CZU: 616-006.441/.442-031.31-07-053.2
https://doi.org/10.52692/1857-0011.2023.2-76.06

DIAGNOSTIC PECULIARITIES OF LYMPHOMAS IN THE CERVICAL REGION IN CHILDREN

URSU Dănis, doctorand, asist. univ.
GUDUMAC Eva, dr. hab. șt. med., prof.univ., acad. AȘM
BERNIC Jana, dr. hab. șt. med., prof.univ.
TÎBÎRNĂ Andrei, dr. hab. șt. med., conf.univ.
RAILEAN Silvia, dr. hab. șt. med., conf.univ.
LUPAN Roman, doctorand, asist. univ.,
LISIȚA Natalia
GOLBAN Rodica

Catedra de Chirurgie, ortopedie și anesteziologie pediatrică „Natalia Gheorghiu" IP USMF „N. Testemițanu,
IMSP Institutul Oncologic, Institutul de Fiziologie și Sanocreatologie, Chișinău, RM,
Catedra de Chirurgie OMF pediatrică și pedodonție „Ion Lupan" IP USMF „N. Testemițanu".

Abstract.
Thisarticle discusses various aspects of pediatric lymphadenopathy, focusing on Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). It outlines common etiologies, diagnostic techniques, and key characteristics of different lymphoma subtypes. HL is classified into classical HL (CHL) and nodular lymphocytic predominant HL (NLPHL), while NHL includes Burkitt lymphoma (BL), lymphoblastic lymphoma (LBL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL). The text emphasizes the importance of accurate diagnosis through various tests, including imaging modalities such as positron emission tomography (PET) and computed tomography (CT). It also discusses the potential use of ctDNA as a prognostic marker and highlights genetic alterations contributing to lymphoma development. The relevance of these findings for pediatric patients and their impact on treatment strategies is emphasized throughout the text.
Key words: pediatric lymphadenopathy, Hodgkin lymphoma (HL), Non-Hodgkin lymphoma (NHL), Diagnosis Imaging techniques.

Rezumat. Particularitățile de diagnostic ale limfoamelor în regiunea cervicală la copii.
Acest articol discută diferite aspecte ale limfadenopatiei pediatrice, concentrându-se pe limfomul Hodgkin (HL) și limfomul non-Hodgkin (NHL). Acesta prezintă etiologiile comune, tehnicile de diagnosticare și caracteristicile cheie ale diferitelor subtipuri de limfom. HL este clasificat în HL clasic (CHL) și HL predominant limfocitar nodular (NLPHL), în timp ce NHL include limfomul Burkitt (BL), limfomul limfoblastic (LBL), limfomul difuz cu celule B mari (DLBCL) și limfomul anaplazic cu celule mari (ALCL). Textul subliniază importanța diagnosticului precis prin diverse teste, inclusiv modalități imagistice, cum ar fi tomografia cu emisie de pozitroni (PET) și tomografia computerizată (CT). De asemenea, se discută despre utilizarea potențială a ctDNA ca marker de prognostic și evidențiază modificările genetice care contribuie la dezvoltarea limfomului. Relevanța acestor constatări pentru pacienții pediatrici și impactul lor asupra strategiilor de tratament este subliniată pe tot parcursul textului.
Cuvinte cheie: limfadenopatie pediatrică, Limfom Hodgkin (HL), Limfom non-Hodgkin (NHL), Tehnici de diagnosticare imagistică.

Резюме. Особенности диагностики лимфом шейной области у детей.
В этой статье обсуждаются различные аспекты детской лимфаденопатии, уделяя особое внимание лимфоме Ходжкина (ЛХ) и неходжкинской лимфоме (НХЛ). В нем представлены общие этиологии, методы диагностики и ключевые особенности различных подтипов лимфом. ЛХ подразделяется на классическую ЛХ (ХЛ) и узловую лимфоцитарную ЛХ (НЛФЛ), в то время как НХЛ включает лимфому Беркитта (БЛ), лимфобластную лимфому (ЛБЛ), диффузную крупноклеточную В-клеточную лимфому (ДКБКЛ) и анапластическую крупноклеточную лимфому (АККЛ)). В тексте подчеркивается важность точной диагностики с помощью различных тестов, включая такие методы визуализации, как позитронно-эмиссионная томография (ПЭТ) и компьютерная томография (КТ). В нем также обсуждается потенциальное использование ктДНК в качестве прогностического маркера и подчеркиваются генетические изменения, которые способствуют развитию лимфомы. Актуальность этих результатов для педиатрических пациентов и их влияние на стратегии лечения подчеркивается на протяжении всего текста.
Ключевые слова: детская лимфаденопатия, лимфома Ходжкина (ЛХ), неходжкинская лимфома (НХЛ), методы визуализации.

