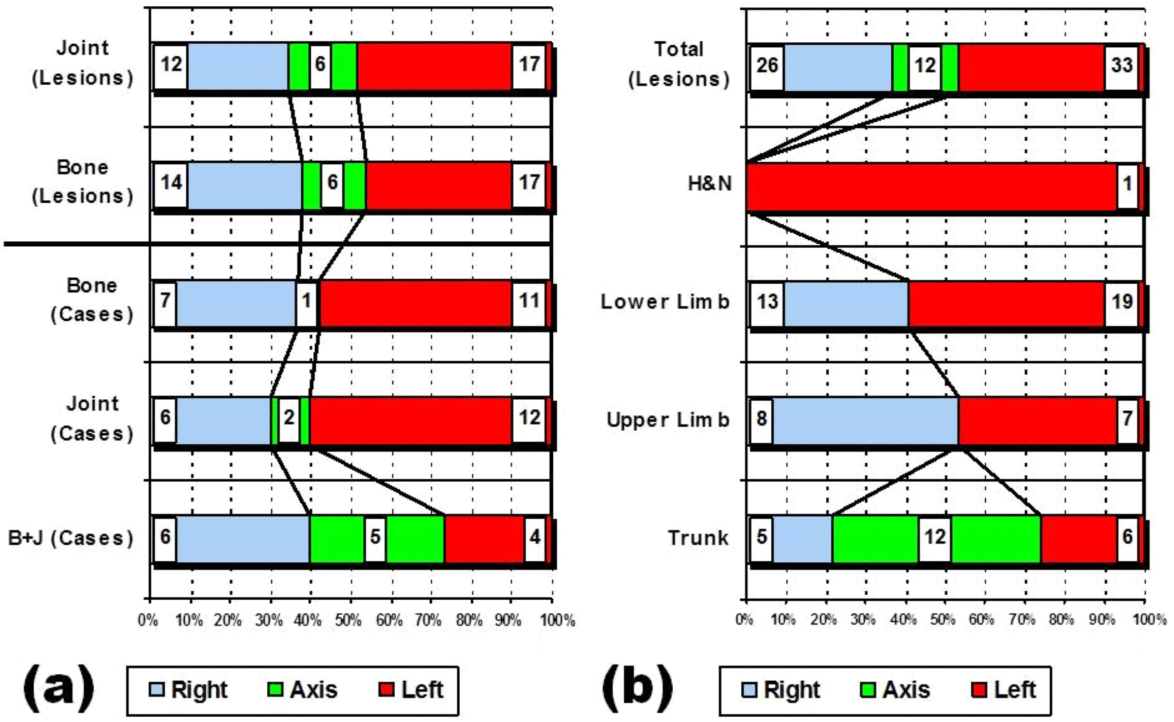

Figure 8 – ***The distribution of body side involvement: (a) Tissue distribution; (b) Body segment distribution. B: Bone; J; Joint; H & N: Head and neck.***

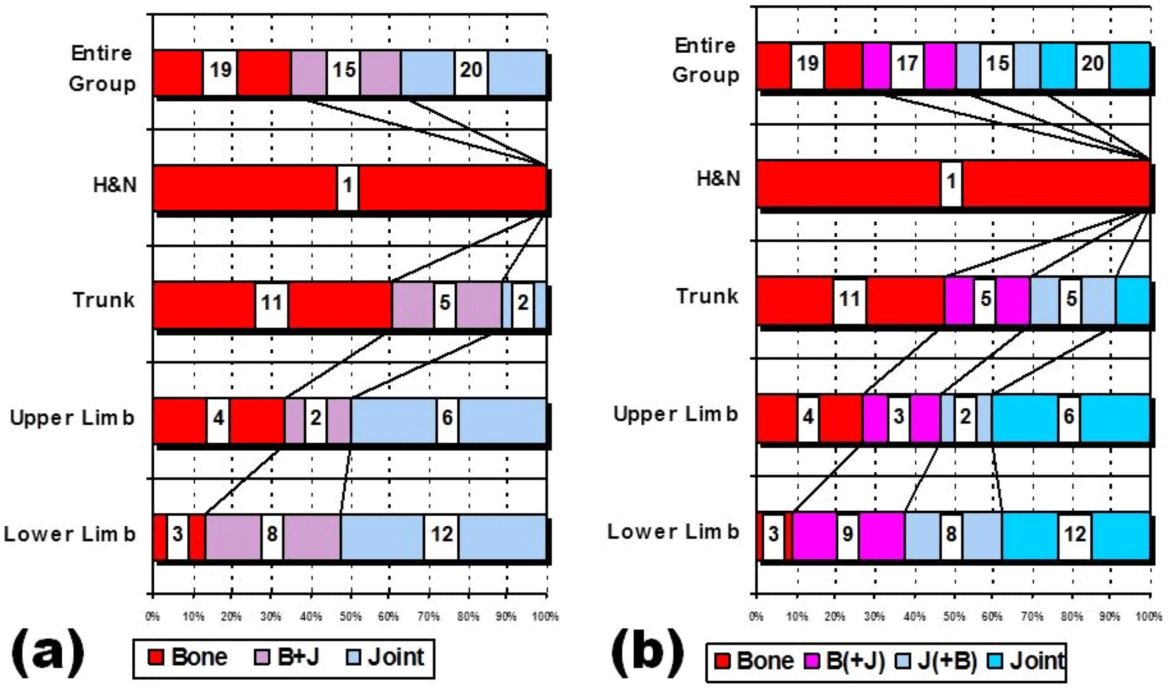

Figure 9 – ***The distribution of cases (a) and lesions (b) on body segments depending on tissue involvement. B: Bone; J; Joint; H & N: Head and neck.***

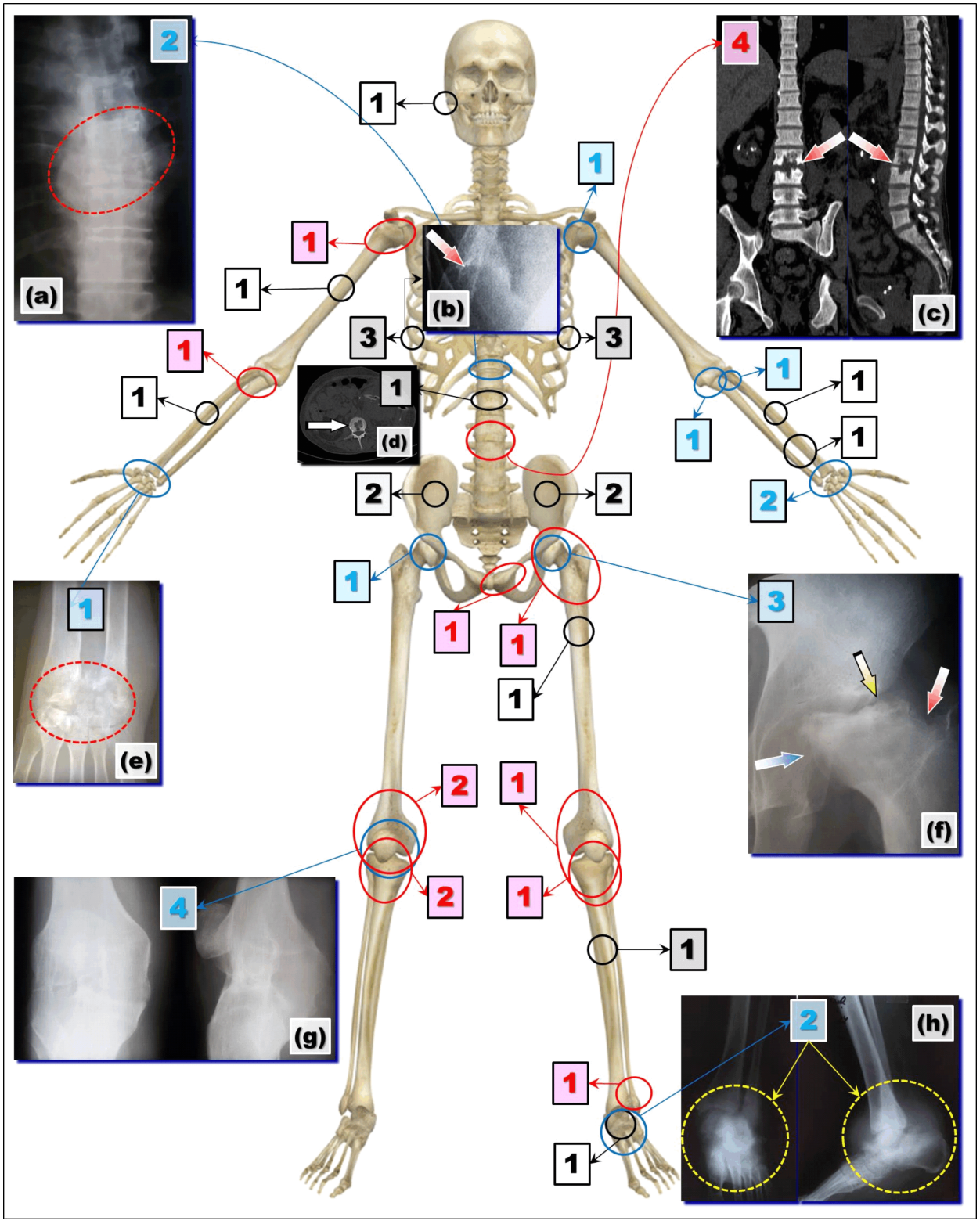

Figure 10 – ***Lesions location: Numbers in squares – number of cases (black – bone lesions; blue – Joint lesions; red – bone and joint lesions); (a) Thoracic spine X-ray: red circle – collapse of the T5 and T6 with paravertebral abscess; (b) Chest X-ray: lytic lesion of the rib (red arrow) associated with chest wall collection; (c) MRI STIR2: "mirror" vertebral caries with dissolution of intervertebral disc (red arrows); (d) CT axial: L2 vertebral body lesion; (e) Wrist X-ray: extensive osteolysis of the carpal bones, distal radial and cubital epiphyses; (f) Left hip X-ray: flattening of the femoral head with extensive epiphyseal osteolysis (red arrow), decrease of the articular space (yellow arrow) and subluxation (blue arrow); (g) Knee X-ray (antero-posterior and lateral view): articular surface destruction and joint space narrowing; (h) Swelling of ankle joint. MRI: Magnetic resonance imaging; STIR: Short tau inversion recovery; CT: Computed tomography.***

