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Cervical lymphadenopathies in children: A prospective clinical cohort study

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ABSTRACT

Aim: Cervical lymphadenopathy (LAP) is a common sign and may raise fears about serious illnesses. The aim of our study was to evaluate the patients with cervical LAPs in a general pediatrics clinic setting, and to evaluate follow-up results for potential causes and risk factors for malignancies.
Material and methods: Two hundred-eighteen patients aged between 79.4 ± 46.7 months with LAP were enrolled in this prospective cohort study. The patients were examined in terms of demographics, clinical, radiologic and serologic aspects like Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19. A lymph node biopsy was performed in selected patients. The patients were followed-up for 8 weeks and risk factors for malignancy were evaluated.
Results: Seventy patients (41.3%) had specific etiology and 6 (2.7%) had malignant causes. The causes were as follows: 27% (n = 59) infections; 2.7% (n = 6) malignancies; 11.4% (n = 25) other causes. EBV was responsible for 27% of infectious causes. The other common infectious etiologies were CMV 4.3%, parvovirus B-19 2.9%, and group-A beta-hemolytic streptococcus (GAS) 10.8%. Four of the six malignancies were lymphomas. Predictive factors for malignancy were having LAP larger than 30 mm, rubbery lymph node, high serum CRP and LDH values, no hilum in ultrasonography, and enlargement of lymph node in follow-up. High uric acid levels and leucopenia were also common in the malignancy group.
Conclusion: Etiology of cervical LAPs was diagnosed in 41.3% patients. Infectious causes were the most common cause with 27%. Malignancy was diagnosed in 2.7% and lymphoma was the most common malignancy.

1. Introduction

Lymphadenomegaly is a palpation examination finding of an enlarged lymph node. The term lymphadenopathy (LAP) is generally synonymously used because diseases often cause enlarged lymph nodes [1]. LAP of the head and neck is a common finding in pediatric ambulatory and emergency departments [1,2]. Lymph nodes react to a new antigen with hyperplasia, which is more excessive in children [3–5]. LAP is often caused by infectious diseases, but malignancies, autoimmune diseases, and chronic inflammatory processes may also be the reason. Mostly self-limited acute upper respiratory viral infections in children may lead to LAP, and these are regresses spontaneously. Some infections may also cause chronic LAPs. Pediatricians differentiate between malignancy and benign causes with clinical and laboratory findings [3,4]. Malignancies that present with LAP may be primary or metastasis. Malignant lymph nodes may enlarge in a rash or with a slow course. Hodgkin's lymphoma (HL)

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shows slow progress in lymph node size, but Non-Hodgkin's lymphoma (NHL) is abrupt [5]. Some clues may be helpful to differentiate benign causes from malignant. LAP located supraclavicular is mostly malign; whereas LAP with concomitant maculopapulary rash is often benign [5–7]. No decrease in size in the follow-up, organomegaly, leucocytosis, leucopenia, high erythrocyte sedimentation rate (ESR), Lactate dehydrogenase (LDH) and uric acid levels may indicate malignancy [8,9].

The aim of our study was to evaluate the patients with cervical LAPs in a general pediatrics clinic setting, and to evaluate follow-up results for potential causes and risk factors for malignancies.

2. Methods

This prospective single-center-cohort clinical study was performed in children who visited Istanbul University, Istanbul Medical Faculty, Ambulatory Clinics of Department of Pediatrics. Informed consent was obtained from all participants' parents. Approval of the Research Ethics Committee of Istanbul University was obtained. This study was supported by Scientific Research Projects Coordination Unit of Istanbul University (project number: 35906).

2.1. The study group and inclusion criteria

Children with LAP of the neck and head who had given informed consent were included in the study group. Lymph nodes that were enlarged more than 10 mm in the cervical, submental, and submandibular region, and 5 mm in the suboccipital, preauriculary and postauriculary region, were accepted as LAP. Any palpable lymph node in the supraclaviculary region was accepted as LAP [3,6,9]. LAP that lasts less than 4 weeks was termed acute LAP and 4 weeks or more as chronic LAP. Patients with any swelling other than lymph node, chronic disease, who were treated or diagnosed in another clinic, or had lymph node enlargement that did not fulfill our LAP criteria were not included in the study.

An anamnesis form were used to collect the following information: age, sex, start date of symptoms, history of travel, animal contact, tuberculosis contact, immunization, B symptoms for lymphoma, medication causing LAP (e.g., phenytoin, allopurinol, valproic acid), dental symptoms and history of upper or low respiratory tract infections.

