Lymph node tuberculosis – an attempt of clinico-morphological study and review of the literature

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Abstract  
Aim: The authors assessed the mycobacterial lesions in the lymph nodes discovered on tissue samples coming from the surgical stage in the Department of Pathology, Emergency County Hospital of Craiova, Romania, starting from 1990 until 2012. Materials and Methods: The studied material consisted of lymph node (LN) tissue samples obtained by biopsy or surgical excision from 362 patients histopathologically diagnosed with tuberculosis. For confirming the diagnosis, Ziehl–Neelsen staining was carried out and, in some cases, PCR technique was used. Results: Patients were mainly women, with a mean age of 35 years. The suspicion of diagnosis at admission was reduced, the most usual diagnosis being a very general and uncertain one of “adenopathy/polyadenopathy”. In only few cases, other tissues/organs have been affected in the same time with the LN determination. Also, multiple LN group involvement was present in only five cases. The most affected LN groups were: the lateral cervical, submandibular, axillary, inguinal, supraclavicular and mesenteric. In paired LN groups, there was no predilection for any of the body sides. Epithelioid cells (ECs) and giant Langhans cells (GLCs) were present together in most of the cases displaying the whole range of morphological features, but usually the acidophilic, microgranular one. Fibrosis was rarely encountered. However, the presence of neutrophils in 10% of the cases should be noticed. Necrosis was present in almost all cases, displaying the whole range of morphological features, but usually the acidophilic, microgranular one. Fibrosis was rarely encountered. As a whole, well-differentiated granulomas were the most frequent but the presence of hyporeactive granulomas in more than a quarter of the cases and that of non-reactive granulomas in more than 10% of the cases should be noticed. The extension of TB process was not a rare event. Conclusion: LNs seem to be the favorite location of TB besides the lung. The overall morphological picture revealed an active and destructive profile of the bacillary aggression in the LN parenchyma, which could mean either a higher sensitivity of the LN tissue or a more vulnerable background of the patients with TBLN lesions.  

Keywords: tuberculosis, morphology, lymph nodes.

Introduction  
Lymph nodes tuberculosis (LNTB) was considered the most common form of extrapulmonary tuberculosis (EPTB) [1]. LNTB continues to be the most common form of EPTB in developing countries, with an estimated incidence of about 28% of cases of EPTB [2–5]. Ilgazli et al. reported, few years ago, an even percentage of 56.3% as having node localization in a study group of 636 cases of EPTB, followed by pleural localization with 31.1% [6]. Recent studies place LNTB on the second position frequency after the pleural determination for HIV-negative EPTB patients, while, in patients with HIV/AIDS it remains the first extrapulmonary determination [7]. Mycobacterium tuberculosis (MT) has been reported to have a remarkable tropism for lymph nodes in children less than five years [8].  

Lymph nodes (LN/LNs) may be affected by tuberculosis: (a) in the primary TB – primary LNTB – as a result of the primary complex development in the pharyngal-cervical territory; (b) in the secondary TB – secondary LNTB – resulting from the secondary location of the TB in the peripheral lymph nodes. It occurs between six and nine months after the initial infection [8].  

It could be said that lymph node involvement is always secondary to the TB development in their tributary organ, or, in other words, LNTB can be considered a local manifestation of a systemic disease.

Our study was a retrospective analysis that targeted the hospitalized cases, diagnosed and recorded in our Department documents between 1990 and 2012.

Materials and Methods  
Our study was carried out on 732 patients hospitalized in the surgical departments of Emergency County Hospital of Craiova, Romania, between 1990 and 2012, whose pathologic diagnostic established in the Department of Pathology of the same hospital was granulomatous inflammatory lesion. We selected 362 of these 732 cases, which showed lymph node tuberculosis granulomatous inflammatory lesions.

The materials were obtained from two different data sources: (a) accompanying notes of tissue specimens
coming from operation theatres; (b) histopathological records and histopathological samples from each case and the paraffin blocks from the Department of Pathology’s archives.

The surgically removed or biopsy samples were processed using the classical histopathological technique (formalin fixation and paraffin embedding) and then stained with Hematoxylin–Eosin (HE). To confirm the etiology, Ziehl–Neelsen staining for acid-fast bacilli was carried out. In some cases, the different lymphocyte and macrophage populations were identified using immunohistochemical staining methods. The used antibodies are listed in Table 1.

### Table 1 – Antibodies used to identify the lymphocyte and macrophage populations

<table>
<thead>
<tr>
<th>Antibody Specificity</th>
<th>Source</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo a Hu CD45.R0 clone UCHL1 T-cells</td>
<td>DAKO</td>
<td>1:100</td>
</tr>
<tr>
<td>Mo a Hu CD20, clone L26 B-cells</td>
<td>DAKO</td>
<td>1:200</td>
</tr>
<tr>
<td>Mo a Hu CD68, clone PG-M1 Macrophages</td>
<td>DAKO</td>
<td>1:50</td>
</tr>
</tbody>
</table>

In other cases, wherein either inflammatory granulomas revealed atypical features or caseous necrosis was dominating the lesion but with a non-specific granulomatous reaction around we used the PCR technique on paraffin-embedded blocks to establish the etiological diagnosis.

