



## Diagnostic approach to lymph node enlargement

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### ABSTRACT

**Background and Objective.** How to reach the correct diagnosis of a lymph node enlargement is still a problem which strongly challenges the knowledge and experience of the clinician. Organized and specifically oriented literature on the right sequential steps and the logical criteria that should guide this diagnostic approach is still lacking.

**Methods.** The authors have tried to exploit available knowledge and their personal experience by correlating a large body of information regarding size, physical characteristics, anatomical location of enlarged lymph nodes, and the possible epidemiological, environmental, occupational and clinical categorization of this condition.

**Results and Conclusions.** It was intended that such material would have constituted the basis of a hypothetical decision-making tree, but this was impossible because of the lack of epidemiological investigation and registry data. Nevertheless, we present this preparatory work here in order to stimulate the interest of concerned readers and because of its possible direct usefulness in hematologic practice.

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In general the question of what to do when a patient presents with lymphadenomegaly (LAM) has no immediate solution. Most of the time the family doctor only participates in the early stages of the diagnostic process, then a specialist is called in – usually a hematologist – whose goal is not only to do his best to reach a diagnosis but to do so in the shortest, most reasonable, least expensive and, above all, least uncomfortable way for the patient.

The clinical approach to LAM follows two main logical steps:<sup>1</sup> first, making a diagnostic distinction between a true lymphadenopathy, with a pathological significance that deserves more detailed diagnostic attention, and a state of exaggerated palpability of normal lymph nodes, due to causes such as a very thin patient or flaccid connective tissue, or a simple LAM – mainly stromal – that is the result of a previous adenopathy and does not require any fur-

ther investigation; second, deciding whether it would be advisable to perform a nodal biopsy when tests and other clinical findings have not provided sufficient diagnostic elements to categorize the LAM with certainty.

It should, however, be noted that all the findings, observations and testing that make up the rational approach to LAM offer no predetermined relationships, but only merely probable ones, and that together they constitute a set of norms in which different factors play significant roles: e.g. the variability of expression of the different possible disorders, individual patient variability, and a hard-to-quantify amount of clinical experience and specific observational expertise on the part of the physicians working on the case. The entire subject matter of this study could be used to outline a decision-making tree that would be extremely complex and quite difficult to construct.

The definition of what constitutes a normal lymph node may in itself frequently be difficult. It is well known that the lymph nodes, together with the spleen, are the peripheral organs of the immune system within which the anatomical and functional interconnections fundamental to immunity occur between the lymphatic and hematic circulations. There are approximately 600 lymph nodes, strategically distributed throughout the human body, each of which consists of a cellular component composed of fibroblasts (whose function is mainly structural), macrophages, dendritic and Langerhans' cells (whose function is to recognize and present an antigen and to activate lymphocytes), T and B lymphocytes (which are the effector cells of cellular and humoral immunity, respectively). All these elements are contained within connective stroma and encased in a capsular shell.

During an immune response the flow of blood and lymph through a lymph node can increase by as much as twenty-five times with a resulting accumulation of activated proliferating cells, and the entire lymph node may swell up to fifteen times its normal volume. When this occurs it is capsular edema and the tension this causes, along with the consequent process of perilymphadenitis, that is responsible for the characteristic pain of inflammatory adenopathy. Moreover, if the etiologic agent is bacterial and reaches the lymph node in large numbers, this can

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cause follicular necrosis with suppuration, transforming the lymph node into a soft, more or less taut, floating mass that is extremely painful and extremely sensitive to the slightest touch. While in time, after every episode of functional hyperplasia, the cellular component returns to its original normal proportions, the same is not always true for the stroma. It is difficult for stromal hyperplasia to return to its original dimensions, especially if there has been conspicuous necrosis or suppuration, and this creates an anatomical basis for greater palpability of the node even under conditions of functional rest. The more times these functional stimuli are repeated, the more pronounced this condition becomes.

A lymph node may be enlarged a) in an immune response to infective agents (bacterial, viral); b) as a result of inflammatory cells in infections involving the lymph node (lymphadenitis); c) by the infiltration of neoplastic cells carried to the node by lymphatic or blood circulation (metastasis); d) due to localized neoplastic proliferation of lymphocytes or macrophages (lymphomas), and e) as a result of an infiltration of macrophages filled with metabolite deposits (lipid storage diseases).<sup>2</sup>

#### **Evaluation of lymphadenomegaly**

It is known that most of the information necessary for formulating a diagnosis of LAM comes from the patient's medical history and a physical examination. In fact, in most cases these two tools are able to provide the following data:<sup>1</sup>

- a. the size of the lymph node in relation to the patient's age;
- b. the characteristics of the lymph node obtained from physical examination (observation, palpation);
- c. its anatomical location;
- d. the epidemiological and clinical categorization that is possible in this patient.