Introduction

Cervical lymphadenopathy in the pediatric population is a common presenting complaint with myriad possible etiologies. The 3 most common etiologies identified include nonspecific diagnosis, Epstein-Barr virus, and malignancy. As with any systematic review, limitations and potential sources of bias exist. By combining these data with the patient's clinical picture, the treating physician can estimate the probability of a specific diagnosis and more accurately evaluate the need for further diagnostic evaluation [7]. Lymphoma comprises 10–15% of childhood malignancy, and the frequency of lymphoma from the SEER database is 0.5–1.2 per 100,000. Although any type of lymphoma can occur in a child, most pediatric lymphomas comprise only a few of the subtypes as defined by the World Health Organization. Aggressive lymphomas such as Burkitt lymphoma, diffuse large B-cell lymphoma, and ALK + anaplastic large cell lymphoma are much more common than indolent lymphomas [1]. The treatment of Hodgkin lymphoma (HL) is one of early success. However, disease-free survival (DFS) does not reflect latent organ injury and its impact on health status and well-being beyond 5 years. In fact, we are at a crossroads, in terms of needing individualized approaches to maintain DFS, while minimizing late effects and preserving health-related quality of life (HRQoL). Premature morbidity and mortality translate to a high societal cost associated with the potential number of productive life years ahead in this population who are young at diagnosis [4]. Prior to starting salvage treatment, a full disease re-assessment is mandatory including biopsy and complete re-staging in all patients. Biopsy is considered mandatory to ensure histologic confirmation and ensures that the type of lymphoma has not changed which is occasionally seen, which is especially important both in unusually resistant patients and in later relapse to exclude second cancers and exclude false positives. Sufficient material must be obtained using either minimally invasive image guided techniques such as "trucut" biopsy or by conventional excision biopsy. Fine needle aspiration (FNA) is strictly not recommend, as this cannot provide sufficient material [5]. There have been tremendous advances in the study of pediatric lymphoma during the past decades, although the pathogenesis of these lymphomas remains not fully understood. These advances have led to optimized treatment strategy and significantly improved therapeutic outcome of these diseases, and the creation of a few new entities in WHO classification. The pathologic features of these lymphomas are well defined, and the diagnosis usually needs the correlation of histology, immunophenotype and the findings of other proper ancillary tests [8].

Hodgkin lymphoma (HL)

HL is a B-cell lymphoma and can be further divided into classical HL (CHL) and nodular lymphocytic predominant HL (NLPHL) based on pathology.

CHL is characterized by the presence of large mononuclear Hodgkin (H) cells and binucleated or multinucleated Reed-Steinberg (RS) cells in a background of mixed inflammatory cells, while NLPHL is characterized by the presence of popcorn-shaped lymphocyte-predominant (LP) cells against the background of a nodular pattern of B-cell growth.

There are four subtypes of CHL: Nodular Sclerosis Classical Hodgkin Lymphoma (NSCHL), Classical Mixed Cell Hodgkin Lymphoma (MCCHL), Classical Lymphocyte Rich Hodgkin Lymphoma (LRCHL) and Classical Lymphocyte Depleting Hodgkin Lymphoma (LDCHL).

Hodgkin's lymphoma presents most frequently in children with asymptomatic cervical and supraclavicular lymphadenopathy, with or without systemic constitutional symptoms (fever, weight loss, and night sweats), which adversely affect the prognosis. The lymphadenopathy is described as firm, rubbery and painless.

CHL involves the cervical lymph nodes and is rarely extranodal, where it can involve the thyroid gland, parotid gland, nasopharynx, and Waldeyer's ring. Painless lymphadenopathy of the neck is the most common presentation of head and neck LCH in children.

Non-Hodgkin's lymphoma (NHL)

NHL is a collection of a heterogeneous group of lymphoid neoplasms originating from B, T, or NK cells. Common NHLs in children include Burkitt lymphoma (BL), lymphoblastic lymphoma (LBL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL).

Histological varieties of NHL are divided into low-grade, intermediate-grade, and high-grade, and the vast majority presenting in childhood are high-grade.

