Cervical Lymphadenopathy-A Clue to Systemic Diseases: A Recent Update

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Abstract

Lymph nodes are distributed along with the lymphatic system all over the body. Enlargement of lymph nodes (lymphadenopathy) may result from an infection, hyperplasia during the immunologic response, and sometimes also by infiltration by cancer cells or lipid cells. Lymphadenopathy may be regional or generalized and or caused by local or systemic factors. Therefore, the differential diagnosis of lymphadenopathy is critical. Oral physician during routine physical examination also includes the examination of any enlarged lymph node in the head and neck region. Lymphadenopathy may be the only clinical presentation or one of the few findings, and enlarged lymph nodes may often raise the suspicion of an underlying pathology like lymphoma, leukemia, and Acquired Immunodeficiency Syndrome (AIDS). This review focuses on the various causes of cervical lymphadenopathy, and the systemic approach to the differential diagnosis and the management along with the health care team.

Keywords: *Cervical lymphadenopathy, Diagnostic aids, Differential diagnosis, Malignancy.*

Introduction

The principal constituents in the lymph system are lymph nodes, the lymphatic vessels as well as the moving cells of immunity which compositely have the basic responsibility to protect the host against infections.[1] Lymphadenopathy frequently occurs as a clinical symptom of an array of disorders. It is described as an alteration in the size, number and consistency of lymph nodes, due to the infiltration or dissemination of either inflammatory cells or malignant cells into the nodal architecture.[2] Cervical lymphadenopathy is described as an enlargement of cervical lymph nodes, with a diameter greater than 1 cm.[3] Cervical lymphadenopathy generally describesa transitory reaction to a non-malignantlocal or generalized infection. However, infrequently, it might be a precursor to an underlying pathological state (autoimmune disorder/malignancy). Lymphadenitis distinctively refers to lymphadenopathies having inflammatory origin.[4] Lymphadenopathy is widely divided into 3 types- localized, generalized, and dermatopathic.[5,6] Generalized lymphadenopathy refers to the enlargement of lymph nodes in more than two noncontinuous areas, whereas, a single site is involved in localized lymphadenopathy. In primary care patients with undiagnosed lymphadenopathy, approximately three-fourths of patients manifest with localized lymphadenopathy and a quarter with generalized lymphadenopathy (Figure 1).[7,8] Dermatopathic lymphadenopathy (DLN) is often seen in patients with skin diseases exfoliative or eczematoid inflammatory erythrodermas, especially mycosis fungoides and Sézary

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syndrome, but has rarely been described in the absence of clinical skin disease.[9] According to its duration, it can be acute, sub-acute, and chronic lymphadenopathy. Acute lymphadenitis is usually seen with bacterial/ viral infections and persists for upto 2 weeks. Subacute lymphadenitis includes a wide array of potential etiologies and lasts between 2-to-6-weeks. Chronic lymphadenopathy persists for more than 6 weeks and occurs due to the infiltration and dissemination of inflammatory/neoplastic cells into the nodal tissues.[4,5,6] Categorizing localized and generalized lymphadenopathy is necessary for making a diagnosis. Thus, a patient presenting with a palpable cervicofacial lymph node poses a significant diagnostic and therapeutic challenge. In most of the cases, without physical examination and investigation result in a delayed incorrect diagnosis and may come as an iatrogenic complication due to misdiagnosis.[10]

Etiology: The Head and neck region is regarded as the commonest site for lymphadenopathy. The spectrum of lymphadenopathy may be represented by the pneumonic "MIAMI" and encompasses malignancies; infections, and autoimmune disorders, miscellaneous and iatrogenic causes.[2] In India, the leading cause for lymphadenopathy is attributed to infection, of which locoregional infections, tuberculosis, and filariasis predominate. According to a study by Iqbal et al., tuberculosis accounts for 70.45% of cervical lymphadenopathy, then comes reactive lymphadenitis (13.63%), metastases (11.36%), lymphomas(4.54%), and chronic nonspecific lymphadenitis (2.27%).[6,11]

Table 1-Depicting etiological factors of cervical lymphadenopathy.