From the point of view of just the size of the node, there is agreement that up to 2 cm in diameter they can be normally palpable – i.e. without carrying definite pathologic significance – only in young children, who readily respond to any number of antigenic stimuli with lymphoid hyperplasia, and in adults at inguinal sites, as evidence of previous infections, even subclinical ones, of limbs, perineum and genitals. It is believed that except for infancy, and in the inguinal area at any age, the presence of one or more lymph nodes larger than 1 cm in diameter calls for further investigation if a definite cause cannot be identified. LAM arising in subjects under 30 years of age have an infectious or inflammatory origin in 80% of the cases, while in people over 50 the enlargement is neoplastic 60% of the time.

#### **Physical diagnosis characteristics and clinical correlations**

Just as the site of the LAM is important, as stated above, for distinguishing between apparent or previ-

ous enlargements and current adenomegalies with clinical significance, the different physical characteristics of the lymph node, as determined by physical examination, are also fundamental to making such a distinction. There are four main types of physical characteristics: 1) enlarged nodes that are the result of a previous inflammatory process are firm, elastic, very mobile, hard to hold in one place and absolutely painless and insensitive to handling; 2) in acute infections lymph nodes are often tender, softly elastic and sometimes asymmetrically enlarged if they are isolated; other times, however, they are confluent, painful and sensitive to touch, and covered by flushed skin. If the infection is localized, a painful red streak (lymphangitis) may connect the site of the infection to the involved lymph node; 3) the lymph nodes of lymphomas are firmer, rigidly elastic with superficial and deep mobility that is less than normal but not completely absent. Often these lymph nodes aggregate to form small packets without modifying their integument; they are only slightly or not at all painful, only slightly or not at all sensitive to handling (tenderness and sensitivity to touch are possible in sites that are readily exposed to repeated infections, such as the tonsils and inguinal lymph nodes); 4) metastatic lymph nodes from solid tumors are typically hard, at times with an irregular surface, not mobile, especially at the deeper levels, painless and insensitive to touch; in extreme cases the overlying skin can take on a bluish-red hue and may become very thin, to the point of ulcerating.

These four types of physical examination findings permit a distinction, albeit not perfect, of the generic etiologic categories to which LAM can be attributed. While rare, it has happened occasionally that lymph nodes showing inflammatory characteristics have been biopsied years after their appearance and found to be lymphomatous. Others, although they are extremely painful and sensitive to touch, prove to be neoplastic, and still others that are hard and fixed in older patients are found to be granulomatous and partially calcified. This must be kept in mind when interpreting the relationships which will be presented below.

The site itself of a LAM is often crucial. *Localized* LAM first requires a scrupulous clinical examination of all the zones that are anatomically afferent to the enlarged lymph nodes, although it cannot be ruled out that they might be the first signs of a precocious clinical manifestation in the course of a progressive systemic process. This is especially true if the physical characteristics of these lymph nodes are of the lymphomatous or metastatic type. The appearance of a *generalized* LAM, on the other hand, will orient the physician more directly toward serological and hematologic testing.

Of the regional types of LAM, occipital and preauricular ones are rarely malignant; the former are often related to scalp and outer ear infections, exanthematous diseases and toxoplasmosis, while the latter

are associated with infections of superficial tissue of the orbit, the middle ear and the parotid glands. They may also be related to oculo-parotid syndromes (e.g. Sjögren's or Heerfordt's syndrome). Submental LAM require a search for disorders in the anterior portion of the mouth and the lower lip, in the submandibular portion of the face, in the nose, the maxillary sinus, the mucosa of the oral cavity, the floor of the mouth, as well as in the submental salivary gland. Retromandibular LAM, besides being involved by the same disorders as the previous two types, can also more directly mirror infectious or neoplastic processes of the rhinopharynx, the supraglottic larynx, the palatine tonsils, the hypopharynx, the base of the tongue and the parotid gland. Laterocervical LAM in the upper portions of the neck can be associated with inflammatory or neoplastic disorders of the hypopharynx, the larynx or the thyroid gland, while those in the lower part of the neck are related to disorders of the hypoglottic larynx, the thyroid and the upper portion of the esophagus. Due to the close anatomical and functional relationships between the lymph node stations and the numerous structures present in the head and neck, it is clear that practically every one of the above mentioned LAM can be associated with almost all of the bacterial, viral, fungal and neoplastic disorders of the upper respiratory tract and the beginning of the digestive tract. Among possible bacterial disorders we should keep in mind the suppurative ones caused by mycobacteria, such as scrofula, which at one time was frequent but has not yet completely disappeared.

