

Peripheral adenopathies in children – an attempt of clinical morphological profile

GEORGETA LIGIA STĂNESCU¹⁾, GIGI CĂLIN¹⁾, IANCU EMIL PLEȘEA^{2–4)}, CĂTĂLINA MARIN⁵⁾, MIRCEA OVIDIU CIOBANU⁶⁾, GEORGE ALIN STOICA⁶⁾, ELENA LOREDANA ȘELARU⁷⁾, REBECA CRISTIANA ȘERBAN⁷⁾, CRISTINA POPESCU⁷⁾, RĂZVAN MIHAIL PLEȘEA⁸⁾, LUCIAN PAUL DRAGOMIR⁹⁾

¹⁾Department of Pediatrics, University of Medicine and Pharmacy of Craiova, Romania

²⁾Department of Pathology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

³⁾Doctoral School, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁴⁾Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania

⁵⁾Department of Pathology, Anton Cincu Municipal Hospital, Tecuci, Romania

⁶⁾Department of Pediatric Surgery, University of Medicine and Pharmacy of Craiova, Romania

⁷⁾PhD Student, Doctoral School, Department of Pediatrics, University of Medicine and Pharmacy of Craiova, Romania

⁸⁾Department of Cellular and Molecular Biology, University of Medicine and Pharmacy of Craiova, Romania

⁹⁾Department of Occlusology and Fixed Prosthetics, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Aim: The authors have proposed to assess peripheral adenopathies in a series of hospitalized children in order to identify and define clinical and morphological profiles of different types of lymph node (LN) diseases. **Materials and Methods:** The studied group consisted of 58 patients less than 18 years of age. The investigation algorithm included: gender, age, site, involvement, side, extension and histopathological (HP) type of LN lesions. Tissue fragments were processed using classical histological techniques (formalin fixation and paraffin embedment) and stained with Hematoxylin–Eosin (HE). In some cases (tuberculous lesions and lymphomas), special stainings (Ziehl–Neelsen) and immunohistochemistry were used. Stratification scales of cases were defined according to each parameter in order to compare the data. All obtained data were assessed individually, compared to each other and with similar data from the literature with the help of a statistical apparatus [χ^2 (chi-squared) test and analysis of variance (ANOVA) test] in some cases. **Results:** The young patients were slightly more frequently boys, of all ages but with a mean age of 10 and half years. The affected LNs belonged most often to neck region, either on the left or on the right side but sometimes bilateral or even on the midline; usually, more than one LN was involved in the area. In most of the cases, the lesions were localized in only one LN area. HP picture was dominated by the inflammatory processes, firstly the nonspecific ones, followed by tuberculosis. **Discussions:** Our observations fitted, for each parameter, with the wide ranges found in the literature. Comparisons between parameters' variations revealed differences, sometimes significant that we tried to organize in clinical and morphological profiles. **Conclusions:** The assessment of our data allowed us to define some clinical and morphological profiles of different types of adenopathy that, by improvement on studies including larger series, could be of real use in daily pediatric practice.

Keywords: peripheral adenopathy, children, clinical profile, histopathology.

Introduction

Peripheral lymph nodes (LNs) are those which are located deep in the subcutaneous tissue and can be clinically identified if any physiological or pathological process causes their enlargement [1]. An updated and modified classification of peripheral anatomical regions/locations of LNs could be as follows [2–4]:

- the *head region groups*: pre-auricular, occipital, posterior auricular, parotid, jugulo-digastric (tonsillar) submaxillary and submental;
- the *cervical (neck) region groups*: anterior (superficial, profound) and posterior;
- the *trunk region*: supraclavicular group;
- the *upper limb region*: infraclavicular, axillary and epitrochlear groups;

- the *lower limb*: inguinal and popliteal space groups.

The change we made to the already recognized distributions of the peripheral LNs locations/regions was to consider the supraclavicular group as being the peripheral LN group belonging to the trunk region.

Lymphadenopathy (LAP) is the term to describe the conditions in which LNs become abnormal in size, considered the most important clinical feature, but also in consistency and number, becoming palpable in peripheral sites [1, 5–7].

In addition to the morphological changes, the degree of extent of LN involvement is another important aspect of LAP assessment. The first step is to establish if only one LN is involved (solitary) or more than one (multiple) [8, 9]. If multiple LNs are involved, the second step

implies to establish how many LN groups are involved. Karadeniz *et al.* [10] defined, around the 2000s, three degrees of extension of the LAP involvement, as follows:

- *localized LAP* – a single anatomic LN area involved;
- *limited LAP* – two or three LN areas involved;
- *generalized LAP* – four or more anatomic LN areas involved [10].

After almost 10 years, Friedmann returns to a simplified scale proposed also around the 2000s by Ferrer, considering as generalized LAP the involvement of two or more noncontiguous anatomic LN areas [5, 11]. Some authors precise in addition the position of the affected LNs in relation to the mid-sagittal plane, that can be *unilateral* (left or right), *median* or *bilateral* [8].

It is a fact that about one-half (38–45%) of otherwise healthy children have palpable LNs at any one time, discovered during common physical examination because, for instance, of intrinsic physiological lymphocyte proliferation of the LN that can result in its volume increase [12, 13]. That is why the morphological clinically evident changes of peripheral LNs represent a challenge for the general pediatrician in order to distinguish non-pathological from pathological situations, and that because these changes may represent:

- normal age related physiological changes;
- transient response to various benign local or generalized infections originating from upper respiratory tract or skin;
- chronic infections like tuberculosis (TB), brucellosis;
- serious conditions like malignancy and autoimmune disorders or other rare causes;
- idiopathic and self-limiting condition, and that frequently enough [11, 12, 14–16].

LAP is associated with numerous disorders both benign and malignant so that it is often difficult to determine clinically the cause in order to establish the appropriate therapeutic strategy [17–20].

Many authors struggled to define a classification as comprehensive as possible of LAPs according to their cause. Habermann & Steensma [20] proposed, in the 2000s, an organization of LAPs causes under the acronym “CHICAGO”:

- **Cancers** (hematological and metastatic);
- **Hypersensitivity syndromes**;
- **Infections** (viral, bacterial, fungal, protozoan, rickettsial, helminthes);
- **Connective tissue disorders**;
- **Atypical lymphoproliferative disorders**;
- **Granulomatous reactions**;
- **Others**.

Almost two decades later, Gaddey & Riegel [21] reorganized the wide range of causes under a simpler mnemonic formula, namely “MIAMI”:

- **Malignancies**;
- **Infections**;
- **Autoimmune disorders**;
- **Miscellaneous and unusual conditions**;
- **Iatrogenic causes**.

The etiological profile varies however from country to country and region to region and, with all efforts, the precise incidence of LAPs remains one of the most common clinical problems encountered in Pediatrics [22, 23].

Starting from these premises, our study intends to define a clinical and especially morphological profile of different types of peripheral LN enlargements.

Materials and Methods

The study was a retrospective one and included 58 patients less than 18 years of age hospitalized in the Surgical Departments of Emergency County Hospital of Craiova, Romania, during a five years’ period (2008–2012), whose clinical diagnosis established in these Departments was a general one – “lymphadenopathy”. The study was performed in agreement with the ethical standards of the Helsinki Declaration. All patients signed an informed consent agreement for the surgical protocol. The main including criterion was the LN degree of enlargement. The thresholds beyond which palpable LNs were considered abnormal were those recommended by Mohseni *et al.* [1] citing Morland [24] and Bazemore & Smucker [4], and listed below in Table 1.

Table 1 – Thresholds for lymph node enlargement

Dimension	Lymph node group
>0.5 cm	Supraclavicular
	Epitrochlear
	Iliac
	Popliteal
>1 cm	Nodes in other areas
>1.5 cm	Inguinal nodes

The studied material consisted of two different types of data: (i) accompanying notes of tissue specimens coming from operation theatres; (ii) histopathological (HP) records and HP samples paraffin blocks of each case from our Department’s Archives.

The assessed parameters were grouped into two main categories (Table 2):

Table 2 – The set of studied parameters

Parameter type	Parameter
<i>Clinical</i>	Gender
	Age
<i>Morphological</i>	Lymph node involvement
	Gross aspects
	Lesion’s side (related to mid-sagittal plane)
	Lesion’s site
	Lesion’s extension
Lesion’s histological type	

The tissue samples consisted of tissue fragments obtained either by surgical removal or by biopsy. Further, they were processed using the classical HP technique (formalin fixation and paraffin embedding) and then stained with Hematoxylin–Eosin (HE). To confirm the tuberculous etiology, Ziehl–Neelsen staining for acid-fast bacilli and immunostaining for *Mycobacterium tuberculosis* (Mt) were carried out. Also, immunohistochemical staining methods were used to identify the phenotype of malignant proliferations [25–28]. The used antibodies are listed in Table 3.

HP aspects were selected with a CX31 Olympus microscope using the ×4 magnification eyepiece. For image acquisition, optical plan-apochromatic corrected objectives with ×4, ×10, ×20 and ×40 magnifications were used.

The most significant features were acquired using a LiveViewPro II digital camera, saved on the computer, and processed using specialized image analysis software: analysis Pro, and ACDSec 4.0.

Table 3 – Antibodies used in the study

Antibody	Clone	Specificity	Source	Dilution	Pretreatment (AR method/time/temperature/pH)
Mo anti-Hu Mt	BGN-3875	Mt	Novus Biologicals	1:500	CB/20 minutes/6
Mo anti-Hu CD20	L26	B-cells	DAKO	1:200	No
Mo anti-Hu CD23	1B12	B-cells	Novocastra	1:100	ERS/20 minutes/95–100°C/ 20 minutes/RT
Mo anti-Hu CD79a	HM57	B-cells	DAKO	1:100	No
Mo anti-Hu CD3	F7.2.38	T-cells	DAKO	1:100	TRS/20 minutes/99°C/6.1
Mo anti-Hu CD5	4C7	T-cells	Vector	1:30	AR/15 minutes/100°C/6.0
Mo anti-Hu CD30	BerH2	Large B-cells dysplastic	DAKO	1:30	TRS/20 minutes/99°C/6.1
Mo anti-Hu CD45.RO	UCHL1	Large B-cells dysplastic	DAKO	1:100	No
Mo anti-Hu Bcl-2	124	Alteration of B-cell lineage	CellMq	1:100	EDTA/15 minutes/100°C/8.0
Mo anti-Hu Ki67	MIB-1	Cell proliferation	DAKO	1:75	EDTA/15 minutes/100°C/8.0

AR: Antigen retrieval; Bcl-2: B-cell lymphoma 2; CB: Citrate buffer; CD: Cluster of differentiation; EDTA: Ethylenediaminetetraacetic acid; ERS: Epitope retrieval solution; Mo: Mouse; Hu: Human; Mt: *Mycobacterium tuberculosis*; RT: Room temperature; TRS: Target retrieval solution.

In order to compare our results with those from the literature, we identified and could access 25 studies related to involvement of LNs of peripheral groups. However, not all these papers evaluated the entire set of parameters we used. Unfortunately, not all studies referred to peripheral groups of LNs as a whole. Six of them included only the

LNs of cervical groups and one study referred only to head and neck region.

We included also in the list a study of peripheral LNs extended beyond the age of 18, including also adults and elderly.

All these studies are listed in Table 4.