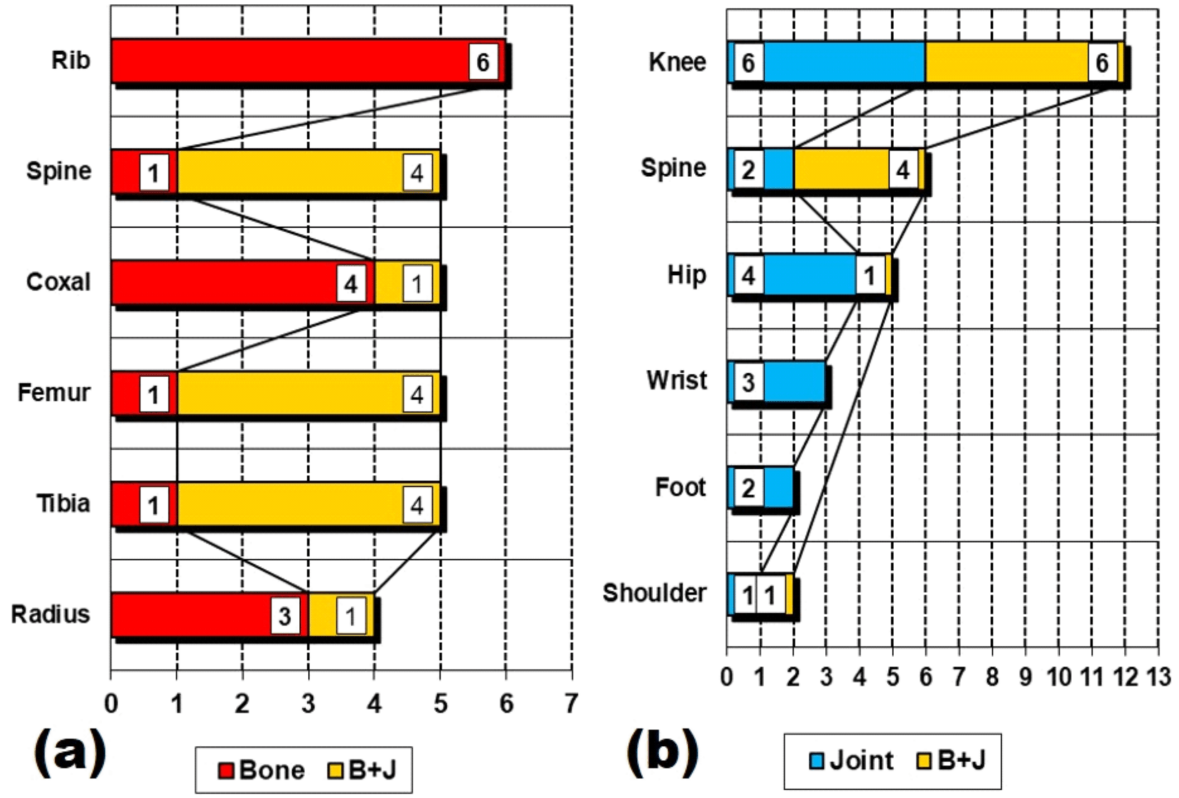

Figure 11 – ***Tissue involvement: (a) Bone (B) involvement; (b) Joint (J) involvement.***

Granuloma cellularity

The great majority of cases presented inflammatory granulomatous reaction with a cell population clearly dominated by mononuclear macrophages of epithelioid (E) type together with multinucleated giant Langhans cells (GLCs) (Figures 12a and 13b). Granulomas with either only epithelioid cells or with the significant presence of polymorphonuclear neutrophils (PMNs) were observed in less than 20% together (Figures 12a, 13a and 13c).

"Pure" epithelioid granulomas were present with a higher frequency (20% of cases) in the group of patients with only joint involvement whereas granulomas with significant number of PMNs were encountered in 10% or less than 10% in all three groups (Figure 12a).

The predominance of granulomas with GLCs in all groups of patients was also statistically confirmed (χ^2 correlation test p-value = 0.291 >0.05).

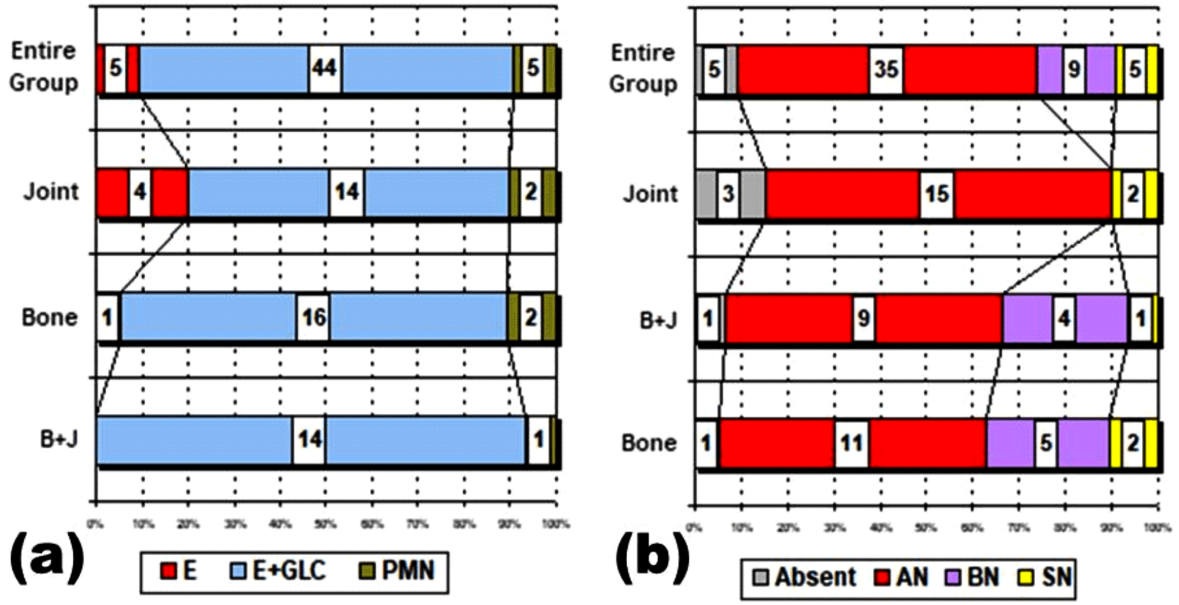

Figure 12 – ***Morphology of TB granulomas: (a) Granuloma cellularity; (b) Types of necrosis. TB: Tuberculosis; B: Bone; J: Joint; E: Epithelioid; GLC: Giant Langhans cell; PMN: Polymorphonuclear neutrophil; AN: Acidophilic necrosis; BN: Basophilic necrosis; SN: Suppurative necrosis.***

Presence and type of necrosis

Tissue destruction, expressed by the presence of necrosis, was a constant component of the inflammatory conflict between Mt and the different tissue structures of the OAS. The most frequently encountered aspect of necrosis was the classical one, intense acidophilic and fine granular (AN) (Figures 12b and 14b).

However, there were some slight but significant differences regarding the morphological appearance of necrosis. Thus, in "joint lesions" group, three quarters of the cases presented the above-described classical aspect. In some of these cases, the necrotic destruction was at the beginning (Figure 14a). Besides this, the group had the highest percentage of cases with no necrosis (15% of all cases). There were also two cases (representing 10%) where the classical aspect of necrotic material was modified by the significant appearance of PMNs. In the other groups, the absence of necrosis or the suppurative transformation (SN) appeared in isolated cases but the AN was replaced in more than one quarter of the cases by coarse granular, basophilic necrosis (BN) (Figures 12b and 14c). However, these differences had no statistical significance (χ^2 correlation test p-value = 0.311 >0.05).

Presence of fibrosis

The fibrosis, considered as a healing process, was absent in more than two-thirds of all cases. However, the percentage of its presence varied from group to group, being encountered in more than 40% of cases in the "Bony" group but significantly less frequent (*i.e.*, 20% of the cases) in the "Joint" group (Figure 15). However, these differences were not validated statistically (χ^2 correlation test p-value = 0.326 >0.05).

Granuloma differentiation

Finally, we assessed the degree of differentiation of the granulomatous reaction, putting together all morphological features of the TB lesions and using Ramanathan *et al.* [32] modified system. The results (Figures 16 and 17) almost overlapped those obtained at the necrosis assessment.