Supraclavicular LAM, together with prescalenic node enlargement, is often indicative of granulomatous (sarcoidosis), neoplastic, intrathoracic, gastrointestinal or retroperitoneal disorders. In particular, left supraclavicular LAM, when it shows the characteristics of a metastatic type (Troisier's or Virchow's lymph node), is a sign of the metastasis of a neoplasm, almost always gastrointestinal, that is no longer surgically operable. In cases of lymphoma, left supraclavicular LAM is often associated with involvement of the lumbo-aortic stations and the spleen, while on the right side it is associated, although less closely, with intrathoracic lymphomatous localizations.

Epitrochlear LAM is often caused by infections in the area of the hand and the forearm or due to brucellosis; however, it can also be the result of non-Hodgkin's lymphoma (Hodgkin's disease is rare in this location). Bilateral epitrochlear LAM raises the suspicion of sarcoidosis, tularemia or even secondary syphilis. This LAM site may also be involved by cat scratch disease, although the localizations of choice for this pathology are laterocervical (40%), axillary (25%) and submandibular (18%).

Axillary LAM is seen in cases of infection or neoplasm localized in the upper arm (melanoma), in the mammary gland, and in intrathoracic localizations

of systemic granulomatoses (tuberculosis, sarcoidosis), as well as in lymphomatous processes. Among possible immune reactions we would like to mention the axillary adenopathy caused by silicon mammary prostheses.<sup>3</sup>

Inguinal LAM can be caused by a variety of venereal diseases such as lymphogranuloma venereum, syphilis and herpes genitalis, disorders whose initial local lesions may not be detectable objectively but can be suggested from a personal medical history. Other possible causes of inguinal LAM include infectious and neoplastic disorders of the perineum and small pelvis (rectum, vagina).

Enlargement of the popliteal lymph nodes is generally associated with infectious disorders of the foot and leg and is rarely caused by neoplasms in these areas or by lymphomatous localization (in which case it is almost always non-Hodgkin's). Adenomegaly of the femoral nodes, besides being associated with the same causes as popliteal LAM, may also be due to *Pasteurella pestis* infection.

Lymphadenomegalies in deep sites (mediastinum, retroperitoneum, mesentery) are usually not detectable at physical examination but they may sometimes be suspected through assessment of indirect signs. Hilar-mediastinal LAM can be suspected upon the appearance of syndromes that involve compression of mediastinal structures: a) compression of the vena cava (headache, congestion of the head and neck, turgor of the jugular veins, congestion of the upper part of the thorax and the arms, small mantle edema); b) compression of the bronchial branches (harsh dry cough, mixed or prevalently expiratory dyspnea) or of the mediastinal nerve trunks (dysphonia, bitonal voice, hiccoughs). Mediastinal LAM is associated with tuberculosis, sarcoidosis, pulmonary mycoses and may be the site of metastases of bronchial, pleural, mammary, digestive, retroperitoneal and genital neoplasms.

Back pains that are more pronounced when lying down, often with sciatic irradiation to one or both lower limbs, muscular weakness of varying degree – from mild all the way to paralysis, dysesthesia and paresthesia – can accompany conspicuous retroperitoneal LAM, in which there is initial compression of the spinal cord or the spinal nerve roots (nevertheless, retroperitoneal LAM is seldom the only finding; if it is not associated with LAM in other sites, as usually occurs, it is at least associated with splenomegaly).

Steatorrhea with intact pancreatic function, or anemia that is resistant to oral iron or vitamin therapy, or even a late case of sprue may be caused by mesenteric LAM associated with hyperplasia of the lymphoid component of the lamina propria of various segments of the small intestine. These conditions are manifest long before mesenteric LAM and intestinal infiltration can provoke direct or zonal symptoms or can be documented by other types of investigation.

