

**UNIVERSITY OF MEDICINE AND PHARMACY  
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**PHD  
THESIS**

***CONTRIBUTIONS TO  
THE STUDY OF CLINICAL AND  
MORPHOLOGICAL PROFILE  
OF OSTEOARTICULAR  
TUBERCULOSIS  
AND SOFT TISSUES***

**ABSTRACT**

Scientific Coordinator:;  
Professor Dr. Iancu Emil PLEŞEA

*PHD - Student:*  
Veronica HUPLEA

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### **KEYWORDS**

Extrapulmonary tuberculosis, osteoarticular system, soft tissue, morfology

## **STAGE OF KNOWLEDGE**

### **TUBERCULOSIS - GENERALITIES**

TB is the second leading cause of death by infectious diseases worldwide after HIV infection [WHO 2012, 2014]. It is more common in men than in women and affects mainly adults in the economically active age groups.

In developed countries, the overall improvement of health status and application of anti TB programs supported successfully by chemotherapy, have led to a sharp drop in the infection rate and mortality. However, the incidence of TB began to grow in these countries in the last years due to many factors correlated between them including: increase of the number of persons in detention, of poor people, of injected drug use, of the number of immigrants from countries where the TB rate is very high, and conurbations. A relaxation of anti TB programs added to this because it was considered that the disease is endangered. All these has led to the emergence of strains resistant to treatment and, ultimately, the emergence of a "superbacteria" resistant to all effective drugs [Iseman 1985].

In addition, the HIV epidemy has had a devastating effect on TB control worldwide, especially in developing countries. While one in ten people with normal immune response and Mt infected will develop the disease during their lifetime, one in ten will develop active TB annually between those infected with HIV.

In 2013, the estimated number of new cases of disease worldwide was of 9 million in a populatin of 7.1 billion inhabitants, with a wide range between 8.6 and 9.4 million, meaning an incidence rate (number new cases reported in the population) of 126 cases/100,000 inhabitants but this rate greatly varied from one country to another and from one region to another [WHO 2014].

TB is an infectious disease spread by air through nuclear droplets dispersed as aerosol containing MT from hosts that are coughing or sneezing. Inhalation of a single droplet containing only a few bacteria (2-5) can lead to infection provided that most of infectious diseases require a higher initial dose of 1000 bacteria, and some of them even  $10^9$  bacteria [Behr et al, 1999 ; Zak and Sande, 1999; Nicas et al, 2005].

The lung is the main gateway for the MT, it penetrates into the body, usually by air.

BT will cause a focal infection where it will be stored after inhalation. Thus, once inhaled, most of tuberculous bacilli are trapped in upper airways trachea and bronchi, mucosa, especially if they are aggregated in groups and are eliminated by the defense mucocilliary mechanisms. However, minsucule particles or droplets of less than 5  $\mu\text{m}$  behave as a gas, overcome this barrier and reach the lower respiratory tract, mainly in the alveoli where are rapidly phagocytised by alveolar macrophages. Tuberculous bacilli can spread from the original site of infection in the lungs through lymphatic or blood pathways to other parts of the body, the apex of the lung and regional lymph nodes being the favorite locations [Kritski and de Melo 2007; Raja 2004; Kuhn and Askin 1990].

Granuloma is the key point of the infection with Mycobacterium tuberculosis and and of tuberculosis pathogenesis. The purpose of its formation is to physically incorporate, centralize in a single hotbed and immunologically restrict bacteria that can not be destroyed, thus preventing the spread of disease to other tissues [Guirado and Schlesinger 2013; Marino et al 2011; Davis 2009].

Granuloma is a dynamic, well-organized structure, containing immune cells in various stages of differentiation. which are highly effective in the control, but not in the elimination of the infection.

Fibrosis is a common and important complication of granulomatous inflammation because it is often responsible for permanent tissue destruction even after the causative agent has been removed. However, until very recently, little was known about the fact that granulomas lead to fibrosis. Studies on integral granulomas have found fibroblast proliferation inducing substances likely produced by Macrophages or lymphoid cells [Wyler et al. 1978; Wyler et al. 1981].