Table 4 – References from the literature used for comparison with our data

Reference No.	Author(s), year	Country	Period	No. of cases	Observations
[29]	Adeniji & Anjorin, 2000	Nigeria	1979–1996	751	All ages
[30]	Obafunwa <i>et al.</i> , 1992	Nigeria	Three years	129	
[10]	Karadeniz <i>et al.</i> , 1999	Turkey	Not mentioned	382	
[31]	Reddy <i>et al.</i> , 2002	India	1995–1998	100	
[32]	Al-Nazer & Al-Salem, 2003	Saudi Arabia	1989–2001	71	
[33]	Okolo <i>et al.</i> , 2003	Nigeria	1988–1997	242	
[34]	Oguz <i>et al.</i> , 2006	Turkey	1996–2004	457	
[35]	Yaris <i>et al.</i> , 2006	Turkey	Three years	98	
[23]	Adesuwa Olu-Eddo & Egbagbe, 2006	Nigeria	1984–2003 (20 years)	126	
[36]	Anunobi <i>et al.</i> , 2008	Nigeria	1991–2004	720	P-LAP
[37]	Hanif <i>et al.</i> , 2009	Pakistan	1999–2007	898	
[38]	Latifagic <i>et al.</i> , 2011	Bosnia and Herzegovina	1998–2003	334	
[39]	De Corti <i>et al.</i> , 2014	Italy	2002 to 2006	217	
[40]	Özkale <i>et al.</i> , 2015	Turkey	Two years	224	
[41]	Gwili <i>et al.</i> , 2014	Egypt	Not mentioned	49	
[42]	Sarsu & Sahin, 2016	Turkey	Not mentioned	1700	
[9]	Singh <i>et al.</i> , 2016	India	2012–2015	498	
[7]	Rao <i>et al.</i> , 2019	India	2015–2017	50	
[6]	Yadav, 2019	India	Not mentioned	126	H&N-LAP
[43]	Citak <i>et al.</i> , 2011	Turkey	Not mentioned	282	
[44]	Al-Tawfiq & Raslan, 2012	Saudi Arabia	1997 to 2008	143	
[45]	Ingolfsdottir <i>et al.</i> , 2013	Denmark	2000–2010	43	C-LAP
[8]	Patar <i>et al.</i> , 2014	India	2012–2014	182	
[46]	Bozlak <i>et al.</i> , 2016	Turkey	Not mentioned	218	
[47]	Khan <i>et al.</i> , 2008	India	2004–2005	89	

C-LAP: Cervical lymphadenopathy; H&N-LAP: Head & neck lymphadenopathy; P-LAP: Peripheral lymphadenopathy.

The assessment of some parameters required the defining of stratification scales of cases according to each of them.

For age evaluation, the scales were those established by Eunice Kennedy Shriver National Institute of Child Health and Human Development in the United States [48, 49] and presented in Table 5.

For site evaluation, the scale included the main anatomical regions of the body: head, neck, trunk (including both thoracic and abdominal regions), upper limb and lower limb.

“Involvement” parameter referred to the number of LNs accomplishing the including criterion. The two categories of this scale were solitary and multiple.

Table 5 – Stratification scale for age

Age period (AP)	Description	
AP1	0–12 months	Infancy
AP2	1–2 years	Toddler
AP3	3–5 years	Early childhood
AP4	6–11 years	Middle childhood
AP5	12–18 years	Early adolescence
AP6	19–21 years	Late adolescence

For “side” evaluation, the scale included: unilateral, right, left and not otherwise specified (NOS), bilateral and midline categories.

For “extension” assessment, we preferred the above-mentioned scale proposed by Karadeniz *et al.* [10] because it is more comprehensive and was used in some of the selected studies.

Finally, for lesions’ HP type, we used the scale summarized in Table 6 that also considers the classification scales used by other authors.

Table 6 – Histopathological types of lymph node lesions

Abbreviation	Our study	Other studies
R	Reactive	+ Sinus histiocytosis
INF	Inflammation	Acute +/- chronic/granulomatous + sarcoidosis
TB	Tuberculosis	
P-NEO	Primary neoplasia	(lymphomas +/- others)
S-NEO	Metastases	
O/U	Other/unknown	

For the morphology of tuberculous lesions, we applied a classification system proposed by Ramanathan *et al.*, in 1999 [50], for tuberculous granulomatous lesions of LNs according to their organization and modified by our group [51]. The scale is presented in Table 7.

Table 7 – Granulomas classification according to their degree of organization {modified by Popescu *et al.* (2014) [51] after Ramanathan *et al.* (1999) [50]*}**

Type	Code*	Code**	Grade*	Cells	Necrosis	
Hyp	G1	la	Well differentiated	EC	Scarce	Absent / IN
		lb		EC + GLC		
R	G2	II		m EC M L and P	EN Mi	
Hypo	G3	III	Poorly differentiated	M i EC L and P	BN Ma	
A	G4	IV	Disorganized	M L, P PMN	NCN	

A: Areactive; BN: Basophilic necrosis; EC: Epithelioid cell; EN: Eosinophilic necrosis; GLC: Giant Langhans cell; Hyp: Hyperplastic; Hypo: Hyporeactive; i: Immature; IN: Incipient necrosis; L: Lymphocyte; m: Mature; M: Macrophage; Ma: Macrogranular; Mi: Microgranular; NCN: Noncaseous necrosis; P: Plasma cell; PMN: Polymorphonuclears (neutrophils); R: Reactive.

Graphs that illustrated evolutionary trends of the different parameters, the statistical comparisons between them, as well as comparisons with other studies were made using the “Graph” tool from “Word” and “Excel” modules of the Microsoft Office 2016 Professional software suite and the XLSTAT 2014 add-on for the “Excel” module.

Statistical tools used were for “age” parameter analysis of variance (ANOVA) test for more than two independent samples and χ^2 (chi-squared) test for all the other parameters.

Results

General description

First of all, we made the assessment of the clinical and morphological parameters related to the entire group of patients.

Clinical aspects

The pathological involvement of peripheral groups of LNs was encountered more frequently in boys than in girls. The age range was extremely wide, from four months infants to 18-years-old adolescents, but with most of the cases grouped in the middle childhood and early adolescence. Thus, the mean age was of 10 and half years.

Gross aspects

Most of the affected LNs belonged to the upper part of the body, more than half of the cases having LNs of the cervical region involved. followed by those of head region and upper limb region. The latter included only LNs from axillary group. LNs from the lower part of the body were affected in only two cases; in both of them, the lesions involved the inguinal group (Table 8).

Table 8 – Assessment of clinical and morphological parameters for all cases

Parameter	Subtype	No. of cases
Gender	Males	31
	Females	27
Age	Infancy (AP1)	2
	Toddler (AP2)	1
	Early childhood (AP3)	7
	Middle childhood (AP4)	24
	Early adolescence (AP5)	24
Site	Head	11
	Neck	34
	Upper limb (UL)	11
	Lower limb (LL)	2
Involvement	Solitary (S)	22
	Multiple (Mp)	36
Side	Unilateral right side (UNI-R)	19
	Unilateral left side (UNI-L)	19
	Unilateral NOS (UNI-NOS)	13
	Bilateral (BI)	5
Extension	Localized (LOC)	49
	Limited (LIM)	8
	Generalized (GEN)	1
Histopathology	Reactive (R)	9
	Inflammatory process (INF)	23
	Tuberculosis (TB)	20
	Neoplasia (NEO)	6

AP: Age period; NOS: Not otherwise specified.

In more than one third of the patients, clinical examination revealed that only one LN was involved. Instead, most patients (62%) had at least two affected LNs, either in the same regional group or in different regional groups (Table 8).

Excepting seven patients, two with midline submental LAP and five with bilateral LAP, the rest of the cases had unilateral involvement of LNs without any predilection for either side (Table 8).

As for the extent of the lesions, they were localized in most patients, affecting one or more LNs of the same group (Table 8).

Histological aspects

“Reactive” LNs

In a significant number of cases (15%), the LN enlargement accompanied the presence of an inflammatory conflict in the draining areas of the affected LN(s). The dominating morphological aspect was the increase in size and number of the B-cells in the germinal centers – **follicular hyperplasia** (Figure 1, a and b) but, sometimes, histiocytic cells expanded in the medullary and cortical sinuses – **sinus hyperplasia**.

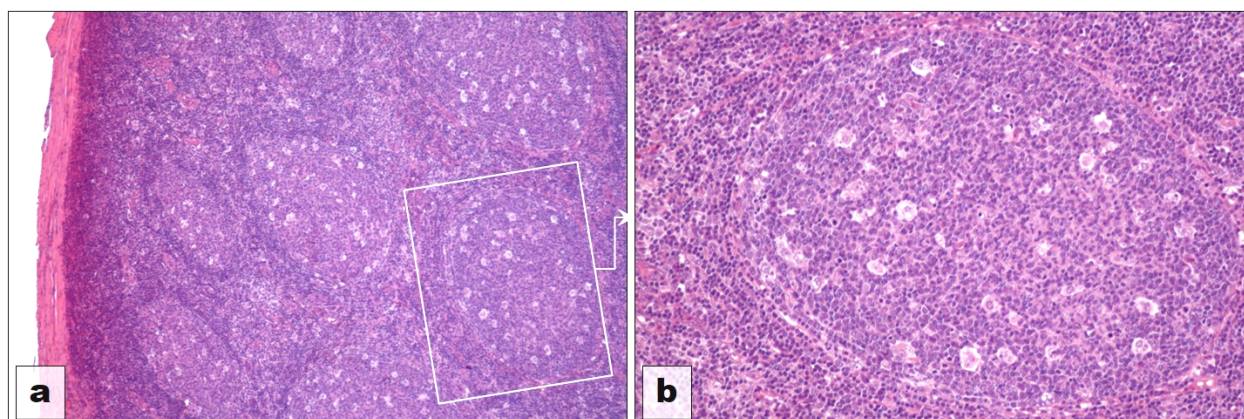


Figure 1 – Reactive lymph node with prominent follicular hyperplasia. HE staining: (a) $\times 40$; (b) $\times 100$.

Lymphadenitis

Inflammatory processes developed within the LN parenchyma represented almost 40% of the investigated lesions. In half of these cases (12 cases), the process was clinically defined as acute, with the presence of cardinal Celsian signs (*rubor, tumor, calor, dolor*). The HP picture

revealed an inflammatory infiltrate rich in neutrophils, rarely generating microabscesses but most often creating large areas of suppurated necrosis with a lot of neutrophils and few lymphoid cells, which tended to be isolated from the healthy parenchyma by a capsule of collagen fibers (Figure 2, a and b).

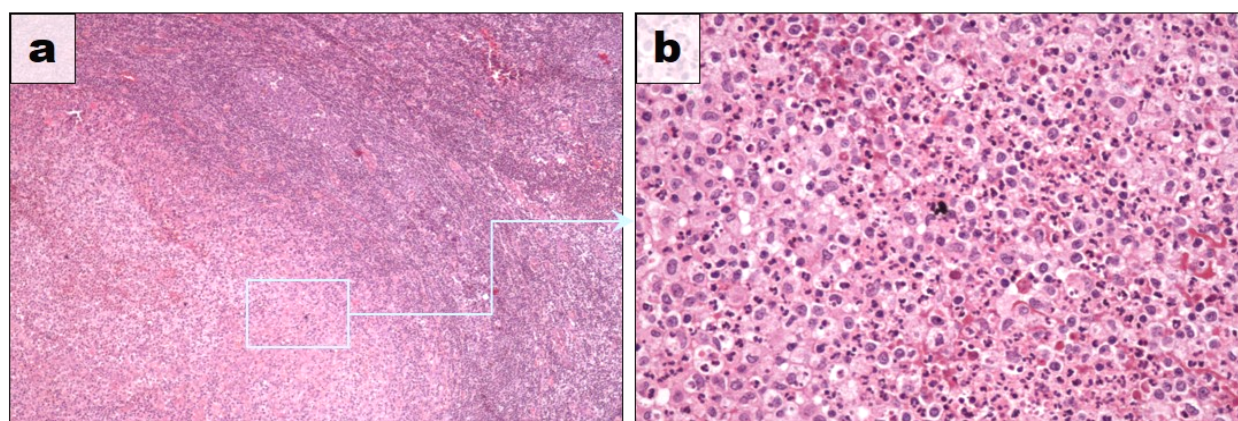


Figure 2 – Suppurated lymphadenitis: (a) General view; (b) Detail – numerous neutrophils. HE staining: (a) $\times 40$; (b) $\times 200$.