There are several newly proposed or revised lymphoma entities in the latest WHO classification, which include Burkitt's lymphoma with 11q aberration, large B-cell lymphoma with IRF4 rearrangement, pediatric follicular lymphoma, and systemic EBV (Epstein-Barr virus). + Childhood T-cell lymphoma. These new entities are relatively common in children.

Childhood NHL

Presents in the head and neck region in 5-10% of cases, most commonly with asymptomatic cervical lymphadenopathy. Reported in children up to 3 years old, with an average age of 15-17 years. There is a strong male predominance with a male:female ratio of 10:1. It most commonly involves the lymph nodes of the head and neck, but also the tonsils and Waldeyer's ring. It has been reported in the cervical, periparotid, postauricular, submandibular, and submental lymph nodes, where it usually presents as an isolated nodule. Other regions that may be involved include the salivary glands, larynx, sinuses, and orbit. NHL can also manifest in the extranodal lymphoid tissue of Waldeyer's ring, presenting as asymmetric tonsillar enlargement or mimicking adenoidal hypertrophy. Therefore, tonsillectomy may not be indicated by asymmetry alone without considering other factors such as constitutional symptoms (fever, weight loss, and night sweats), history of rapid unilateral enlargement, or associated cervical lymphadenopathy or hepatosplenomegaly.

Burkitt's lymphoma

BL is frequently an extranodal disease and may involve the head and neck region. In endemic BL, ~50–70% of cases involve the jaw or other facial and orbital bones, but may also involve other extranodal sites, including the thyroid gland, nasopharynx, jaw, sphenoid, and salivary glands. Lymph node involvement of BL is less common, especially in children. Symptoms for cases in the head and neck region may include swelling in the jaw region, jaw pain, nasal obstruction, facial edema, headache, and proptosis.

On CT, Burkitt lymphoma appears as a large osteolytic lesion near the angle of the mandible with an associated soft tissue mass without osteoid or cartilaginous matrix (Aiken and Glastonbury, 2008). Burkitt's lymphoma can also affect the jaw.

Lymphoblastic lymphoma (LBL)

Lymphoblastic lymphoma (LBL) is the second most common type of non-Hodgkin's lymphoma (NHL) in childhood and adolescence, accounting for 25-35% of all cases. The majority, 70-80%, are of T-lymphoblast origin, while 20-25% are of B-lymphoblast origin.

T-LBL affects men 2.5 times more often than women, and the average age of T-LBL diagnosis is about 9 years. T-LBL can occur in any lymph node in the body, but the mediastinum and cervical nodes are involved in the vast majority of patients. Adolescent and young adult patients most commonly present with an anterior mediastinal mass arising from the thymus, which may cause airway compression or superior vena cava syndrome and is frequently accompanied by pleural or pericardial effusions. Symptoms include shortness of breath, cough, stridor, dyspnea and acute respiratory distress. Edema of the neck and face and jugular venous distension should raise the suspicion of superior vena cava syndrome.

Most precursor B malignancies present as B lymphoblastic leukemia (B-ALL), with only 10-20% of cases presenting as pB-LBL. B-ALL/LBL is primarily a disease of childhood, with 75% of cases occurring in children under 6 years of age. Similar to T-LBL, there is a slight male predominance. Osteolytic bone lesions (26%) and skin or subcutaneous lesions (23%) are the most common sites of disease.

Diagnosis

Laboratory tests include the following:

• Complete blood cell count for anemia, lymphopenia, neutrophilia, or eosinophilia

• Erythrocyte sedimentation rate and C-reactive protein, serum copper and ferritin levels.

• Lactate dehydrogenase

• Serum creatinine

• Alkaline phosphatase

Imaging studies include the following:

• Plain radiographs

• Computed tomography

• Positron emission tomography, which is considered essential for the initial staging of Hodgkin's lymphoma

Head and neck lymphadenopathy

Palpable cervical lymph nodes, which are commonly appreciable throughout childhood, were noted in 56 percent of adult physicals in one outpatient primary care study, although the incidence declined with age. The most common cause of cervical lymphadenopathy is infection, which in children is typically an acute and selflimited viral infection. While most cases resolve quickly, some entities such as atypical mycobacteria, cat-scratch disease, toxoplasmosis, Kikuchi's lymphadenitis, sarcoidosis, and Kawasaki's syndrome can create persistent lymphadenopathy for many months, and may be confused with neoplasms. Among this group, supraclavicular nodes are the most likely to be malignant, and should always be investigated, even in children. Overall, the prevalence of malignancy in this presentation is unknown, but rates of 54 to 85 percent have been seen in biopsy series reports [2].