## **EXTRAPULMONARY TUBERCULOSIS**

Since patients with EPTB rarely present positive smears, it is generally accepted that the contagion potential of this form is negligible and thus has never been a priority of the campaigns undertaken within the national TB control [Caminero 2003; World Health Organization 1994].

In the past, TBEP was the disease of children, was decreasing with age and was culminating again in elderly people. In the post-AIDS era, TB with multiple determinations predominates among the elderly and people with immune deficiency, especially those infected with both HIV and M. tuberculosis [Barbu 1977; Chaisson et al. 1987; Pitchenik et al. 1988; Kim et al. 1990].

EPTB diagnosis, especially that located in deeper and less accessible regions is very difficult. The shortest delay in diagnosis is in pleural disease, and longest in skeletal disease, probably because the tissue is easily accessible and the symptoms are more subtle [Marini 1988].

TBEP incidence rate varies in different countries, because it is closely correlated with the prevalence of TB in a given region [Fuentes and Caminero 2006].

In 2011, 6.2 million TB cases were notified worldwide of which 0.8 million with TBEP [WHO 2012].

In the European Union, 72.334 TB cases have been notified in 2011 of which, 16.116 cases, meaning 22% had TBEP. TBEP percentage ranged between 4% and 48% depending on the country. This difference could be explained by differences in exposure to risk factors or difficulties in diagnosis [Solove et al 2013].

Patients with TBEP often accuse nonspecific symptoms such as changes of general status, decreased appetite, low grade fever, weight loss, night sweats and lymphadenopathy [Milburn, 2010].

It is particularly difficult to differentiate between TB osteomyelitis and bacterial osteomyelitis or bone tumors [Nakazawa et al 2013]

## **OSTEOARTICULAR AND SOFT TISSUE TUBERCULOSIS**

Bone tuberculosis remains a major disease wich leave behind significant disabilities all over the world. This secondary tuberculosis results from the location of tuberculous process in bones, joints or both. It was representing the third type of EPTB in the US in 1997. It represents between 20 - 33% and 11,2% of the total extrapulmonary tuberculosis, and, according to some authors, up to 35% of the cases of extrapulmonary disease and about 1-3% of all cases of tuberculosis [Davidson and Horowitz, 1970; Golden and Vikram 2005].

The co-existence of an active intrathoracic tuberculosis is present in less than 50% of these patients [Davidson and Horowitz, 1970].

In the past, bone and cartilage were affected in children with pulmonary tuberculosis [Lincoln, 1963]. Today is a disease of the elderly in America and Europe, but still affects the children in developing countries [Gorse and 1983].

Osteoarticular tuberculosis usually develops as a result of paucibacillary hematogenous dissemination by setting of a colony in active bone marrow [Sharma and Mohan, 2004].

The more dissemination occurs at a younger age, the more spinal location or the small bones are dominating. Late disseminations - a consequence of the primary infection movement to adulthood - result in the prevalence of large joints of the pelvis determinations. The current maximum frequency age is around 30 years.

Bone and joint accidental or surgical trauma seem to play a significant role in the rebound of hematogenous metastases besides the normal risk factors. They act by destroying the barrier represented by the encapsulated hematoma that occurs around the latent focus.

Tuberculosis of spine or Pott's disease is the most common form of skeletal tuberculosis effectively, representing approximately 50% of cases with bone and joints location [Sharma and Mohan, 2004, the Moon, 1997]. It results from lymphatic dissemination from a primary focus such as the lung. It can also result from direct invasion of a paravertebral focus or from lymphatic spread from a paravertebral lymph node or pleural space [Davidson and Horowitz, 1970]. Mechanical factors seem to play an important role in the pathogenesis and it was suggested that this trauma is responsible for the increasing susceptibility of supporting cartilage disease.

TB osteomyelitis can mimic and can be mimicked by chronic osteomyelitis of other causes (pyogenic infections or fungal). An useful aspect to differentiate tuberculosis from pyogenic infection is that in the former case, the expansion is in the growth area; fungal infections can also extend, along growth zones [Malaviya and Kotwica 2003; Bhan and Nag 2001; Engin et al. 2000].