The study was of retrospective type and had two components, depending on the assessed parameters: [I] a clinical study including: department where the patient was hospitalized, gender, age, suspicion of the etiological diagnosis at admission and the lesion’s location; [II] a histopathological study, focused on: (a) the clarification of borderline cases using the immunohistochemical and PCR techniques; (b) the assessment, on routine stained samples, of: the granuloma cellularity, the presence and type of necrosis, the presence of fibrosis, the degree of differentiation of the granulomatous lesions and extension of the lesions.

### Results

#### Clinical data

**Lymph node involvement**

Lymph node involvement represented almost half of the initial group of 732 cases identified with extrapulmonary tuberculous lesions (Figure 1).

![Figure 1 – Lymph node involvement in studied group.](image)

Although in most of the cases the TB inflammation was located only in one or more of the lymph nodes, it was anyway a total of 23 cases, meaning a proportion of around 6% where other tissues/organs have been affected in the same time (Figure 2).

![Figure 2 – Association of lymph node involvement with other sites involvement.](image)

In half (12) of these cases, the different segments of digestive system have been affected, the lymph nodes involved being the regional ones of the digestive segment harboring the TB lesion.

In another third of the cases, either the soft tissues (five cases) or the integument (two cases) near the involved lymph nodes have been affected too.

Other sites with concomitant involvement were: upper airways – two cases, urinary system – one case and male genital system – one case.

**Temporal evolution**

The cases grouping in five years period revealed a fluctuating incidence of the LNs determinations discovered during the hospitalization, with two peaks between 1995 and 1999 and between 2005 and 2009, a period that saw the largest number of cases.

However, the general trend has been the decrease in the number of cases from the beginning to the end of the studied interval (Figure 3).

![Figure 3 – Temporal evolution of cases incidence.](image)

**Origin of the specimens**

Lymph node specimens came from no less than 12 surgical and clinical departments of the hospital.

The majority of cases were hospitalized in the two departments related to the head and neck surgery, i.e., Department of Oral and Maxillofacial Surgery (83 cases) and Department of Otorhinolaryngology (70 cases). Then around one third (125 cases) belonged, somehow expected, to the three Departments of General Surgery of the hospital. A significant number of cases – 35 – was hospitalized in the Department of Pediatric Surgery, the same number coming also from Departments of Internal Medicine and Hematology (26 and nine cases respectively).

The rest of 14 cases came from other different departments, half of them from Thoracic Surgery (seven cases), Plastic Surgery and Autopsy with two cases each,
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and Orthopedic Surgery, Urology and Nutrition Diseases with one case each.

**Gender distribution**

The analysis of the gender distribution showed that while almost two thirds of the cases with only LNs involvement were women, more than one half of the cases with concomitant involvement of other tissue systems were men (Figure 4).

![Figure 4 – Gender distribution.](image)

**Age distribution**

The tuberculous lesions affected mostly younger ages, more than 60% of patients being aged up to 44 years.

The analysis of the LNs involvement amount in different age groups in patients with single determinations and in those with associated determinations showed a more uniform distribution in different age periods, in patients with determinations of only LN structures, with a significant impairment of childhood age groups of almost 20%.

In return, in patients with LN determinations associated with tuberculous lesions localized in other tissue structures almost half of the cases were young adults (Figure 5).

![Figure 5 – Age group distribution.](image)

**Table 2 – Comparative statistical parameters of the age in the two groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LN</th>
<th>LN + Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of determinations</td>
<td>339</td>
<td>23</td>
</tr>
<tr>
<td>VMAX</td>
<td>86</td>
<td>73</td>
</tr>
<tr>
<td>AV + STDEV</td>
<td>57.04</td>
<td>59.2</td>
</tr>
<tr>
<td>AV</td>
<td>35.2</td>
<td>41.9</td>
</tr>
<tr>
<td>AV - STDEV</td>
<td>13.36</td>
<td>24.7</td>
</tr>
<tr>
<td>VMIN</td>
<td>0.3</td>
<td>14</td>
</tr>
<tr>
<td>STDEV</td>
<td>21.8</td>
<td>17.3</td>
</tr>
<tr>
<td>VAR</td>
<td>476.9</td>
<td>298.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Values</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student’s t-test</td>
<td>t-critical value =1.96</td>
<td>0.166 (&gt;0.05)</td>
</tr>
<tr>
<td>Kolmogorov–Smirnov test</td>
<td>D=0.293</td>
<td>0.046 (&lt;0.05)</td>
</tr>
</tbody>
</table>

The mean age moved this range towards the lower end of the age variation range for the group with determinations strictly in the LN, proving that, although the mean age values were relatively similar (p>0.05, Student’s t-test), the patients with associated determinations were older than those with determinations strictly in the LNs (p<0.05, Kolmogorov–Smirnov test) (Table 2).

