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**PHD
THESIS**

**CLINICAL AND
MORPHOLOGICAL STUDY OF
LYMPHADENOPATHY OF
TUBERCULOUS ETIOLOGY**

ABSTRACT

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KEYWORDS

Extrapulmonary tuberculosis, lymph node, morphology

STAGE OF KNOWLEDGE

TUBERCULOSIS - GENERALITIES

TB is an infectious disease spread by air by nuclear droplets dispersed as aerosol containing *Mycobacterium tuberculosis* (MT) from hosts that are coughing or sneezing. Worldwide, TB is a disease that is "a dynamic equilibrium between body and MT" [Bates and Stead 1993].

In Europe and the US, the overall improvement of health helped to the reduction of TB problem long before the appearance of specific drugs. The disease has become increasingly better controlled but never really disappeared.

Mycobacterium tuberculosis is an intracellular, mandatory aerobic pathogen with affinity for lung tissue, rich in oxygen. *Mycobacteria* occupy a taxonomic niche between eubacteria and actinomycetes [Kuhn and Askin 1990]. It seems that *mycobacterium* is a very old type of bacteria.

Typically, BT enters the body by air. They disseminate from the original place of pulmonary infection via lymphatic and blood circulation in other regions of the body, the apex of the lung and regional lymph nodes being the favorite locations.

Granuloma is the main feature of the original host immune response to TB and many efforts have been made to understand its formation and role in immune defense against MT [Saunders and Cooper 2000; Mohan et al. 2001].

Inflammatory reaction occurring during primo-infection is nonspecific, similar to the reaction triggered by any bacterial invasion.

The first phase of TB infection begins once the *mycobacterium* is inhaled and results in a LT-mediated immune response which determines the sensitivity to microorganisms and controls 95% of infections.

Inhaled bacilli are phagocytosed by alveolar macrophages, most often on the periphery of one of the lungs, and transported by these cells in hilar lymph nodes.

"Indifferent" (non-activated) macrophages are not capable to destroy *mycobacterium* that are multiplying, lyse host cells, infect the other M and sometimes disseminate through hematogenous pathway in other areas of lungs or the body.

In some situations, it may cause reinfection or reactivation of dormant bacilli or change directly from primary lesions to secondary tuberculosis. This can happen either because the bacillary population has a particular virulence or because the host has a particular susceptibility.

In mice, susceptibility to TB infection - as in the case of *Salmonella* and *Leishmania* - is determined by an autosomal gene named *Bcg*, which codes for a membrane transport protein. MT can affect all organs; however lung is the most common location. Between 1993 and 1998, 83% of cases had pulmonary localization. The remaining 17% can have any other location. EPTB can be locally confined but usually affects multiple organs with or without concomitant pulmonary effects.

TB is a global pandemic disease. More than two billion people, representing one third of the world population are infected with BT. One of ten people infected with BT reach manifest disease during life, people infected with HIV having a even higher risk.

It is a disease of poverty, affecting mostly young adults in the most active period of their lives. The highest rate is in Africa (29% of all cases), and half of the new cases are in 6 Asian countries (Bangladesh, China, India, Indonesia, Pakistan, Philippines) [WHO 2006 and 2009]. The number of newly registered TB cases worldwide is closely linked to economic conditions, the highest incidence being

observed in countries in Africa, Asia and Latin America which have the lowest gross domestic product.

EXTRAPULMONARY TUBERCULOSIS

TB can involve any organ or tissue in the body, the disease can have a non-pulmonary location [Caminero 2003; Farga 1992; Dannenberg and Tomashefki 1988; Murray and Nadel 1988]. The classic definition of extrapulmonary tuberculosis (EPTB) is tuberculous involvement of an organ outside the lung [Sharma and Mohan 2004]. However, when extrapulmonary localization is evident in a patient with pulmonary tuberculosis (TBCP), these patients were taken out from pulmonary tuberculosis group according to WHO rules [Maher et al. 1997].

