

Review Article

Clinician's guide to lymphadenopathy- A review

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ABSTRACT:

Lymphadenopathy is benign and self-limited condition in most patients. Cervical lymphadenopathy is a common problem encountered by dental clinicians in patients seeking oral health care. It can present as an incidental finding on examination or may be the patient's main reason for the visit to the health professional. Usually, cervical lymphadenopathy represents a transient response to a benign local or generalized infection, but occasionally it might be a sign of the presence of a more serious disorder. However, a systematic approach to diagnosis of lymphadenopathy can cause a better treatment, minimal discomfort to the patient and good prognosis. This article reviews the anatomical sites, staging, etiology of lymphadenopathy and presents a systematic clinical approach to a patient with cervical lymphadenopathy.

Keywords: Lymphadenopathy, Cervical nodes, TNM staging, Lymph nodes

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INTRODUCTION

Lymphadenopathy is a routinely encountered clinical sign and symptom depicting a minimal inflammation to malignancy. The lymph nodes(LNs) of the human body represent a complex lymphatic system where lymph fluid is filtered and cleared as it circulates throughout the body. The human body consists of about 800 lymph nodes and forms a part of the immune system whose prime function is to deal with antigen be it organisms, particulate material or soluble antigen to fight off disease and infections.^[1] The cervical area of the human body contains nearly 300 lymph nodes (Figure 1).^[2] When lymph nodes are detected clinically it is termed as lymphadenopathy, this phenomena can occur due to two entities, that is, infiltration of the node and hyperplasia of the node. In both of these, there is increase in size, consistency and the number. Immunostimulation or an infectious stimuli can cause hyperplasia of the node. Whereas, infiltration of the lymph node occurs by various types of cells including macrophages, cancer cells or lipid cells.^[3] Lymphadenopathy is not a disease by itself, but it can be a sign of many possible underlying pathologies. The term lymphadenitis specifically refers to enlargement caused due to inflammation of

the lymphnode. A thorough detailed medical history, complete physical examination, judicious selection of specific investigations and, if needed, a lymph node biopsy and histopathological examination will determine the cause of the lymphadenopathy.^[1] This review attempts to summarize the importance of cervical lymphadenopathy, its significance, interpretation and diagnosis since it can be an index of spread of spectrum of infection and malignancy and also aid in enhancement of the understanding of the clinician.

DEFINITION

Lymphadenopathy is a pathological process exhibited by abnormal increase in size or number and changes in the consistency and the texture of the lymph node. Cervical lymphadenopathy refers to increased size of lymph nodes in the head and neck region with a diameter more than 1cm. However, palpable supraclavicular nodes of any size are considered abnormal. Lymphadenopathy in an individual signifies underlying pathology from a simple infection to a metastatic malignancy.^[4]

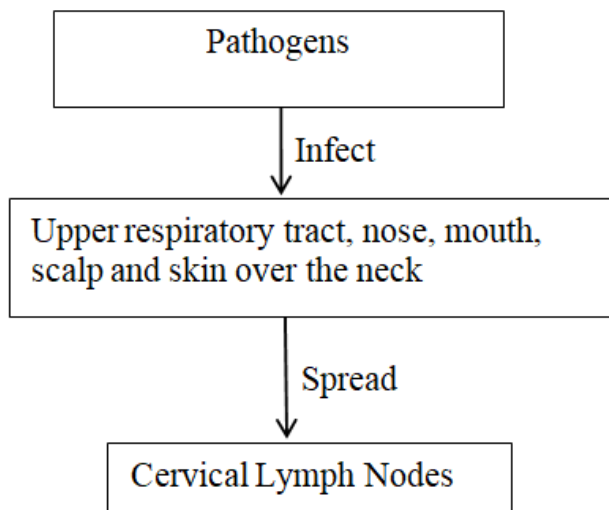
EPIDEMIOLOGY

In a health care set up, the yearly incidence of indcipherable lymphadenopathy is 0.6%, only 1.1% of these cases are due to malignant causes and an increase in this percentage is seen as age advances. Malignancies are identified in 0.4% below the age of 40 years and 4% of patients in the fourth decade of age and above who present with unexplained lymphadenopathy. Usually, 38% to 45% of children have palpable cervical lymph nodes as a normal finding.^[5]