In another three cases, the lesion appearance was different, namely, the necrotic areas, full of mainly altered neutrophils, had an irregular, stellate contour and were surrounded by palisading histiocytes (Figure 3, a and b), to which paracortical vascular proliferation was added. This picture was suggestive for “cat scratch” disease (produced by the *Bartonella henselae* coccobacillus).

Only four cases were out of the suppurated pattern. An 8-year-old boy had a solitary right cervical enlarged LN that showed a neutrophil rich infiltrate but with no pus formation. Another 13-year-old boy had a solitary firm

submental LN that became fluctuant. The histological examination showed an area of suppurated necrosis surrounded by a lymphoid parenchyma with extended fibrosis. Another 13-year-old boy with a submandibular block presented a nonspecific granulomatous infiltrate. Last, but not least, the fourth patient, a 10-year-old girl, had bilateral cervical and submandibular adenopathy in which HP examination revealed areas of lymphocyte depletion on a background of unequal follicles, some of them confluent and sinus histiocytosis, suggesting the human immunodeficiency virus (HIV) infection, confirmed later.

Finally, in five cases, the LN enlargement, unilateral and localized in four of them and bilateral and localized in the fifth, was the consequence of the extensive

interfollicular sclerosis, associated sometimes with the follicular replacement with adipose tissue (Figure 4, a–f), histological features suggestive for chronic lymphadenitis.

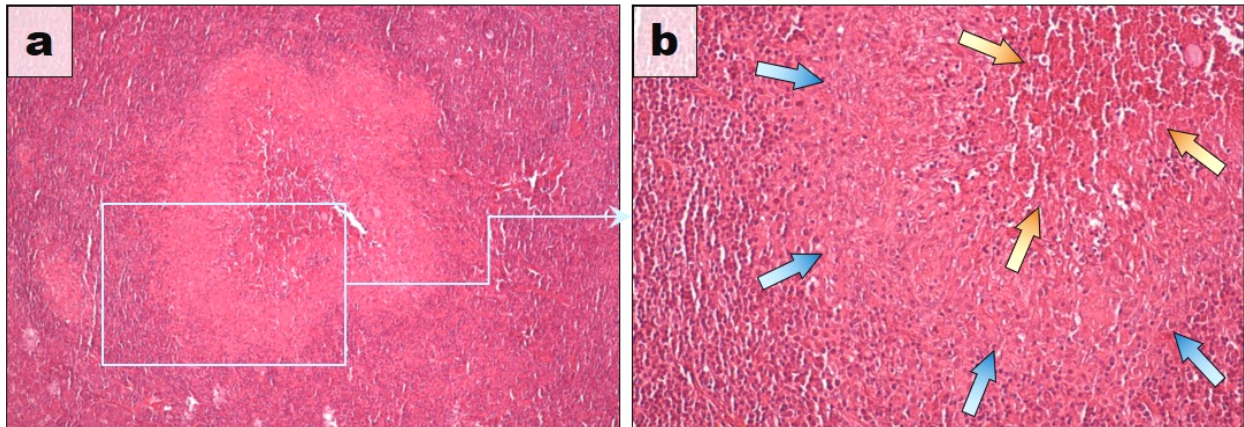


Figure 3 – “Cat scratch” disease: (a) General view; (b) Detail – central necrosis (orange arrows), palisading histiocytes (blue arrows). HE staining: (a) $\times 40$; (b) $\times 100$.

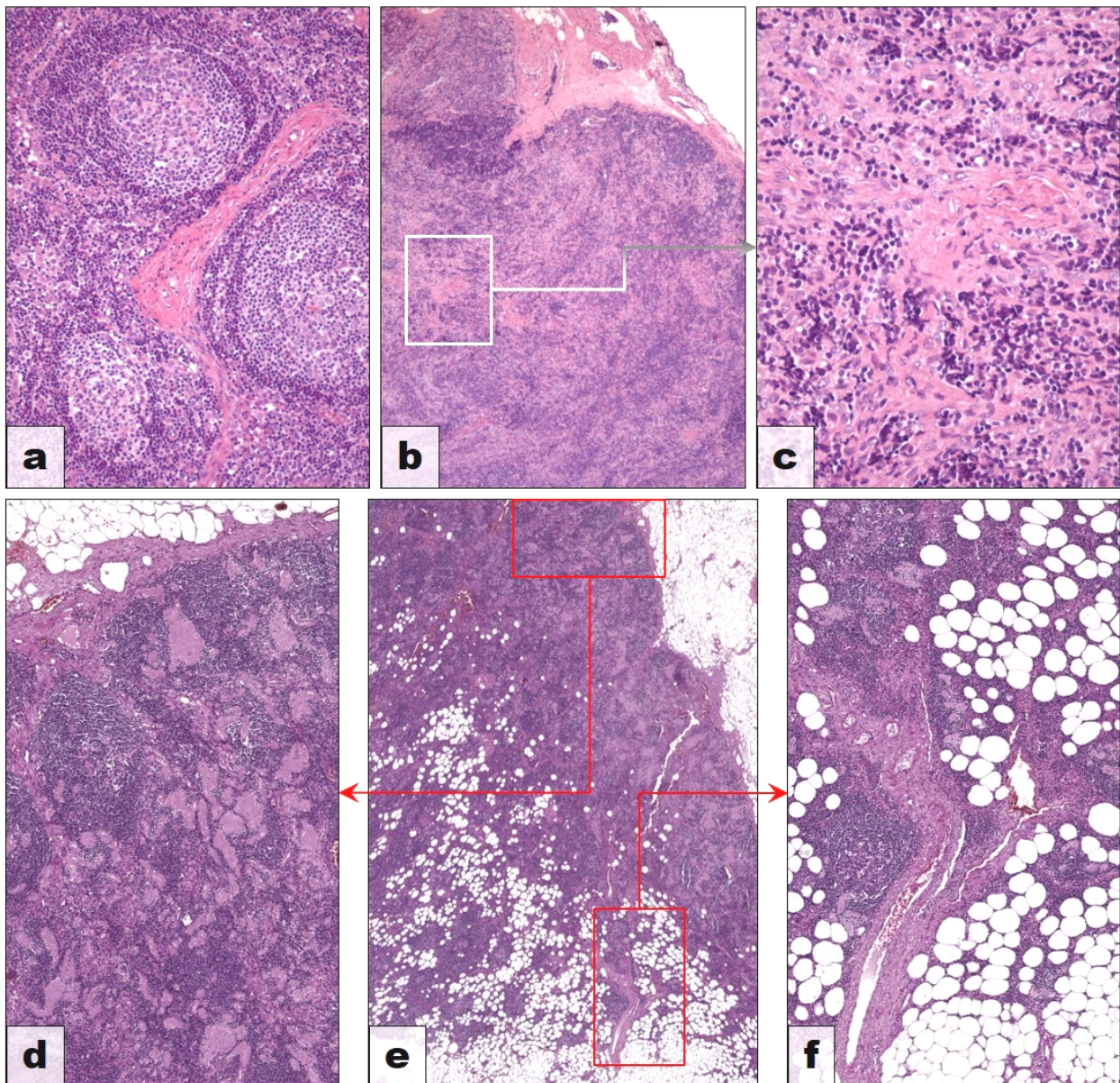


Figure 4 – Chronic lymphadenitis: (a) Follicular hyperplasia; (b) Intrafollicular fibrosis; (c) Detail of previous image; (d) Follicular and sinus fibrosis; (e) General view; (f) Adipose degeneration. HE staining: (a and f) $\times 100$; (b, d and e) $\times 40$; (c) $\times 200$.

Tuberculous lymphadenitis

Inflammation caused by Mt occupied a special place, accounting for one third of the cases alone and just under half of all cases with inflammatory processes.

The morphological analysis revealed that cellular population of the granulomas was dominated (almost two thirds of the cases) by the tandem epithelioid cell – Langhans multinucleated cell. However, in one quarter of the cases, Langhans cells were missing, macrophage population being represented only by epithelioid cells.

There were also three cases in which neutrophils joined the cell population of granulomas (Figure 5a).

The second main morphological aspect, necrosis, had in many cases the classical acidophilic, fine granular appearance. It was interesting to observe, however, that necrosis was either absent or incipient in one third of the cases. It is also worth mentioning the two cases with basophilic necrosis and the three cases with unstructured noncaseous necrosis (Figure 5b). Putting together the composition of cellular population and the aspect of necrotic areas, we observed that well differentiated granulomas clearly dominated the morphological picture (Figure 6a). However, in almost one-half of these cases and one third of all cases, the granulomas were of hyperplastic type, betraying a recent active conflict between Mt and the LN tissue (Figure 6, b and c).

It is also worth mentioning the two cases with hypo-reactive granulomas and the three cases with areactive granulomas, betraying a prolonged and aggressive evolution. In the cases with no necrosis and cellular population made only of epithelioid cells and in those with extensive, modified necrosis, the diagnosis had to be confirmed using specific stainings as Ziehl–Neelsen (Figure 6e) or/and anti-Mt immunostaining (Figure 6f).

Neoplastic lesions

Although they were few, neoplastic proliferations covered the whole range of types: benign, primary malignant, metastases (Table 9).

Table 9 – Types of neoplastic lesions

Type	Lesion	No. of cases
Benign	Cavernous hemangioma	1
	Lymphoma	3
Malignant	Metastases	2

The only one benign tumor identified in the studied group was a cavernous hemangioma, discovered in an enlarged solitary right axillary LN of a 17-year-old girl.

Malignant neoplasms were rather primitive than secondary. All three primitive malignancies were non-Hodgkin's lymphomas. One of them was a small lymphocytic lymphoma discovered on biopsy of a solitary enlarged (1.5 cm) painless right cervical LN of a 6-year-old boy. The microscopic picture revealed the effacement of nodal architecture that was replaced by a monomorphic proliferation of small lymphocytes alternating with areas of lymphocyte depletion. The immunohistochemical profile – cluster of differentiation (CD)5+, CD23+, CD79a+, B-cell lymphoma 2 (Bcl-2)+ –, oriented the diagnosis.

The other two cases (a 17-year-old boy with a solitary large left cervical LN and a 9-year and 9-month-old girl with multiple right cervical LNs of 3/2 cm) presented a different histological picture also with the effacement of nodal architecture but by a diffuse proliferation of large dysplastic B-cells with pale or basophilic cytoplasm, vesicular chromatin due to chromatin margination, and 2–3 visible nucleoli.

The immunohistochemical profile – CD20+, CD79a+, Bcl-2+, CD30+, CD 45+, CD3-, CD5- and Ki67 index >40% (Figure 7) – oriented the diagnosis towards diffuse large B-cell lymphoma.

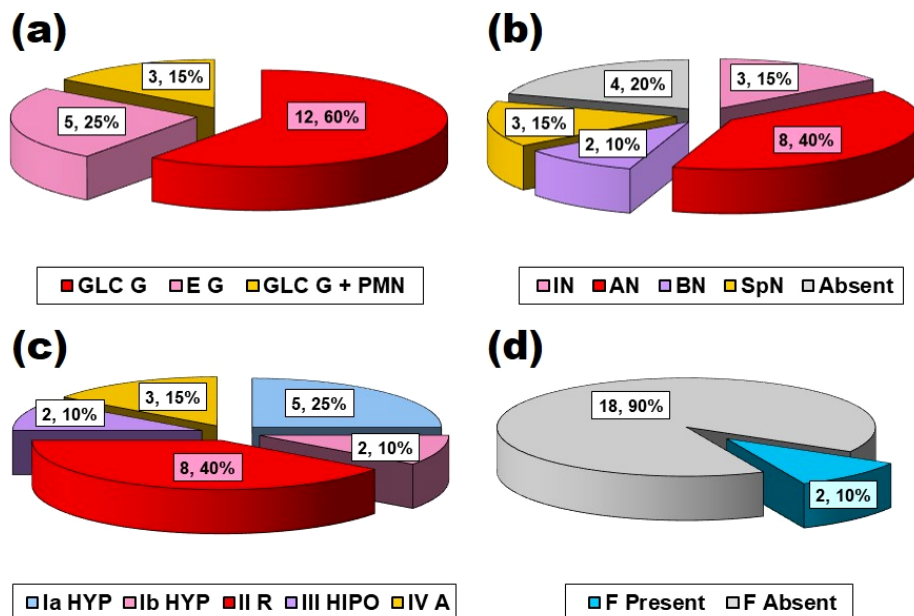


Figure 5 – Tuberculous lymphadenitis: (a) Granuloma cellularity; (b) Types of necrosis; (c) Types of granulomas; (d) Presence of fibrosis. A: Areactive; AN: Acidophilic necrosis; BN: Basophilic necrosis; E G: Epithelioid granuloma; F: Fibrosis; GLC G: Giant Langhans cell granuloma; HYP: Hyperplastic; HIPO: Hyporeactive; IN: Incipient necrosis; R: Reactive; SpN: Suppurated necrosis.