As the initial diagnostic imaging of choice for cervical lymphadenopathy, the role of conventional ultrasonography is well established, and malignant cervical lymph nodes with typical imaging features

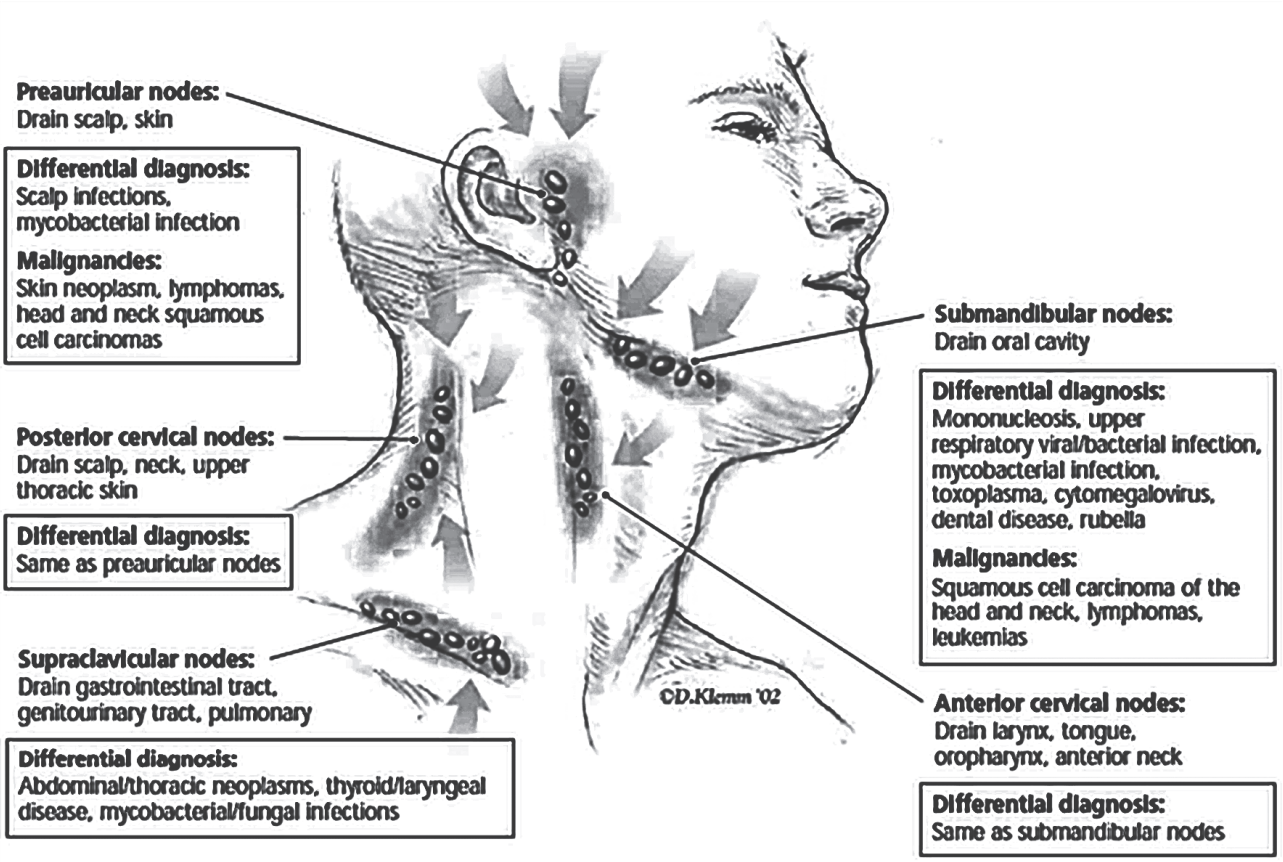

Figure 1. Lymph nodes of the head and neck, and the regions that they drain [2].

are not too difficult to differentiate from benign lymph nodes. On ultrasonography, metastatic lymph nodes are usually hypoechoic and round with hilar loss. Internal necrosis of metastatic nodes can be seen either as an echogenic focus or as a cystic or hypoechoic area, depending on the type of necrosis.