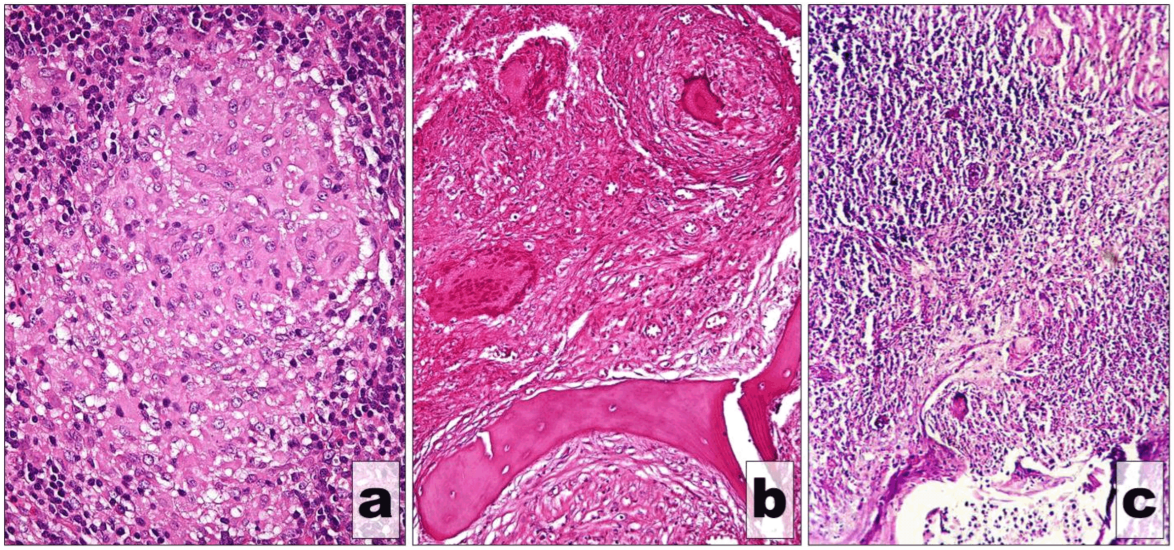

Figure 13 – ***Granuloma cellularity: (a) Epithelioid granuloma in synovial tissue; (b) Giant Langhans cell granuloma in bone tissue; (c) Granulomas with giant Langhans cells and neutrophils. HE staining: (a) ×200; (b and c) ×100.***

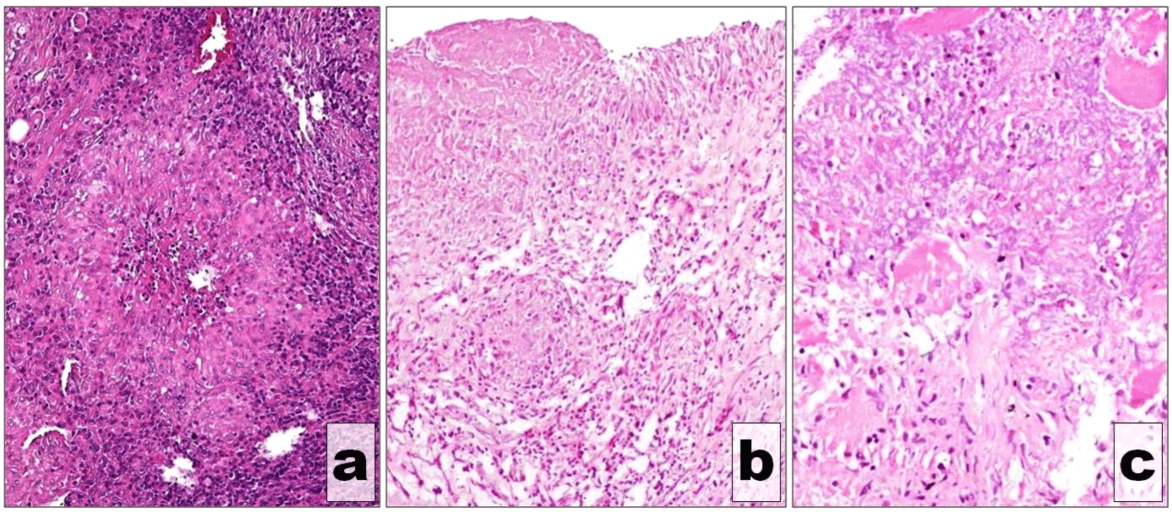

Figure 14 – ***Types of necrosis: (a) Granuloma with incipient acidophilic fine granular necrosis in synovial tissue; (b) Acidophilic fine granular necrosis (top left) of the synovial epithelium (top right) and underlying tissue; (c) Basophilic coarse granular necrosis extended in the muscular tissue (top right) and bordered by Langhans cell granulomas (bottom left). HE staining: (a–c) ×100.***

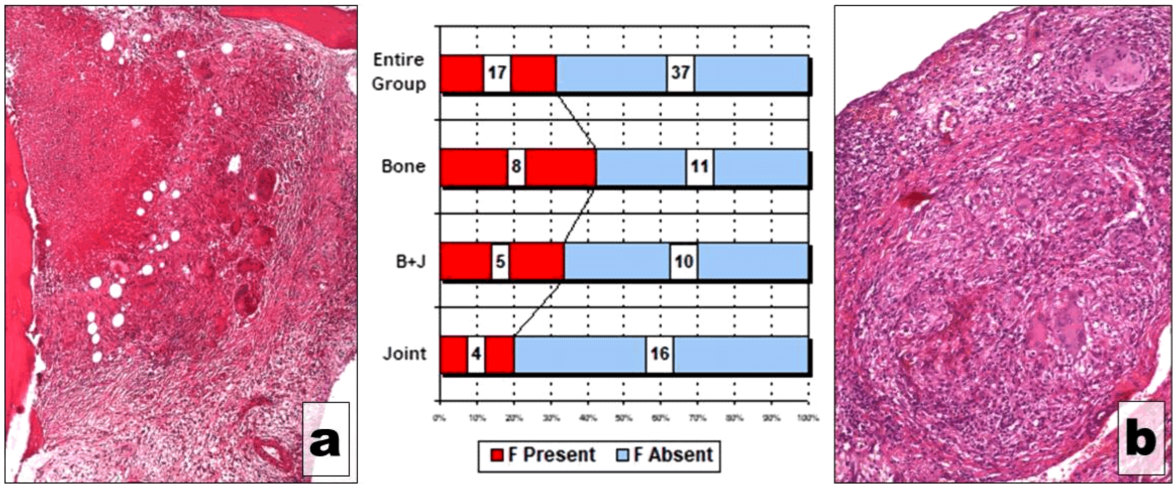

Figure 15 – ***Presence of fibrosis: (a) Bony granuloma with acidophilic surrounded by E and GLCs and a rim of fibroblasts; (b) Group of E and GLC granulomas in the synovial tissue surrounded by fibroblasts and collagen fibers. HE staining: (a and b) ×100. B: Bone; J: Joint; E: Epithelioid; GLC: Giant Langhans cell.***

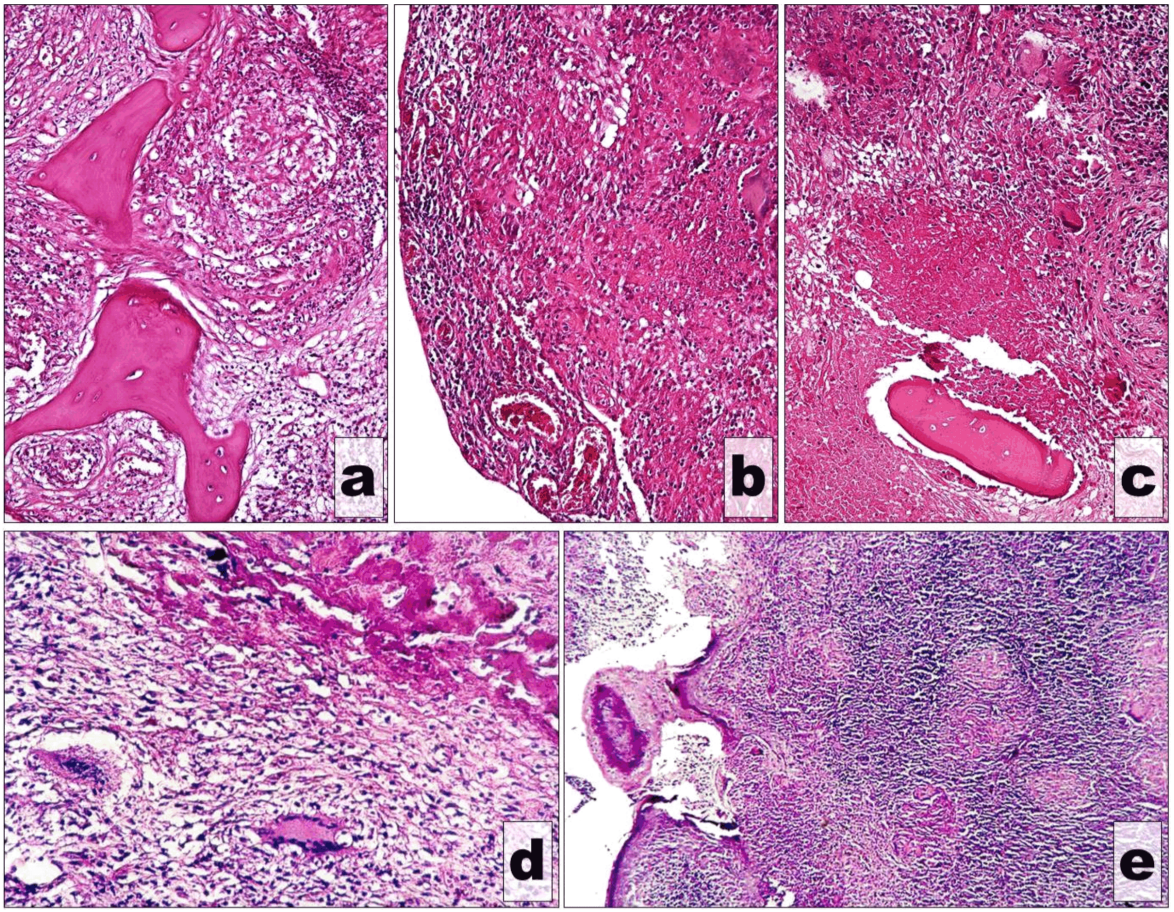

Figure 16 – ***Granuloma differentiation: (a) Type Ia – Hyperplastic granuloma in the bony tissue; (b) Type Ib – Hyperplastic granuloma in the synovial tissue; (c) Type II – Reactive granuloma in the bony tissue; (d) Type III – Hyporeactive (poor differentiated) granuloma; (e) Type IV – Areactive (disorganized) granuloma. HE staining: (a–c) ×100; (d) ×200; (e) ×40.***

We found all types of degrees of granuloma differentiation although the one who dominated in general and in all three groups was the type II Reactive granuloma, with acidophilic fine granular necrosis and GLCs (Figure 16c). In all four cases from "Joint" group and the only one case from "Bone" group with hyperplastic granulomas, these were of subtype "Ia" with no necrosis and containing only epithelioid cells. The only one case with hyperplastic granulomas had subtype "Ib" granulomas, with incipient necrosis and GLCs. In "Joint" group, there were no cases with hyporeactive granulomas, these types of granulomas being encountered. In turn, in the other two groups in more than 20% of the cases. The areactive granulomas, with the appearance of PMNs as a marker of the superinfection, were found in isolate cases in all groups.