ANATOMIC CONSIDERATIONS AND PATHOPHYSIOLOGY

Lymph nodes are small oval to bean shaped connective tissue capsulated masses of lymphatic tissue which are widely distributed in the body measuring approximately 1mm in diameter. The human body has three superficial regions, the groin, armpit and the neck on each side where the lymph nodes tend to cluster known as inguinal nodes, axillary nodes and the cervical nodes respectively. The connective tissue encapsulating the node divides the node into sections called lymph nodules. These nodules are separated by lymph sinuses which contain macrophages. From the periphery of the lymph node the afferent lymphatics enter the lymph node on the convex side carrying lymph into the node. As the lymph passes through lymph sinuses the pathogens are phagocytised and at the hilum the lymph fluid enters an efferent lymphatic vessel which carries the it away from the node. The lymph nodes of the human body drains lymphatic fluid from areas exposed to external environment and its pathogens. The lymphatic system is so strategically placed in the body that the pathogens that gain access are restricted to enter the circulation. Although the process of pathogen dissemination through lymphatics is a common occurrence, the available literature is limited. The lymph node contains localized sources of innate immune cells which respond to pathogens immediately which restrict the pathogens until acquired immunity is activated. It is well known that acquired immunity cells need specific antigen, co-stimulation to activate an immune response and then time for rapid cell division. Hence, lymph nodes play a crucial role as active barriers, preventing spread of pathogens via lymphatics. Once there's a break through the skin and the mucous membrane, the innate immunity which is the first line of defence against any pathogen comes into action and keeps the

pathogen contained. There's also a possibility that the pathogen could enter into lymphatics or blood that's where lymph nodes function as the next sequential barrier.^[6] The lymph node functions as a pathogen filter for the reticuloendothelial system of the body. It exposes the defense cells to harmful pathogens where the immune system can recognize and react to the foreign materials and cause an immune response thereby maintaining the equilibrium of the human body. The lymph nodes are arranged in series, so that if the initial lymph node is overwhelmed, any pathogens that escapes gets held up in the following lymph node.^[7] The lymph nodes of the head and neck region are grouped as superficial and deep nodes placed in the superficial and deep fascia, respectively. The superficial nodes are placed on the surface of the sternocleidomastoid muscle along the external jugular vein. The deep cervical nodes are further grouped as median and lateral group. The median group of deep cervical nodes are located anterior to the larynx and trachea. The lateral group of the deep cervical nodes are further divided as upper and lower groups and are placed along the internal jugular vein at the side of the neck. All the lymph from the head and neck region drains into deep cervical lymph nodes. The lymph from the head and neck area drains into the upper deep cervical lymph nodes which in turn drains into the lower deep cervical. The lymphatic drainage can also be divided as horizontal and vertical groups. The vertical group are (i) Tracheal which drains the trachea, larynx, thyroid, and superficial neck and below hyoid, (ii) retropharyngeal nodes which drain the nasopharynx, auditory tube, and middle ear, (iii) superficial cervical nodes drains the lower parotid, auricle, mastoid, and angle of mandible, the deep cervical nodes drains the entire head and neck. (iv) Superior group with jugulodigastric node which drains the palatine tonsil and posterior 1/3 of the tongue, larynx,pharynx and (v) Inferior group draining the ant 2/3 of tongue, larynx, thyroid gland. The horizontal group include (a)Suboccipital which drains the back of scalp and neck, (b) Mastoid which drains the posterior scalp, auricle, and auditory meatus (c) Parotid nodes draining the anterior scalp, external and middle ear and parotid gland (d) Submandibular nodes draining the scalp, face, and tongue and (e) Submental nodes draining the tip of the tongue, floor of the mouth, lower lip, and chin. The lymphatic system in the head and neck area acts as a barrier to prevent further invasion and dissemination of these organisms.