1. **Infectious Etiology-** Various infectious etiologies like viral, bacterial, fungal, protozoal and pararsitic infectious may result in cervical lymphadenopathy.

(a) Viral infections- Herpes group of viruses (HSV, Varicella, EBV, CMV), HIV, Rubella, Measels, Adenovirus, Rhinovirus, enterovirus, Parvovirus B19etc may cause lymphadenopathy.

(b) Bacterial infections- Staphylococcus, Streptococcus, Tuberculous mycobacteria, Non Tuberculous mycobacteria, Treponema, M. leprae, corynobacterium diphtheria, Brucellosis, yersinia pestis, tularemia, mycoplasma pneumoniaetc may cause lymphadenopathy.

(c) Fungal infections- Candida, histoplasmosis, blastomycosis, dermatophytes (linea), coccidoimycosis.

(d) Parasitic/protozoal infections- Toxoplasmosis, trapanosoma, leishmania, rickettsia, microfilaria.

2. **Neoplastic Etiology-** A wide array of neoplastic conditions may have associatedlymphadenopathies.

(a) Squamous cell carcinoma- Odontogenic etiology (chronic irritation due to sharp tooth cusp, ill-fittingdentures), Tobacco induced conditions, SCC with Lichen planus of lip.

(b) Malignanat lymphomas- Hodgkin's & Non-Hodgkin's lymphoma (burkitt lymphoma).

(c) Leukemias- Acute myeloid leukemias, .Acute lymphoblastic leukemia

(d) Lymph node metastasis from solid tumors- Neuroblastoma, Rhabdomysarcoma, Nasopharyngeal carcinoma, metastatic lung, breast, thyroid, renal carcinoma.

3. **Metabolic Disorders-** A wide array of metabolic conditions may have associated lymphadenopathies.

(a) Inborn metabolic storage disorders- Niemann-Pick disease, Gaucher disease, Amylodosis, Tangier disease, Glycogen storage diseases are associated with cervical lymphadenopathy.

(b) Endocrine disorders- like Thyrotoxicosis, Adrenal insufficiency.

4. **Drugs & Lifestyle Exposure-** A variety of drug and lifestyle induced entities may have associated lymphadenopathy.

(a) Drug induced- A number of drugs like Isoniazid, Phenytoin, Allopurinol, Captopril, Penicillin, Cephalosporin, Carbamezipine, Heparin,,Gold, Hydralazine, Primidone, Pyrimethamine, Quinidine, Sulphonamides causes cervical lymphadenopathy.

(b) Lifestyle exposure- Alcohol, ultraviolet (UV) radiation, and tobacco can cause cancers with secondary lymphadenopathy.

5. **Miscellaneous-**A number of miscellaneous entities may cause cervical lymphadenopathy.

(a) Granulomatous infections- like Mycobacteria (M. tuberculosis, M. leprae, M. avium, M. kansai, M. marinum, BCG vaccination) spirochaetes (T. pallidum, T. pertenue, T. carateum) actinomycosis,

brucellosis, yersinia, nocardia, histoplasmosis may cause cervical lymphadenopathy.

(b) Vasculitis- like Wegener's granumatosis, Giant cell arteritis, Systemic lupus erythematosus(SLE), Rheumatoid arthritis, Polyarteritis nodosa, Churg-Strauss

(c) Immunologic abberrations- like Sarcoidosis, Orofacial granulomatosis, Crohn's disease, Primary biliary cirrhosis

(d) Hypersensitivity pneumonia (farmer's lung) & chemicals (beryllium & silicon) may also cause lymphadenopathy.