Positron emission tomography complements CT and MRI results as it provides information on metabolic activity. Positron emission tomography (PET) has been shown to be more reliable than CT and MRI in detecting residual or recurrent disease, as well as in distinguishing post-treatment fibrosis from active residual tumors.

Common lymphadenitis is characterized by the following characteristics:

1) the presence of a "causal" tooth (complicated caries) or any other inflammatory process in the organs and tissues of the head and neck;

2) lesions of the lymph nodes, which represent the first stage of lymphatic drainage for the organs of the oral cavity (submandibular and upper cervical), while with lymphomas, as a rule, the supraclavicular lymph nodes are affected;

3) swelling of the tissues in the area of the lymph nodes, painful to palpation;

4) the pasty consistency of the lymph nodes;

5) a pronounced effect of the anti-inflammatory treatment already in the first 5-7 days after the onset of the disease

In the differential diagnosis with tuberculous lymphadenitis, it should be remembered that the latter is characterized by:

1) the adhesion of the lymph nodes to each other and to the surrounding tissues, the skin;

2) the tendency to form fistulas with their subsequent scars;

3) when examining patients with tuberculin tests are usually strong

For infectious mononucleosis, which also affects the peripheral lymph nodes and most often the upper cervical region, it is characterized by:

1) a swelling, primarily in the postauricular and posterior neck lymph nodes, as well as other groups of peripheral lymph nodes;

3) the acute onset of the disease, which can appear with symptoms of tonsillitis, and in children who have undergone tonsillectomy, hyperemia of the throat mucosa;

4) pain in the abdominal cavity, enlargement of the spleen and liver, sometimes jaundice;

5) an increase in peripheral blood lymphocytes, the appearance of large protoplasmic lymphocytes

Histologic subclassification can be challenging, and open excisional lymph node biopsy is considered the gold standard for diagnostic evaluation. Recently, publications have supported the diagnosis and classification of lymphomas using less invasive techniques, benefiting from image-guided cutting needle biopsies and advances in the use of cytopathological and immunohistochemical techniques with small specimens. These techniques have been applied with great success to cervical lymphadenopathy in some units, but remain controversial and may not be applicable to the pediatric population. Biopsy tissue should be sent fresh to the pathologist to facilitate flow cytometry, immunohistochemical staining, electron microscopy, and molecular genetic testing.

In current practice, 18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) is the reference standard for both staging and follow-up of Hodgkin lymphoma. Although FDGPET/ CT is the current preferred imaging modality, ultrasonography (US) and magnetic resonance imaging (MRI) are increasingly used in both staging and follow-up since a substantial dose of radiation is used in FDG-PET/ CT. Depending on the child's age and weight, and the local imaging protocols, estimated doses have been described to be around 9.3 ±2.3 mSv [10].

For both staging and treatment response assessment, [18F] FDG-PET/CT is considered the technique of choice for the vast majority of lymphoma subtypes, according to the guidelines of the International Conference on Malignant Lymphoma (ICML), because they show a high glucose metabolism. For lymphoma, on the other hand, WB-MRI is presently not recommended by clinical guidelines, and is merely regarded as an alternative technique to [18F] FDG-PET/CT when radiation exposure is a concern, as for instance in pediatric patients, or when CNS involvement is suspected. Despite their high sensitivity, WB-MRI, and especially DWI, is currently not recommended in patients with non-FDG-avid lymphoma subtypes such as MALT lymphoma and SLL. [9].

Waldeyer's ring and posterior cervical nodes can be difficult to interpret in children, especially on the interim and end of treatment 2-[18F] FDG PET/CT. Children are prone to viral and bacterial infectionswhich frequently involve the upper air ways. Recent chemotherapy reduces the patient's immunity further, which increases the risk for infections. The use of 2-[18F] FDG PET/CT in combination with MRI is useful to identify pathology in Waldeyer's ring [3].

Persistence of ctDNA detection during curative-intent therapy is proposed as a dynamic prognostic marker for clinical outcome that can anticipate and complement interim PET/CT results. ctDNA is the portion of cell free DNA (cfDNA) which derives from tumor apoptotic cells, and which can be distinguished from cfDNA released by normal cells by using the tumor mutation profile as a fingerprint. Being influenced by disease type and stage, the mean concentration of cfDNA in lymphoma patients is 30 ng/mL, Levels of ctDNA correlated with tumor burden assessed by measuring metabolic tumor volume (MTV) in baseline FDG-PET/CT, and International Prognostic Index (IPI) and could be detected up to 3–3.5 months before overt disease manifestation. However, the diagnostic and prognostic value of VDJ profile of the heavy chain (IgH) tracking has some disadvantages when applied to HL, including the need for analyzing micro dissected HRS cells. In HL, ctDNA can be explored using two main techniques: polymerase chain reactions (PCR) and next-generation sequencing assays [8].