CLASSIFICATION OF LYMPHADENOPATHY^[3]

I	Generalized	Lymph node enlargement of more than two isolated groups.
	Localized	Lymphadenopathy of only one group; cervical involved more than others.
II	Dermatopathic	Lymph node enlargement associated with dermal diseases
III	Acute	Lymphadenopathy duration of less than 2 weeks.
	Subacute	Lymphadenopathy duration of 2-6 weeks.
	Chronic	Lymphadenopathy duration of more than 6 weeks.

The most commonest cause of localized lymphadenopathy in adults and children in the cervical area is infection and acute self-limiting viral illnesses, respectively. Supraclavicular adenopathy (Virchow’s node) in adults and children is associated with high risk of intra-abdominothoracic malignancy and must be evaluated promptly. Generalized Lymphadenopathy is more likely seen in conditions like chronic and serious infections, autoimmune diseases, and disseminated malignancy.

ETIOLOGY

There can be numerous causes cervical lymphadenopathy, among them reactive hyperplasia of the node as a result of a viral infection of the upper respiratory tract is the most commonest cause. Other viruses that maybe strongly associated with cervical lymphadenopathy include herpes virus, enteroviruses, human papilloma virus, coxsackievirus and human immunodeficiency virus.^[5] The bacterias responsible for the inflammation of the lymph node are usually Streptococcus pyogenes or Staphylococcus aureus.^[12] Dental decay, periodontal disease, infections caused Mycobacterium tuberculosis cause cervical lymph adenopathy.^[13] In 50% of acquired toxoplasmosis cases, chronic posterior cervical lymphadenitis is the only presenting symptom.^[8] One of the important diagnostic criteria for Kawasaki disease is the presence of cervical lymphadenopathy. It is noted that cervical lymphadenopathy in the first six years of life is most commonly associated with neuroblastoma, leukemia, rhabdomyosarcoma and non-Hodgkin’s lymphoma. After 6 years of age in a child, the most common tumor associated with lymph node

enlargement is Hodgkin’s lymphoma, followed by non-Hodgkin’s lymphoma and rhabdomyosarcoma.^[6] Generalized lymphadenopathy can be caused by autoimmune disorders, certain anticonvulsant drugs like phenytoin and carbamazepine, vasodilator hydralazine, and isoniazid. In children, cervical lymphadenopathy has been reported after immunization for poliomyelitis, typhoid and for diphtheria-pertussis-tetanus.^[5] Several causes can be attributed for lymphadenopathy and they can be categorized based on the 1) area of involvement of lymphadenopathy and its localization. 2) Using the acronym "CHICAGO" (Table I).^[3]

EVALUATION OF LYMPHADENOPATHY

History taking

The diagnostic skill of a clinician is strongly based on the ability to elicit a complete history and the details of present illness from the patient. The age of the patient, time since the lymphnode enlargement was noticed and its associated symptoms, environment changes, history of travel, animal and insect exposures, location, time of presentation, underlying systemic diseases, and the circumstances in which lymphadenopathy was detected play a vital role in diagnosis. Adverse habits such as tobacco and alcohol use as well as occupational history, chronic medication use, infectious exposures, immunization status adds a great value in diagnosis.^[3] The family history identifying the familial causes of conditions, syndromes and malignant disorders should also be reviewed. A history of malignancy or infection could point to a recurrence.^[14]

Physical Examination

The anatomical location of the lymphadenopathy(cervical, submandibular, submental, supraclavicular, occipital, preauricular, auricular) should be identified and a complete lymphatic examination along the lymphatic drainage patterns should be performed to assess whether multiple nodal sites are involved. The consistency of the nodes should be ascertained as soft, rubbery, Stony hard, fixed to the underlying structures and skin or movable. The size of the lymph node needs to be determined whether its less/more than 1 cm². If bilateral; check for symmetry. The lymph node has to be evaluated for presence or absence of tenderness and also associated with systemic symptoms. A skin examination should be done to assess clinical signs of bruises, wounds, growths, nodules or colour changes to rule out any trauma or malignant changes that could be the source of lymphadenopathy. A thorough intral oral examination has to be carried out to rule out any dental caries, pulpal and periapical infections, soft tissue infections, periodontal complex infections and infections of the oro pharynx. The air sinuses should be examined and evaluated to rule out infection, malignancy and lodgement of foreign objects.