Clinical Evaluation: Since the diagnosis changes with age, sex, location, duration of symptoms, shape, and size an organized and detailed history, thorough clinical correlation and tissue diagnosis are mandatory.[12]

History: Factors which aid in classifying the cause of lymphadenopathy should include patient's age, location (localized vs. generalized) and duration of lymphadenopathy, foreign travel history, drug history, exposures, and associated symptoms.[13]

Age And Duration: About half of the healthy children demonstrate palpable lymph nodes. Most lymphadenopathy in children is non-malignant or due to infection.[14] The incidence of childhood neoplasms change with the age. In general, lymphadenopathy secondary to neoplasia arise in the adolescents.[4] The majority of acute lymphadenitis cases have an infectious etiology and subside after 2 weeks. This is in contrast to chronic lymphadenopathy, which persists for more than 6 weeks and has an underlying pathology (malignancy, metabolic disease or opportunistic infections).[15]

Associated Symptoms: A detailed review of systems helps in knowing any red flag symptoms. Upper respiratory tract infections encompass constitutional symptoms of fever, chills, sore throat, cough, and body ache. Along with fever, sweating in the night and unknown weight loss (< 10% of body weight) is suggestive of Hodgkin/non-Hodgkin lymphoma. Persistent productive cough lasting more than 3 weeks,evening rise of temperature, hemoptysis, and weight loss are suggestive of tuberculosis. Idiopathic fever, rash, fatigue, and pain in bones increase the suspicion of any autoimmune disease.[13,16]

Concurrent Illness and Past Health: A detailed and meticulous history is mandatory taking in account history of foreign travel, animal/insect contact (esp. cats, dogs, rodents and ticks), preceding infection (tonsillitis and periodontal infections), occupational history (mining and metal industries like lead, beryllium, and silicon), chronic use of medications (Isoniazid, phenytoin, and allopurinol may cause lymphadenopathy), immunization status (lymphadenopathy may occur after diphtheria-pertussis-tetanus, Polio and typhoid fever vaccine), sexual history (genital sores may have accompanying lymphadenopathy) and family history (few diseases have a familial predisposition, like lipid storage diseases and Li-Fraumeni syndrome).[13,15,16]

Physical Examination: General Malnutrition or poor height and weight indices are suggestive of underlying chronic disorders such as tuberculosis, immunodeficiency, or malignancy.[17] Physical examination usually includes inspection, palpation, and ENT assessment. However, cases with suspected systemic disorders would necessitate palpation of lymph nodes of the region.

Characteristics of the Lymph Tissue: A meticulous and comprehensive lymphatic examination should be carried out to eliminate generalized lymphadenopathy.[6] Lymphadenopathy in the supraclavicular region poses the highest risk for malignancy. Elderly individuals > 40 years of age have 90% risk and 25% risk is associated with individuals <40 years.[18] The lymph nodes when examined for tenderness, mobility, and consistency with adjoining tissue/adjoining lymph nodes.[19,20] Any acute infection is known by localized lymphadenopathy in which the lymph nodes are distinct, soft, tender, and mobile. However, firm and mildly tender/non-tender lymph nodes represent chronic infections.[21,22] In lymphadenopathy of metastatic cancer, the lymph nodes may bepainless, stony hard, and are fixed to adjacent tissues; but in lymphoma, they are larger, distinct, not tender, rubbery, and not fixed.[21,23] Firm, discrete, and mobile nodes with free overlying skin are typically seen in the initial stages of TBlymphadenitis. The nodes may become matted with inflamed overlying skin in the later stages. Advanced stage of TB lymphadenitis is marked by softened nodes with abscess and sinus tract formation.[24]

Figure 2- show lymphatic drainage patterns, and etiologies of lymphadenopathy of the regions.[6]

If a group of lymph nodes may betender and bigger, but several – mostly bilateral – are involved, other

situations should be taken into consideration inthe differential diagnosis. In infections bilateral growth suggest a viral or streptococcal infection.[15] (Figure 3)

Diagnostic Aids: Apparent benign causes (such as infection) of cervical lymphadenopathy do not require further investigations. However, ancillary aids like serological studies, imaging, and biopsy are recommended for idiopathic conditions. Imaging shows the dimension and spread of the node more accurately than palpation. Ultrasonography is done to study lymph nodes of superficial parts like the neck.[25] Computed tomography determines lymphadenopathy in the thorax or abdomen and pelvic region.[26,27] Diagnosis through Fine needle aspiration cytology (FNAC) or excisional biopsy is the only gold standard for diagnosing lymphadenopathy.[6] In India tuberculosis predominates among the granulomatous infections.