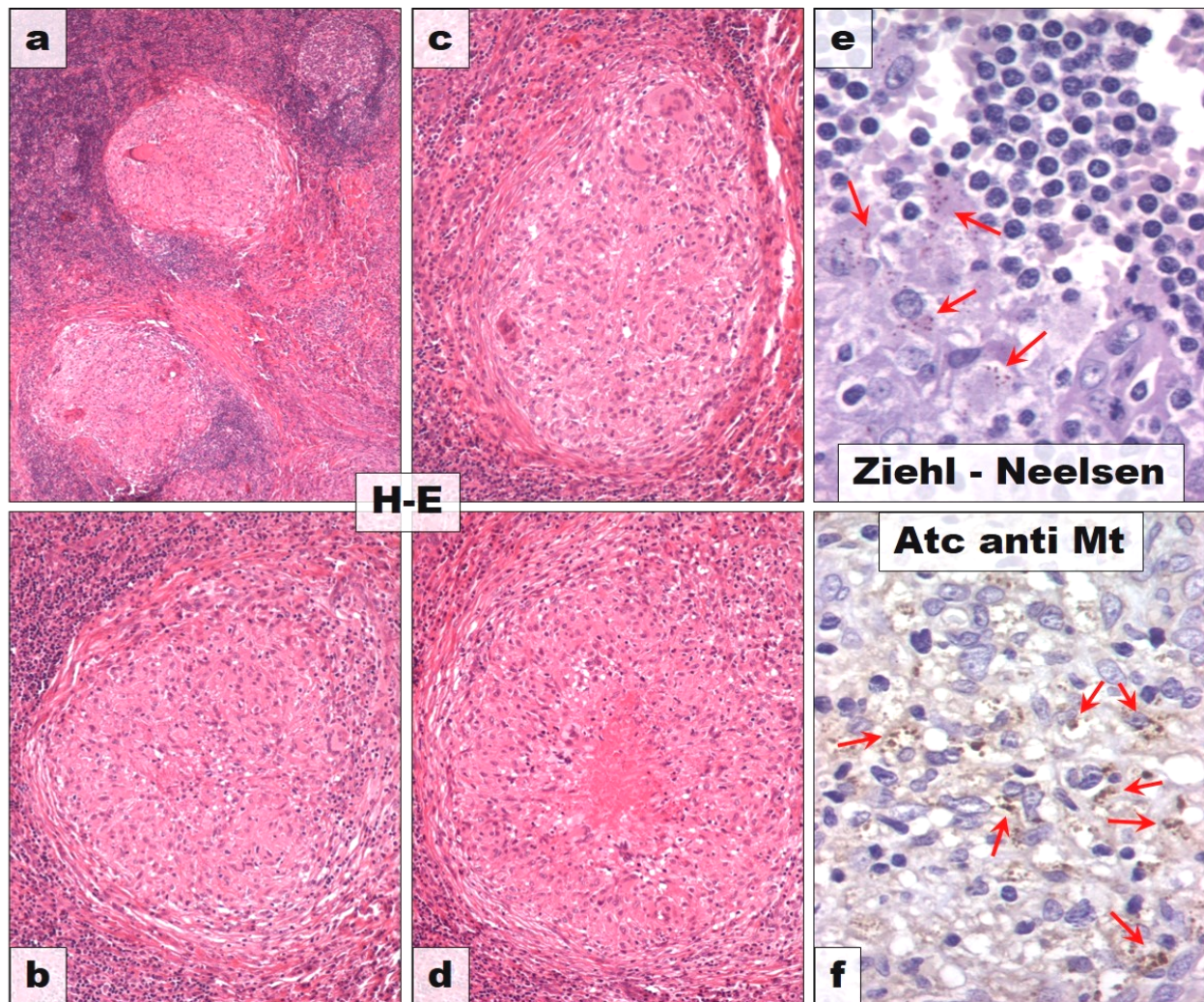


Figure 6 – Tuberculous lymphadenitis: (a) General view; (b) Type Ia hyperplastic granuloma; (c) Type Ib hyperplastic granuloma; (d) Type II reactive granuloma; (e) Acid fast Mt in mononuclear macrophages (red arrows); (f) Anti-Mt + antibody (red arrows), $\times 200$. HE staining: (a) $\times 40$; (b–d) $\times 100$. Ziehl–Neelsen staining: (e) $\times 200$. Mt: *Mycobacterium tuberculosis*.

Correlations between clinical and morphological parameters

In the second step of our study, we looked for the correlations between all parameters taken in pairs and grouped these comparisons in four categories:

- (I) Correlation between clinical parameters;
- (II) Correlations between clinical parameters and gross morphological parameters;
- (III) Correlations between gross morphological parameters;
- (IV) Correlations between HP type and all the other parameters.

As we already mentioned, the relationship between

parameters was checked with χ^2 test. The tests were grouped in the four categories mentioned above and the p -values were recorded in Table 10.

Correlation between clinical parameters (I)

Comparison between distributions of age groups in boys and girls revealed, in general, an almost similar distribution but with more frequent lesions in “early childhood” group of girls than in that of boys and, in turn, with more frequent lesions in “early adolescence” group of boys than in that of girls (Figure 8). These small differences were, however, not validated statistically [Table 10 – (I)].

Table 10 – P-value of χ^2 test for all correlations between clinical and morphological parameters

Correlation	Parameter	Gender	Age	Site	Involvement	Side	Extension
(I)	Age	0.5345					
	Site	0.5524	0.4868				
	Involvement	0.3400	0.5622	0.5836			
(II)	(III)	Side	0.8865	0.7820	0.0851	0.0540	
		Extension	0.3271	0.7503	0.2330	0.0386	0.0014
		HP	0.4270	0.6996	0.8611	0.0792	0.5737

(I) – Correlation between clinical parameters; (II) – Correlation between clinical and gross morphological parameters; (III) – Correlation between gross morphological parameters; (IV) – Correlation of histopathological (HP) type with other parameters.

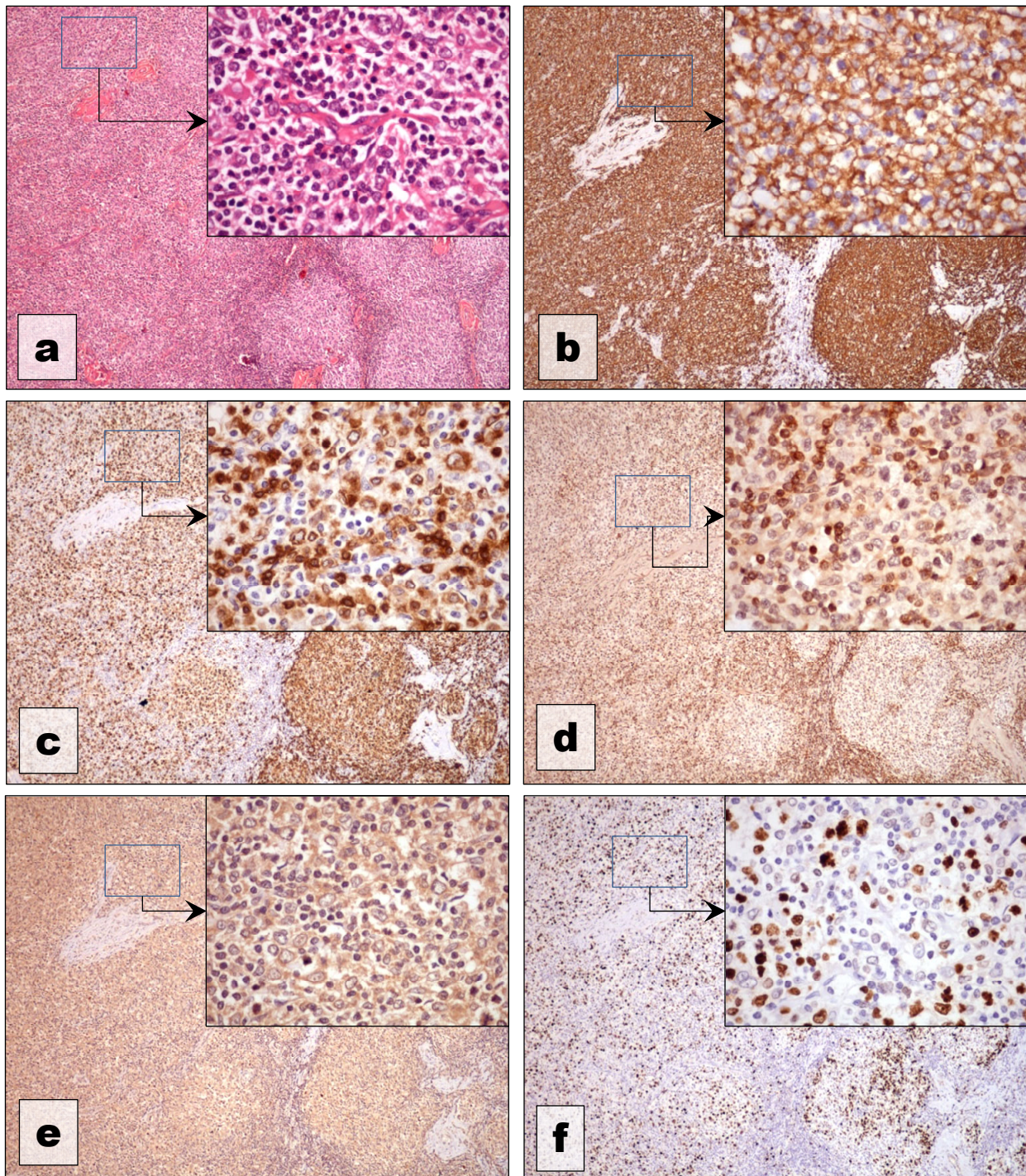


Figure 7 – Diffuse large B-cell lymphoma [$\times 40$ and $\times 200$ (detail frame)], immunohistochemical panel of positive antibodies used: (a) HE staining; (b) CD20+; (c) CD79a+; (d) Bcl-2+; (e) CD30+; (f) Ki67 index. Bcl-2: B-cell lymphoma 2; CD: Cluster of differentiation; HE: Hematoxylin–Eosin.

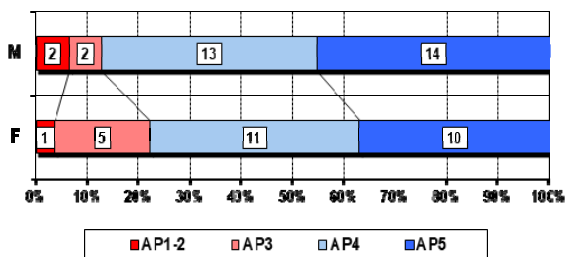


Figure 8 – Gender distribution related to age. AP1-2: 0–2 years; AP3: 3–5 years; AP4: 6–11 years; AP5: 12–18 years.