**Clinical suspicion**

TB infection was suspected in a reduced number of cases, although, as it will be shown below, an important proportion of bacillary lesions were confined to some LN groups accessible for the physical examination (Figure 6).

![Figure 6 – Suspicion of TB distribution.](image)
Only in 40 of the 362 cases with lymph node lesions, which meant a rate of only 11%, there was a suspicion of tuberculous lesion before histopathology.

In the remaining 323 cases, the suspicion diagnosis was extremely varied (Figure 7).

**Figure 7 – Suspicion of diagnosis distribution.**

In a significant proportion of nearly two thirds of the cases, the met suspected diagnosis, very general and uncertain was that of “adenopathy/polyadenopathy”.

When there was a suspicion, it was directed equally to an inflammatory process or to a neoplastic proliferation but even in this latter case, the diagnosis had a high degree of generality – tumor formation.

In the group of patients that had associated TB determinations with the main LN determination, the suspected diagnosis turned to a neoplastic proliferation in 40% of cases and only in 20% of cases to an inflammatory process (Figure 7).

**Morphological profile**

**Site**

**Single lymph node/LN group involvement**

In most of the cases, the specific TB lesions were identified to only one LN group of the same segment. TB affected simultaneously the LN groups located in several segments in only five of the 362 studied cases (Table 3).

The lesions were located in the LN groups of the head and neck region, groups of LNs accessible to the clinical examination in more than three-quarters of cases.

The cervical region was the segment with the most numerous cases, concentrating alone about two thirds of the cases. The most affected LN groups at this level have been the lateral – cervical lymph groups – 91% of the patients with TB LN lesions at this site (Figure 8), followed by supraclavicular LN groups.

**Figure 8 – Lateral cervical LN group involvement (red arrow) – LN swelling; a fistulizing LN (blue arrow); the scar of a previous LN biopsy (black arrow).**

**Table 3 – The synopsis of single lymph node/lymph node group involvement**

<table>
<thead>
<tr>
<th>Group of lymph nodes</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submandibular</td>
<td>45</td>
<td>12.4</td>
</tr>
<tr>
<td>Retromandibular</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Submental</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Preauricular</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Neck</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral cervical</td>
<td>217</td>
<td>54.4</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>20</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Upper limb</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>34</td>
<td>9.4</td>
</tr>
<tr>
<td>Arm</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Thorax</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavicular</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Inguinal</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Spleen</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Mesocolon</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepatic hilum</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Perithecocystic</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Periappendicular</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepatic hilum</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Periappendicular</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Epiploic</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Paratubal</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Lower limb</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Multiple lymph node groups involvement</strong></td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>362</td>
<td>100</td>
</tr>
</tbody>
</table>

The next region with a significant number of cases was the cephalic region, which gathered together another 14% of the cases with LNTB. The most commonly affected LN group of this region was, by far, the submandibular group, with 88% of the patients with LN lesions in this region.

Of all cases in which upper limb LNs were affected, in only one case the TB lesion was located in the arm.
In all the other cases, the axillary LN group was the interested one.

In the abdominal region, the most frequently affected LN group was the inguinal one which gathered together almost 50% of all the cases in this region, followed, with a significant frequency – almost a quarter of the region cases – by the mesenteric LN group.

In five cases – one diagnosed with pigmented cirrhosis in a female patient of 62 years, one diagnosed with hypersplenism, two diagnosed with splenomegaly including one from a 13-year-old girl, cases in which a splenectomy was performed and, finally, the fifth case which was found at the necropsy – the histopathological examination revealed multiple confluent, granulomatous TB lesions, with areas of caseous necrosis in splenic parenchyma (Figure 9).

In the case of two female patients, one of 84 years and one of 71 years, the granulomatous inflammation affected the LNs from the hepatic hilum.

**Paired lymph node groups**

In 330 of the 362 cases with LNTB, paired lymph node groups were involved. In most of the cases, the involvement was unilateral. Bilateral determinations were found just in nine cases, meaning 3% of paired LN groups’ involvement (Table 4).

Except for the 31 cases, in which in the biopsy material accompanying record it was not specified the side of the TB process in the paired LN groups, there was not any affecting predominance of the right side or the left side group of paired lymph nodes. However, trends were noted in the different LN groups for the right or left side of the body. Thus, if the right submandibular and supraclavicular LN groups were affected more frequently than the left ones, left inguinal and axillary LN were affected more frequently than the right ones. The 31 cases in which left or right location was not mentioned belonged to the most commonly affected LN groups: lateral-cervical, submandibular, axillary, supraclavicular and inguinal ones.

**Unpaired lymph node groups**

In 32 cases, there were affected lymph nodes or lymph node groups with no symmetrical position in relation to the mid sagittal plane (Figure 10).

The mesenteric LNs were the most commonly involved. In six of these cases, the LN involvement was secondary to a TB injury in the drained digestive tract segment.