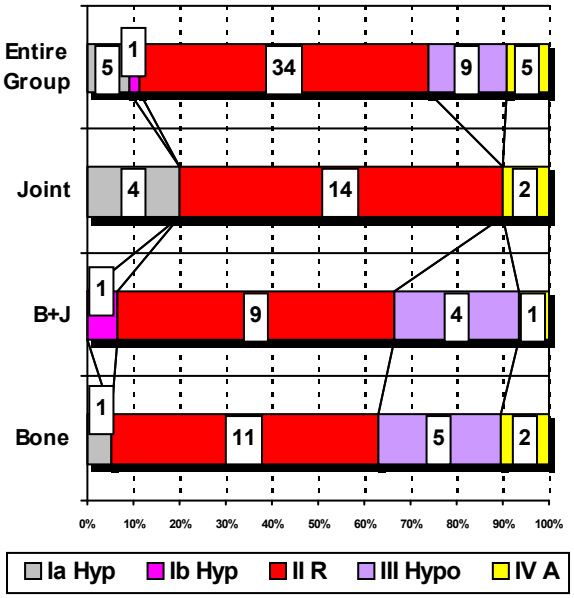

Figure 17 – ***Degree of granuloma differentiation. B: Bone; J: Joint; Hyp: Hyperplastic; R: Reactive; Hypo: Hyporeactive; A: Areactive.***

These small differences between the three groups in the range of different types of granulomatous reactions had however no statistical significance (χ^2 correlation test p-value = 0.130 >0.05).

Lesions extension

We considered as extensions of the TB lesions the spread of the infection outside the OAS structures in the neighboring soft tissues, skeletal muscles and even further towards the integument. This extension was not so frequent, being observed in slightly more than 20% of the cases (Figure 18).

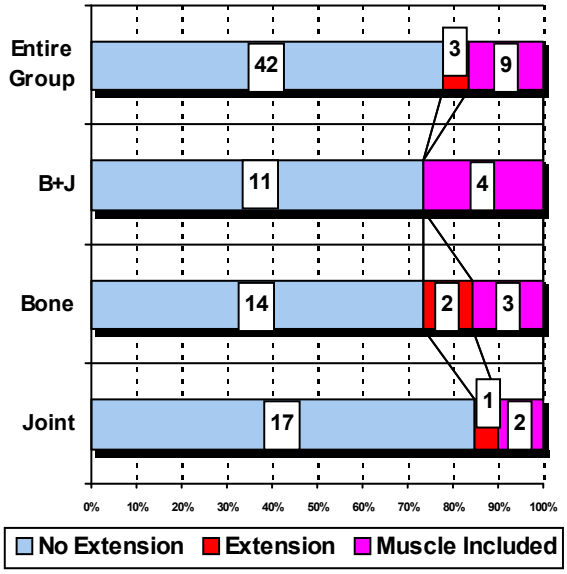

Figure 18 – ***TB lesions extension. B: Bone; J: Joint.***

Muscle involvement

In three quarters of these cases (*i.e.*, nine cases), the TB inflammatory process extended to the muscles placed around the affected osteoarticular tissue (Figure 19).

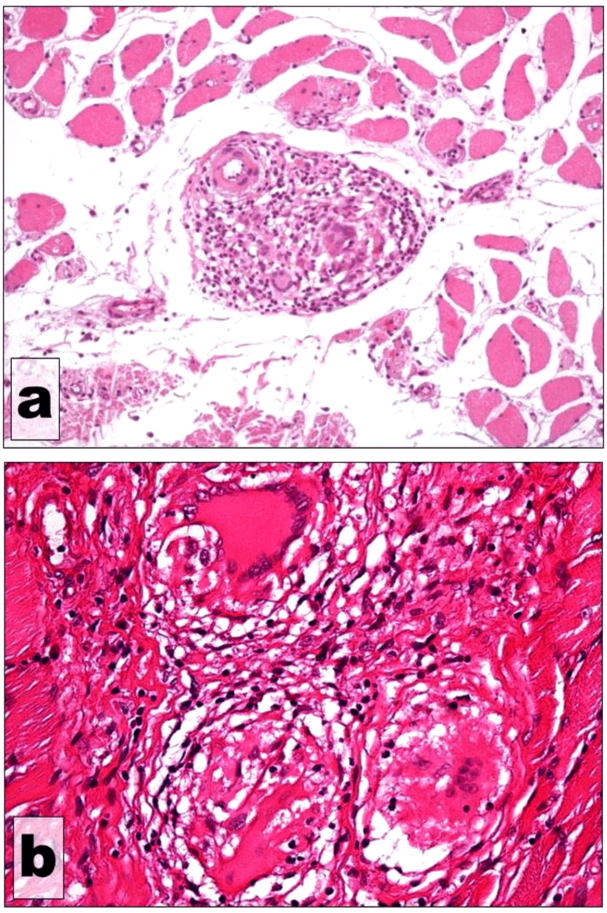

Figure 19 – ***Muscular involvement: (a) Perivascular granuloma with Langhans cells; (b) Confluent giant cells granulomas between striated muscle fibers. HE staining: (a) ×40; (b) ×400.***

In the "Bone and Joint" group, the extension involved the neighboring muscles in all four cases, in one of them being affected in addition two regional lymph nodes – male, 55 years old, T6–T8 osteomyelitis and arthritis with accompanying cold abscess).

Cold abscesses

Another way of extension was the formation of cold abscesses in the soft tissues around the osteoarticular lesions. There were six such pus formations. Five of these cases belonged to the "Bone and Joint" group and the primary TB lesion was placed in the spine, in two of them in thoracic spine and in three of them in the lumbar spine (Figure 20).

In one of these cases (male, 56 years old, with L4–L5 Pott's disease complicated with spastic paraparesis) the pus collection was bilateral. In the sixth case (female, 44 years old) the cold abscess appeared in the left chest region, the initial TB lesion being rib osteomyelitis.

Sinus formation

In three cases, two belonging to "Bone" group and one belonging to "Bone and Joint" group, blind tracks lined by granulation tissue formed leading from the TB lesion to the epithelial surface. The primary TB lesions were placed in the rib, knee joint and neighboring bones and in the coxal bone (ischion).

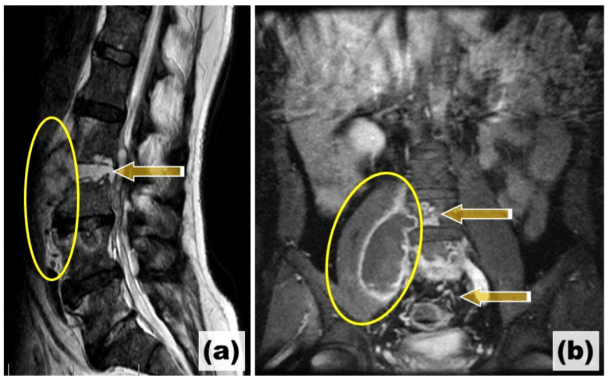

Figure 20 – ***Cold abscesses: (a) Anterior cold abscess (yellow circle); L2–L3–L4 arthritis (arrow). MRI STIR2 sagittal; (b) Right paravertebral abscess (yellow circle). L4 osteomyelitis and L5–S1 arthritis. MRI STIR1 frontal. MRI: Magnetic resonance imaging; STIR: Short tau inversion recovery.***

Identification

The classical morphological examination, coupled with clinical examination led to the diagnosis of TB. However, in almost one quarter of the cases, the morphological investigation needed additional investigations like Ziehl–Neelsen staining or immunohistochemistry (IHC) for Mt in order to establish the etiology. There were some differences between the groups meaning that the need for confirmation was significant in the "Bone and Joint" group (40% of the cases), whereas in "Bone" group only one patient needed further morphological investigation to confirm the presence of Mt (Figures 21 and 22).

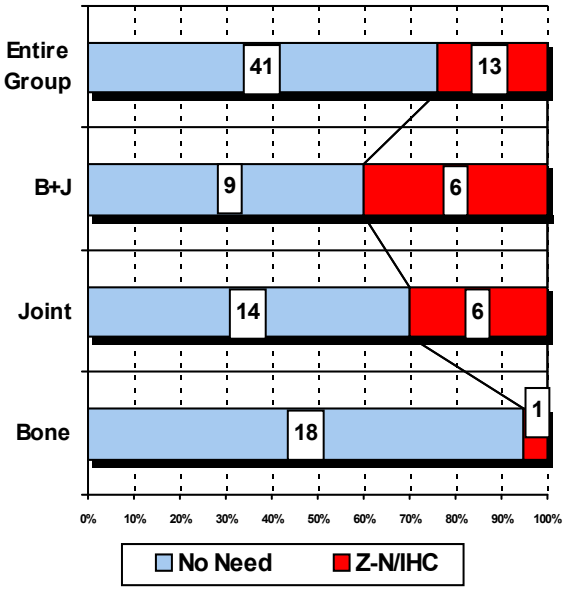

Figure 21 – ***Identification of Mt. Mt: Mycobacterium tuberculosis; B: Bone; J: Joint; Z-N: Ziehl–Neelsen staining; IHC: Immunohistochemistry.***

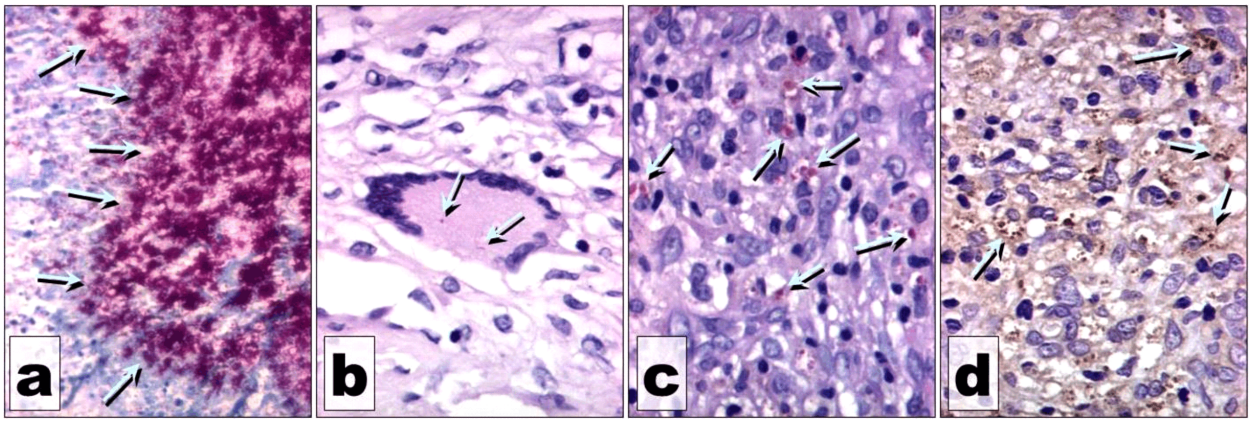

Figure 22 – ***Mt identification: (a) Extensive necrosis in synovial tissue with lot of Mt (blue arrows); (b) Giant Langhans cell with two Mt (blue arrows); (c) Atypical granulomatous reaction with Mt inside macrophages; (d) Atypical granulomatous reaction with Mt inside macrophages (Immunomarking for Mt, ×40). Mt: Mycobacterium tuberculosis. Ziehl–Neelsen staining: (a) ×200; (b and c) ×400.***

Situations that led to the use of additional staining were: too large regions with tissue destruction and necrosis, atypical granulomatous reactions as poorly differentiated (hyporeactive) or disorganized granulomas or "young" granulomas with no necrosis.