Correlations between clinical parameters and gross morphological parameters (II)

Gender–gross morphological parameters correlations

Gender–site correlation

The site distribution was almost similar in both genders but with some small differences. Thus, in girls’ group, lesions were more frequent in head and neck regions as compared to the same regions in boys while, in boys’ group, lesions were more frequent in upper limb region as compared to the same region in girls

(Figure 9a). These small differences were not validated from statistical point of view [Table 10 – (II)].

Gender–LN involvement correlation

Distribution of LN involvement in the two gender groups was somehow similar to the distribution according to site. Thus, in general, multiple LN involvement was more frequent in both groups. However, solitary lesions were more frequent in girls than in boys while multiple lesions were more frequent in boys' group as compared with girls' group (Figure 9b). Nevertheless, these differences were also not validated from statistical point of view [Table 10 – (II)].

Gender–LN side correlation

Position of the affected LNs relative to the midline revealed also similar distributions in the two gender

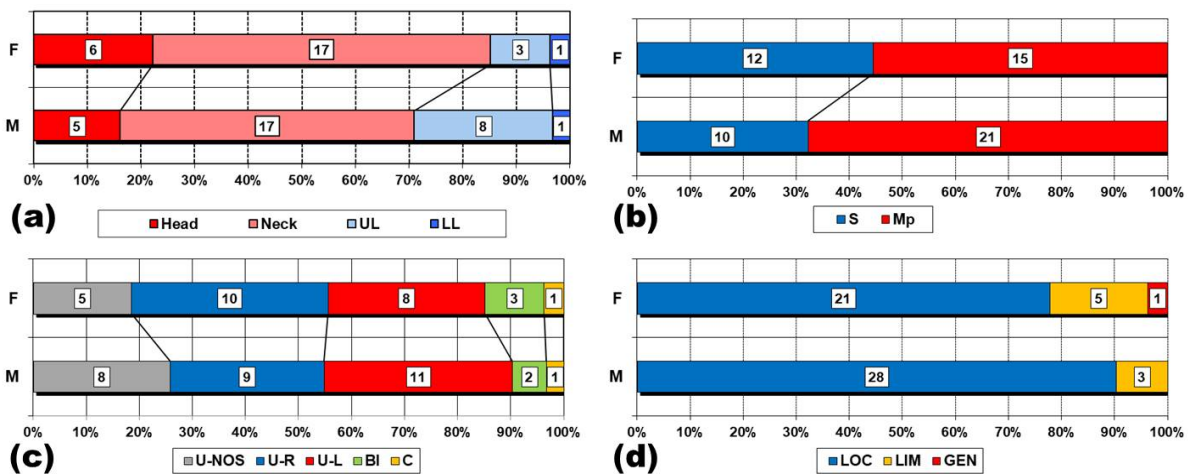


Figure 9 – Correlations between gender and gross morphological parameters: (a) Gender–site correlation; (b) Gender–LN involvement correlation; (c) Gender–LN side correlation; (d) Gender–LN extension correlation. BI: Bilateral; C: Center; GEN: Generalized; LIM: Limited; LL: Lower limb; LN: Lymph node; LOC: Localized; Mp: Multiple; S: Solitary; U-NOS: Unilateral – not otherwise specified; U-L: Unilateral – left; U-R: Unilateral – right; UL: Upper limb.

Age–gross morphological parameters correlations

Age–site correlation

Overall, lesions' distribution according to site was following the same pattern with some variations from one age group to another. Thus, in middle childhood (AP4) and early adolescence (AP5), the lesions were located predominantly in the neck region whereas in early childhood (AP3), the lesions were present more frequently in the upper limb and head regions together (Figure 10a). The statistical assessment did not validate these differences [Table 10 – (II)].

Age–LN involvement correlation

LN involvement was often solitary in middle childhood (AP4) while in the other periods of life was predominantly multiple (Figure 10b) but even this difference was not statistically valid [Table 10 – (II)].

Age–LN side correlation

Lesions' side (relative to the midline) analysis could not offer a correct assessment if in three of the four groups of age there was a significant number of cases with no specification concerning the side the lesion was placed. Lesions placed on the midline appeared after the

groups. However, there were some small differences, not validated by the statistical instrument used [Table 10 – (II)]. Thus, unilateral – right lesions and bilateral lesions were more frequent in girls as compared with boys while unilateral – left lesions were more frequent in boys as compared with girls (Figure 9c).

Gender–LN extension correlation

Finally, the distribution of lesions' extension was almost similar in the two gender groups, fact confirmed by statistical analysis [Table 10 – (II)].

There were, however, some slight differences in the sense that localized lesions were more frequent in boys as compared with girls while limited lesions were more frequent in girls as compared to boys. The only case with generalized LN extension was a 13-year-old girl (Figure 9c).

three years of age and those placed bilaterally were present after age of six years (Figure 10c).

Even these small variations were not statistically validated [Table 10 – (II)].

Age–LN extension correlation

Finally, there were no significant differences between the age groups concerning the lesions' extension distribution because, in most of the cases, the lesions were localized and the only few cases with extension to more than one LN area were present in patients older than six years (Figure 10d). The χ^2 test had a *p*-value greater than the significance level alpha of 0.05 [Table 10 – (II)].

Correlations between gross morphological parameters (III)

Site–involvement correlation

In head and lower limbs regions, the distribution of LN involvement was balanced, meaning that either only one LN was involved, or more than one LN were involved. In turn, in upper limb region and neck region especially, more than half of the cases presented more than one LN affected (Figure 11a).

Statistical assessment, however, did not validate these differences [Table 10 – (III)].

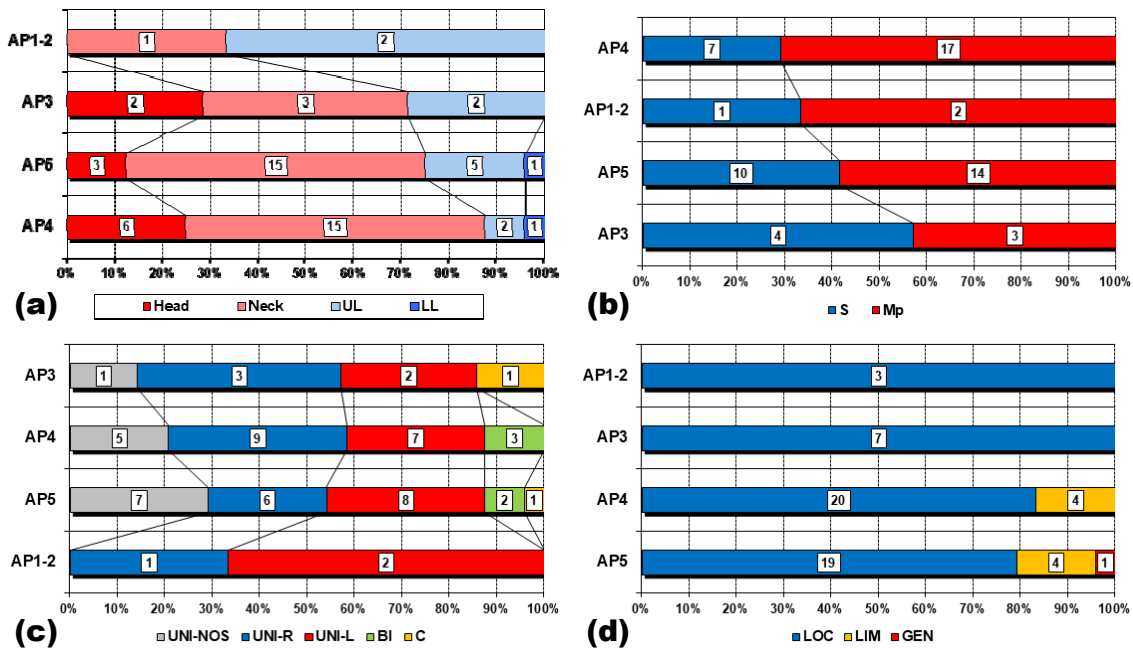


Figure 10 – Correlations between age and gross morphological parameters. (a) Age-site correlation; (b) Age-LN involvement correlation; (c) Age-LN side correlation; (d) Age-LN extension correlation. AP1-2: 0–2 years; AP3: 3–5 years; AP4: 6–11 years; AP5: 12–18 years; BI: Bilateral; C: Center; GEN: Generalized; LIM: Limited; LL: Lower limb; LN: Lymph node; LOC: Localized; Mp: Multiple; S: Solitary; U-NOS: Unilateral – not otherwise specified; U-L: Unilateral – left; U-R: Unilateral – right; UL: Upper limb.

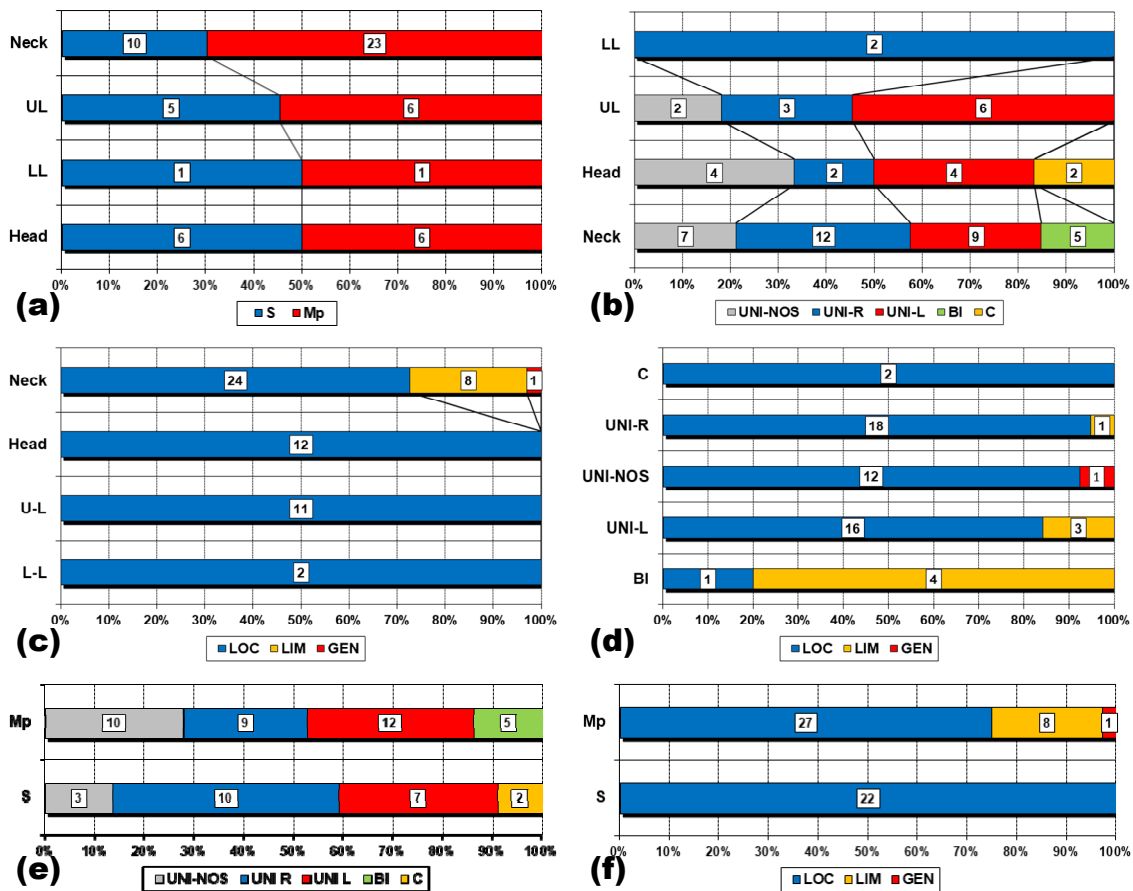


Figure 11 – Correlations between gross morphological parameters. (a) Site-involvement correlation; (b) Site-side correlation; (c) Site-extension correlation; (d) Side-extension correlation; (e) Involvement-side correlation; (f) Involvement-extension correlation. BI: Bilateral; C: Center; GEN: Generalized; LIM: Limited; LL: Lower limb; LOC: Localized; M: Multiple; S: Solitary; U-NOS: Unilateral – not otherwise specified; U-L: Unilateral – left; U-R: Unilateral – right; UL: Upper limb.