Tuberculosis in organs other than the lung was observed for centuries but was not recognized as such. In the skeleton, TB was present in Egypt in 3500 BC [Morse et al. 1964]. Ancient doctors divided TB (phthisis, consumption level) in several distinct diseases. Throughout history, EPTB was named in many ways such as: Pott's disease of the spine, lupus vulgaris of the skin and cervical lymph nodes scrofula. It was described as "a sign of evil" as a disease "that was carrying the people in the other world after their candle burned only a short period."

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].

EPTB, on the one hand, has become more common with the advent of the possibility of HIV infection and, on the other hand, has become a significant cause of morbidity and mortality in HIV-positive patients in the 90s [Rieder et al. 1990; Talavera et al. 2001].

It is interesting to note that, while in some areas AIDS did not affect the EPTB frequency [Viskum Kok-Jensen, 1994; Mehta et al. 1991], in most regions, HIV infection is the main risk factor for progression from TB infection to active disease [Calpe et al. 2005; Aaron et al. 2004; Caminero 2003; Daley et al. 1992; Elder 1992; Raviglione et al. 1992].

Immunodeficiency also influences the EPTB location. In extrapulmonary TB in immunocompetent patients lesions are most often located in the pleura, lymph node system and urogenital system [Caminero et al. 2005; Ozbay and Uzun 2002; Lenk et al. 2001; Lado et al. 2000a; Morehead 1998]. In HIV-positive patients, the most frequent location of EPTB is, as outlined above, the lymphatic system [Caminero et al. 2005; Sharma and Mohan 2004; Mohan and Sharma 2001; Lado et al. 2000a; Lado et al. 2000b; Cremades et al. 1998; Hsieh et al. 1996; Kok-Jensen and Viskum 1994; Carcaba et al. 1993].

EPTB diagnosis, especially of 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].

Patients with EPTB present with general symptoms like fever, anorexia, weight loss, fatigue. In India for example, patients with EPTB, especially when the disease is obscurely localized, may present with pyrexia of unknown origin and this may be the only sign for diagnosis.

Patients may present, sometimes, sensitivity changes, cranial nerve palsy, seizures, monoarticular inflammation and painless lymphadenopathy. In addition, EPTB patients have signs and symptoms organ or system related. The spectrum of

clinical symptoms can mimic other systemic diseases and is partially responsible for misdiagnoses and delay diagnosis.

LYMPH NODE TUBERCULOSIS

From a historical perspective, lymph node TB (LNT), more precisely the cervical disease was recognized in the eighteenth century in Europe, being called "the king's devil" (the belief that could be cured by hands of a sovereign) or scrofula or "full necked sow" [Kumar 2001; Talavera et al. 2001].

BK enters the body in the respiratory tract and then disseminates in a hematogenous and lymphatic way. Hilar and mediastinal nodes are the first to suffer. These first two steps can be traveled in either primary infection or later in life in reinfection or reactivation of a previous infection. From the first lymph node stations affected, the infection then spreads in the cervical lymph nodes through lymphatic pathways [Sharma and Mohan 2004].

Intrathoracic lymphadenopathy (LA) is an unusual manifestation of adult TB, but it is fairly common in children [Powell 1993]. In a study by Silver and Steel, intrathoracic LA TB was more common in Asians and Blacks. [Kent et al. 1967].

Although mediastinal lymph nodes are usually the main drainage station, they are affected in only 5% of cases of LA TB [Farer et al. 1979]. In 2/3 of cases, mediastinal lymph nodes affected are situated in the right paratracheal site [Im et al. 1987].

HIV positive patients with suspected intrathoracic LA TB have frequently extrathoracic lymph nodes palpable [Artenstein et al. 1995].

Spleen TB is presented either with hypersplenism or splenic abscesses or as a solitary splenic lesion. Isolated splenic TB is very rare in immunocompetent individuals [Sheen-Chen et al. 1995; Sharma and Mohan 2004].