Investigations

A complete blood picture, specific markers and imaging provide a great value in accurately diagnosing the cause of lymphadenopathy. Extra oral radiography, Intraoral imaging, Chest radiography helps to know the underlying causes or metastases.

Ultrasonography is the most useful diagnostic imaging modality in lymph node assessment in terms of number, site, size, external and internal structure and the texture of the lymph node.^[1] This imaging modality helps to evaluate and differentiate a cystic and a solid mass. Also, ultrasonography establishes the presence of suppuration or infiltration and its tissue involvement.^[6] Color Doppler ultrasonography is a non invasive modality which gives a detailed information on blood flow, vascular resistance, displacement of vascularity, pulsatility index and can differentiate between chronic and acute lymphadenopathy. Ultrasonography guided core-needle biopsy is indicated for cervical lymphadenopathy in patients with suspected malignancy. For enlarged lymph nodes of 2-6 weeks and not responding to medical line of treatment, Fine Needle Aspiration and Core Needle Biopsy aids in the diagnostic evaluation.^[10] CT and MRI are the modalities of choice in evaluation of the thoracoabdomeninal, pelvic, and retropharyngeal cavity. Tissue diagnosis is considered as the gold standard in the evaluation of lymphadenopathy.^[11] When the Fine Needle Aspiration cytology result is negative and the clinical findings strongly suggest malignancy or if the clinical diagnosis remains a doubt, excisional biopsy with histopathological examination has to be performed. The biopsy should ideally be taken on the most suspicious, largest and firmest node that is most accessible, and the node should be removed intact with the capsule.^[5]