Discussion

General involvement of OAS

Excepting one study which referred to the situation of EPTB in the European Union (EU) and mentioned also the OATB [33], no other official paper of *World Health Organization* (WHO) contained data on OATB incidence neither as part of TB infection or as part of extrapulmonary sites of TB. There was a great variability concerning the size of the studied group, the size of the studied period of time, and even the geographical extension of the study in all the papers consulted, which make the comparative analysis very difficult (Figure 23). In Figure 23, blue rectangle covers data from papers published in Europe, pink rectangle covers data from papers published in Americas, yellow rectangle covers data from papers published in Asia, light green rectangle covers data from papers published in Australia and orange rectangle covers data from papers published in Africa.

However, most of the studies were national; some of them were regional, one of which referring only to the children population (Figure 23 – [6]R*) and fewer were series registered in hospitals, among the latter being also our study. The variation of OATB among the EPTB cases was very wide. It ranged between 0.3% in national study in Qatar [49] and 20.6% in Estonia [40]. In Europe, the

mean percentage calculated during a 10 years period was low – 5.8% [33] but the variation among different countries was wide (Figure 23, blue rectangle). Studies from Spain reported the lowest values [34, 35] and, besides the 10 years Estonian study, national studies from Denmark [38] and England & Wales [39] reported high values (15% and 16% respectively).

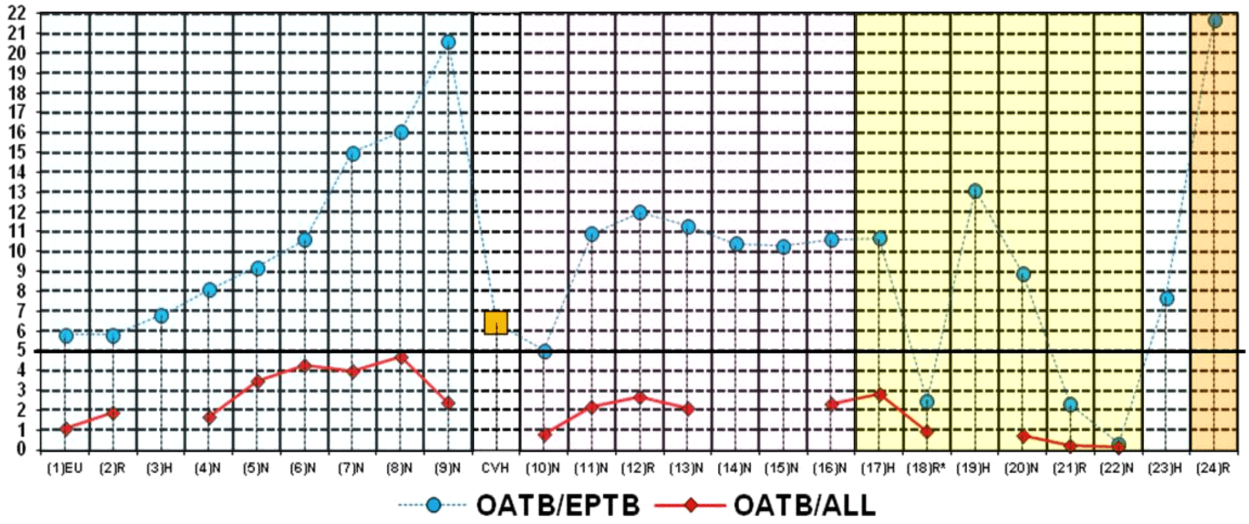

Figure 23 – ***Comparison with other studies of OATB incidence among EPTB cases and all TB cases: (1): [33]; (2): [34]; (3): [35]; (4): [36]; (5): [37]; (6): [8]; (7): [38]; (8): [39]; (9): [40]; (10): [41]; (11): [42]; (12): [43]; (13): [10]; (14): [44]; (15): [45]; (16): [46]; (17): [11]; (18): [6]; (19): [19]; (20): [47]; (21): [48]; (22): [49]; (23): [50]; (24): [51]. Small orange square: Our study (CVH); EU: European Union; H: Hospital; N: National; R: Regional; TB: Tuberculosis; OATB: Osteoarticular tuberculosis; EPTB: Extrapulmonary tuberculosis.***

From the Americas region, there were only one national study from Brazil [41], which reported a low incidence of OATB among EPTB cases (5%) and another national study from Canada [46], which reported an incidence of 10.6%. All the other studies came from USA, and had an incidence value ranging between 10.1% and 12% [10, 42–45]. In Asia region, the variation was wide as in Europe but with lower limits of the range (0.3% in Qatar [49] and 13.1% in South Korea [19]). As compared with Europe region, most of the studies were regional or concerning hospital series. There was only one study from Africa region, we found with references to OATB incidence among EPTB cases. It was a regional study from Togo [51] and it reported the highest incidence among the consulted data (21.7%).

The incidence of OATB in our study (to mention: a hospital but widely extended in time study – 26 years) was placed in the inferior region of the range, around the European mean incidence [33] and the incidence values reported in Spain [34, 35].

The OATB incidence of all TB cases was significantly lower and with more narrow boundaries of variation (Figure 23). It was not reported in all consulted studies and an interesting observation was that European studies from developed countries [8, 38, 39] reported the highest values (between 10.6% and 16%).

Clinical data

Temporal evolution

The comparison of temporal evolution trend was also a difficult task because there were only four studies among those we could consult that mentioned the evolution in time of OATB cases. All these studies only partially overlapped over the period of time we have studied. Two of them, a Dutch study [8] and an Estonian study [40], both national, concurred with the first half of our period of time; a third regional study from India [52] concurred with the interval 2005–2011 of our study and finally, the fourth study concerning a regional Spanish series covered the period of time between 1991 and 2008 (Figure 24). Taking into consideration that our series had a descending trend from 1991 to 2000 and an ascending trend from 2001 until the end – 2015 (Figure 2), our data had a similar decreasing trend with the Estonian study [40] and increasing trend with the Indian study [52] and contrary trends with the Dutch study [8] (decreasing *vs.* increasing) and with the Spanish study. In the latter, the trend was slightly ascending in the first part of the time interval and decreasing in the second part whereas in our study the trend was slightly decreasing in the first part of the overlapping interval and increasing in the second part (Figure 24).

Gender

Male/female ratio was another parameter with a wide range of variation from one world region to another and even inside of the same region (Figure 25). This time we tried to select for comparison, with few exceptions, studies with significant number of patients in the presented series. In Figure 25, blue rectangle covers data from papers published in Europe, pink rectangle covers data from papers published in India, light green rectangle covers data from papers published in Asia, yellow rectangle covers data from papers published in Korea, and orange rectangle covers data from papers published in Africa.

In all world regions, there were studies reporting more women affected than men [19, 29, 37, 39, 61] but in the majority of studies, the M/F ratio was in favor of men

(Figure 25). Excepting an Iranian study [48], on a very small series (only 10 cases), the value of M/F ratio ranged between 1.12 and 2.27. Our series was close to the upper limit of this range with a value of 2.37 (Figure 25). Therefore, we could speak about a variable but obvious propensity of OATB lesions for males.

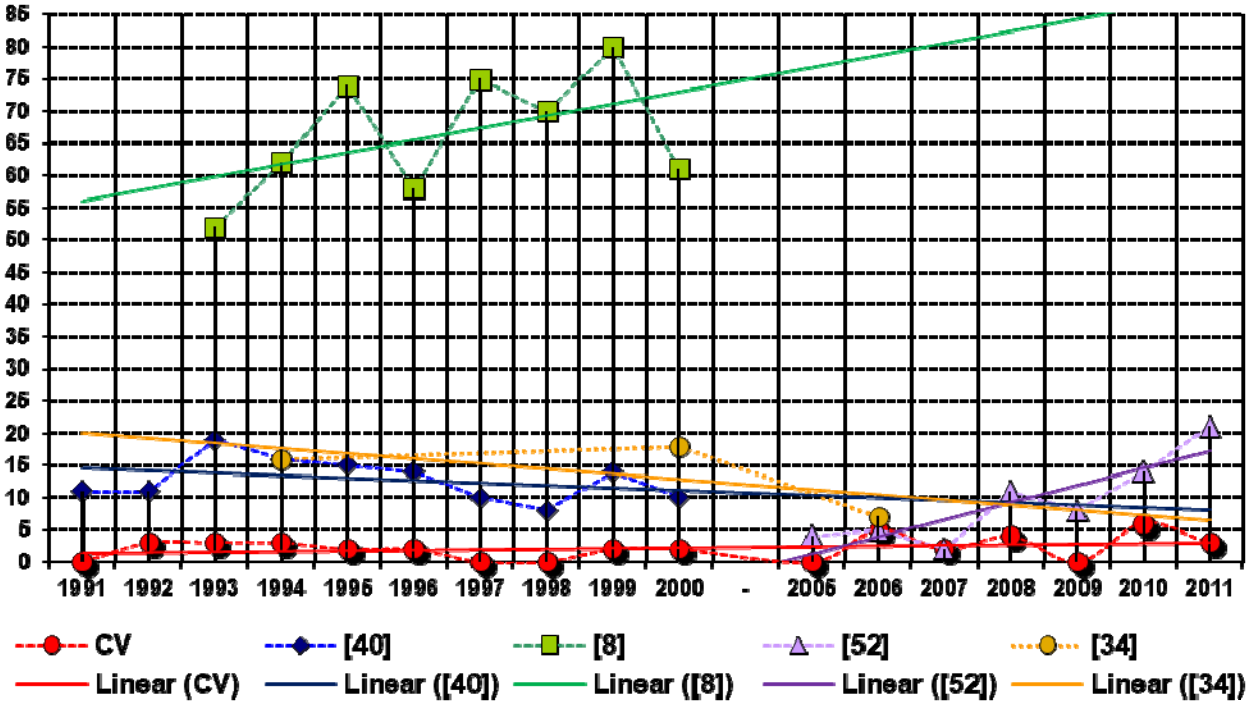

Figure 24 – ***Comparison with other studies of temporal evolution of cases incidence. Red: Our study (CV); Indian blue: Pehme et al., Estonia [40]; Light green: Jutte et al., Netherlands [8]; Orange: García-Rodríguez et al., Spain [34]; Mauve: Prakasha et al., India [52].***