Spleen involvement may be the result of miliary tuberculosis, in which case is frequent in immunocompromised individuals, or may be the only manifestation of TB, without evidence of other tuberculous lesions elsewhere in the body.

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 382 of these 774 cases, which showed granulomatous inflammatory lesions of tuberculous lymph nodes. 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.

Samples surgical biopsies were obtained or 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 culture acid-alcohol resistant bacilli from a necrotic material. In other cases, the inflammatory granulomas revealed caseous necrosis or atypical features

or dominant appearance of the lesion, but with a non-specific 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

From the initial group of 774 cases that were identified microscopically as tuberculous type of inflammation, lymph node structures were placed on first place as frequency of TB localization, followed at a big difference by the digestive system and the male genital.

A comparison of the data obtained by us with similar studies in the literature is difficult because, on the one hand, the angle of our approach is a particular one, namely the inventory of cases hospitalized in general surgical clinics of the hospital to which histopathological examination revealed the presence of reactive and destructive tuberculous lesions, most often, as we show below, was in disagreement with the clinical evaluation of first impression at the patients admission.

Grouping cases for periods of 5 years revealed an fluctuating incidence of lymph nodes determinations discovered during hospitalization, with two peaks between 1995 and 1999 and between 2005 and 2009, a period which saw the biggest number of cases.

However, the general trend of the cases number was decreasing from the beginning to the end of the studied period.

It should be stressed once again that accurate comparison was affected by a number of inconsistencies between studies regarding criteria for inclusion in EPTB categories, its different locations and ways of ranking the importance of the types of sites.

Among international studies taken as a comparison, only those of Yoon et al Forssbohm and PHEME et al included the evaluation of gender distribution.

The gender distribution varied in a very wide range but the M/F ratio was subunitary in all studies, ie, the number of affected women was higher. The limits were, on the one hand, the net effect on female preponderance of the Korean group (Yoon et al.) and, on the other hand, almost equal gender ratio - 0.97 - the Estonian group (PHEMA et al.). In our study female preponderance was moderate with a value of 0.63 of the M / F ratio or reversing the report for a more suggestive representation, a value of 1.57 the ratio F/M.

MORPHOLOGICAL STUDIES

Analysis of damage distribution in the lymph node groups from different parts of the body revealed that in only 15 of the 382 studied cases (namely 4%), the tuberculous process affected simultaneously lymph nodes groups located in several segments.

Cervical region was the most frequent site of TB inflammation, concentrating alone almost two thirds of cases.

Cephalic region followed as significant number of cases, which concentrated another 14.1% of the cases.

Thus, over three quarters of cases with nodal lesions were located in the cephalic extremity lymph node groups, namely groups accessible for the clinical examination.

In the cervical region most affected groups in the studied cases were laterocervical lymph node groups - 94%.

However, In no case was mentioned by the clinician which group of the laterocervical region was affected (superficial or deep, etc.). In very few cases, less than 10% (exactly 13 cases), the seat of tuberculous process was supraclavicular lymph.

In the abdominal region, the lymph node group most commonly affected was the inguinal one which accounted for nearly 50% of all locations in this region. In five cases - one diagnosed with cirrhosis pigmentosa in a patient of 62 years, a diagnosis of hypersplenism, two diagnosed with splenomegaly, one of them a girl of 13 years, who underwent splenectomy and, finally, the fifth case found in necropsy - histopathological examination revealed multiple, confluent, tuberculous granulomatous lesions and areas of caseification necrosis in the splenic parenchyma.

Except the 33 cases with deeply situated lymph involvement, most of them in the abdominal cavity, the remaining cases, representing more than 90% of patients had impairment of the lymph node groups available for clinical examination.

In 340 of the 382 cases of tuberculosis paired lymph node groups were involved.