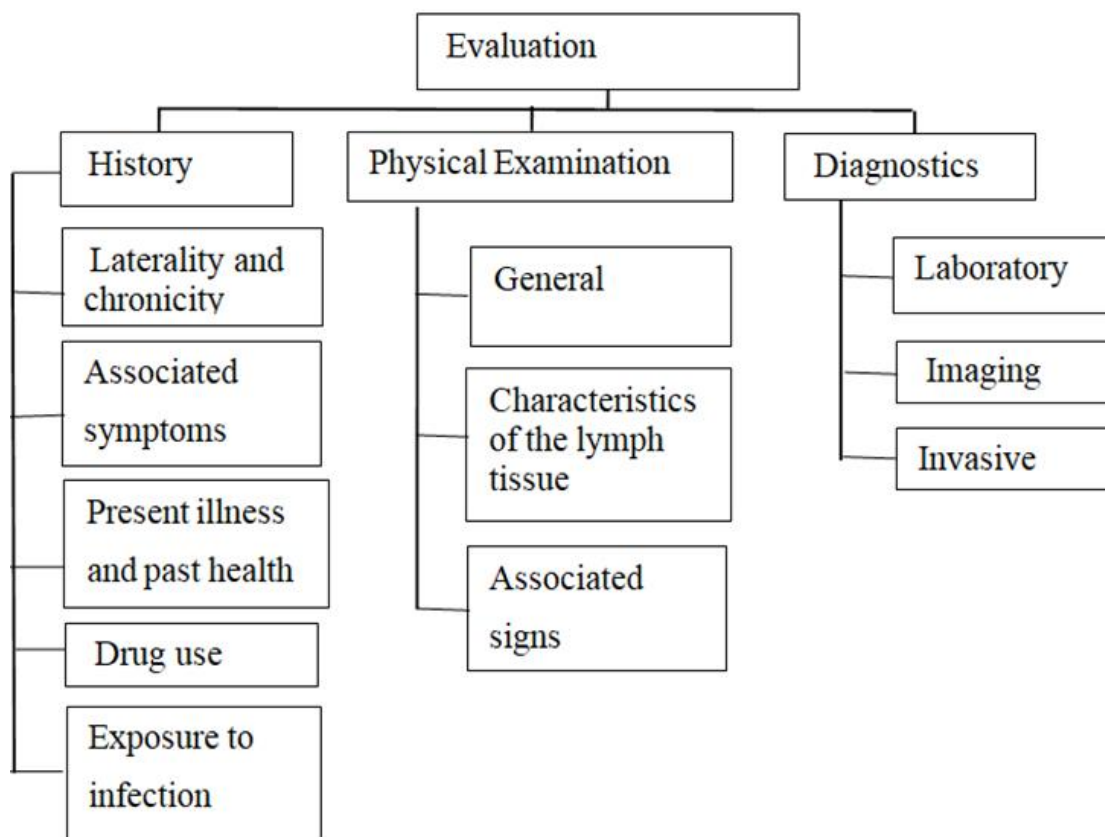


FIGURE 1: Lymph Nodes of Head and neck region.[2]