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**Figure 9** – Tuberculous nodules with confluent epithelioid and giant cell granulomas in the spleen. (a) Under the organ capsule; (b) In parenchyma. HE staining; (a) and (b) ×100.

**Table 4** – The synopsis of paired lymph node groups involvement

<table>
<thead>
<tr>
<th>Group of lymph nodes</th>
<th>Right side</th>
<th>Left side</th>
<th>Bilateral</th>
<th>Not specified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submandibular</td>
<td>20</td>
<td>17</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Retromandibular</td>
<td>0</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preauricular</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neck</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral cervical</td>
<td>89</td>
<td>95</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>11</td>
<td>7</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Upper limb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>12</td>
<td>19</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Arm</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thorax</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavicular</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td>9</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Parasternal</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower limb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Multiple lymph node groups involvement</strong></td>
<td>145</td>
<td>145</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>290</td>
<td></td>
<td>9</td>
<td>31</td>
</tr>
</tbody>
</table>

---
The mesenteric location was followed, as frequency, by spleen and mesocolon LNs (Figure 10).

**Multiple lymph node group involvement**

The five cases in which TB process affected at the same time LN groups located in more than one segment of the organism were as follows:
- a 60-year-old aged man, whose clinical examination revealed the existence of a sessile tumor formation in the left palatine tonsil, accompanied by the morphological change with macroscopic individualization of the homolateral group of lateral-cervical LNs;
- a 54-year-old aged man, whose clinical examination revealed a sessile tumor formation at the left hemitongue accompanied by a homolateral reaction in the lateral-cervical LN group;
- a 35-year-old young man, whose clinical examination revealed changes of latero-cervical bilateral lymph nodes which led the clinicians to extend the investigation by using imaging techniques that have “complicated” a little doctors’ initial suspicion, revealing, in addition, changes of mediastinal and pelvic LNs;
- a 36-year-old young woman, in which the bilateral involvement of the lateral-cervical and axillary groups determined the clinicians to make a suspicion diagnosis of “generalized polyadenopathy”;
- a 61-year-old aged man who presented at the clinical examination, changes of the right side lateral-cervical and submandibular LNs, suggesting an acute inflammatory process.

In all these cases, however, the decision to perform a LN biopsy was salutary because, after the histological examination, the diagnosis was clarified, eliminating, at least for the first four patients, the suspicion of a proliferative process and allowing the setting of a correct treatment.

**Granuloma cellularity**

Inflammatory lesions were dominated by granulomatous type reactions where the main cell population was composed both from epithelioid cells (ECs) and giant Langhans’ cells (GLCs).

The latter are placed usually in the center of the macrophage cell agglomeration (Figure 11; Figure 13, a and b).

The constant presence in most of the patients included in the study of GLCs betrays an active, ongoing conflict, between the body’s defense mechanisms and the BK’s skills to avoid these mechanisms.

Granulomas composed of epithelioid cells only, which means an inflammatory conflict in its early phase, or, in other words, recent TB lesions with an effective macrophage response, were present as the single morphological aspect at a significant percentage of 10% of the cases (Figure 11; Figure 13, c and d).

In a small percentage of the cases, the morphological picture of TB inflammation in the LN parenchyma was noticed in a transitional phase between the early stage and the “illness” stage, phase characterized by the coexistence of the two major types of granulomas: those containing only ECs and those containing both ECs and GLCs (Figure 11; Figure 13, e and f).

Finally, the lesions containing neutrophils (NC), which could mean the reduction of the defense capacity in these patients, were found in over 10% of cases (Figure 12).

**Necrosis**

The cases where we have not identified the presence of the necrosis were very few – 41 in number. The remaining cases showed foci of necrosis in various stages of development and with different degrees of extension. The necrosis displayed the whole range of morphological features from early necrosis to the so-called “non-caseous” necrosis or bacterial superinfected necrosis (Figure 15).
A small number of cases with necrosis (under 10%) presented an incipient necrosis feature (Figures 14a and 15).

The classic, acidophilic necrosis was the most frequent among the lesions with necrotic foci within the LN parenchyma, half of the cases presenting only this type of necrosis (Figures 14b and 15).

Foci of macrogranular, basophilic necrosis, were found in one third of the cases (Figures 14c and 15) and the areas of “non-caseous” necrosis, with altered appearance due to the influx of NCs were found in a small percentage of the cases, namely 14% (Figures 14e and 15).

Both these two latter forms of necrosis are the expression of a more severe bacillary aggression.

In 15 of the cases with modified necrosis, the necrotic foci were large, occupying almost the entirely nodal parenchyma.

**Fibrosis**

The fibrosis was identified in only 14% of the studied LNTB lesions (Figure 16, a and b).

**Degree of differentiation**

For a better assessment of the TB lesions, Ramanathan et al. have proposed, in 1999 [9], an evaluation system of the granulomatous lesions localized only in the LN, which takes into account the whole TB lesion, which includes both the identification of all the cellular components of the inflammatory complex (macrophages, ECs, GLCs, Ns and Lys) and their proportions as well as the tissue destruction (the necrosis) presence, appearance and degree of extension.