## **PERSONAL CONTRIBUTION**

### **MATERIAL AND METHODS**

Our study was performed on 774 patients hospitalized in surgical departments of Emergency County Hospital Craiova, Romania, between 1990 and 2013, whose clinical and laboratory diagnosis established by the Department of Pathology was tuberculous granulomatous inflammatory lesion. We selected 99 of these 774 cases, which showed tuberculous granulomatous inflammatory lesions of osteoarticular and soft tissue structures. Rating Scale age was as follows: P1 = 0-14 years, P2 = 15-24 years P3 = 25-44 years, P4 = 45-64 years and P5 => 65 years. The materials were obtained from two different data sources: (a) notes in tissue samples coming from the surgery; (b) histological records in each case from the archives of the Department of Pathology. For the timing, time interval studied was divided into five-year period since 1990.

Surgical samples or biopsies were processed using conventional histological techniques (formalin fixation and paraffin embedding) and then stained with hematoxylin eosin (HE). To confirm etiology, Ziehl Nielsen staining was performed for acid-fast bacilli culture resistant alcohol a necrotic material. In other cases, the inflammatory granulomas revealed caseous necrosis or atypical features or dominant

appearance of the lesion, but with a nonspecific granulomatous reaction around we used PCR on paraffin-embedded blocks to determine the etiologic diagnosis.

The study was retrospective and parameters evaluated were those used in the department where the patient was hospitalized, general involvement of the lymph nodes, the time evolution of the number of cases, sex, age, suspected etiologic diagnosis at admission and lesion site.

## **CLINICAL STUDY**

TBCOA incidence is widely fluctuating depending on the source data, which in turn is conditioned by the time considered, the geographic area, the study group structure, etc.

In our study, the percentage of SOA lesions was lower than those found in all consulted and cited sources, and less than 5%. This low percentage could be explained by the fact that, as it will be explained in more detail in the next chapter, there was only one case with spine involvement between our cases.

Another group of lesions that we have defined for our study and that we have not encountered in the literature was the group of "soft tissue" lesions. We have included here all lesions found in common connective tissue or adipous tissue, generally located under the integument and lesions discovered in the mammary gland.

In the literature, lesions with such locations are probably included in the "bag" called "other injuries" which represent, sometimes, 15% of all EPTB lesions.

In our study, this somehow heterogeneous group, was quite large, accounting for 5.5% of the studied cases if only bacillary lesions strictly localized in soft tissue are considered but 8.5% if cases where there was an association between soft tissue injuries and lesions in other tissue structures located elsewhere in the body were taken into account.

Currently, the age distribution of the musculoskeletal TB lesions is influenced by socio-economic status of the geographical area. Thus, underdeveloped countries, children are still frequently affected while in developed countries, osteoarticular location is encountered more frequently in adults and particularly the elderly [Joachim 1983; Talavera et al. 2001; Kritski and Melo 2007].

Concerning the osteoarticular lesions, our data are in disagreement with the literature in the sense that even our region is a developing one, the pattern of injuries age distribution is closer to that of industrialized countries in that two-thirds of the patients were adults, especially mature adults (between 45 and 64 years) which them alone accounted for 45% of cases.

The TBOA diagnosis is usually delayed because it is often overlooked in the differential diagnosis of joint disease. Systemic symptoms are usually absent. There are, however, characteristic symptoms and signs for each of the two major sites: spinal and extraspinal and that may suggest the etiology of spinal TB.

## **MORPHOLOGICAL STUDY**

In just over a third of the studied cases (37%), only the TB process affected only bone structures, and in less than a third of cases only joint structures.

The remaining one third of cases, tuberculous lesions were found in two different tissue structures. Associated lesions were located more frequently in SOA structures, with simultaneous involvement of bone structures and neighboring joint

structures. In a twice smaller percentage, associated lesions were located, one at the bone and the other outside the SOA, in the soft tissues.