The *epidemiological, environmental, occupational and clinical categorization* of each individual patient also pro-

vides important elements of probability with which to search for a LAM.

Age is an important factor to consider because of the progressive quantitative reduction in and diminished reactivity of lymphatic tissue which occurs during the aging process. On biopsy specimens, 17% of the LAM in subjects under 30 years old show a picture of aspecific reactive hyperplasia or complete normality, while these findings occur in only 2% of the LAM biopsied after age 30.<sup>2</sup> Moreover, LAM with an inflammatory etiology are much more frequent during infancy, whereas those with a neoplastic cause predominate in people over 40 years old.

Thus, factors such as the fact that the patient is an infant and the presence of exanthematic diseases among his/her playmates or school friends, especially during their most common period of diffusion (end of winter, spring), will make it easy for the physician to orient his diagnostic suspicions in the case of an occipital or nuchal LAM with or without fever. Generalized LAM with fever, accompanied by splenomegaly, in adolescents who sleep in school dormitories or who frequent other types of young people's organized activities (e.g. social clubs, sports, military service) should bring to mind infectious mononucleosis. Generalized LAM in homosexuals, heroin (or other drug) addicts, hemophiliacs or other chronic users of blood derivatives will lead the physician to run serological tests for positivity to the acquired immune deficiency syndrome (AIDS) virus or to AIDS-related syndromes. Regional or generalized LAM in hunters, shepherds, cow milkers, veterinarians and farmers raise the possibility of infections such as tularemia, brucellosis, tuberculosis, nocardiosis. Erythema with generalized LAM following treatment with heterologous sera points to serum sickness. The presence of LAM in an epileptic patient could be related to previous ingestion of hydantoins, especially phenytoin, or of carbamazepine; the same lymph node enlargement in a chronic arthritis sufferer could be due to phenylbutazone, while in a tuberculosis patient the cause could be para-aminobenzoic acid, when the LAM are not the direct result of rheumatoid arthritis or tuberculosis, respectively.

The symptoms associated with LAM can be very enlightening. Fever and weight loss alone cannot be considered indicative of a neoplasm, given the frequency with which these symptoms occur in a variety of infectious, inflammatory and neoplastic disorders; however, coupled with unwarranted, profuse sweating, especially at night, they could indicate a neoplastic etiology. Fever of unknown origin associated with laterocervical lymphadenopathy, neutropenia and lymphocytosis in a young woman could be correlated not only with a lymphoma but also with necrotizing lymphadenitis (Kikuchi's disease).<sup>4</sup> This condition can account for a considerable proportion of the lymphadenopathies encountered in systemic lupus erythematosus (SLE).<sup>5</sup> Unexplained itching resis-

tant to antihistamines points toward a possible lymphoma; deep abdominal or thoracic pain following alcohol consumption, albeit rare, can be considered pathognomonic for Hodgkin's lymphoma. The association of uveitis or erythema nodosum and LAM suggests sarcoidosis, while that of LAM and chorioretinitis points to toxoplasmosis or even Waldenström's macroglobulinemia. The presence of various types of dermatological disorders can, by itself, support the diagnosis of a simple dermatopathic lymphadenitis, which most of the time will resolve spontaneously upon remission of the dermatosis; in rare cases this association is found in mycosis fungoides. LAM and arthritic disorders can lead the physician to suspect SLE or rheumatoid arthritis. If LAM is associated with proteinuria and renal insufficiency, this could signal the presence of myeloma or amyloidosis. LAM plus hemolytic anemia may be a sign of lymphoma, especially the low-grade malignancy form, or of angioimmunoblastic lymphadenopathy. Diabetes insipidus and LAM can be associated with Hand-Schüller-Christian disease.

Except in rare cases (e.g. spleen extremely soft in systemic infections, or extremely voluminous in chronic leukosis, lymphocytic lymphoma, hairy cell leukemia and – in particular pediatric patients – lipid storage diseases), assessing the spleen is not very helpful in determining the nature of the LAM; naturally, encountering splenomegaly in the course of evaluating a localized LAM should orient the initial hypothesis toward a systemic disorder.

#### **Instrumental investigations**

In the majority of cases, surgical biopsy excluded, instrumental investigations can only enrich the information already obtained on the basis of the medical history and physical examination or make the judgement already formed more certain.

The elements of evaluation offered by each investigative procedure should be integrated with one another, beginning with those presented by the simplest and most generalized procedures and then continuing on with the more particular and more complex ones, unless of course the diagnosis has emerged in the meantime.