The system includes four types of granulomas:

- G1 – hyperplastic granuloma;
- G2 – hyperreactive granuloma;
- G3 – hyporeactive granuloma;
- G4 – non-reactive granuloma.

Furthermore, the authors introduce the notion of granulomatous lesion “degree of differentiation” and group the four types into three groups:

- Well differentiated granuloma (G1 and G2 granulomas);
- Poorly differentiated granuloma (G3 granuloma);
- Disorganized granuloma (G4 granuloma).

![Figure 13](image-url) - *The main types of TB granulomas: (a and b) Granulomas with ECs and GLCs; (c and d) Epithelioid granulomas; (e and f) Mixture of epithelioid granulomas with granulomas with ECs and GLCs. HE staining: (a) and (c) ×200; (e) ×100. CD68 immunomarking: (b) and (d) ×200; (f) ×100.*
Figure 14 – Morphological types of caseous necrosis: (a) Incipient necrosis; (b) Acidophilic, fine granular necrosis; (c) Basophilic, coarse granular necrosis; (d) Basophilic necrosis (left) and acidophilic necrosis (right); (e) Non-caseous necrosis. HE staining: (a), (c), (d) and (e) ×100; (b) ×200.

Figure 15 – Distribution of granulomas according to their necrosis type.

Figure 16 – (a) Massive peri- and intra-granulomatous fibrosis within a lymph node (HE staining, ×100); (b) Highlighting of intra- and peri-granulomatous collageneic network within a lymph node (van Gieson staining, ×100).
We applied the classification system to all the studied lesions, however, after a careful evaluation of all the cases, we modified the scale for a finer discrimination, namely we subdivided the category of hyperplastic granuloma of Ramanathan et al. classification [9] into two subgroups according to the presence or absence of GLC from the granuloma cell population as follows:

- Well differentiated granuloma:
  - Grade IA: hyperplastic granuloma with EC ± incipient necrosis;
  - Grade IB: hyperplastic granuloma with EC and GLC ± incipient necrosis;
  - Grade II: hyper-reactive granuloma with EC and GLC + acidophilic necrosis.
- Grade III: hyporeactive/poorly differentiated granuloma with EC and GLC + basophilic necrosis;
- Grade IV: non-reactive/disorganized granuloma with Ns.

Following this modified classification, the morphological profile of the LN lesions covered the entire range of morphological types described above from the hyperplastic one to the non-reactive one.

The patients with well-differentiated granulomas were the largest contingent of cases, with a proportion of nearly two thirds of the cases.

The Grade IA granulomas, regarded as early stages of the granulomatous lesions formation process were found in a significant proportion of about 10% of cases (Figures 17 and 18a).

The Grade IB granulomas, composed of ECs and, in addition, GLCs, and, more frequently incipient necrosis, were found in a lower proportion than the others, meaning less than 10% (Figures 17 and 18b).

The Grade II granulomas, the classical ones, containing foci of smooth granular acidophilic necrosis in the center, were the most numerous, the percentage being of about 45% of the cases (Figures 17 and 18c).

Grade III hyporeactive granulomas, with foci of modified caseous necrosis, basophilic and macrogranular (which is the indicator of an increased aggressiveness of MT on the background of a decrease of the organism mechanisms of defense), was present in almost one third of the cases, which should be considered a significant proportion (Figures 17 and 18d).

Grade IV non-reactive granulomas, with a significant NC component (a sign of a superinfection) were present in the group of studied lesions, in a surprising proportion, even higher than 10% (Figures 17 and 13).
**Local extension of TB infection**

The local extension of the LNTB lesions was relatively frequently encountered, almost one third of the cases presenting bacillary lesions in more than one LN simultaneously or beyond LN’s capsule (Figure 19).

In two cases, the TB process extended beyond the LN capsule, generating a fistulous tract, opened on the integument surface. Thus, in 14 years aged patient one of the simultaneously affected LN of the left lateral cervical group fistulized in the posterior triangle of the neck (Figure 8) and in a 65-year-old woman the right lateral cervical LNs fistulized in the anterior triangle of the neck.

![Figure 19 – The steps of TB lesions extension beyond the LN capsule (LN C). HE staining, ×40.](image)

**Discussion**

**Clinical profile**

As we mentioned above, on one hand, the study was a retrospective one and based only on records and materials (slides and paraffin blocks) belonging to our department and, on the other hand, the diagnosis of TB was an incidental discovery of the histological examination in most of the cases. After the diagnosis was sent to the surgical and medical departments, we had no feedback from them concerning the patient and, therefore, we had no information about the primary of secondary character of the LNTB lesions, excepting those cases that we already mentioned where we had surgical specimens including both the lymph nodes and the fragment of the drained organ with lesions to be cleared up by the histological examination.

**Lymph node involvement**

The comparison of our data with similar studies in the literature was quite difficult because the cases inclusion criteria in the study groups were often different from one study to another.