Following history taking and examination, (Figure 4) can show the wayto physicians for further evaluation with peripheral LAP.[6,26,29]

Differential Diagnosis: Differential diagnosis of cervical lymphadenopathy is essential to rule other diseases that present with overlapping features. Pain (tender/non-tender), location (unilateral/bilateral), relation with underlying structures (mobile/fixed nodes), consistency (rubbery/matted), and associated constitutional features (fever, cough, weight loss, arthralgias, rash, etc.) may help in arriving at a definitive diagnosis.

Table 2- Differential diagnosis protocol for cervical lymphadenopathy.[29]

Majority of the disorders are associated with generalized lymphadenopathies. Mononucleosis like syndrome present with Fatigue, malaise, fever, atypical lymphocytosis, and splenomegaly in around 50% of patients. Diagnostic tests are Monospot, IgMearly antibody or viral capsid antigen test. 80 to 90% of patients are asymptomatic in toxoplasmosis, often present as mild symptoms; few patients may have hepatitis, and IgM toxoplasma antibody is the diagnostic test.Tuberculosis lymphadenitis usually present with painless, matted cervical nodes and purified protein derivative(PPD), Fine needle aspiration cytology (FNAC), and biopsy are the diagnostic aids. Secondary syphilispresent with painless, shotty nodes, typical cutaneous rash, condyloma lata, mucous patches in the mouth,and Rapid plasma regain (RPR) is the test of choice. Initial stages of HIV infection manifest as “Flu-like” illness, rashand HIV antibody testing is done. Lymphoma present with fever, night sweats, weight loss in 20 to 30% of patients, along with nodal involvement, and biopsy is used for diagnosis. Leukemia present as blood dyscrasia and bruising. Blood smear and bone marrow aspiration are the investigative test. Measels and rubella present with fever, conjunctivitis and rash and Clinical criteria, serology is used for diagnosis. Hepatitis B present with Fever, nausea, vomiting, icterus, and Liver function tests, HBsAg are used as diagnostioc aids.

Management: Management of Cervical lymphadenopathy is based on the underlying pathology. Usually, the condition is self-limiting and necessitates regular surveillance.[17] Vigilantreview at a 2-to 4-week time is generally recommended for benign lymphadenopathy.[13] Antibiotic treatment targeting Staphylococcus aureus and streptococci (cephalosporins, amoxicillin/clavulanate, or clindamycin) should be given to patients who exhibitunilateral, acute anterior cervical lymphadenitis, and systemic conditions.[30] Corticosteroids therapy should not be given until a definitive diagnosis, as it may potentially mask

