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Review article ■

Palpable Lymphadenopathy in Primary Care

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SUMMARY

Palpable lymphadenopathy presents a serious diagnostic and therapeutic problem in primary care. The patients are often referred to a specialist with delay and even more often they are referred to unneeded diagnostic and therapeutic procedures. Empiric treatment with antibiotics and corticosteroids and extraction of often healthy teeth commonly leads to delay in establishing the diagnosis and sometimes even to iatrogenic complications. Because of the aforesaid factors, the authors of this paper decided to review the available literature and try to quantify the characteristics of primarily malignant lymphadenopathies hoping to contribute to the making of a better and more cost-effective system for diagnosing these patients.

Key words: lymphadenopathy, lymph node, lymphoma, metastatic cancer

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INTRODUCTION

The human body contains about 500-600 lymph nodes. These organs are susceptible to pathologic and physiologic changes and can, very commonly, be the first hallmarks of a disease.

Palpable lymphadenopathy is a very common finding in children and can be observed in 38-45% of the pediatric general population (1), however, according to Fijten et al. (2) the adult population has a 0.6% annual incidence of lymphadenopathy. The same paper by Fijten reported that 10% of those patients were referred to a specialist who performed a biopsy in 3.2% of the cases and found malignancy in 1.1% of the analyzed samples; another author (3) found that 3 out of 238 lymph nodes biopsied had a malignant cause. A recent paper by I Chau et al. (4) analyzed a population of 2.2 million people during the period of 1996-2001, and out of that population only 550 were referred to a specialist because of lymphadenopathy, of which 17.3% were eventually diagnosed with malignancy.

Because of the aforementioned statistical discrepancies and partly due to our clinical experiences with lymphadenopathy, we decided to review all the literature we could find on this topic and try to formulate a plan for a reasonable and cost-effective approach to lymphadenopathy.

PREDICTING FACTORS

Our review of previously published papers produced a number of factors that were best at predicting a possible malignant cause of lymphadenopathy. Those factors produce a mnemonic "A MODAL" and are summarized in Table 1. Other studies have also found similar factors and the most widely known is "ALL AGES" which was invented by Haberman et al. (5). A third system was published in 2000 by Vassilakopoulos and Pangalis (6) and it revolves around a formula devised by the two authors, thus predicting the need for a lymph node biopsy. Some factors, predominantly from the "A MODAL" system, concerning these systems will be discussed in this section.

Age

The age of the patient is a very important factor in establishing a clinical suspicion of malignancy in patients with lymphadenopathy. Lee et al. analyzed 925 pathology reports from lymph node biopsies done at the Los Angeles County Hospital from 1973-1977 and found that the cause of lymphadenopathy was benign in 79% of the patients under 30, in 59% of the patients aged 31-50 and only 40% of the patients aged 51-80 had a benign cause for their lymphadenopathy (7). The rule of 4's says that of all patients presenting to the primary care with a lymphadenopathy 0.4% of those younger than 40 years will have a malignancy and 4% of

those over 40 will have a malignancy (1, 3, 8, 9). The reason for the statistical difference in the Lee et al. study and the rule of 4's is that Lee et al. analyzed patient findings in a secondary referral center where patients were referred with a high suspicion of malignancy whilst the rule of 4's applies to primary practice.