In all the studies we compared with, the percentage of lymph node involvement was generally over 30%, with only one exception, the South Korean study of Yoon *et al.* (Table 5).

### Table 5 – The share of LN involvement in different other studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>No. of cases</th>
<th>LN%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>1990–2012</td>
<td>732</td>
<td>49.45</td>
</tr>
<tr>
<td>CDC, 2004 [15]</td>
<td>2003</td>
<td>3029</td>
<td>43.2</td>
</tr>
<tr>
<td>CDC, 2008 [16]</td>
<td>2007</td>
<td>2697</td>
<td>42.5</td>
</tr>
</tbody>
</table>

**Temporal evolution**

The only study that analyzed the time evolution of the LNTB was an Estonian study led by Pheme *et al.* [11], but we had to select of our studied cases only the time interval that overlapped the one of Estonian researchers (Figure 20). Comparing the evolution of the LNTB incidence on the interval of time that the two studies overlapped (between 1991 and 2000), one can see an almost parallel evolution, with a peak incidence between 1996–1998 and a significant decrease of cases with more than 50% at the end of the common interval (i.e., in 2000). However, the evolutionary trend of LN involvement was a negative one in our study and a positive one in the Estonian study group (Figure 20).
Lymph node tuberculosis – an attempt of clinico-morphological study and review of the literature

Figure 20 – Comparison of the temporal evolution with the Estonian series.

Gender

In all the consulted studies it was considered that both gender and ethnicity play a major role in the development of LNTB. Most of the studies have shown a prevalence of females to males with a ratio greater than 2:1 [1, 2, 4, 17–22]. This female preponderance appears somehow paradoxical given that pulmonary TB has a higher incidence in males [23].

Of the international studies taken for comparison, only those of Pheme et al. [11], Forssbohm et al. [12] and Yoon et al. [14] included the evaluation of LN involvement gender distribution. The gender distribution varied in a very wide range, however, the M/F ratio was subunitary in all studies, and in other words, the number of affected women was greater.

The limits were, on one hand, the net predominance on the female affecting in the Korean group [14] and, on the other hand, the almost equal gender ratio – 0.97 – in the Estonian series [11].

In our group, the female predominance was moderate with a 0.63 value of the M/F ratio, or, reversing the ratio, for a more suggestive representation, a value of 1.57 for the F/M ratio (Figure 4).

Figure 21 – The gender distribution in other studies.

The value of the F/M ratio obtained by us is consistent with the three studies where we found explicit data (Figure 21) but also with the retrospective mentioned studies.

Age

Although LNTB has been described and, for a long time, regarded as a disease that occurs most frequently in children and most often in the first six months after the primary infection, since the '70s, the epidemiological studies began to show that LN involvement peak of incidence gradually moved to young adults, aged between 20 and 40 years, although it is still frequently present in children [1, 2, 4, 20, 24–27].

A study which falls within this new pattern of distribution is the Turkish one of Ilgazli et al. [6] which, in a group of 636 cases, found that, although the age range which was including all the cases was from 1 year to 86 years, the mean age was of 22.5 years, with a STDEV of 17.1 years, with about three quarters of the cases concentrated before 40 years, of which 41.4% aged under 15 years, and the remaining 30.9% between 20 and 39 years.

Our study is close enough to this pattern of distribution, with almost two thirds of cases under the age of 44 years but only 18% of cases under the age of 15 years, with a mean age of 35 years and a STDEV higher than 21.63 years, meaning a larger and more uniform age group dispersion.

Of the all consulted international studies, only those of Forssbohm et al. from Germany [12] and of Yoon et al. from Korea [13] included the evaluation of LN involvement age distribution. There are significant differences between LN involvement age group distributions in our series and the German one (Figure 22).

Figure 22 – Comparison of age groups distribution with Forssbohm et al. [12] series.

Thus, while in our series, with a somehow more homogenous distribution, around half of the cases were aged between 25 and 40 years, the age periods of the adult, in German series, the distribution was polarized towards the age variation range ends, more than 40% of cases being children and adolescents and another more that 30% of cases being elderly.

The comparison of our data with those of the Korean study revealed a higher mean age in the Korean series (mean age – 38.4 years; STDEV – 16.1) but a larger dispersion of the majority of cases in our series (mean age – 33.5 years; STDEV – 21.6).

However, if we put together the results of German and Korean studies, we will observe, in both of them, a larger group with ages higher than 44 years and a reduced group of children. Therefore, if we take into consideration the fact that the populations to whom these trials were addressed to had a more favorable economic and social context while the populations to whom our study and the Turkish study were addressed to are the beneficiaries of some more unfavorable social and economic conditions, we could say that the economic and social disadvantaged status moves the LN involvement
incidence towards the young ages and especially towards childhood.

**Clinical diagnosis**

Patients usually come to the doctor because they present visible and palpable LNs, which are painless and slowly enlarging and, complaining of fever as general manifestation [7, 28–30]. Other systemic manifestations include weight loss, fatigue and night sweats but these symptoms may also be missing. However, fever, night sweats and weight loss, are usually present in patients with HIV infection [7, 30–32].