In particular, ultrasonography is easily able to distinguish the lymph nodal nature of a tumefaction that was difficult to diagnose differentially at palpation; furthermore, this procedure also provides an accurate picture of the dimensions of a LAM, defines its relationships with contiguous structures, and offers information as to the content of the LAM (solid, liquid, gas; homogeneous or nonhomogeneous). Ultrasonography can also reveal the presence of other enlarged lymph nodes that are near the LAM but were not detected at palpation; in the abdomen, it is able to put mesenteric, mesocolic and retroperitoneal lymph nodes, which cannot be evaluated by physical examination, into relation with the superficial LAM,

which could be the revealing element of a generalized lymphadenopathy. In special conditions Doppler-ultrasonography can supply indications about the vascularization of a lymph node, thereby helping to distinguish between an old LAM due to a condition in the past and a current LAM that is still active.

Needle biopsy should be considered when a LAM has not been able to be categorized clinically or diagnostically. Many superficial LAM can be needle biopsied just by using palpation as a guide; all superficial and many deep nodes can be needle biopsied under the guidance of ultrasonography, and virtually all deep nodes can be needle biopsied by using tomography. The problem arises from the diagnostic reliability of the procedure itself, which, first of all, can be considered in direct relation to the diameter of the needle employed: the bigger the needle, the more abundant and the better the quality of the material that will be obtained, and the less difficulty the cytologist who must evaluate the specimen (and whose expertise is crucial) will have.<sup>6</sup>

In fact, in about 20% of cases the needle-biopsied material is not adequate for cytohistologic interpretation when needles with a diameter of 14-18 gauge are utilized; the percentage of unsuccessful biopsies rises when narrower needles are employed. The benefits of needle biopsy are to spare the patient from surgical biopsy, more so if the LAM is in a deep site (mediastinum, abdomen), and to offer a possibility of carrying out immunophenotypic studies as well. On the other hand, the disadvantages of this procedure, besides the above mentioned problems with being able to obtain an adequate specimen, are the reduced feasibility of conducting immunophenotype investigations and hemorrhagic lesions provoked in the lymph node. The latter can be very important if there is only a single LAM and surgical biopsy becomes necessary.

In other words, especially for the purposes of an initial diagnosis, needle biopsy is completely justified as a substitute for surgical biopsy only when the LAM is located in a deep site and the surgical risk is high. In such cases it is nevertheless necessary to employ no smaller than a 14-gauge needle, otherwise surgical biopsy is preferable. In general, for superficial LAM, needle biopsy cannot replace surgical biopsy as the means of primary diagnosis; only in cases of positivity during the course of a disease that has already been diagnosed does needle biopsy offer a simpler and more rapid way of indicating the need to continue or resume treatment. Otherwise, at disease onset and without a certain diagnosis, needle biopsy negativity should still indicate the need for a surgical biopsy.

Surgical biopsy should be effected when all other procedures have failed to elucidate the nature of the LAM, or when this condition persists following therapy based on a previous diagnostic hypothesis. In order to arrive at a correct diagnosis, it is very important to

select the best node to remove (this choice must be clinical) and to handle the specimen properly. The lymph node to biopsy is not simply the one most surgically accessible, but the biggest one or the one that has undergone the greatest and most recent changes in volume (as a rule, retromandibular and inguinal lymph nodes under 3 cm in diameter are not chosen).

Computerized axial tomography (CAT) is particularly useful for visualizing deep lymph nodes, especially in those situations in which ultrasonography presents technical limits, namely in the mediastinum in general and in retroperitoneal sites in heavier patients. CAT offers only an evaluation of the size of the nodes; however, deep lymph nodes in the adult that exceed 1.5 cm in diameter are considered pathologic, while those between 1 and 1.5 cm are dubious. For this reason, especially in the evaluation of retroperitoneal lymph node involvement in patients with lymphoma or genital neoplasms, until recently a procedure called abdominal lymphography was employed. This examination allowed assessment of the parenchymal tissue structure of the lymph node, but it is no longer being used for various reasons: its complexity and elevated cost, unwanted side effects, the lack of personnel with the necessary manual and diagnostic expertise required to carry it out and the difficulty in training such personnel.