Morphology

DIAMETER: The most important factor considering the morphology of lymph nodes is size. Although most clinicians and some textbooks claim that the size of lymph nodes should be less than 1cm that is not entirely true. Pangalis (10) conducted a study in which he analyzed lymph nodes of 220 patients. Biopsies produced no malignancies in lymph nodes smaller than 1 cm², 8% of the lymph nodes sized between 1-2.25 cm² were malignant, and 38% of patients whose lymph nodes were larger than 2.25 cm² were found to have a malignant disease. Another publication (11) found that in patients aged 9-25, lymph nodes larger than 2 cm were predictive of granulomatous diseases or cancer. Even though these two studies are considered a definite work on the topic at hand, other authors reveal that the previously mentioned diameters cannot be applied to every lymph node and advocate that if supraclavicular, epitrochlear, iliac or popliteal nodes are larger than 0.5 cm, that should greatly alarm the physician (12-15). Several studies (16, 17) have reported on radiologic characteristics of lymph nodes and the unanimous conclusion was that one of the most important predictive factors for lymph node malignancies is the Long/Short axis ratio (L/S) where if that ratio is less than 2.0 malignancy is highly likely, the rough clinical conclusion from those studies is that if the width of the lymph node approaches its length malignancy should be suspected, this finding cannot be used for submandibular and parotid lymph nodes which can normally be round in shape (18). Even though these studies used ultrasound and found that ultrasound was superior to clinical examination in detecting lymphadenopathy (96.8% vs. 73.3%) (19), the authors of this paper believe that the L/S measurement could be used in a clinical practice as a sensitive but not a specific finding, meaning that a L/S ratio less than 2 should be considered highly risky while a normal L/S ratio should not be taken for granted. All of the findings considering the size of the lymph node or the L/S ratio of the affected lymph node warrant a very important recommendation. The lymph nodes should always be measured in centimeters or millimeters with a ruler (or a Vernier caliper if possible) and both the length and width should be measured. Comparing lymph node sizes to common household items (i.e. coin, battery, strawberry, and pear) should never be used in clinical practice as it is: inaccurate, prone to subjectivity and opens the examiner to litigation.

TEXTURE AND TENDERNESS: While little reliable statistical data exists on tenderness and texture as a

predictive factor for malignancy Vassilakopoulos and Pangalis (6) used the hard texture as a positive predictor of a need for a biopsy and tenderness as a negative predictor in their formula.

Other

SEX: We were able to find only one study that found sex as a significant malignancy prediction factor in lymphadenopathy and that paper reported the male gender a relative risk of 2.72 (CI 95%) (4).

HISTORY: Past medical illnesses which might have recurred such as tuberculosis, cancer, leukemia or lymphoma should always be on top of everyone's mind. A family history of malignant diseases should raise the physician's suspicions. History of risky environmental or sexual exposure could raise the risk of malignant and/or infectious diseases which might cause generalized or localized lymphadenopathy (20, 21).

MEDICATIONS: The medications summarized in Table 2 are known to cause lymphadenopathy.

Duration

The general rule (5) is that a lymphadenopathy which lasts less than 4 weeks (according to some authors 2 weeks (22, 23) or more than 1 year should, at least for the time being, be considered benign. This rule should not be considered absolute and patients that have other risk factors must be referred for further testing regardless of the duration of their lymphadenopathy. Also, certain diseases such as low grade Hodgkin's (HD) and non-Hodgkin's (NHD) lymphoma and chronic lymphocytic leukemia (CLL) can present itself as a long- standing (>1year) lymphadenopathy (5).

Associated signs and symptoms

Lymphadenopathy is frequently accompanied by a wide variety of symptoms and signs but for the purpose of this paper we decided only to explore the more straightforward ones. Lymphangitic streaking can be a manifestation of a cutaneous infection (5). Splenomegaly in the presence of lymphadenopathy is a rare occurrence (4.5% of the cases according to one study (10). The most likely causes for the splenomegaly and lymphadenopathy appearing together are: infectious mononucleosis, HD, NHD, CLL and some acute leukemias (5). The presence of splenomegaly is rare in metastatic cancer (24). Constitutional symptoms such as malaise, fatigue and fever are usually not very helpful but coupled with a cervical lymphadenopathy and atypical lymphocytosis they are most commonly seen in mononucleosis (23). The "B symptoms" (fevers >38C, drenching night sweats, unexplained loss of more than 10% of body weight) are usually present in 8% of patients in Stage I HD and 68% of patients in Stage IV of HD (25), these sym-