Sometimes, clinical examination can detect nothing but the palpable lymphadenopathy, the disease being completely asymptomatic. However, it should not be forgotten that, although rarely, abscesses in the LN can fistulize, causing the formation of non-healing chronic fistulae and ulcerative lesions [30].

Therefore, given that there is sufficient evidence to draw attention to the clinician about the possibility of LN structures tuberculous involvement, we will make further some remarks about the diagnosis written on the LN tissue specimen accompanying records received in the histopathology department.

The only consulted study that assessed the suspected diagnosis at admission was the study of Yoon et al. [14]. The difference is significant, i.e., while in the Korean study suspected diagnosis was present in two thirds of the cases in our study, it practically did not exist (Figure 23).

![Figure 23 – Comparison of the diagnostic suspicion with the Korean series.](image)

If we exclude from our cases those diagnosed with “adenopathy/polyadenopathy”, the ratio between the suspicion of inflammatory lesions and tumor lesions is almost similar to that in the Korean group but with a slight predominance for the diagnosis of tumor lesion (Figure 24).

![Figure 24 – Comparison of the suspected diagnosis with the Korean series.](image)

From the 221 cases with an uncertain diagnosis, 207, meaning 94%, have had TB lesions developed in superficial LN groups, accessible to the clinical examination. In the other 14 cases, the involved LNs were situated in the abdominal cavity, so inaccessible to the direct clinical examination.

In 19 of the 48 cases with suspicion of inflammatory process, the diagnosis was of suppurative adenitis. The site was, with four exceptions (located in the inguinal region), the head and neck region, mostly lateral cervical LN groups. In other words, we identified 19 cases in which a careful and thorough clinical could have raised the suspicion of TB.

We want to insist, however, on the 206 cases where the suspicion diagnosis was extremely elusive – adenopathy/polyadenopathy. Only six of these cases had deep located LN lesions. The remaining 200 cases had lesions of the LN groups superficially located, so accessible for the careful physical examination, and, moreover, the vast majority of these were lateral cervical LN groups. Nevertheless, in all these cases, which represented about two thirds of the cases with mismatch diagnosis, there was at least no attempt of classification in the two major categories of differential diagnosis, namely inflammatory processes of other origin (either acute or chronic), or neoplastic proliferative processes (whether benign or malignant).

This lack of minimal clinical information forwarded to the pathologist can sometimes put its imprint negatively on the pathological diagnosis elaboration.

**Morphological profile**

**Location**

The profile of the LNs/LN groups involvement of our series is not different from that outlined by the numerous studies published over time in the literature.

Thus, it has been demonstrated that the TB inflammatory process affects the LN groups following a certain hierarchy, dictated by the relation of BK with the entrance gate, irrespective of whether it is about primary or secondary infection. The most commonly affected peripheral LN are the cervical ones. Of these, the favorite locations are anterior cervical and posterior LNs, and supraclavicular LNs. According to some authors, TB cervical lymphadenitis would be the most common or among the most common forms of EPTB. Submandibular and submental LNs are rarely affected. The following LN groups are the axillary, the mesenteric and the peripancreatic ones (most commonly affected groups in the abdominal LNTB), then inguinal, epitrochlear, mediastinal, intramammary groups [20, 28, 29, 33–44].

Other less common locations of the abdominal TB lymphadenitis include the retroperitoneal LNs, the hepatic hilum LNs and the generalized lymphadenopathy with discrete swelling of all the peripheral LNs, which mimics neoplasia. However, the generalized micropolyadenopathy regarded once as a specific manifestation of TB, has nowadays exceptionally a bacillary etiology [33, 45].

In our study, the lymph node involvement falls within this classic pattern, being firstly the most common site of the EPTB process and in a significant proportion (about half of the patients).
Secondly, the hierarchy of the main LN groups’ predilection of involvement is generally the same as defined in the literature, with lateral cervical LNs on the first place, followed by the submandibular and the axillary groups.

However, in our hierarchy a reversal of seats between inguinal LNs and the mesenteric ones appeared which has not, anyhow, a major significance because it follows the variability trend, sometimes significant, of the data reported by various studies.

If, as we have already underlined above, the LN percentage of involvement itself is highly variable – between 18.2% and 52.9% in the cited studies (Table 5) – the LN involvement hierarchy is, in the same way, subjected to the same phenomenon of study to study variability.

An example in the support of this assertion is the study of Ilgazli et al. [6] already mentioned. If the LN location represented more than half of cases (56.3%), following somehow the general rule, the most commonly affected LN group, in a significant percentage of 71.5%, was the intrathoracic one, cervical and axillary groups coming in the next positions but at a great distance – 25.7% and 2.8%. The explanation could be the significant prevalence of patients under 15 years – 41.4% – in the Turks authors study, being known that, in children, the percentage of involvement hierarchy is, in most of the cases, modified in the following somehow the general rule, the most commonly involved LN group, in a significant percentage of 71.5%, was the intrathoracic one, cervical and axillary groups coming in the next positions but at a great distance – 25.7% and 2.8%. The explanation could be the significant prevalence of patients under 15 years – 41.4% – in the Turks authors study, being known that, in children, the percentage of involvement hierarchy is, in the same way, subjected to the same phenomenon of study to study variability.