#### **Laboratory investigations**

Evaluation of laboratory indices of inflammation is of little help. Erythrocyte sedimentation rate, C reactive protein, measurement of the individual glycoproteins migrating into the  $\alpha_1$  and  $\alpha_2$  regions at electrophoresis, fibrinogenemia and blood copper levels demonstrate aspecific alterations, both regarding each single value and for all of them as a group pattern, without offering the possibility of making even a rough distinction between benign and malignant conditions. A clear increase in  $\beta_2$  microglobulinemia or serum lactate dehydrogenase is associated with lymphoproliferative diseases: the former with myeloma in particular, and the latter with lymphomas (more often non-Hodgkin's than Hodgkin's type, and more often the high-grade malignancy subtypes than intermediate- or high-grade ones). The particular iron picture, with low blood iron levels, low transferrin and normal or high ferritin – typical of the anemia of chronic diseases – and hypoalbuminemia (without concomitant liver disease or other cause of albumin loss), only signal that the disorder in question is not recent but has been present for some time. Biochemical and immunologic alterations can be useful in various cases: e.g. when serum protein electrophoresis reveals a monoclonal band (lymphocytic, lymphoplasmacytoid and immunoblastic lymphoma), or a polyclonal hypergammaglobulinemia (angioimmunoblastic lymphadenopathy), or even a hypogammaglobulinemia (chronic lymphatic leukemia, non-Hodgkin's lymphomas); another useful finding is a reduction in the T lymphocyte ratio OKT4/T8 (AIDS

and AIDS-related syndromes).

Common hematologic parameters are also aspecific (anemia, leukocytosis, leukopenia, etc.) except in particular cases. The finding of a substantial lymphomonocytoid cell component ( $> 1 \times 10^9/L$ ) on a peripheral blood slide is practically diagnostic of mononucleosis; when the proportion of these cells is less conspicuous, it could be indicative of a cytomegalovirus or toxoplasma infection. Finding medium to large-sized lymphocytes that can be classified as *in transformation* or *activated* is useful in any case as an indicator of viral infection. On the other hand, monomorphic lymphocytosis with small lymphocytes or centrocytes or lymphoplasmacytoid elements (with or without hairs) should definitely lead the physician to suspect chronic lymphatic leukemia, leukemized lymphoma or hairy cell leukemia. The documented presence of atypical blast cells should orient the doctor toward either lymphoid or non-lymphoid leukemia, while considerable granulocytosis with thrombocytosis must cast suspicion on chronic myeloid leucosis. Furthermore, a finding of *myeloid* alteration, with the presence of even a few myelocytes, metamyelocytes and an occasional orthochromatic or polychromato-philic erythroblast, suggests a possible neoplastic bone marrow infiltration (myelophthisis).

#### **Indications for lymph node biopsy**

Even though a physician keeps in mind and tries to apply all of the above mentioned possible indications and associations of signs and symptoms, it is a foregone conclusion that there are no criteria or combinations of findings able to lead to a satisfactory clinical classification or to specifically indicate a biopsy (or other invasive procedure) for every LAM encountered.<sup>7</sup> Given the present state of the art, it should be accepted as inevitable that a certain proportion of patients will be submitted to biopsy when in fact (but *a posteriori*) it will prove to have been unnecessary (19% of all cases biopsied), the biopsy will not indicate any specific therapy and the LAM will undergo spontaneous remission within 6 months. Nevertheless, the alternative to this risk seems to be less acceptable since it could mean an increase in the percentage of neoplastic illnesses that go undiagnosed or diagnosed late.

During the physical examination phase of patient evaluation it is particularly important to remember that a localized LAM may possibly represent the revealing manifestation, or at least the earliest sign, of a systemic oncohematologic disorder. The presence of particular symptoms, of possible splenomegaly, of elevated indices of inflammation should all be evaluated very carefully in order to avoid unnecessarily spending time investigating a restricted area for a LAM that actually only appears to be localized and to begin more specific testing for systemic conditions.

In the presence of a laterocervical LAM whose physical characteristics are of the inflammatory type, in a subject under 30 years of age with a history of recent or recurring infection of the upper respiratory tract, normal inflammation indices and negative results to serological tests for the most likely and most common infectious agents, the physician is justified in attempting empirical broad spectrum antibiotic therapy – provided it is carried out under close surveillance – before resorting to invasive testing procedures.

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*MLG contributed to the layout of the paper and wrote it. VJ discussed all surgical aspects and many logical steps in the diagnostic sequence. PGG was responsible for the conception and the supervision of the study. All authors were equally responsible for the general design of the paper.*

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