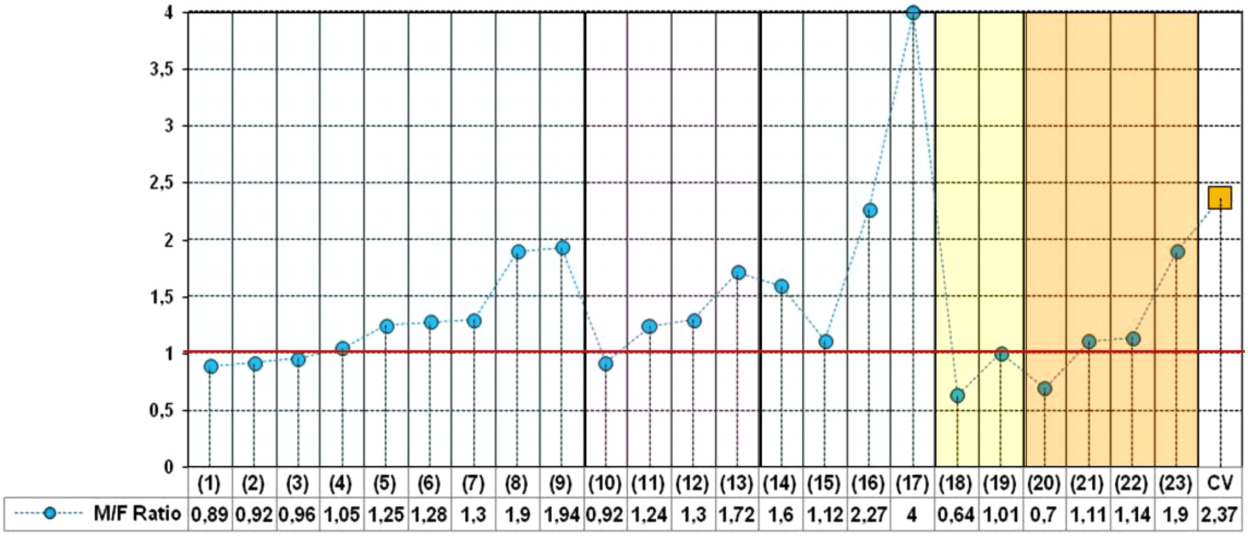

Figure 25 – ***Comparison with other studies of OATB male/female (M/F) ratio: (1): [39]; (2): [37]; (3): [8]; (4): [36]; (5): [39]; (6): [40]; (7): [38]; (8): [35]; (9): [53]; (10): [29]; (11): [54]; (12): [55]; (13): [56]; (14): [57]; (15): [58]; (16): [59]; (17): [48]; (18): [19]; (19): [60]; (20): [61]; (21): [62]; (22): [63]; (23): [64]; CV: Our study; OATB: Osteoarticular tuberculosis.***

Age

The assessment and the comparison of distribution by age was also a difficult task because different authors use different scales for grouping the patients by age. In Table 4, the studies are split depending on the scale they used (age group or age period) and we compared our data using both scales.

There were four distinct trends of distribution observed in the consulted studies.

The first trend was the propensity of OATB lesions for people younger than 40 years, meaning, children, adolescents and young adults (studies from Denmark, India and Pakistan) [38, 54, 55, 65].

The second trend was the presence of OATB lesions in active people, between 25 and 64 years (studies from Netherlands and Saudi Arabia) [8, 56].

The third trend was the bimodal distribution, with picks in adolescent/young adult live and in elderly/mature adult life

(studies from India, Netherlands and England) [29, 37, 39].

Finally, our study could be considered as a fourth trend, with the majority of cases grouped in the mature adult and elderly periods of life.

Table 4 – ***Comparison with other studies of OATB age distribution***

Age group	Study				Our study	Age period	Study				
	[38]	*[29]*	*[54]*	*[55]*			*[56]*	*[8]*	*[37]*	*[39]*	*[65]*
0–9			1		4	5 Child		93	14	10	*26*
10–14	9	1	*7*	24	2						
15–19						1 Adolescent	9 (13–25)		66	*63*	
20–24	*26*	*24*	*6*	*43*	3						
25–29						10 Young adult	*24*	*149*	*105*		*36*
30–34	*17*	*21*	1	*46*	5						
35–39								*72*	75	*50*	
40–44	10	18	0	0	5						1
45–49						28 Mature adult	*15*	*63*	*97*		
50–54	8	*23*	1		*18*						
55–59								43		*63*	
60–64	10	*25*		7	*13*						3
65–69						10 Elderly	4	52	*108*		
70–74	8	11			4						
75–79								*60*			
>80	7	1									

OATB: Osteoarticular tuberculosis.

Clinical suspicion

Everybody is agreeing that the diagnosis of OATB is still a real challenge. There are several reasons that support the difficulty in recognizing OA involvement. One of them is, as mentioned above (Figure 23), that it is much less common than pulmonary involvement and, therefore, it could be less familiar to clinicians who do not suspect it and, consequently, many cases are missed [7, 10, 41, 66, 67]. Another reason is the chronic nature of the disease with insidious and variable clinical presentation consisting often in infrequent and nonspecific symptoms that can mimic other infective conditions, such as acute bacterial osteomyelitis and septic arthritis [5, 7, 26, 67]. Finally, as many forms of EPTB, bone and joint lesions are paucibacillary [67]. Therefore, again, everybody is agreeing that, in order to avoid destruction, neurological complications and, consequently, disability and need of surgery, a high index of clinical suspicion is not only required but critical in contact with the patient, especially in non-endemic areas [3–5, 15, 19, 21, 37, 54, 68, 69–71].

Natheless, only one Indian study [55] among those consulted mentioned the degree of clinical suspicion of TB lesion at the admission. The result was a good one – 44%, comparable with our results but the series was small, only 16 cases. Therefore, we could not have a picture of the degree of suspicion at admission of OATB lesions.

Morphological data

Lesion site

The topography of TB lesions in the musculoskeletal system is well known as well as the propensity of Mt for the bones and joints of the axial segment of the system – the spine. Most of the studies, and we mentioned some of them in Figure 26a [38, 54, 72, 73], are stating that spine lesions represent half or around half of all OATB lesions. However, there are studies that report a higher incidence of spine involvement, going even to more than 80% [8, 29, 35, 57, 74] or, on the contrary, a lower incidence [26, 39]. Our study belongs to the latter category, with a very low percentage of spine involvement (only 13%). The explanation that supports this variability is the type of medical institution that makes the report. For instance, in our case, the lack initially and then the small number of cases with spine lesions we previously reported [30, 31] is determined by a peculiarity of the Romanian health care system that still has medical institutions dedicated to the surgical treatment of TB lesions and especially of those of the spine.

In the spine, not all authors use the same classification scale of the spinal segments and some of them let some cases not included in the scale they use. However, except the Indian study of Sharma *et al.* [54], in all the other consulted studies the group of thoracic (dorsal) +/-, sometimes, dorsolumbar lesions is larger (from slight to obvious) than the group of lumbar +/- lumbosacral lesions [29, 35, 57, 59, 60–64,73, 75]. The cervical involvement rarely has risen until around 10% of the cases [54, 57, 61]. Moreover, in an African study [64] and in our study there were no cervical lesions (Figure 26b).

Regarding the distribution of TB lesions in extraspinal segments of OAS, most of the studies reported a predominance of the TB lesions developed in the limbs. They represented from 64% [35] to around 90% of all extraspinal sites [29, 38, 74] and even over [65]. In all these studies, the lesions affected more often and sometimes predominantly the lower limb. Our study fitted in this distribution pattern. There was only one study that reported a higher proportion of TB of the upper limb than the lower limb [73]. Lesions of the head and neck region are very rare [26, 65]. We found only one case, a 58 years old woman with a suppurative TB osteomyelitis of the left mastoid process. We found also an Indian study [57] with only eight extraspinal lesions, six of which were placed in the trunk and only two in the lower limb. We mention finally a Serbian study [72] with no

specification of the lesion site in 40% of the cases (Figure 26c).

The studies do not always clearly specify which of the OAS tissues is affected (bone, joint or both). However, regarding the joint involvement, most of the studies are reporting lower limb joints as the most frequent sites of extraspinal OATB, representing between 44% [72] and 74.3% [65] of all extraspinal cases and if we add the sacroiliac joint lesions the percentage can rise up to 84.6% [54].