In general, impairment was unilateral, bilateral determinations being seen in only 9 cases, ie 2.64% of paired lymph node groups involvement.

Apart from the 26 cases in which in the biopsy material accompanying statement was not specified the location of the tuberculous process within paired groups, there was a preponderance of lymph node groups located on the right side.

Analysis of the incidence of the major cell types with phagocytic function revealed that granulomatous inflammatory lesions were dominated by granulomatous type reactions whose cell population was composed of epithelioid cells as well as cell giant cell in the center of the macrophages bulk.

In tuberculosis lesions that contained foci of necrosis, it displayed the whole range of morphological aspects, from early necrosis to so-called bacterial overgrowth noncaseating necrosis.

Thus, it can be observed that 6% of necrotic caseous lesions showed the appearance of early necrosis. The classical, acidophilic necrosis, was the most frequent outbreaks of necrotic lesions localized in the lymph node structures, half of cases showing such a necrosis.

Fibrosis was identified in only 15% of tuberculous lesions located in various lymph node groups.

The fibrilogenetic process is controversial. On the one hand it is its role original of isolating the inflammatory focus and containing the spread of infection. On the other hand is its constant destructive action on the tissue where is triggered.

Morphological profile of lymph node lesions covered the whole range of morphological types of tuberculous granuloma from the hyperplastic to the non reactive one.

Patients with well-differentiated aspects of TB granulomas were the largest contingent of cases, with a rate of almost 80%.

Granulomas of "Ia" type, consisting only of mononuclear cells EC and M, considered as initial stage of the of granuloma formation process were found in a significant proportion of nearly 10% of cases.

Local extension in the lymph node structures was relatively frequent, almost a third of cases revealing bacillary lesions in more than one lymph node capsule or beyond them.

Fistula formation was encountered in four cases: one patient of 14 years, which has spread beyond the capsule of left supraclavicular lymph nodes in the subcutaneous adipose tissue, creating a fistula which opened to the skin in the supraclavicular fossa, a patient 65 years old who presented a laterocervical lymph fistula, a 78 years old patient with left laterocervical lymphadenopathy block and, finally, a patient of 44 years with chronic fistulising submental adenitis.

CONCLUSIONS

Our study resulted in the following conclusions:

The analysis results obtained in the two studies outlined some conclusions which may be relevant and applicable in the future handling of TB lymph node localization of in medical practice:

The lymph node was found to be the preferred location of the tuberculous process besides the lung parenchyma.

TB incidence had a somewhat stationary general trend, but amid an oscillating evolution.

Usually, nodal involvement was solitary. But there was also a small number of cases in which TB affected simultaneously the structures of another organ/system.

Patients with nodal determinations only were usually young women with a mean age lower than patients with associated determinations which were rather men.

Bacillary aggression was mostly confined to one group in the ganglion, located usually superficial, in the cephalic end, but should not be neglected deep locations.

Despite directly accessibility of clinical examination to the vast majority of patients, TB suspicion was very low, the diagnosis being oriented towards a nontuberculous inflammatory reaction or towards a proliferation of neoplastic type or to an expectant conduct, the decision being transferred to the pathologist. The lack of minimal clinical information can, sometimes, negatively put its imprint on the development of histopathological diagnosis.

Granulomatous reaction was, in almost half of the cases, of poorly differentiated or disorganized type, with EC and CGL predominance but also of the PMN, with more basophilic and noncaseating necrosis when existed, and reduced perifocal fibrillary reaction.

The morphological general picture did not put the problem of establishing the pathological diagnosis but only in very rare cases. However, it revealed an active, destructive profile of the bacillary aggression, raising the suspicion of either a greater sensitivity of lymph node tissue that would lead to a higher susceptibility to aggressive and extensive forms of TB infection, or the existence of a more vulnerable background in patients with lymph node lesions.

It is essential that clinicians know and refresh their knowledge about different locations of TB manifestation, 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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