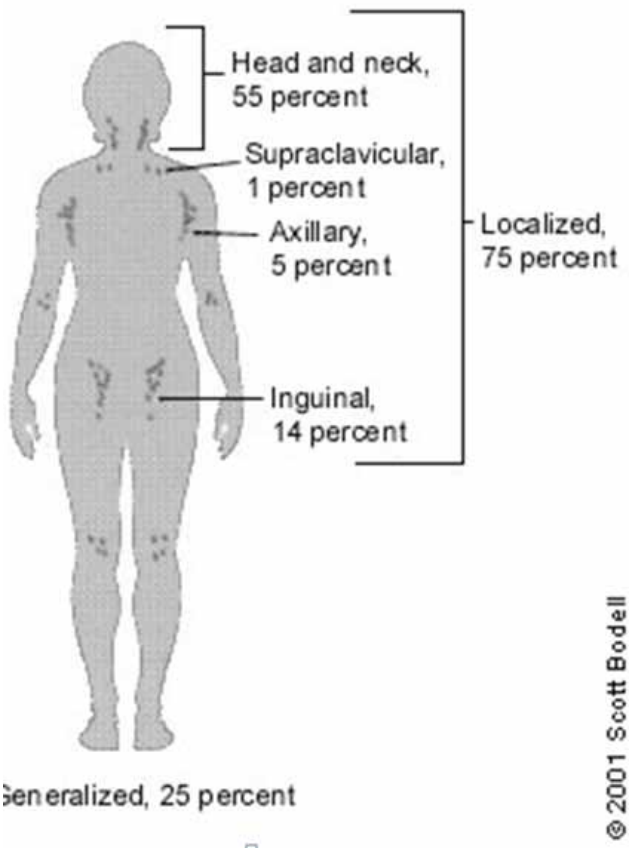

Figure 1: Distribution of lymphadenopathy

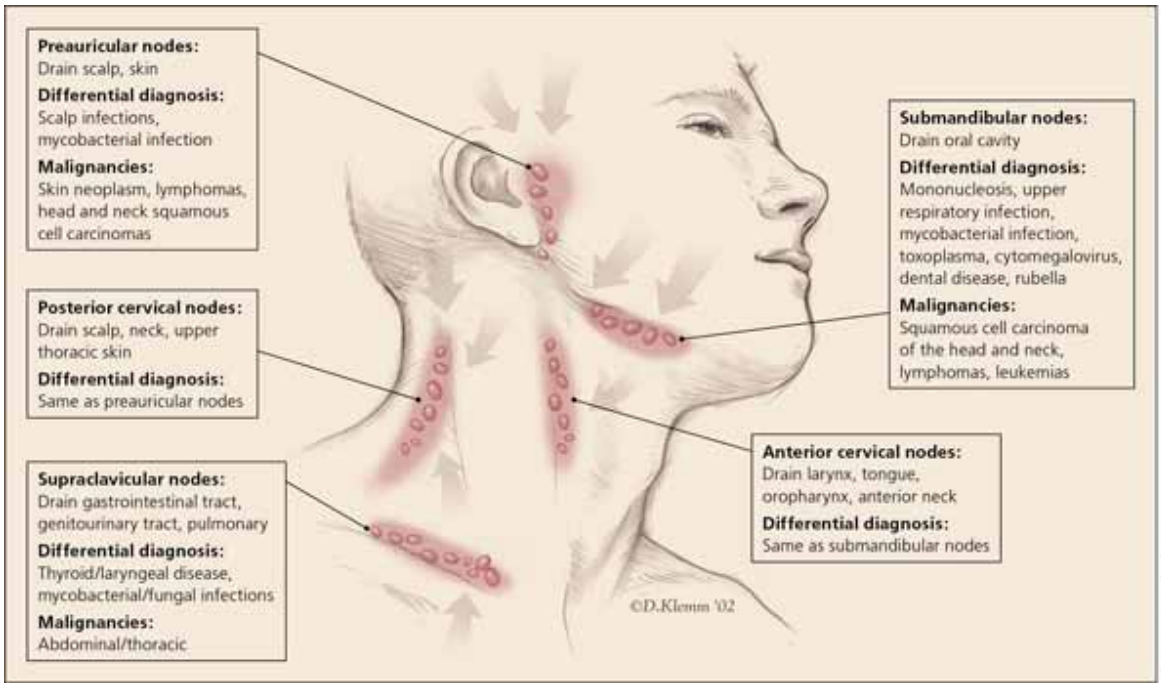

Figure 2: Lymphatic drainage pattern and associated lymphadenopathy

Origin	Side	Course	Frequent	Rare
Infectious	unilateral	acute	Staphylococcus aureus[A,B,F,G]; serogroup A streptococci [A,B,F,G]; anaerobic organisms [A,B,F]	Serogroup B streptococci [A,B,F,G]; tularemia[E,F,G,H], Pasteurella multocida; Yersinia; gram-negative bacteria[A,B]
		chronic	Non-tuberculous mycobacteria (NTM)[B,C]; bartonellosis	Toxoplasmosis; TBC[F,G,H]; actinomycosis
	bilateral	acute	EBV[F,G]; CMV[F,G]; rhinovirus[A,B,F,G]; adenovirus[A,B,F,G]; enterovirus; serogroup A streptococci	Parvovirus B19; rubella virus[D,E], HS, mycoplasma pneumoniae
		chronic	EBV[F,G]; CMV[F,G]	HIV; toxoplasmosis; TBC[F,G,H]; syphilis
Immunologic	unilateral	acute	Arthritis, systemic lupus erythematosus, dermatomyositis	Chronic granulomatous disease
		chronic		Hyper-IgM syndrome, Kawasaki syndrome[F,H]
	bilateral	acute	Arthritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis	Common variable immunodeficiency
		chronic	Sarcoidosis	HLH, Langerhans cell histiocytosis, Castleman's disease, Rosai-Dorfman disease, Kikuchi-Fujimoto disease [G]
Metabolic	unilateral	acute	Adverse drug reaction	
		chronic		
	bilateral	acute	Adverse drug reaction, serum sickness	
		chronic	Gaucher's disease; Amyloidosis	Niemann-Pick disease, Tangier disease
Neoplastic	unilateral	chronic	Rhabdomyosarcoma, non-Hodgkin lymphoma; Hodgkin's lymphoma	Neuroblastoma, nasopharyngeal carcinoma
	bilateral		Acute lymphoblastic leukemia	Acute myeloid leukemia
			Non-Hodgkin lymphoma; Hodgkin's lymphoma	Nasopharyngeal carcinoma

Figure 3: Origin, localization and course of disease distribution.