ptoms also occur in 10% of patients with NHD (10). Although the presence of B symptoms is usually associated with lymphoproliferative disorders we remind the physician that these symptoms, together or separately, may be present in many other diseases one of which is tuberculosis (8). Symptoms and signs such as arthralgias, muscle weakness, and/or unusual rash may indicate an autoimmune condition such as rheumatoid arthritis, systemic lupus erythematoses, or dermatomyositis (23). The rate of malignancy in patients presenting with generalized pruritus is 1-8% (26) and even though that rate is not high, the appearance of lymphadenopathy concomitant with pruritus is a very concerning symptom because 35% of patients with HD (27) and 10% patients with NHD (26) exhibit pruritus and it may even precede the diagnosis of lymphoma by 5 years (26, 28). Vassilakopoulos and Pangalis also found generalized pruritus as a positive predicting factor for the need for a lymph node biopsy in lymphadenopathy (6).

Location

Lymphadenopathy can be classified as generalized or localized with a prevalence of 25% and 75%, respectively (8).

Generalized lymphadenopathy is defined as the enlargement of 2 or more non-contiguous node sites. It's most commonly caused by mononucleosis, toxoplasmosis, AIDS, systemic lupus erythematoses, mixed connective tissue disorder, acute and chronic lymphocytic leukemia lymphomas and other diseases. According to Chau, the rate of malignancy in high risk patients with lymphadenopathy referred for lymph node biopsy was 34.8% (4). Considering the most common causes of generalized lymphadenopathy we believe that a complete blood count (CBC) would be the reasonable first step in a cost-effective diagnostic approach, serology should be reserved as a second step and only if there is a valid suspicion of a specific infectious disease. If the need arises for biopsy the largest lymph node other than inguinal should be biopsied (8).

Localized lymphadenopathy is far more common and the location of the enlarged lymph node yields a lot of information of diagnostic value. The enlarged lymph node location points to its area of drainage and usually, i.e. if it is not a primary lymph node disease, enables the visualization of the primary process. The clinical characteristics of localized lymphadenopathies, sorted by location, are given in Table 3.

Final Comments

The "A MODAL" and the "ALL AGES" systems are very similar and rely heavily on individual factors and the statistical analysis of those factors. One drawback is that none of these systems have been tested in a clinical setting let alone in a clinical trial and the other drawback is that these systems are currently not quantified

and remains to be seen if they are quantifiable. The only positive side to these systems is that it leaves the physician room for creative thinking giving him a possible chance to establish an early diagnosis of a malignant disease. The third system by Vassilakopoulos and Pangalis (6) is relatively easy to use, and any clinician can calculate it very rapidly. The system is clinically tested by the authors and yielded a sensitivity/specificity of 95%/81% when $Z > 1$ was taken as a cut-off point, another study found the sensitivity/specificity to be 97%/56% for $Z > 1$ (34). Although this system is yet to be thoroughly tested we believe that the Vassilakopoulos and Pangalis formula is clearly superior to previous systems but that it should not be used as a blind substitute for the clinicians knowledge, experience and the other systems so that we recommend that the abovementioned formula should be used with one of the previously mentioned systems as an adjunct tool. Aside from all the data and recommendations presented in this review the authors have three more recommendations to make or reiterate:

1. Lymph nodes should be measured with a ruler or a Vernier caliper and their length and width should be noted in millimeter or centimeter.
2. Patients should not be started on antibiotics except if obvious signs of bacterial infection exist. Steroids should not be introduced except if breathing is compromised because of lymph node obstruction of airways. Steroids can falsely and temporarily reduce the size of lymph nodes thus prolonging the time to diagnosis (5, 9, 10).
3. "Blind" teeth extraction is not comfortable for the patient and yields little information of diagnostic value. Teeth extraction can introduce an infection in a possibly immunocompromised individual and even produce prolonged bleeding in a thrombocytopenic patient and it prolongs the time to diagnosis. Ultrasound is far more specific and sensitive and the price may even be lower.