Many authors found the knee joint as the most frequently affected joint [38, 39, 65, 73] but there are studies that found the hip joint on the first place [54, 72] and studies where the ankle joint appears involved in a significant number of cases [35, 39, 65]. Our data are fitting with the range and pattern of distribution described above (Figure 27a). Most of the studies report, regarding the bone involvement, a propensity of TB lesions for the small bones of the limbs, the incidence varying between 36% [35] and 68% [39]. Sometimes small bones of the foot are more affected [38, 54, 65], sometimes small bones of the hand are more involved [35, 39]. Next bones that appear to be affected more frequently are the femur [35, 38, 39] and the humerus [38, 65, 73].

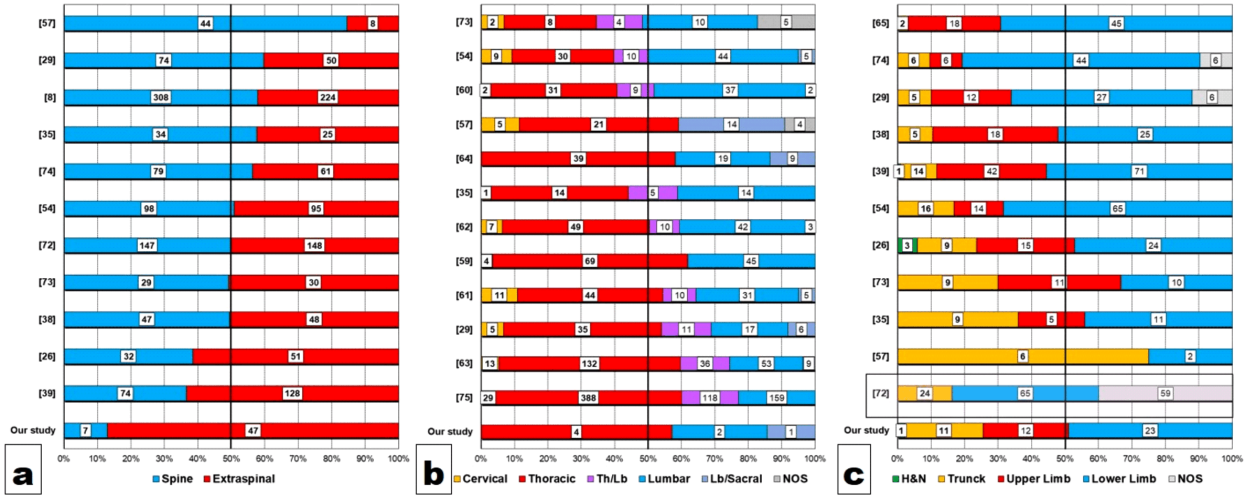

Figure 26 – ***Comparison with other studies of OATB location: (a) Location in the main skeletal regions; (b) Location in the main extraspinal segments; (c) Location in the spine segments. OATB: Osteoarticular tuberculosis; Th: Thoracic; Lb: Lumbar; NOS: Not otherwise specified; H & N: Head and neck.***

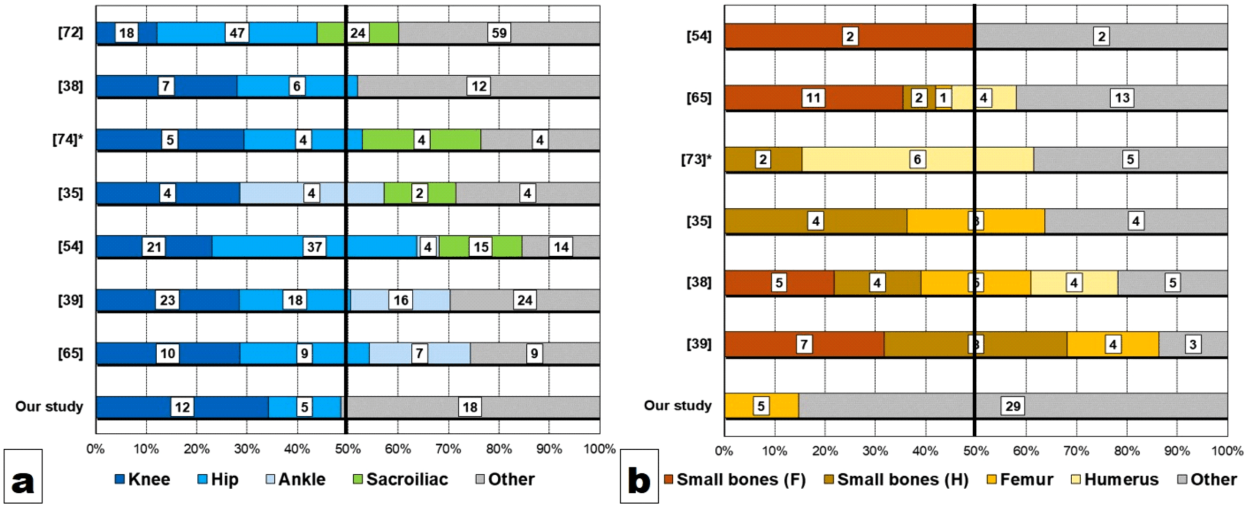

Figure 27 – ***Comparison with other studies of OATB tissue location: (a) Location in the joints; (b) Location in the bones. (*: Tissue not clearly specified). OATB: Osteoarticular tuberculosis; F: Foot; H: Hand.***

In our study, except for the femur, the ribs, coxal bone and tibia were the most frequently affected bones.

So, as a final remark, the spine seems to be the most affected segment of OAS, followed by the lower limb in both bony and joints structures but an uniformity in the use of site classification scales and a clear specification of the tissue involved are still required.

Lesions extension

In our study, we separated from the beginning the lesions according to their extension in the component tissues of the OAS. Thus, almost one third of our cases were gathered in a group in which each case had lesions involving neighboring bones and joints.

In the consulted studies, we found references to the extension of TB lesions only in series including spine involvement [60, 76–82].

The number of vertebral bodies involved varied between 1 and 15, with an average value ranging between 2 and 4.7 vertebrae involved (Figure 28), our data being and this time within the range of above-mentioned variation.

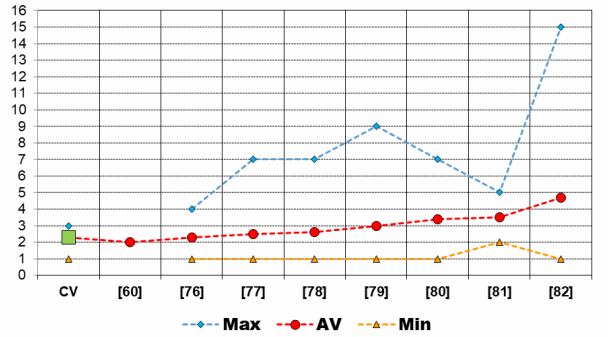

Figure 28 – ***Degree of extension in the spine. CV: Our study; Max: Maximum; AV: Average; Min: Minimum.***

Presence of abscesses

Abscess formation is an event that accompanies often enough TB lesions of the OAS.

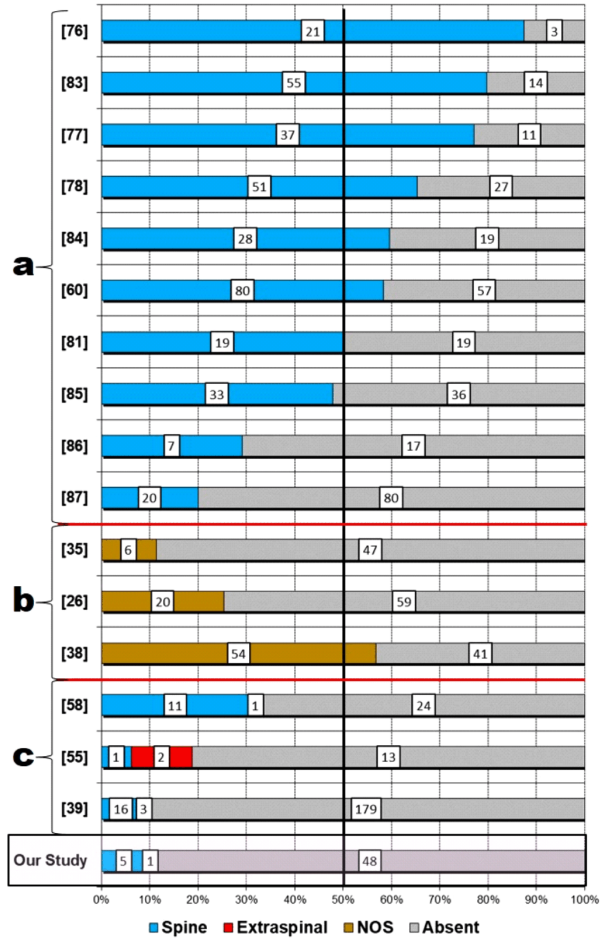

Figure 29 – ***Presence of abscesses: (a) Series with only spine cases; (b) Series with site no specified; (c) Series with spinal and extraspinal cases. NOS: Not otherwise specified.***

In spinal lesions for instance, the presence of abscesses (epidural, paraspinal or psoas abscesses) varies between 20% and almost 90% of all cases (Figure 29, section a) [60, 76–78, 81, 83–87].

In studies reporting both spinal and extraspinal involvement (Figure 29 – sections b and c), the presence of abscesses was lower, varying between 9.5% [39] and 57% [38] of all cases and abscesses accompanying extraspinal lesions were rare.

In some of these latter studies, the site of the OATB lesion accompanied by abscess was not specified [26, 35, 38].

Histopathological examination

Histopathological (HP) examination is gold standard in diagnosis of OATB when biopsies or surgical specimens are available. However, the biopsy should be done only in selected patients, namely in cases in which microbiological tests give negative results in order to confidently exclude TB [3, 4, 54, 88].

Granulomatous inflammation with lymphocytes, giant Langhans cells and typical caseating necrosis, often found in the center of granulomatous lesion is considered as a highly specific and very characteristic histological finding [3, 88, 89].

The studies consulted present again a great variability regarding the use of HP examination (Figure 30a). Thus, there are studies that report the performing of the investigation in all or almost all patients [76, 77, 81, 84, 85, 90]. Other studies are reporting the performing of the investigation in a consistent number of cases, varying between 58% and 85% [53, 83, 86, 91, 92]. Finally, there are studies in which the HP examination was done in less than 10% of the cases [63, 93, 94]. It is true that these latter studies come from African region (two from Morocco and one from Senegal) but, between the studies with HP examination of all patients, one is from Colombia [90] and another from Iran [85]. Therefore, one could conclude that the possibility of covering a complete diagnostic algorithm is depending also on local conditions offered by the medical institutions.