Site-side correlation

There were some differences in distribution related to midline of LN lesions between different LN regions. Thus, the two cases with lesions in the lower limb region were located on the right side. Lesions in the upper limb region, in turn were located predominantly on the left side.

Lesions in the head region were placed more frequently in the left side or bilaterally whereas lesions in the neck region were more frequently located on the right side or on the midline (Figure 11b).

The statistical assessment was very close to validate these differences – p -value of the χ^2 was 0.0851 [Table 10 – (III)] – but we have to take into account the presence of a significant number of cases with no specification of the side in three of the four groups of the side classification (Figure 11b).

Site-extension correlation

Analysis of this correlation revealed that in three of the four regions the lesions were localized and all the lesions with limited or generalized extension were

harbored by neck region where, however, dominated localized lesions (Figure 11c).

Side-extension correlation

Statistical assessment revealed a high significant correlation only between the side and the extension of lesions [Table 10 – (III)]. Thus, all midline lesions were localized. In turn, all except one of the bilateral lesions were placed in more than one region. Lesions placed unilaterally were predominantly localized but limited extension was more frequently encountered in lesions placed on the left side than those on the right side (Figure 11d).

Involvement-side correlation

Although the significant number of cases with an unspecified position should not be lost sight of, there were notable differences between the side distributions of solitary and multiple lesions. Thus, while solitary lesions were predominantly on the right side, multiple lesions were more frequent on the left side or bilaterally (Figure 11e) so that the χ^2 test had a p -value almost equal to the significance level alpha of 0.05 [Table 10 – (III)].

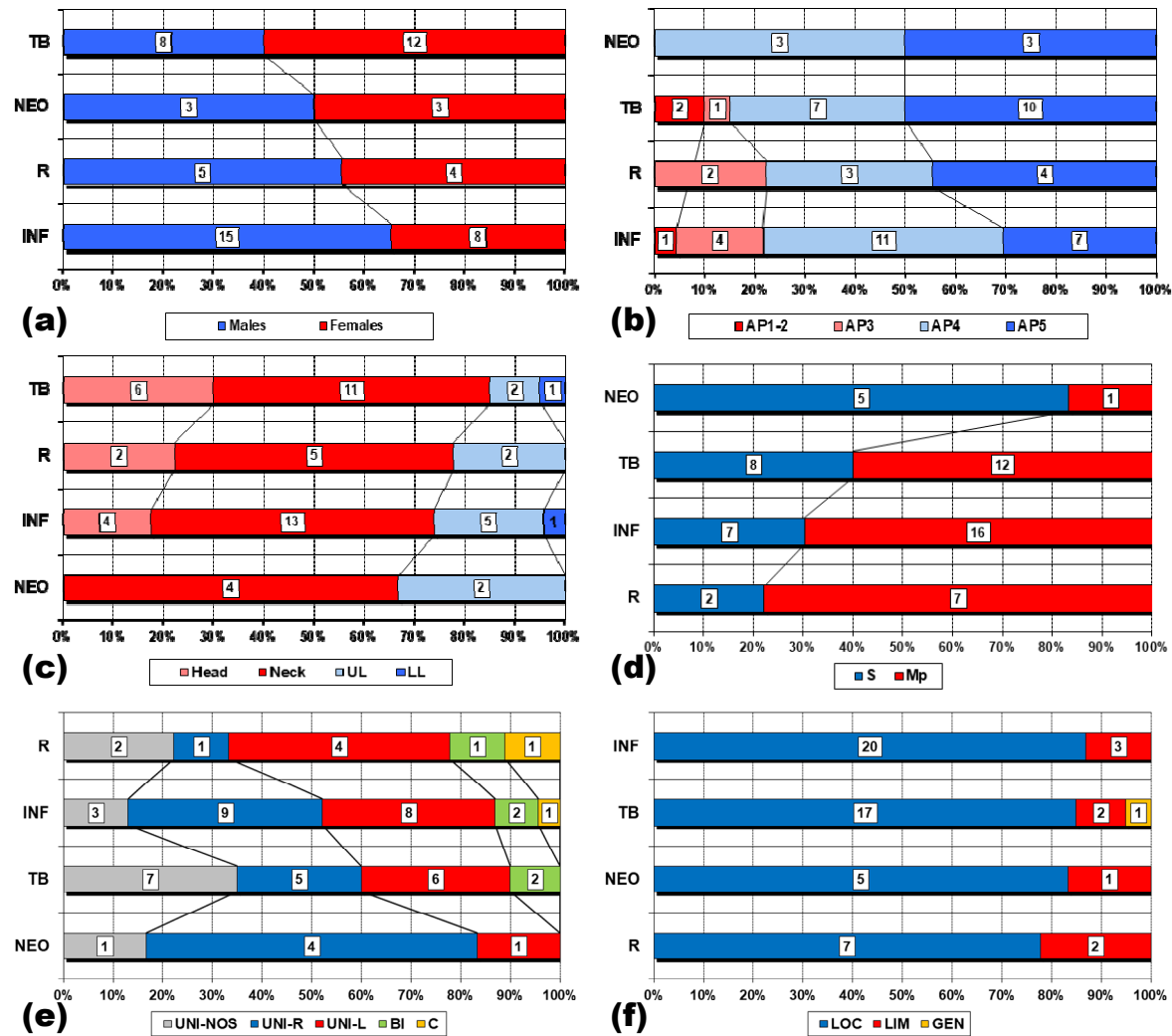


Figure 12 – Correlations between histological type and all other parameters: (a) HP type-gender correlation; (b) HP type-age correlation; (c) HP type-site correlation; (d) HP type-involvement correlation; (e) HP type-side correlation; (f) HP type-extension correlation. AP1-2: 0–2 years; AP3: 3–5 years; AP4: 6–11 years; AP5: 12–18 years; BI: Bilateral; C: Center; GEN: Generalized; LIM: Limited; INF: Inflammatory process; LL: Lower limb; LOC: Localized; Mp: Multiple; NEO: Neoplasia; R: Reactive; S: Solitary; TB: Tuberculosis; U-NOS: Unilateral – not otherwise specified; U-L: Unilateral – left; U-R: Unilateral – right; UL: Upper limb.

Involvement–extension correlation

As for the relationship between LN involvement and the degree of lesion extension, there was a clear difference between solitary and multiple lesions. Thus, all solitary lesions were localized whereas limited and generalized lesions belonged to the group of lesions with more than one LN involved (Figure 11f), the difference being statistically validated by the p -value of the χ^2 test [Table 10 – (III)].

Correlations between HP type and clinical and morphological parameters (IV)

HP type–gender correlation

There were significant differences between gender distributions of different HP types of lesions. Thus, while nonspecific inflammations predominated in boys (around two thirds of the cases), TB was obviously more frequent in girls. Reactive LNs were also slightly more frequent in boys while neoplasia had no gender predilection (Figure 12a). However, the χ^2 test did not validate these differences [Table 10 – (IV)].

HP type–age correlation

Age distribution had also differences between the HP types of lesions. Neoplastic lesions appeared only after six years of life whereas all the other types of lesions were also found under this age (Figure 12b).

The analysis of mean ages in the four HP groups revealed an ascending trend from inflammatory lesions that appeared at younger ages to neoplastic lesions that appeared at older ages (Table 11; Figure 13).

Table 11 – Mean age distribution in the four groups

Parameter	Values			
	INF	TB	R	NEO
No. of determinations	24	20	8	6
VMAX	18	18	18	18
AV + STDEV	13.95	15.51	15.95	17.97
AV	9.76	10.43	11	12.96
AV - STDEV	5.56	5.35	6	7.96
VMIN	2	0.3	4	6
STDEV	4.19	5.08	4.95	5

AV: Average; INF: Inflammatory process; NEO: Neoplastic lesion; TB: Tuberculosis; R: Reactive; STDEV: Standard deviation; VMAX: Maximum value; VMIN: Minimum value.

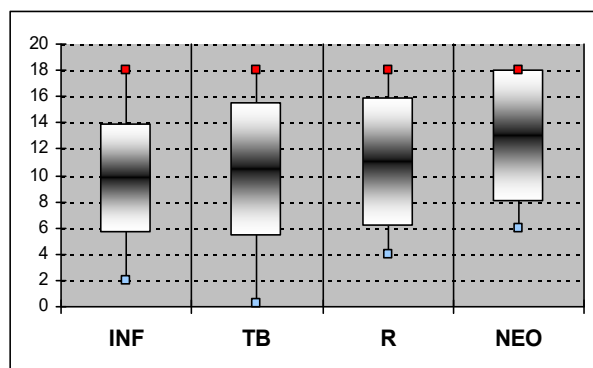


Figure 13 – Graphical representation of age distribution in the four groups. INF: Inflammatory process; NEO: Neoplastic lesion; TB: Tuberculosis; R: Reactive.

Neither these differences were validated by either the χ^2 test [Table 10 – (IV)] or ANOVA test (Table 12).

Table 12 – P-value of ANOVA test for mean ages

ANOVA test						
Source of variation	SS	df	MS	F	P-value	F crit.
Between groups	51.79	3	17.26	0.78	0.509508	2.77

ANOVA: Analysis of variance.

HP type–site correlation

Although neck region was the most frequently affected in all four groups of HP lesions, there was a descending trend of lesions from head region towards lower regions. Thus, TB lesions were located especially in the head and neck regions while neoplastic lesions were located in the neck and upper limb regions (Figure 12c), but statistical instrument did not validate these differences [Table 10 – (IV)].

HP type–involvement correlation

Differences were present in the involvement distribution too. Thus, while reactive lesions affected more than one LN in most of the cases, neoplastic lesions were found in only one LN in most of the cases. Inflammatory lesions (TB and nonTB) involved more frequently many LNs but to a lesser extent than reactive lesions (Figure 12d). These differences are the only ones validated by the statistical apparatus [Table 10 – (IV)].

HP type–side correlation

There were differences also between the side distributions in the four HP groups. Thus, neoplastic lesions were found predominantly on the right side and were never bilateral or on the midline while reactive lesions were usually placed on the left side and were also bilateral and on the midline (Figure 12e). Statistical assessment, however, considered these differences as insignificant but we must not forget that there was a significant number of cases with no side specification.

HP type–extension correlation

There were no differences between extension distributions of the HP groups [Table 10 – (IV)]. In all of them, localized lesions dominated. However, limited or/and generalized lesions were more frequently encountered (slightly more than 20%) in reactive group than in the other groups, the lowest percentage being registered in the group of inflammatory lesions (Figure 12f).

Discussions

The final step of our study consisted in the comparison of our data with those we could consult in the literature, on one hand and, on the other hand, in the attempt of defining the clinical-morphological profile for each of the parameters we have taken into consideration. Apart from the differences between the consulted studies already mentioned above in the “Materials and Methods” section concerning the site of peripheral lesions, the region/country the cases belonged, and the number of cases included in each study, we must not forget to mention that not all the authors used the same algorithm of parameters

for the assessment of peripheral lymphadenopathies (P-LAPs). Therefore, each of our comparisons referred to a different number of external publications and not always the same.

Clinical aspects

Patients' gender

Concerning the gender distribution, we had access to two categories of studies: the first category included studies dedicated to all P-LAPs; the second category included studies dedicated only to cervical lymphadenopathies (C-LAPs). We compared the male/female ratios found in these studies with that of our group.

The first observation was that there were only few studies – one on P-LAPs [36] and three on C-LAPs [6, 8, 47] – with a male/female ratio <1. In rest, all studies reported a male/female ratio >1.

The second observation was that the variation ranges were wide in both P-LAPs and C-LAPs. However, the range was wider in P-LAPs (0.6–3.7) than in C-LAPs (0.7–1.9) (Figure 14).