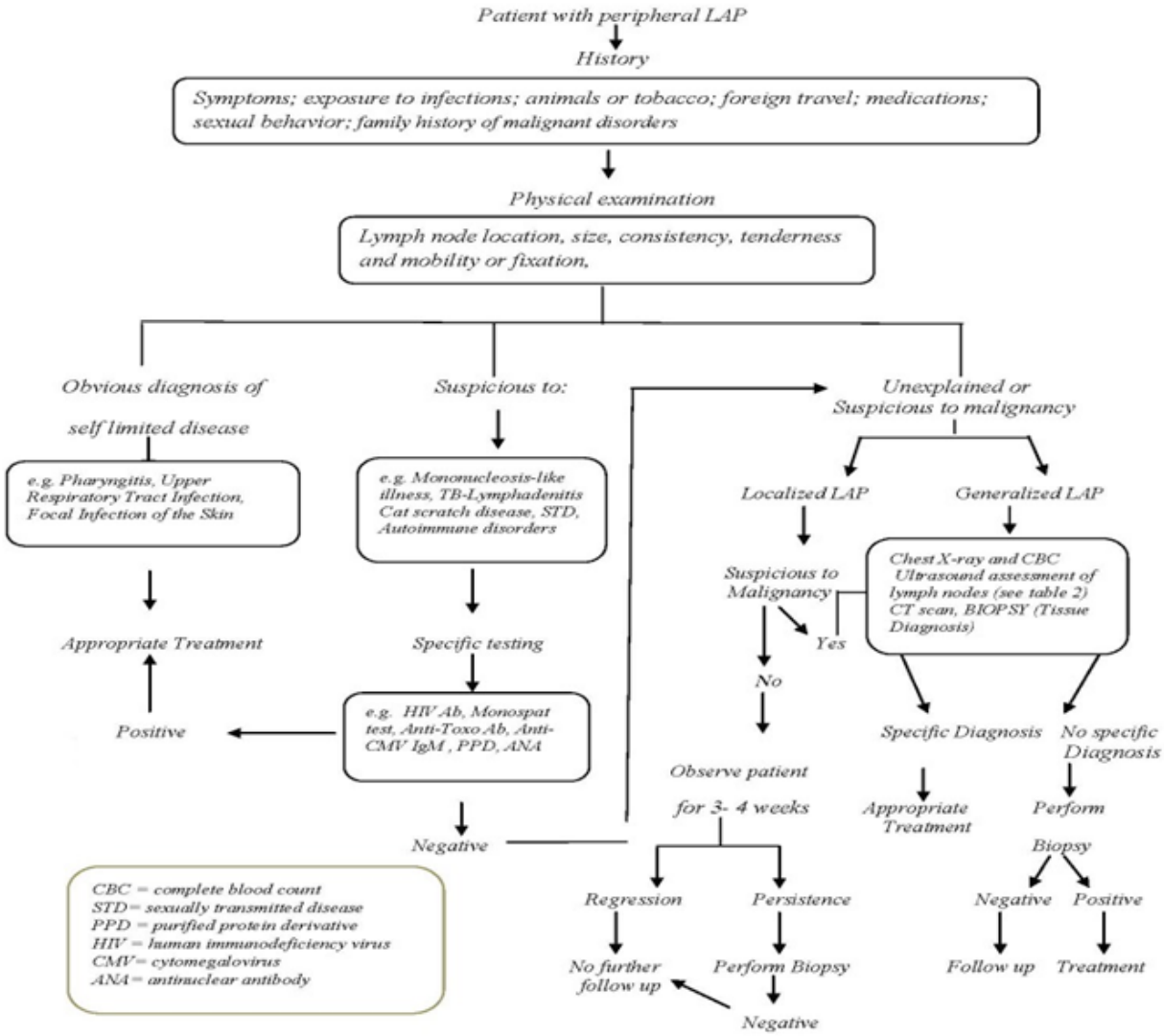

Figure 4: Diagnostic evaluation of cervical lymphadenopathy. histopathology of leukemia or lymphoma.[31]

Conclusion

Cervical lymphadenopathy may be a manifestation of benign pathology or may present as a sign of an underlying systemic disorder. Detailed history, meticulous clinical examination, and a plethora of diagnostic modalities are required for a confirmatory diagnosis. An Oral physician should be aware of the various etiologic causes of cervical lymphadenopathy and understand the significance of cervical lymphadenopathy as a clue to systemic pathologies.

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References

1. Bozlak S, Varkal MA, Yildiz I, Toprak S, Karaman S, Erol OB, et al. Cervical lymphadenopathies in children: A prospective clinical cohort study. Int J Pediatr Otorhinolaryngol 2016;82:81-87.
2. Kulal PR, Shanbhag SR, Dontamsetty SK, Madhu BS, Ramu BK. Clinicopathological Study of Cervical Lymphadenopathy. Journal of Evolution of Medical and Dental Sciences 2015;4(54): 9437-48.
3. Darville T, Jacobs RF: Lymphadenopathy, lymphadenitis and lymphangitis. In Pediatric Infectious Diseases: Principles and Practice. Edited by Jenson HB, Baltimore RS. Philadelphia: WB Saunders; 2002: 610-29.