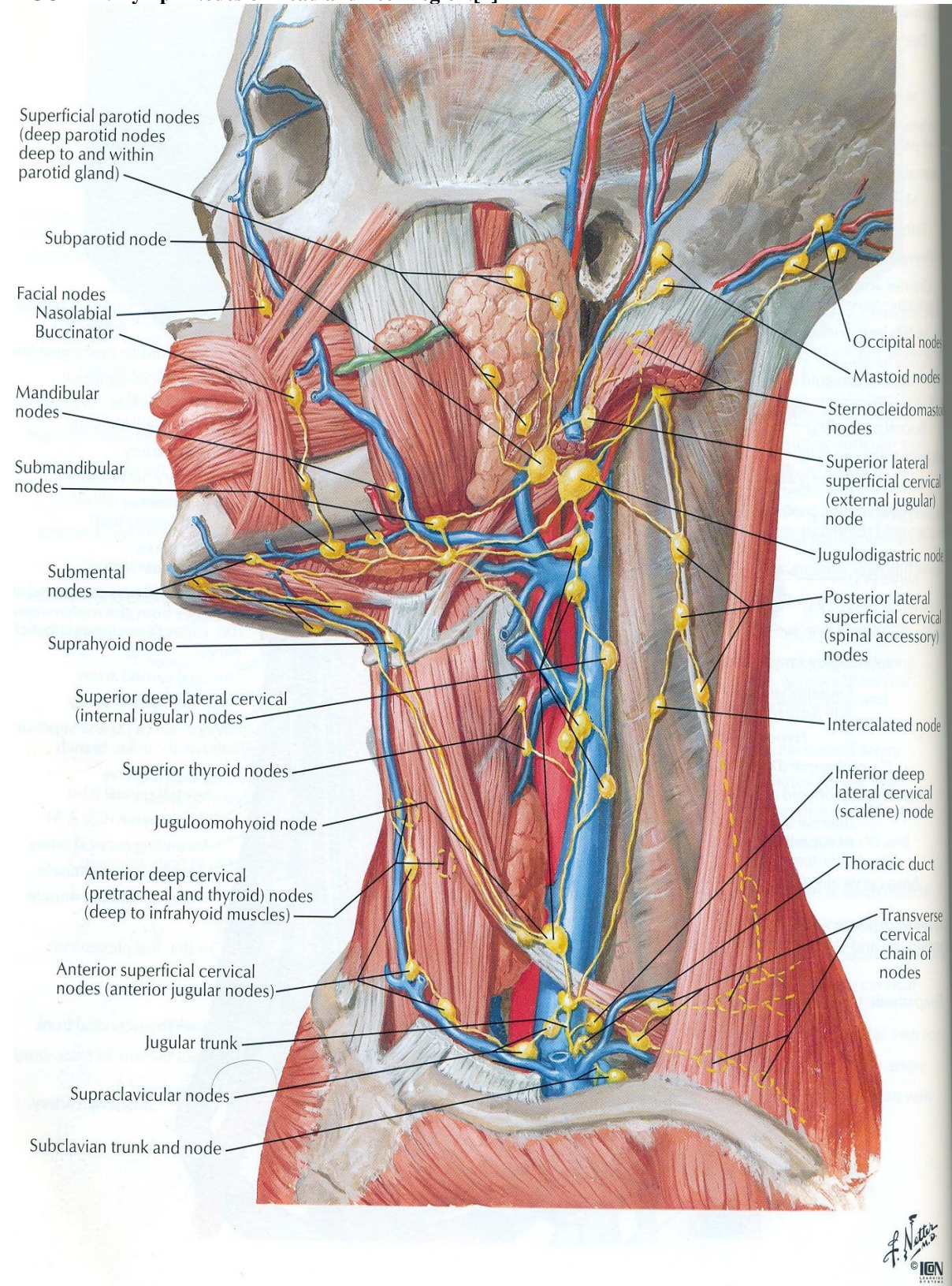


Figure 2. Algorithm for evaluating lymphadenopathy.^[9]