Further, when performed, the histopathological examination could be negative and, again, we found a great variability of the positive results from one study to another (Figure 30b). Thus, there were studies with all HP examinations positive for TB [76, 93]. It is interesting to note that in one of the Moroccan studies [93], although only 19% of the cases had biopsies, all of them were positive. Then, there were studies in which HP examination, when performed, was positive in more than 70% of the cases [53, 81, 83, 84, 91] but also studies with less than 50% [63, 77, 85, 90, 94] or even less than 20% of the cases positive [86, 92].

Therefore, even if it is considered the gold standard, the HP examination is not unfailing and should be part (a mandatory one) of a complete algorithm of investigation for diagnosing as early as possible the TB infection involving the OAS structures.

Except the mention of HP examination importance and of its presence and efficiency in the algorithm of diagnosis, we found only one study from India on a small number of cases [55] that made short references to the morphological features of TB infection. One of the observations was that necrosis was present in almost 69% of the cases, but with no specification concerning the necrosis type. Other observation was that in 81% of the cases the granuloma cell population included giant Langhans cells, the rest of cases presenting epithelioid cell granulomas. We can speculate that around 30% of the cases had type I, hyperplastic granulomas of which two-thirds were type Ia (with epithelioid cells and no

necrosis) and the other one third were type Ib (with no necrosis but with giant Langhans cells). In the majority of cases, the granulomas were of type II – reactive.

As a final remark, we could state that our study is the first one making a detailed morphological analysis of the TB inflammation involving the OAS tissue structures.

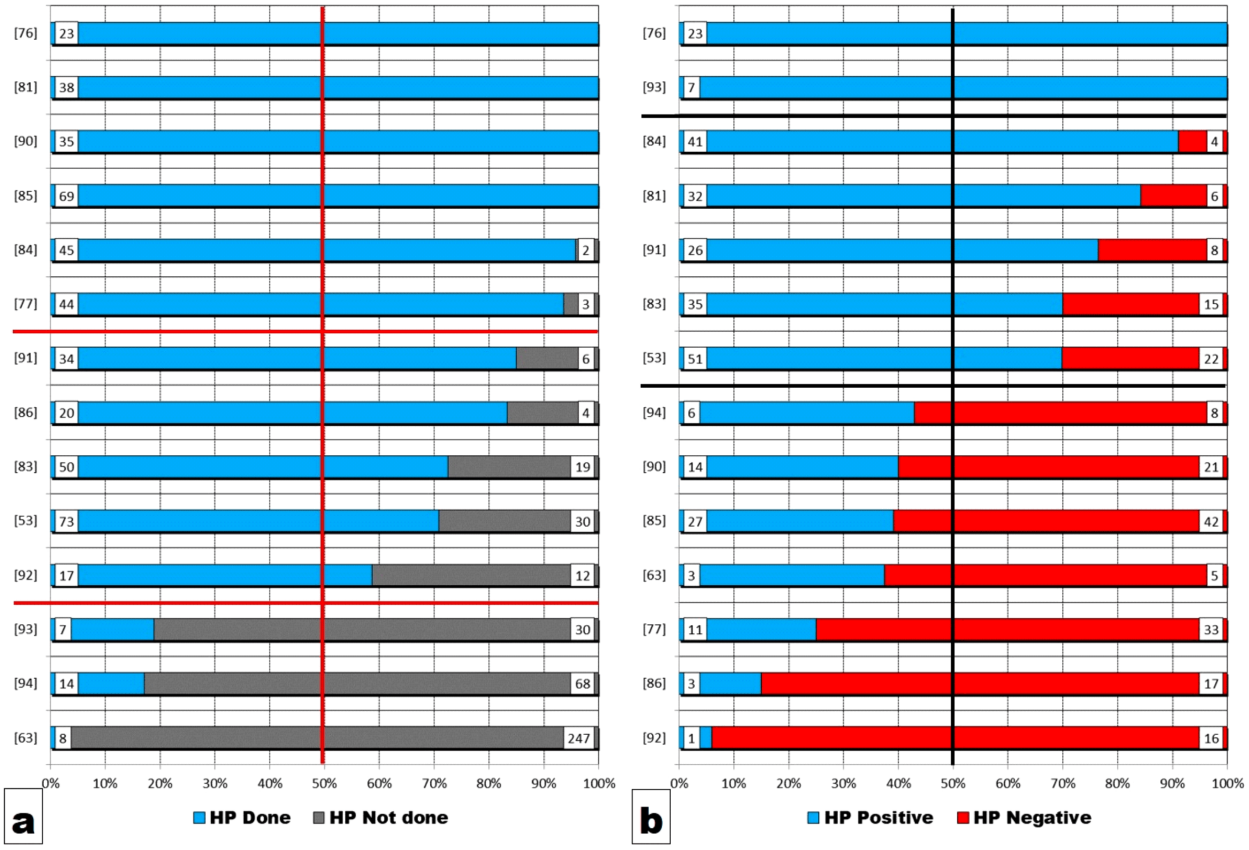

Figure 30 – ***Comparison with other studies of OATB histopathological (HP) confirmation: (a) Achievement of HP examination; (b) Positivity of HP examination. OATB: Osteoarticular tuberculosis.***

We could go further in the end and try to design the clinical-morphological profiles if only bones are involved, if only joints are involved or both tissue structures are involved.

Thus, in our series, the patient with bony lesions was most often male, aged either under 44 years or over 65 years, suspected of TB in less than half of cases and, when not suspected, the diagnosis was most of the time oriented toward tumor formation. Trunk bones, like ribs and coxal bone, often from the left side, were more frequently involved. The recognition of TB etiology did not need (except one case) the use of special staining techniques. Although the great majority of granulomatous reactions had giant Langhans cells in the inflammatory cellular population, almost 40% of the granulomatous reactions were poorly differentiated (type III – hypo-reactive) or even disorganized (type IV – areactive), with basophilic or suppurative necrosis respectively. These morphological features together with the presence of lesion extension in the neighboring tissues could plead for higher aggressiveness of Mt and superinfection respectively. However, the presence of fibrosis in more than 40% of cases is an argument for lesion stabilization.

The profile of patient with lesions of the joints was a little bit different. The patient was also male in the majority of cases but mature adult (aged between 45 and 64 years). The TB suspicion was present in almost half of the cases but, when not, the diagnosis is mainly oriented toward an inflammatory process. Lower limb and especially knee and hip joints on the left side were predominantly affected. Rarely extended, the TB lesions had a significant percentage of granulomas with epithelioid cells only and without necrosis, meaning well differentiated (hyperplastic – type Ia) granulomas, that pleaded for a recent and active conflict, fact confirmed also by the lower percentage of fibrosis. Unlike the bony lesions, joint lesions required special techniques of Mt identification in one-third of cases.

Finally, the patients with mixed bone and joints lesions were females in one third of the cases, young (less than 44 years old) in one quarter of the cases. They had also the highest clinical suspicion at admission (almost two-thirds of the cases) and, when not, the diagnosis was oriented towards an inflammatory disease. The lesions involved most often the right lower limb, particularly the knee joint, the neighboring bones and the spine. Almost all granuloma contained giant Langhans cells. In one-third of the cases, the necrosis was basophilic or suppurative, meaning a significant percentage of poorly differentiated or disorganized granulomatous reaction. The inflammatory process was also extended in the neighboring tissues other than bone and joint in an important number of cases (one quarter) although one-third of the cases had stabilizing fibrotic reaction. The poorly differentiated aspect of the lesions and their extension required in a very significant percentage of

cases (40%) the use of special techniques in order to elucidate the mycobacterial etiology. Therefore, although the number of cases is small in the three subgroups, we defined within our series, in each tissue belonging to OAS, some particularities of the clinical morphological profile of the conflict between Mt and that tissue.

Our attempt of comparing our results with literature was a very difficult task first of all because our study was the only one that separated the cases depending on the type of OAS tissue involved. Then, apart from few generally accepted facts like variable male predominance and most frequent involvement of the spine and then of the weight bearing joints, the literature reveals a wide range of information. Thus, there are variable trends in the temporal evolution and different trends of the age distribution. Clinical suspicion is only stated not analyzed in detail. Apart from studies dedicated to only one of the tissues that are part of the OAS, in the other studies it is not always specified which and how much of these tissues (bone, joint or both) is involved.

It seems that some details offered by the HP examination do not raise the curiosity of the investigators although our study showed that these details could define differences between the different ways in which TB can affect OAS tissue components. Excepting the Indian study of Ramanathan *et al.* [32] dedicated to lymph node TB, we have not found any other study focused on the analysis of morphological aspects of the conflict between Mt and the tissue involved. As we observed in our previous studies [95, 96], this conflict could present on one hand particular morphological profiles depending on the tissue involved. On the other hand, the morphological picture could provide clues about Mt aggressiveness, quality of host reaction or temporal evolution of the lesions (the propensity for extension for instance), information that should not be overlooked or underestimated.

Conclusions

Tuberculosis of the musculoskeletal system is a spectrum of dynamic clinical morphological pictures in close relation with the OAS tissue involved, the mycobacterial aggressiveness or the host immune status, which is still partly known, described and understood especially in the field of morphological changes. The disease is well known as an invalidating one. Therefore, in order to improve the therapeutic outcome, further detailed and integrative analysis of both clinical and morphological aspects is required so the suspicion of diagnosis at the admission becomes as soon as possible certitude. We come again and insist with the idea of designing a unifying and complete way of presenting and reporting such cases on one hand and, on the other hand to share this valuable information as much as possible.

Before ending

This article continues the series of articles about extrapulmonary tuberculosis, dedicated to the memory of our colleague and friend, Dr. Stelian Dănuţ Enache (1953–2012), a true example of passion, devotion and respect for the profession of pathologist and the suffering patient.

Conflict of interests

The authors declare that they have no conflict of interests.

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