Patients have genetic alterations in their HRS cells that may also be present in their circulating mononuclear B cells, possibly due to telomere dysfunction. The genetic basis for immune evasion and the anti-apoptotic signaling mediated by NF-κB and PI3K/AKT/mTOR pathways play a key role in cHL survival, while JAK/STAT signaling is known to sustain tumor growth. A reduced MHC Class I and/or Class II antigen expression and a reduced antigenic peptide/MHC complex presentation, which often correlates with worse prognosis, is reportedly common in HL, affecting from 40% to 70% of cases [6].

Conclusion.

A lot of different illnesses with different causes that can produce a similar clinical picture must be taken into account when making a diagnosis of HL or NHL in a child. To correctly make the differential diagnoses for this pathology, specialists must be aware of it and have access to sufficient clinical and paraclinical evidence. Although HL and NHL diagnostic and treatment methods have advanced significantly in recent years thanks to various technologies, literature still stresses the need for further development and the creation of more straightforward and effective diagnostic techniques so that HL and NHL can be predicted and detected earlier in order to increase survival rates of the patients.

Programul de stat 2020-2023. *Proiectul de cercetare „Chirurgia modernăpersonalizată* ***în*** *diagnosticul* ***și*** *tratamentul complex al tumorilor la copii" cu cifrul 20.80009.8007.06*

References

1. Auerbach A, Schmieg JJ, Aguilera NS. Pediatric Lymphoid and Histiocytic Lesions in the Head and Neck. Head Neck Pathol. 2021 Mar;15(1)41-58. doi 10.1007s12105-020-01257-6. Epub 2021 Mar 15. PMID 33723759; PMCID PMC7959275.
2. Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. Am Fam Physician. 2002 Dec 1;66(11)2103-10. PMID 12484692.
3. Brink A, Hlongwa KN, More S. The Impact of PETCT on Paediatric Oncology. Diagnostics (Basel). 2023 Jan 5;13(2)192. doi 10.3390diagnostics13020192. PMID 36673002; PMCID PMC9857884.
4. Chantada G, Lam CG, Howard SC. Optimizing outcomes for children with non-Hodgkin lymphoma in low- and middle-income countries by early correct diagnosis, reducing toxic death and preventing abandonment. Br J Haematol. 2019
5. Daw S, Hasenclever D, Mascarin M, Fernández-Teijeiro A, Balwierz W, Beishuizen A, Burnelli R, Cepelova M, Claviez A, Dieckmann K, Landman-Parker J, Kluge R, Körholz D, Mauz-Körholz C, Wallace WH, Leblanc T. Risk and Respon
6. De Re V, Repetto O, Mussolin L, Brisotto G, Elia C, Lopci E, d'Amore ESG, Burnelli R, Mascarin M. Promising drugs and treatment options for pediatric and adolescent patients with Hodgkin lymphoma. Front Cell Dev Biol. 202
7. Deosthali A, Donches K, DelVecchio M, Aronoff S. Etiologies of Pediatric Cervical Lymphadenopathy A Systematic Review of 2687 Subjects. Glob Pediatr Health. 2019 Jul 27;62333794X19865440. doi 10.11772333794X19865440. PMID
8. Li W. Pathogenesis and Pathology of Pediatric Lymphoma. In Gallamini A, Juweid M, editors. Lymphoma [Internet]. Brisbane (AU) Exon Publications; 2021 Dec 28. Chapter 1. PMID 35226433.
9. Mayerhoefer ME, Archibald SJ, Messiou C, Staudenherz A, Berzaczy D, Schöder H. MRI and PETMRI in hematologic malignancies. J Magn Reson Imaging. 2020 May;51(5)1325-1335. doi 10.1002jmri.26848. Epub 2019 Jul 1. PMID 3126015
10. Spijkers S, Littooij AS, Humphries PD, Lam MGEH, Nievelstein RAJ. Imaging features of extranodal involvement in paediatric Hodgkin lymphoma. Pediatr Radiol. 2019 Feb;49(2)266-276. doi 10.1007s00247-018-4280-z. Epub 2018 De