As previously mentioned, our series included five spleen determinations, discovered incidentally either after the splenectomy (performed in four cases based on the clinical suspicion of pigmented cirrhosis or neoplastic proliferation) or at necropsy (in one case). Although it is an important manifestation of EPTB [46–49] isolated splenic TB is a rare entity and the clinical morphological form of tuberculosis is even more rare, with only a few cases reported in the literature in recent decades in Western countries. Nevertheless, it should be included in the differential diagnosis of the unknown origin fever in patients from an endemic area [47, 50, 51]. However, the splenic involvement is usually more frequent in patients with disseminated miliary tuberculosis that were diagnosed based on other locations [52].

**Granuloma cellularity**

The assessment of the granuloma cell population allows us to say that if the GLC granulomas together with early CE granulomas dominated the morphological picture of the majority of the cases (88% of cases), then the conflict between MT and the inflammatory and immune defense systems of the patient was an active one, in full swing.

**Necrosis**

The presence of the necrosis is one of the important indicators of the TB infection degree of aggressiveness, signifying either a strong toxic effect of the pathogen agent on the macrophage either a vigorous delayed hypersensitivity type response of the host to the action of that agent [53]. The high percentage of cases in which necrosis was part of the morphological picture is consistent with the above observation concerning the cellular population of the granuloma, pleading once again for the active trait of the conflict between BK and the LN tissue in most of our cases.

**Fibrosis**

The fibrillogenetic process is a controversial one. On one hand is its original role – to isolate the inflammatory focus and limitate the infection spread. On the other hand is its continuous and permanent destructive action on the tissue where it starts.

The high number of cases in which this process was not found is another argument for the active trait of the TB process when it was discovered.

**Degree of differentiation**

Morphological analysis of the granulomatous reaction as a whole, showed that granulomas developed in the studied LN structures were, in almost two thirds of the cases, granulomas with an obvious destructive component, in other words, aggressive and advanced lesions, with extensive trend, meaning lesions with a high grade of severity.

The analysis of granulomatosus lesions morphological profile, taking also into consideration their mode of organization, could lead to the assumption that LN tissue could present a higher susceptibility to the aggressive, destructive and extensive forms of TB infection, assumption sustained by the significant presence of hyporeactive an non reactive granulomas.

As we already mentioned, the only study in the literature that makes an analysis of the morphological microscopic features of the TB granulomatous lesion and which is dedicated only to the granulomatous lesions localized in the lymph nodes is that of Ramanathan et al. [9].

Comparing our data with those of the Indian authors, following both the granuloma type criterion and the granuloma organization criterion, we found that, while in our study the percentage of the various types of granulomas is somehow homogeneous, with the dominance of reactive and hyporeactive granulomas, in the Indian group the reactive granulomas were the dominant ones, representing alone more than a half of the cases (Figure 25).

**Figure 25 – Comparison of the suspected diagnosis with the Indian series.**

It also can be noted, in the Indian series, the change of the incipient/superinfected granulomas ratio in favor of the former. If we consider the mode of organization, we can see that in the Indian group the well differentiated granulomas clearly dominated, signifying recent, evolving...
TB lesions, while in our group the proportion of poorly differentiated and non-reactive granulomas has grown to almost 40% (almost twice as in the Indian group) revealing a more vulnerable background of the patients with LN lesions (Figure 25).

Conclusions

Lymph node system proved to be, at least in our series, the favorite site for TB process development outside the lung parenchyma. The clinical profile is most often the one a young woman, presenting almost always only a LN involvement, usually of only one LN group, situated in most of the cases superficially in head and neck region. However, associations with other extranodal locations and deep locations should not be neglected. In spite of the direct clinical examination accessibility in most of the patients, TB infection was only rarely suspected, the diagnosis at admission inclining either towards a neoplastic type proliferation or towards an expectative attitude with the transfer of the decision to the pathologist. However, any clinician has to have in mind that the lack of minimal clinical information can, sometimes, to negatively influence the elaboration of the pathological diagnosis. Granulomatous reaction was in a significant number of cases of poorly differentiated or disorganized type, with necrosis rather basophilic and non-caseous when existed and with a reduced perifocal fibrillary reaction. The morphologic picture put in rare cases the problem of correctly establishing the diagnosis, but revealed an active and destructive profile of the bacillary process, when existed and with a reduced perifocal fibrillary reaction.

Before ending

This article is the first from project consisting of a series of articles about extrapulmonary tuberculosis, and being dedicated to the memory of our colleague and friend, Dr. Stelian Dănuț Enache (1953–2012), a true example of devotion, and respect for the profession of pathologist and the suffering patient.

References

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