The analysis of bacillary lesions distribution among different OAS structures in different parts of the body showed that they particularly affected the limbs, and especially the lower limb.

Bacillary lesions localized in the trunk's osteoarticular system structures were found in over a quarter of patients. In most cases TB process was stuck in the bone structures, ribs being the most commonly affected.

In one case, a patient aged 72 years, T12 vertebral body was affected, the patient being admitted following the radiological discovery of an area of osteolysis in the vertebral body.

In general, the left upper limb was more affected than the right.

We noticed, however, that solitary joint involvements were significantly more common in the left upper limb while solitary bone lesions had no predilection for either of the upper limbs.

In almost two thirds of the studied cases, tuberculous lesions were confined only to the soft tissue, whether it was common supporting connective tissue, whether it was the fat. However, the remaining one third of cases, the lesion TM either represented extension of a preexisting lesion in the neighboring tissue or expanded itself to surrounding tissues.

The classical division of tuberculous granulomas used as a criterion, the cell type with predominant phagocytic function. Using this classification, we noticed that the overwhelming majority of SOATB and TMTB cases presented the classical granulomatous lesion described by Köster, with giant cell centrally located surrounded by a bulk of epithelioid type mononuclear cells and a peripheral layer of lymphocytes with variable density. Such granulomas were seen more frequently in cases with osteoarticular lesions - almost 90% of them - and less frequently in cases with soft tissue injury - less than 80% of them. Granulomatous infiltrate was frequently dominated by giant Langhans cells which presented degenerative lesions.

Granulomatous reaction, usually localized, presented however in a high proportion of about one third of cases, either a poorly differentiated pattern, with basophilic necrosis, either a disorganized pattern, with PMN dominating the cellular complex and unstructured necrosis. Atypical lesions showed a somewhat significant share of over 10%, being, most often, changes in morphology granuloma. The perilesional fibrilogenetic process was seen more rarely than in the osteoarticular lesions.

## **CONCLUSIONS**

Our study resulted in the following conclusions:

The incidence of tuberculosis have had different patterns of temporal evolution over the studied time interval. Thus, if in the osteoarticular forms, the temporalevolution had an oscillating trend with a general decending trend in the localized forms of soft tissues lesions, the temporal evolution was an ascending one with a slight regression toward the end of the interval.

There are differences in terms of gender, age, and clinics where the patients have been hospitalized. Thus, if in the group of patients with osteoarticular lesions patients were, in most cases, adults and elderly men, hospitalized somehow naturally, in clinics which deal with osteo-articular pathology, in the the group of patients with tuberculous lesions in the TM, patients were rather women, in adulthood, and, because lesions in the majority of cases were located in the trunk, mainly in the thoracic region, they were

hospitalized in surgical clinics, especially general surgery and the thoracic surgery.

The suspicion of etiologic diagnosis at clinical examination was reduced in the group with tuberculous lesions in the soft tissues, whether they were solitary or associated, but raised to more than one third of cases in patients with osteoarticular lesions, especially those associated.

When TB was not suspected, suspicion was directed rather to a tumor formation than to an inflammatory process.

Granulomatous reaction was usually in both groups of well differentiated type, active, with predominance of EC and CGL, with classical acidophilic caseous necrosis, centrally located and with reduced perifocal fibrillary reaction. It is reported, however, a significant contingent of poorly differentiated or disorganized type granulomas in the group of soft tissue lesions.

The morphological picture did not rize the problem of pathologic diagnosis but in very rare cases andrevealed the active and destructive profile of the bacillary aggression, raising suspicion of either a greater sensitivity of the two tissue types that would lead to their higher susceptibility to aggressive and extensive forms of tuberculosis infection, or the existence of a background more vulnerable particularly in patients with soft tissue injuries.

It is essential that clinicians know and refresh their knowledge about manifestations of different TB locations, so they can recognize and diagnose this curable disease before definitive surgery is practiced in order to protect patients from the application of inappropriate therapies. The surgery should be limited to the diagnosis or treatment of life-threatening complications.

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