Table 1. The "A MODAL" and "ALL AGES" diagnostic systems and the "Vassilakopoulos and Pangalis" formula for lymphadenopathy

A MODAL	ALL AGES (5)	Vassilakopoulos and Pangalis formula (6)
Age	Age	Age: $x_1 = 0$, if $<$ or $= 40$ years and 1 , if > 40 years.
Morphology	Location	Tenderness in palpation: $x_2 = 0$, if absent and 1 , if present
Other (sex, history, medications)	Length of time present	Size of the largest lymph node: $x_3 = 0$, if < 1.0 cm^2 , 1 if $1.0-3.99$ cm^2 , 2 if $4.0-8.99$ cm^2 , and 3 if $>$ or $= 9.0$ cm^2
Duration	Associated signs and symptoms	Generalized pruritus: $x_4 = 1$, if present and 0 , if not.
Associated signs and symptoms	Generalized lymphadenopathy	Supraclavicular lymphadenopathy: $x_5 = 1$, if present and 0 , if not.
Location	Extranodal Associations	Texture: $x_6 = 1$, if nodes are hard and 0 , if not.
	Splenomegaly and Fever	$Z = 5x_1 - 5x_2 + 4x_3 + 4x_4 + 3x_5 + 2x_6 - 6$; if $Z > 1$ a lymph node biopsy is warranted.

Table 2. Medications known to cause lymphadenopathy (8, 10, 22)

Allopurinol	Carbamazepine	Hydralazine	Penicillin	Primidone	Sulfonamides
Atenolol	Cephalosporins	Isoniazid	Phenytoin	Pyrimethamine	Sulindac
Captopril	Gold	Mephenytoin	Phenylbutazone	Quinidine	

Table 3. Localized lymphadenopathy sorted by location, drainage of clinically significant lymph node groups, diseases causing the lymphadenopathy and comments (4, 5, 8, 9, 20, 23)