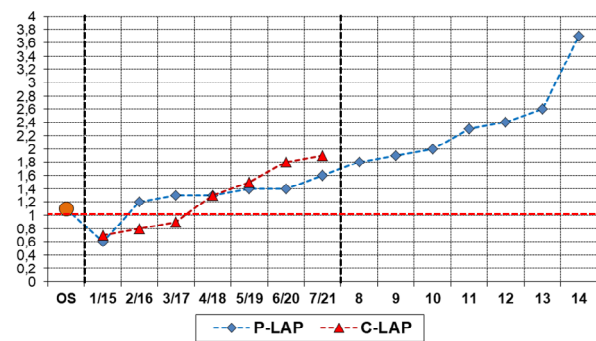


Figure 14 – Comparison of male/female ratio with other studies. OS: Our study. Blue dotted line: Peripheral lymphadenopathy (P-LAP) – 1: [36]; 2: [37]; 3: [7]; 4: [40]; 5: [39]; 6: [42]; 7: [29]; 8: [38]; 9: [32]; 10: [23]; 11: [9]; 12: [41]; 13: [10]; 14: [31]. Red dotted line: Cervical lymphadenopathy (C-LAP) – 15: [6]; 16: [47]; 17: [8]; 18: [43]; 19: [44]; 20: [45]; 21: [46].

The gender ratio of our study group was just slightly >1, being however, placed within the range observed in the literature.

Table 13 – Comparison of age distribution by age groups with other studies

Age [years]	Study									
	OS	Peripheral LAPs					Cervical LAPs			
		1	2	3	4	5	6	7	8	9
<1	2		38	9		73			6	
1	1	30			80		10			
2			68							
3				14						
4	7								53	
5										
6		55					17	30%		
7				29	242	329				69
8	24		61							
9										
10										
11		15		19			23			
12			19		176	236				
13	24							50%		

Patients' age

The way the different authors reported the age of patients included in their groups was extremely varied. Some of them reported only the limits of the age range; few of them reported only the mean age. Finally, there were some of them who reported both: the range with its limits and the mean age (Figure 15).

Our results were comparable with the picture offered by these disparate data.

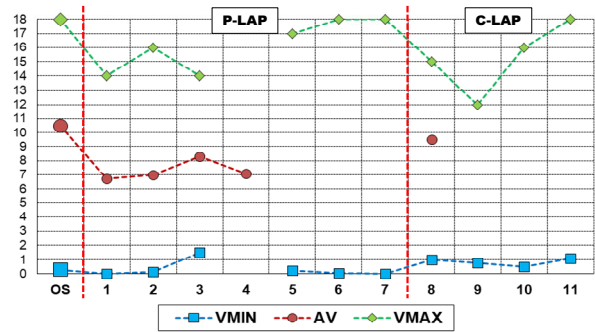


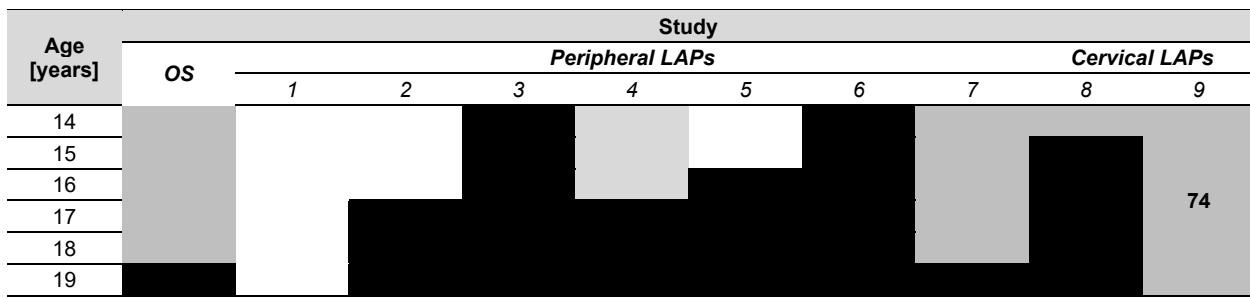
Figure 15 – Comparison of mean age and age range with other studies. OS: Our study; Peripheral lymphadenopathy (P-LAP) – 1: [38]; 2: [10]; 3: [23]; 4: [35]; 5: [39]; 6: [41]; 7: [42]; Cervical lymphadenopathy (C-LAP) – 8: [45]; 9: [47]; 10: [43]; 11: [46]. AV: Average; VMAX: Maximum value; VMIN: Minimum value.

Comparison with age assessments using age groups was even more difficult because, on one hand, there were not at least two authors to use the same system of defining age groups, and, on the other hand, the age ranges differed from one study to another (Table 13).

In many of these studies, most of the patients were younger, being included in early childhood or/and middle childhood [9, 31, 32, 37, 40].

In other studies, most of the patients belonged to early adolescence and/or middle childhood periods of age [6, 8]. Finally, there were studies where most of the patients belonged to early adolescence period [30, 44].

Our study fitted somehow in this wide range of dispersions according to age periods, being comparable with the second category of data described above (early adolescence and middle childhood periods).



1: [31]; 2: [40]; 3: [32]; 4: [9]; 5: [37]; 6: [7]; 7: [30]; 8: [8]; 9: [44]; LAP: Lymphadenopathy; OS: Our study.

Morphological gross aspects

Lesion's site

Of the eight studies with which we compared our data concerning site distribution, the first included patients of all ages [29] and the eighth included patients with lesions located only in the head and neck regions [6]. In all consulted studies, the most frequently affected region was the cervical region, with at least around 40% of the cases and going towards around three quarters of the cases (Figure 16).

It is interesting that in the study of Yadav [6], that included only LN lesions placed in the head and neck regions, cervical lesions were on the second place, as frequency, almost two thirds of the studied lesions being located in the head area.

Anunobi *et al.* [36] mentioned in their study that cervical lesions were the most numerous (almost 40% of cases) without any reference to the degree of LN impairment of other sites.

So, one could observe the great variability of site distribution from one study to another. In this respect, our study was in line with this general variable trend of case distribution by site.

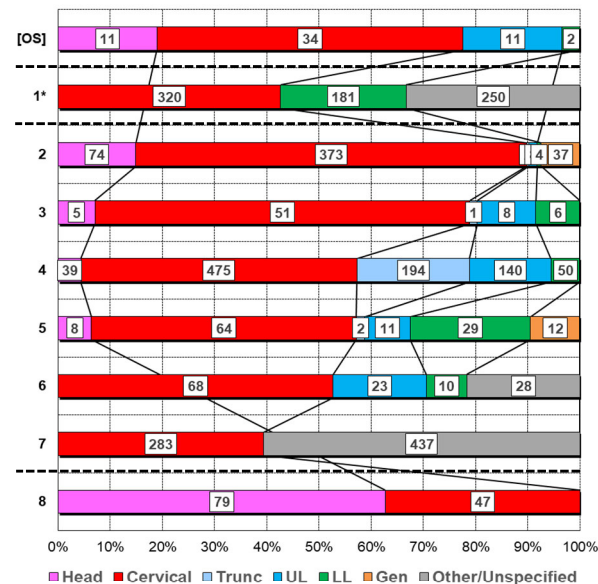


Figure 16 – Comparison of LAP site with other studies. OS: Our study; P-LAP: Peripheral lymphadenopathy (P-LAP) – 1: [29]; 2: [9]; 3: [32]; 4: [37]; 5: [23]; 6: [30]; 7: [36]; Head and neck lymphadenopathy (H&N-LAP) – 8: [6]. GEN: Generalized; LL: Lower limb; UL: Upper limb.

Lymph nodes' involvement

For the assessment of LNs' involvement, we found

only two Indian studies to compare with. One of them included all peripheral LNs regions [9] and the other included only lesions of the LNs in the cervical region [8].

In all studies, including ours, the involvement of more than one LN was more frequent, slightly over 50% of cases (Figure 17).

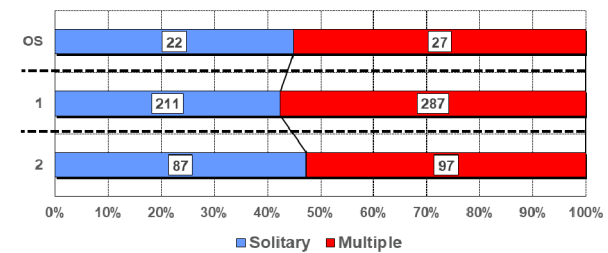


Figure 17 – Comparison of LAP involvement with other studies. OS: Our study; P-LAP: Peripheral lymphadenopathy – 1: [9]; C-LAP: Cervical lymphadenopathy – 2: [8].

Lesions' extension

Of the six studies with which we compared our data concerning extension distribution, the sixth referred only to the cervical region lesions [8].

The scale for assessing the extension of LN lesions was used differently. Some authors described only localized and generalized lesions, without defining what “localized” means [8, 34, 38, 40]. Other studies, including ours, used the scale with three degrees of extension (including also “limited” step).

The comparison revealed a great variability of the lesions' extension distribution. Thus, in some of the studies [38, 40], localized lesions dominated obviously. In other studies [10, 34] lesions in more than one single anatomical LN area dominated. Patar *et al.* mentioned that they found only two cases with generalized LAP, without mentioning how the rest of their 180 cases were distributed [8]. Our study was included in the first category described above (Figure 18).

Lesions' HP type

For the distribution of different HP types of LAPs, we had the widest range of studies to compare with. Most of these studies were like ours, meaning that they included LN lesions from all peripheral regions. Few of them referred only to lesions belonging to the cervical region [8, 44, 47]. One study [29] included lesions belonging to head and neck regions and, finally, one study included not only children but patients of all ages.

The HP profile of different studied groups was extremely varied. Thus, in the largest group of studies (P-LAPs), reactive lesions dominated in many of these

series [7, 9, 31, 32, 35, 37, 40] as there were studies without reactive lesions [30, 36]. TB lesions were the most frequently present in two studies [23, 30] but there was one study without TB lesions [35]. Nonspecific inflammatory lesions dominated in one study [38] and have missed in three studies [30, 31, 44].

Finally, neoplastic lesions did not miss from any study and even they were the most frequent in two studies [33, 36] (Figure 19).

It is interesting to point out that, in the Nigerian study of Anunobi et al. [36] who reported the greatest number of neoplastic lesions (almost 50% from all cases), 70% of all neoplastic lesions were metastases.

The Nigerian study of Adeniji & Anjorin [29], that included patents of all ages, had no nonspecific inflammatory lesions, had almost 50% of cases with neoplastic lesions both primary and secondary and had almost one third of the cases with TB lesions.

Our study included all four types of lesions and was dominated by the nonspecific inflammatory lesions and TB lesions (Figure 19).

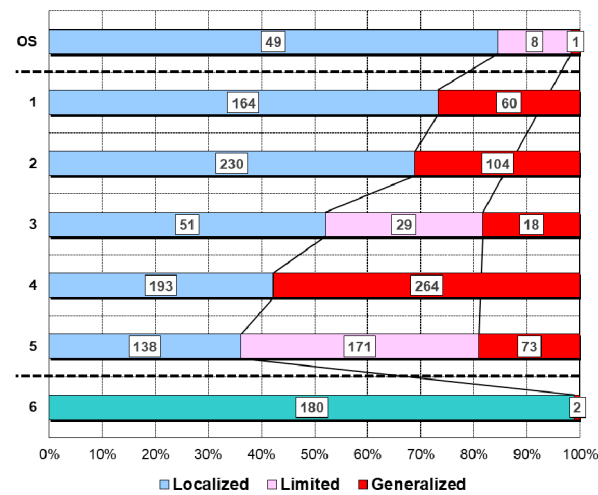


Figure 18 – Comparison of LAP extension with other studies. OS: Our study; P-LAP: Peripheral lymphadenopathy – 1: [40]; 2: [38]; 3: [35]; 4: [34]; 5: [10]; C-LAP: Cervical lymphadenopathy – 6: [8].