LAP was classified depending on location, size, and existence of inflammation findings (redness on the skin, pain on palpation, tenderness and increased heat on the skin), relationship with peripheral tissue, like as fixed or not, and consistency. LAP was grouped depending on its consistency as soft, rubbery or hard. Other signs like arthritis, splenomegaly or rash were noted.

B symptoms include: fever greater than 38 °C with no known cause, drenching night sweats, and unintentional weight loss of more than 10% of body weight over a period of 6 months or less. Presence of one was accepted as B symptom positive. Patients left study for any reason before 8 weeks were excluded.

2.2. Laboratory tests

Investigation of hemogram (CBC), C-reactive protein (CRP), ESR, LDH, serum uric acid level, and blood smear were routinely performed all patients. Other diagnostic tests such as throat cultures, viral serological analysis, ultrasonography of LAP, tuberculin skin test, bone marrow aspiration, and excisional biopsy were undertaken if necessary.

Patients were followed-up for 8 weeks after the diagnosis. If there was no suspicion of malignancy after the first-step evaluation, we treated patients with appropriate antibiotics against probable Gram-positive bacteria with as amoxicillin, amoxicillin–clavulanate, cefuroxime or ampicillin–sulbactam for 14 days and called them for a follow-up check afterwards. If there was no regression after two weeks, the patients underwent further examinations like tuberculin skin test, ultrasonography, chest radiography, and serology for EBV, CMV, Parvovirus B19, and Mycoplasma pneumonia. If there was still no suspicion for malignancy after reevaluation, we followed-up the patient routinely. In the event that we found a risk for malignancy, we contacted the Division of Pediatric Hematology–Oncology of Istanbul Medical Faculty for additional opinions.

All biochemical analyses were undertaken in the Department of Biochemistry of Istanbul Medical Faculty, Istanbul University. Venous blood samples were taken in appropriate tubes and centrifuged. Uric acid, CRP, and LDH enzyme activities were measured using a Cobas Integra 800 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Hemograms were measured using an LH 780 (Beckman Coulter, USA) and ESR with THERMA NE (Linear Chemicals S.L, Spain). All serologic analyses were studied in specific ELISA kits [10,11].

2.3. Radiologic investigations

All radiologic images were taken in the Department of Radiology, Istanbul Medical Faculty, Istanbul University. Ultrasonography for LAP was performed with the patient in the supine position with their neck slightly extended. A Logiq 9 with 13–5 mHz probe (GE Healthcare, Milwaukee, WI, USA) was used. Bilateral submandibular, submental, postauriculary and preauriculary nodes, posterior cervical triangle, midjugulary chain area and lower jugulary chain area were checked. Long axis/short axis ratio of lymph node (L/S), echogenicity of hilum, vascular pattern were checked. If L/S around 1, and on echogenicity showing deformation, irregular margins, and chaotic vascular patterns were determined, these are defined as compatible with malignancy [12–15].

2.4. Histopathologic evaluation

Lymph node excisional biopsies were performed under general anesthesia [16–18]. Pathologic examination of bone marrow and lymph node tissues were performed in the Department of Pathology in Istanbul Medical Faculty, Istanbul University. All specimens were evaluated by a senior pathologist expert on hematology. Bone marrow aspiration was done in some patients with any clinical symptoms considered acute lymphoblastic leukemia or lymphoma. We had not any complication for excisional lymph node biopsies. Average time referral to biopsy and diagnosis were 2–3 weeks.

2.5. Statistical analysis

Number Cruncher Statistical System 2007 (NCSS) and Power Analysis and Sample Size (PASS) 2008 statistical software 2008 were used for statistical analyses. In the evaluation of the qualitative and quantitative parameters, descriptive methods (mean, standard deviation, median, and frequency) were used. Mann–Whitney *U* test was used for quantitative parameters with non-normal distribution. Fisher's exact test and Fisher–Freeman–Halton test were used for qualitative evaluation. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed for diagnostic tests. Risk factors for malignancy were estimated with Multivariate logistic regression analysis. Significance were taken as $p < 0.01$ and $p < 0.05$.

3. Results

Two hundred eighteen patients were enrolled in the study (Fig. 1). Among all groups, 34.4% ($n = 75$) were girls, and the mean age of all groups was 79.4 ± 46.7 months (range, 13–215 months)