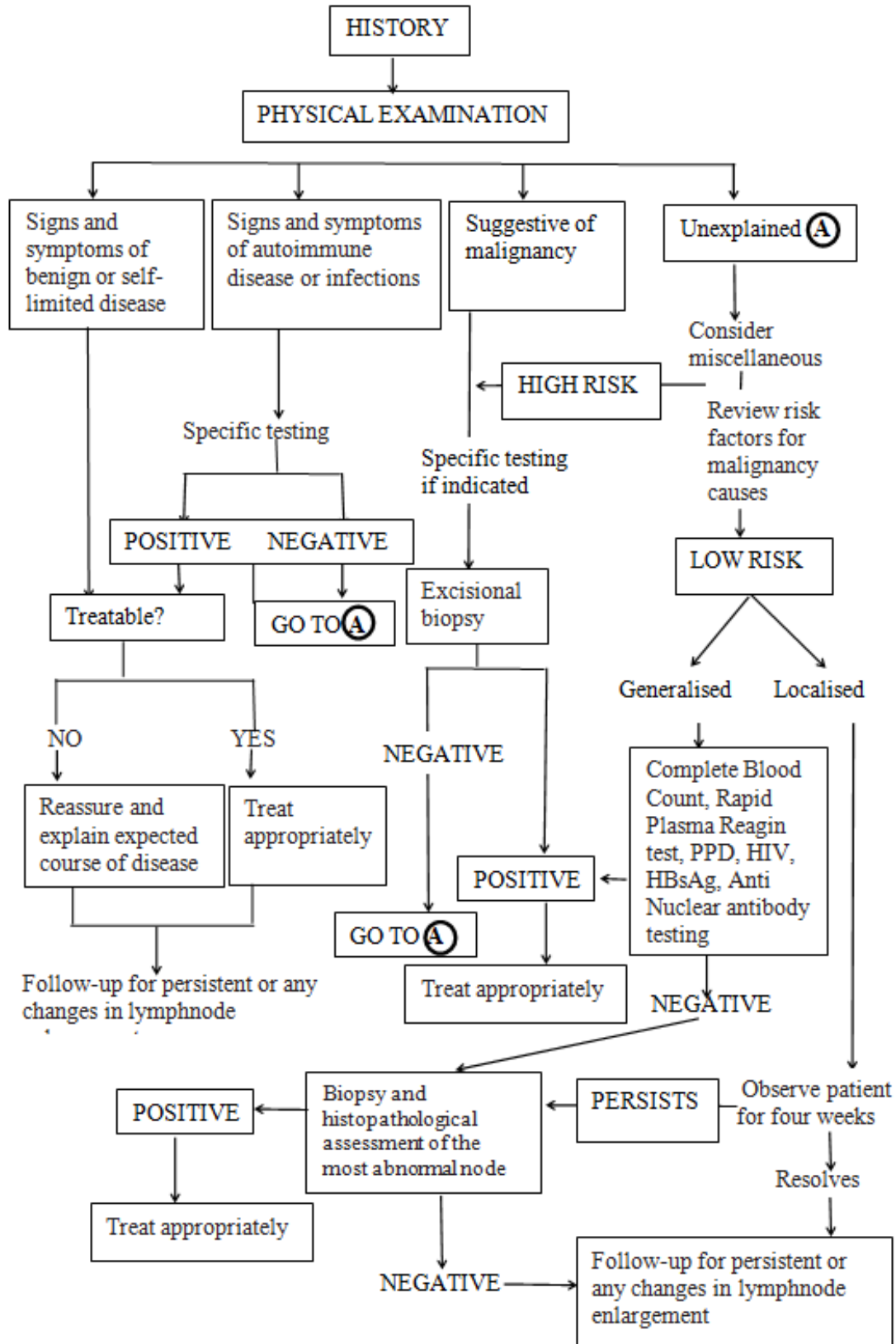


Table 2: Etiology of lymphadenopathy ‘CHICAGO’ Acronym^[3]

C	Cancers	Malignancies	Hodgkin's and Non Hodgkin's lymphoma, Skin neoplasms, Leukemia, Kaposi's sarcoma
		Metastatic	Tumors of Breast, Lung, Kidney, others
H	Hypersensitivity syndromes		Serum sickness, Drugs
I	Infections	Viral, Bacterial, Fungal, Protozoan Rickettsial, Helminthes	Infections by Epstein Barr Virus, Cytomegalo Virus, Human Immunodeficiency Virus, Tuberculosis, Typhoid fever, Syphilis, Pharyngitis, Dental infections
C	Connective Tissue disorders	Systemic Lupus Erythematoses, Rheumatoid Arthritis, Dermatomyositis	
A	Atypical lymphoproliferative disorders	Castleman's Disease, Wegener's.	
G	Granulomatous	Histoplasmosis, Mycobacterial infections, Cryptococcus, Berylliosis, Cat scratch disease, Silicosis	
O	Others	Medications, Iatrogenic	

Table 2: Differential diagnosis of lymphadenopathy, ‘MIAMI’ acronym.^[9]

M	Malignancies	Kaposi sarcoma, leukemias, lymphomas, metastases, skin neoplasms
I	Infections	Brucellosis, cat-scratch disease, chancroid, cutaneous infections, lymphogranuloma venereum, primary and secondary syphilis, tuberculosis, tularemia, typhoid fever, berylliosis, coccidioidomycosis, cryptococcosis, histoplasmosis, silicosis, adenovirus, cytomegalovirus, hepatitis, herpes zoster, human immunodeficiency virus, infectious mononucleosis, rubella, fungal, helminthic, Lyme disease, rickettsial, scrub typhus, toxoplasmosis
A	Autoimmune disorders	Dermatomyositis, rheumatoid arthritis, Sjögren syndrome, Still disease, systemic lupus erythematosus
M	Miscellaneous	Angiofollicular lymph node hyperplasia, histiocytosis, Kawasaki disease, Kikuchi lymphadenitis, Kimura disease, sarcoidosis, Storage disease, Angioimmunoblastic lymphadenopathy
I	Iatrogenic	Medications, serum sickness

DIAGNOSTIC APPROACH AND DIFFERENTIAL DIAGNOSIS

If the detailed history and the clinical examination findings advocate a benign or self-limited process, the patient can be reassured and a follow-up has to be scheduled after four weeks if lymphadenopathy persists. Disease or condition related specific investigations may be required for confirmation and treatment. In any case, generalized lymphadenopathy should prompt a routine and specific laboratory testing. Figure 2^[9] provides an algorithm for evaluating lymphadenopathy. The differential diagnosis of lymphadenopathy can be strategised as a Mnemonic ‘MIAMI’ (Table II).^[9]

CONCLUSION

A myriad of lesions of the head and neck as well as the whole body causing cervical lymphadenopathy is

a common occurrence and should be duly noted by a oral health physician. A systematic guide and approach will diagnose the cause aptly. A right diagnosis determines the proper approach to the treatment resulting in a better prognosis for the patient. A detailed history and physical examination with careful attention to the areas drained by the involved lymph node or mass of nodes often leads to the appropriate diagnosis.

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