Attempt of a clinical morphological profiles

Even if our study group is not so large, we tried to see if a clinical-morphological profile can be outlined for each of the main clinical and morphological parameters observed to young patients with P-LAP we introduced in our study.

Gender profile

Male patients

In most of the cases, they were older than six years and presented multiple lesions, but localized, slightly more on the left side of the neck region or the limbs regions. The pathological process identified at HP examination was usually a nonspecific inflammation or a tuberculous conflict.

Female profile

Girls, in turn, were in more than 20% of cases younger than six years and were presenting more frequently than boys solitary lesions, usually localized but also limited

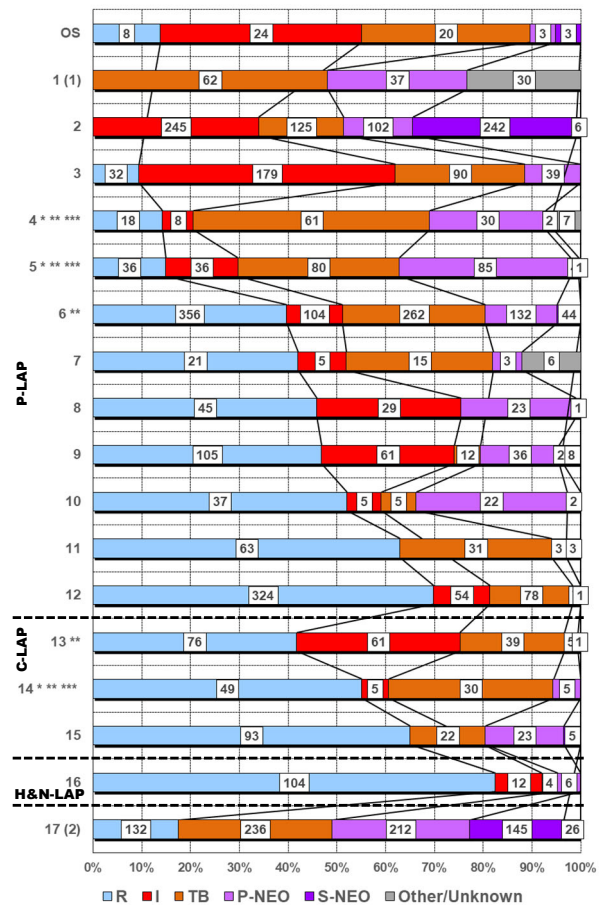


Figure 19 – Comparison of HP types’ distribution with other studies. OS: Our study; P-LAP: Peripheral lymphadenopathy – 1: [30]; 2: [36]; 3: [38]; 4: [23]; 5: [33]; 6: [37]; 7: [7]; 8: [35]; 9: [40]; 10: [32]; 11: [31]; 12: [9]; C-LAP: Cervical lymphadenopathy – 13: [8]; 14: [47]; 15: [44]; H&N-LAP: Head and neck lymphadenopathy – 16: [6]; 17: [29]; (1): Primary sarcomas or carcinomas were excluded; (2): Age range – one year to 80 years; *: Reactive + Sinus histiocytosis; **: Inflammation (acute, chronic, granulomatous) + Sarcoidosis; ***: Lymphoma + other. HP: Histopathological.

or generalized, slightly more on the right side of the neck region, but also bilateral and on the midline. The pathological process identified at HP examination was this time TB, followed by nonspecific inflammations.

Age profile

Infancy +/- Toddler

Patients less than two years of age were boys rather than girls and presented only localized lesions, more frequently with multiple LN involvement, placed usually on the left side of the body, most frequently in the limbs’ region. The most frequently diagnosed disease was TB.

Early childhood

Patients aged between three and five years were usually girls and presented also only localized lesions but more frequently involving more than one LN, placed rather on the right side than on the left side of the neck region. The most frequently diagnosed pathological process was nonspecific inflammation, followed by reactive LNs.

Middle childhood

Patients aged between six and 11 years were rather boys than girls and presented most often localized lesions, more frequently with multiple LN involvement, placed slightly more frequently on the right side than on the left side of the neck region. The most frequently diagnosed disease was nonspecific inflammation, followed by TB.

Early adolescence

Patients aged between six and 11 years were also rather boys than girls and presented usually localized but sometimes also limited and generalized lesions, often with multiple LN involvement, placed more frequently on the right side of the neck region and then of the limbs' region but sometimes bilaterally and on the midline. The most frequently diagnosed disease was TB, followed by nonspecific inflammation.

Site profile**Head region**

Patients with lesions in the head region were rather girls than boys, usually aged between six and 11 years. The lesions were only localized either with solitary or with multiple involvement of LNs most often on the right side but also on the midline. TB was more frequently diagnosed than nonspecific inflammations and there were no neoplastic lesions.

Neck region

Patients with lesions in the head region were either boys or girls, in most of the cases aged either between six and 11 years or between 12 and 18 years. Lesions were most often localized but also limited, with multiple involvements of the LNs in most of the cases, rather on the right side but also bilateral. TB was diagnosed rather than nonspecific inflammations.

Upper limb

Patients with lesions in the upper limb region were more frequently boys than girls, usually aged between 12 and 18 years. Lesions were all localized, rather with multiple involvements of LNs than solitary and on the left side in most of the cases. Nonspecific inflammation was the most frequent HP diagnosis.

Lower limb

There were only two patients with lesions in the lower limb region, in both cases being affected LNs of the inguinal group, as we mentioned above. First patient was an 11-year-old boy with a localized lesion affecting many LNs of the right inguinal group, with local Celsian signs that proved to be a suppurated lymphadenitis. The second patient was an 18-year-old girl with also a localized lesion affecting many LNs of the right inguinal group that proved to be a tuberculous lymphadenitis.

Side profile

We excluded from the analysis of the side profile the thirteen cases with unilateral involvement but without mention of the side.

Side profile**Right side**

Patients with lesions placed on the right side were rather girls than boys, aged more frequently between six and 11 years and then between 12 and 18 years. Lesions were all localized except one that was limited, rather solitary than multiple and located mostly in the neck region. With one exception, lesions were half nonspecific inflammations and half tuberculous lesions and neoplasms.

Left side

Patients with lesions placed on the left side were rather boys than girls, aged rather between 12 and 18 years than between six and 11 years. Lesions were mostly localized but sometimes limited, most often with multiple LN involvement, and located firstly in the neck region and then in the upper limb region. The most frequently diagnosed disease was TB followed by nonspecific inflammations.

Bilateral lesions

Patients with bilateral lesions were rather girls than boys, aged more frequently between six and 11 years and then between 12 and 18 years. Lesions were mostly limited to two or three LN areas, all with multiple LN involvements and placed in the neck region. None of them was of neoplastic type.

Midline region

There were only two patients with lesions placed on the midline. One patient was a 13-year-old boy with a solitary submental LN with Celsian signs that proved to be an acute inflammatory episode developed on a pre-existent chronic lymphadenitis. The second patient was a 4-year-old girl also with a solitary submental LN but without Celsian signs that proved to be a reactive LN.

Extension profile**Localized lesions**

Patients with localized lesions to only one LN area were the most numerous and were more frequently boys than girls, in most of the cases older than six years. The lesions were more often multiple and placed rather on the right side of the neck region. The most frequently diagnosed disease was nonspecific inflammation, followed by TB.

Limited lesions

Patients with limited lesions were more frequently girls than boys, aged either between six and 11 years or between 12 and 18 years. The lesions were all with multiple LN involvements, more frequently bilateral than placed on the left side, and all placed in the neck region. The most frequent lesion was the nonspecific inflammation followed closely by TB and reactive LN.

Generalized lesions

There was only one patient with generalized extension, a 13-year-old girl, with multiple LN involvement in the neck region, suspected of lymphoma but finally diagnosed

as TB with the help of special staining for Mt and immunohistochemistry (Figure 6).

Histopathological profile

Reactive LAP

The patient with reactive LAP is rather a boy than a girl, in early adolescence but sometimes in early childhood also. He is presenting most often with localized multiple adenopathies, placed on the left side of the neck region. The microscopic morphological picture is that of a follicular hyperplasia with or without sinus histiocytosis.

Lymphadenitis

The patient with inflammatory processes is usually a boy in early adolescence who is presenting most often with localized multiple adenopathies, placed either on the left or on the right side of the neck region. The microscopic morphological picture is usually that of a suppurated process (microabscesses or extended suppurated necrosis in the LN parenchyma), followed by the picture of chronic inflammation, with different degrees of fibrosis. Other inflammatory processes could be found, as “cat scratch” disease or inflammatory response to HIV infection, situations we encountered in our patients.

Tuberculous lymphadenitis

The patient with tuberculous involvement of the LNs could have any age in the range but usually is older than 12 years (early adolescence). Most often is a girl who presents in most of the cases, localized, multiple adenopathy on the left side of the neck region. The inflammatory reaction is usually dominated by well differentiated granulomas, but most often surrounding foci of classical acidophilic fine granular necrosis.

Not to be overlooked that, quite often, granulomatous reaction is of hyperplastic type, betraying an active process, in other words, a recent infection/reinfection.

Neoplasia

Patients with neoplastic proliferations were either boys or girls older than six years, with a mean age of 12 years who presented in most of the cases, localized solitary modified LNs, usually placed on the right side of the neck.

HP examination revealed (even in this small number of cases) a wide range of histological aspects, namely primary malignant tumors (lymphomas), secondary malignant tumors (metastases) and even benign tumors.

The main observations are summarized in Table 14.

Table 14 – Synthesis of clinical morphological profiles of LAPS HP types

	Reactive LAP	Lymphadenitis	Tuberculosis	Neoplasia
Clinical				
Gender	M>F	M	F	M=F
Age	AP5 but 20% AP3	AP4 but all ages	AP5 but all ages	AP4=AP5 (>6 years)
Morphological				
Site	Neck >50%	Neck >50% followed by limbs	Neck >50% followed by head 30%	Neck >60% followed by limbs
Involvement	Multiple almost 80%	Multiple 70%	Multiple 60%	Solitary >80%
Side	UNI-L >50%	UNI-R=UNI-L	UNI-L 30% but UNI-NOS >30%	UNI-R >60%
Extension	LIM >20%	LOC >85%	LOC 85%	LOC >80%
Histopathology	Follicular hyperplasia +/- Sinus hyperplasia	50% Acute suppurative 20% Chronic Three cases “cat scratch” disease One case HIV	75% Well differentiated granulomas 35% Hyperplastic granulomas (active conflict)	Both primary and secondary neoplasms

AP3: Early childhood (3–5 years); AP4: Middle childhood (6–11 years); AP5: Early adolescence (12–18 years); HIV: Human immunodeficiency virus; LAP: Lymphadenopathy; LIM: Limited; LOC: Localized; M: Male; F: Female; UNI-R: Unilateral right side; UNI-L: Unilateral left side; UNI-NOS: Unilateral not otherwise specified.

Conclusions

Each of the clinical and morphological parameters we have considered varied within the large limits of the ranges we found in the literature. Comparisons between the descriptive clinical and morphological parameters we used in the investigation of our series of P-LAPs revealed differences more or less significant between them. These differences, however, allowed us to define clinical profiles for different types of P-LAPs that could orient the diagnosis towards the type of disease harbored by the modified LNs. Therefore, we consider that our attempt should be extended to larger series of study so that the defined profiles get more accuracy in order to become reliable tools in assessing the situation of P-LAP in daily pediatric practice.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

The first and the second authors had equal contribution to the achievement of this paper.

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Corresponding author

Iancu Emil Pleșea, Professor, MD, PhD, Departments of Pathology, Carol Davila University of Medicine and Pharmacy, and Fundeni Clinical Institute, 258 Fundeni Road, Sector 2, 022328 Bucharest, Romania; Phone +40722–992 511, e-mail: emil.plesea@umfcd.ro

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