4. Gosche JR, Vick LV: Acute, subacute, and chronic cervical lymphadenitis in children. SeminPediatrSurg 2006;15:99-106.
5. Upadhyay N, Chaudhary A, Alok A. Cervical lymphadenopathy. J Dent Sci Oral Rehabil 2012;3:30-33.
6. Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. Am Fam Physician 2002;66:2103-10.
7. Allhiser JN, McKnight TA, Shank JC. Lymphadenopathy in a family practice. J FamPract. 1981;12:27-32.
8. Williamson HA Jr. Lymphadenopathy in a family practice: a descriptive study of 249 cases. J FamPract. 1985;20:449-58.
9. Herrera GA. Light microscopic S-100 immunostaining and ultrastructural analysis of dermatopathic lymphadenopathy, with and without associated mycosis fungoides. Am J ClinPathol 1987;87: 187-95.
10. Ramadas AA, Jose R, Varma B, Chandy ML. Cervical lymphadenopathy: Unwinding the hidden truth. Dent Res J 2017;14:73-8
11. Iqbal M, Subhan A, Aslam A. Frequency of tuberculosis in cervical lymphadenopathy. J Surg Pak Int 2010;15:107-09.
12. Showkat SA, Lateef M, Wani AA, Lone SA, Singh K, Yousuf I. Clinicopathological profile of cervicofacial masses in pediatric patients. Ind J Otolaryngol Head & Neck Surg 2009;61:141-46.
13. Gaddy HL, ReigelAM. Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis. Am Fam Physician. 2016;94(11):896-903.
14. King D, Ramachandra J, Yeomanson D. Lymphadenopathy in children: refer or reassure? Arch Dis Child EducPract Ed. 2014;99(3):101-110.
15. Lang S, Kansy B. Cervical lymph node diseases in children. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2014;13:1-27.
16. Leung AK, Davies HD. Cervical lymphadenitis: etiology, diagnosis, and management. CurrInfect Dis Rep. 2009;11(3):183–89.
17. Leung AK, Robson WL: Childhood cervical lymphadenopathy. J Pediatr Health Care 2004, 18:3-7.
18. Unexplained lymphadenopathy in family practice. An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. Fijten GH, Blijham GH J FamPract. 1988 Oct; 27(4):373-76.
19. Vassilakopoulos TP, Pangalis GA. Application of a prediction rule to select which patients presenting with lymphadenopathy should undergo a lymph node biopsy. Medicine (Baltimore) 2000 Sep;79(5):338–47.
20. Ghirardelli ML, Jemos V, Gobbi PG. Diagnostic approach to lymph node enlargement. Haematologica. 1999;84(3):242–47.
21. Henry PH, Longo DL. Enlargement of lymph nodes and spleen. In: Kasper DL, Hauser J, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine. United States of America: Mc-Graw Hill; 2015. 407-13.
22. Aster JC. Diseases of white blood cells, lymph nodes, spleen and thymus. In: Gruliow R, editor. Robbins and Cotran Pathologic basis of disease: Elsevier Saunders; 2005. 661-63.
23. Scully C. Haematology. In: Scully C, editor. Scully's medical problems in dentistry. Seventh Edition ed. London: Churchill Livingstone Elsevier; 2014. 212-22.
24. Hasan S, Saeed S. Conventional and recent diagnostic aids in Tuberculous lymphadenitis: A Brief Overview. Asian Journal of Pharmaceutical and Clinical Research 2017;10(2):78-81.
25. Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. AJR Am J Roentgenol. 2005;184:1691–99.
26. Richner S, Laifer G. Peripheral lymphadenopathy in immunocompetent Adults. Swiss Med Wkly. 2 010;140:98–104.
27. Chau I, Kelleher MT, Cunningham D, Norman AR, Wotherspoon A, Trott P, et al. Rapid access multidisciplinary lymph node diagnostic clinic: analysis of 550 patients. Br J Cancer. 2003;88:354-61.
28. Hasan S, Khan MA. Tuberculosis - A common disease with uncommon oral features Report of two cases with a detailed review of the literature. Proceedings of the World Medical Conference 2011 ISBN: 978-1-61804-036-7:156-66.
29. Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. Am Fam Physician. 1998; 58(6):1313-20.

30. Meier JD, Grimmer JF. Evaluation and management of neck masses in children. AmFam Physician. 2014;89(5):353–58.

31. Salzman BE, Lamb K, Olszewski RF, Tully A, Studdiford J. Diagnosing cancer in the symptomatic patient. Prim Care. 2009;36(4):651–70.