Location	Area of drainage	Most common causes of enlargement	Epidemiology, recommendations and comments
Submandibular	Tongue, submaxillary gland, lips and mouth, conjunctivae	Infections of head, neck, sinuses, ears, eyes, scalp, pharynx, mononucleosis upper respiratory tract infection, dental disease, rubella, squamous cell carcinoma of the head and neck, lymphoma, leukemia	
Submental	Lower lip, floor of mouth, tip of tongue, skin of cheek	Mononucleosis syndromes, cytomegalovirus, toxoplasmosis, dental disease, lymphoma, oral carcinoma	Head and neck lymphadenopathy represents 55% of all lymphadenopathies. It is usually of benign etiology, most commonly viral infections, especially in children. Malignancy represents 13.8%. It is not commonly caused by dental infections. In the absence of high risk factors waiting is recommended. Examination of the tissues drained by the enlarged lymph node and CBC should be the first step. If lymphadenopathy is persistent (>2 weeks) or more risk factors perform an ultrasound (sensitivity 98%, specificity 95%) (29) or refer for biopsy ^c . "Blind" dental extraction ^p is not recommended because it prolongs the time to diagnosis if a malignancy is present.
Anterior cervical	Tongue, tonsil, larynx, oropharynx, parotid, anterior neck	Pharyngitis, upper respiratory disease, mononucleosis, squamous cell carcinoma of the head and neck, lymphoma, skin neoplasms	
Posterior cervical	Scalp and neck, skin of arms and pectorals,	Tuberculosis, lymphoma, head and neck malignancy, ear infections, scalp infections	
Suboccipital	Scalp and head	Scalp and head infection and rubella	
Retroauricular	External auditory meatus, pinna, scalp	Ear infections and scalp infections	
Preauricular	Eyelids and conjunctivae, temporal region, pinna	Conjunctivitis, and ear infections, lymphoma, skin neoplasms, head and neck squamous cell carcinoma	
Right supraclavicular	Mediastinum, lungs, esophagus	Lung, retroperitoneal or gastrointestinal cancer , tuberculosis	Represents 1% of all lymphadenopathies in primary practice but 6.4% in referral centers. Enlarged supraclavicular lymph nodes are most commonly malignant (34-90%) (2,4,7) Biopsy ^c should be sought immediately.
Left supraclavicular (Virchow node)	Thorax, abdomen via thoracic duct	Lymphoma, thoracic or abdominal cancer , tuberculosis, bacterial or fungal infection.	
Infraclavicular		Highly suspicious for HD	Biopsy ^c should be sought immediately.
Axillary	Arm, thoracic wall, breast	Infections, silicone implants, brucellosis, cat-scratch disease, lymphoma, breast cancer, melanoma	Represents 5% of lymphadenopathies. Most commonly reactive. Malignancy represents 15.1%. Arm and breast examination should be performed. If coupled with other high risk factors perform ultrasound of the axillary lymph nodes (specificity 50-82%, sensitivity 40-100%) (30,31) and breast. If further examination is needed refer for mammography and/or lymph node biopsy ^c .
Epitrochlear	Ulnar aspect of forearm and hand	Infections, sarcoidosis, tularemia, secondary syphilis, lymphoma, melanoma	Should be considered abnormal if over 0.5cm. Always perform examination of the arm. Most common cause is CLL and infectious mononucleosis (32). The first step is to order a CBC and refer for biopsy ^c .
Inguinal	Penis, scrotum, vulva, vagina, perineum, gluteal region, lower abdominal wall, lower anal canal	Infections of the leg or foot, STDs lymphoma, squamous cell carcinoma of penis, vulva and anus, skin neoplasms, melanoma, Kaposi sarcoma	Most adults have some degree of inguinal lymphadenopathy. Reactive hyperplasia is the most common cause of enlargement (71%) (33). Malignancy represents 17.1%. Can be mistaken for inguinal hernia or vice versa. Ultrasound has a sensitivity of 95% and specificity of 97% in metastatic inguinal lymphadenopathy (16).
St. Mary Joseph node (Umbilical node)		Abdominal or pelvic carcinoma with metastasis	Considered by some a lymph node and by others a metastatic lesion to the umbilicus. The node is believed to almost always be malignant but the node is mostly enigmatic as little data on it exists. Can be mistaken for a hernia or vice versa.

a - The percentage of malignancy was derived from Chau et al study (4) which determined those rates in a secondary referral center in patients with lymphadenopathy and a high enough risk stratification to warrant a biopsy.

b - "Blind" teeth extraction is a term coined by the authors of this study and refers to the practice of extracting multiple teeth with/without evidence of infection in an attempt to cure the lymphadenopathy.

c - Excisional biopsies should be performed as fine needle aspiration (FNA) biopsies require a specialized laboratory with a highly experienced and very prudent staff. PCR can aid the diagnosis by determining the clonality of cells and flowcytometry can also be used in sorting and counting the number of cells according to their biomarkers in samples acquired by FNA.

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PALPABILNA LIMFADENOPATIJA U PRIMARNOJ NEZI

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Sažetak

Palpabilna limfadenopatija predstavlja ozbiljan dijagnostički i terapijski problem u primarnoj nezi. Ovi bolesnici se često upućuju specijalisti sa zakašnjenjem a još češće se upućuju na nepotrebne terapijske i dijagnostičke procedure. Empirijsko lečenje antibioticima i kortikosteroidima, kao i ekstrakcija često zdravih zuba, dovode do kašnjenja u postavljanju dijagnoze a ponekad i do jatrogenih komplikacija. Zbog prethodno navedenih faktora, autori ovog rada odlučili su da izvrše pregled dostupne literature i pokušaju da kvantifikuju karakteristike prvenstveno malignih limfadenopatija, u nadi da će time doprineti stvaranju boljeg i jeftinijeg sistema za dijagnostikovanje ovih bolesnika.

Ključne reči: limfadenopatija, limfni nodus, limfom, metastatski karcinom