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Peripheral lymphadenopathy in immunocompetent adults

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Summary

Although unexplained lymphadenopathies are not particular prevalent in the general population (<1%), they represent a diagnostic dilemma. The differential diagnosis is broad, and although only few diseases will be either severe or treatable, patients as well as their doctors are in fear of missing a relevant diagnosis such as a malignancy.

For the differential diagnosis it is prudent to distinguish between localised and generalised lymphadenopathy. Seventy-five percent of all lymphadenopathies are localised and often caused by a specific pathology in the area of drainage, which can be diagnosed without additional investigations. If the diagnosis is unclear, the patient is clinically stable and there is no suspicion of malignancy, it is safe to wait for three to four weeks and observe the clinical course. Exceptions are supra- and infraclavicular lymph nodes, which are always suspicious of an underlying malignancy.

Twenty-five percent of lymphadenopathies are generalised and are often a sign of a significant underlying disease. A diagnosis of lymphoma, malignancy, HIV infection or tuberculosis should not be missed. Excisional biopsy is regarded as the diagnostic method of choice, since it allows an assessment of the architecture of the lymph node as well as histological, immunohistochemical, cytogenetic and molecular investigations.

Key words: lymphadenopathy; adults; immunocompetent; algorithm

Introduction

The human body harbours more than 600 lymph nodes, which – together with the spleen and the mucosa-associated lymphatic tissue – represent the secondary lymphatic organs characterised by antigen depending cell proliferation. In a Dutch study providing population-based estimates, the prevalence of an unexplained lymphadenopathy in the general population was 0.6% [1]. Lymph nodes less than 1 cm are frequently palpable in the cervical, axillary or inguinal region in healthy individuals. Only few diseases present predominantly as a peripheral lymphadenopathy, defined as enlarged (>1 cm) lymph nodes or lymph nodes altered in number or consistency. Ten percent of patients with lymphadenopathy in the series cited above were referred to a specialist and biopsy was performed in 3.2% [1].

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Unexplained peripheral lymphadenopathies represent a diagnostic dilemma since the differential diagnosis is broad and, although only few diseases are either severe or treatable, patients as well as doctors are afraid of missing or delaying a diagnosis of malignancy. The prevalence of a malignancy in this setting depends on the site of care. In primary care the prevalence is low (0.4% in patients aged <40 years to 4% in patients >40 years [1, 2]). In referral clinics the prevalence rises to 17% [3] and up to 40–60% in patients referred with a high suspicion of malignancy [4].

This review will focus on the challenge of diagnosing malignancies and treatable infectious or non-infectious diseases in a cost-effective way in immunocompetent adults with peripheral lymphadenopathies.

Clinical algorithm to evaluate peripheral lymphadenopathies in immunocompetent adults

For clinical purposes it is useful to distinguish between localised (only one anatomic region of nodal drainage involved) and generalised (>1 anatomic region involved) lymphadenopathy [5]. In primary care 75% of all unexplained lymphadenopathies are localised: of these, more than half are found in the head and neck region, followed by the inguina (14%) and axilla (5%). Supra- and infraclavicular or epitrochlear lymphadenopathies are rare [5]. Generalised lymphadenopathies are present in approximately 25% of cases and must be considered as a clue to a systemic disease.

The differential diagnosis of an unexplained lymphadenopathy in immunocompetent adults is broad. In table 1 selected diseases are listed according to their frequency and clinical relevance. The patient's age is most important, because the risk of malignancy increases proportionally.

There are *5 key questions*:

- Are there local symptoms in the area of nodal drainage as a clue to a local infection or malignancy?
- Are these symptoms acute or chronic?
- Does the patient complain of constitutional symptoms (fever, night sweat or weight loss) as a clue of a systemic disease?
- Are there epidemiological clues (travel history, contact with animals, tick bites, consumption of raw meat, unsafe sexual behaviour, use of illicit drugs or an immunosuppressive state)?
- Does the patient take any medication?
- For how long do the symptoms last?

The *physical examination* should focus on:

- the presence of a local pathology in the area of drainage of the affected lymph nodes;
- the documentation of number, texture, and character of the lymph nodes. Soft and tender nodes favour an infectious cause whereas a hard consistency and fixation to the underlying tissue is suspicious for malignancy. The prevalence of malignancy raises with increased size of the affected lymph node from 8% (1–2.25 cm^2) to 38% (>2.25 cm^2) [6];
- a careful examination of the skin, joints, liver and spleen in case of a generalised lymphadenopathy.

One must be aware that all these signs do not reliably differentiate between benign and malignant causes of lymphadenopathies.

After a complete history and physical examination, the following algorithm (fig. 1) can guide the investigations in patients with an unexplained lymphadenopathy. Trials of empirical therapies – either with antibiotics or steroids – are not recommended in this setting.

Table 1

Causes of peripheral lymphadenopathy in adults.

Infections
Pharyngitis (GrA Strep)*
Skin infections*
Syphilis*
Tuberculosis*
nontuberc. Mycobacteria
Cat-scratch disease
Tularaemia
Brucellosis
Leptospirosis
Rat-bite fever
Chancroid
Lyme disease
Diphtheria
Plague
HIV*
*EBV**
*CMV**
HSV*
*Toxoplasmosis**
Leishmaniasis
Mumps
Measles
Rubella
Hepatitis B
Dengue fever
M. Castleman
Dimorphe fungi (Histoplasmosis, Coccidiomycosis)

Lymphoproliferative disease / cancer
Non-Hodgkin lymphoma*
M. Hodgkin*
Leukaemia*
Squamous-cell CA*
Metastatic disease*
Angioimmunoblastic LAP
Rosai-Dorfman disease
Haemophagocytic Lymphohistiocytosis

Miscellaneous
Drug reactions*
Serum sickness
Kikuchi's disease
Hypothyroidism
Addison's disease
Sarcoidosis
Still's disease
Rheumathoid arthritis
Lupus erythematosus
Histiocytosis
Amyloidosis
Rheumathoid arthritis
Kawasaki disease
Dermatomyositis
Churg-Strauss-Syndrome

bold	common and treatable diseases
italic	diseases causing mainly generalised lymphadenopathies
non italic	diseases causing mainly localised lymphadenopathies
*	more common diseases
GrA Strep	Group A Streptococci
HIV	Human Immunodeficiency Virus
EBV	Epstein Barr Virus
CMV	Cytomegalovirus
HSV	Herpes Simplex Virus
LAP	Lymphadenopathy

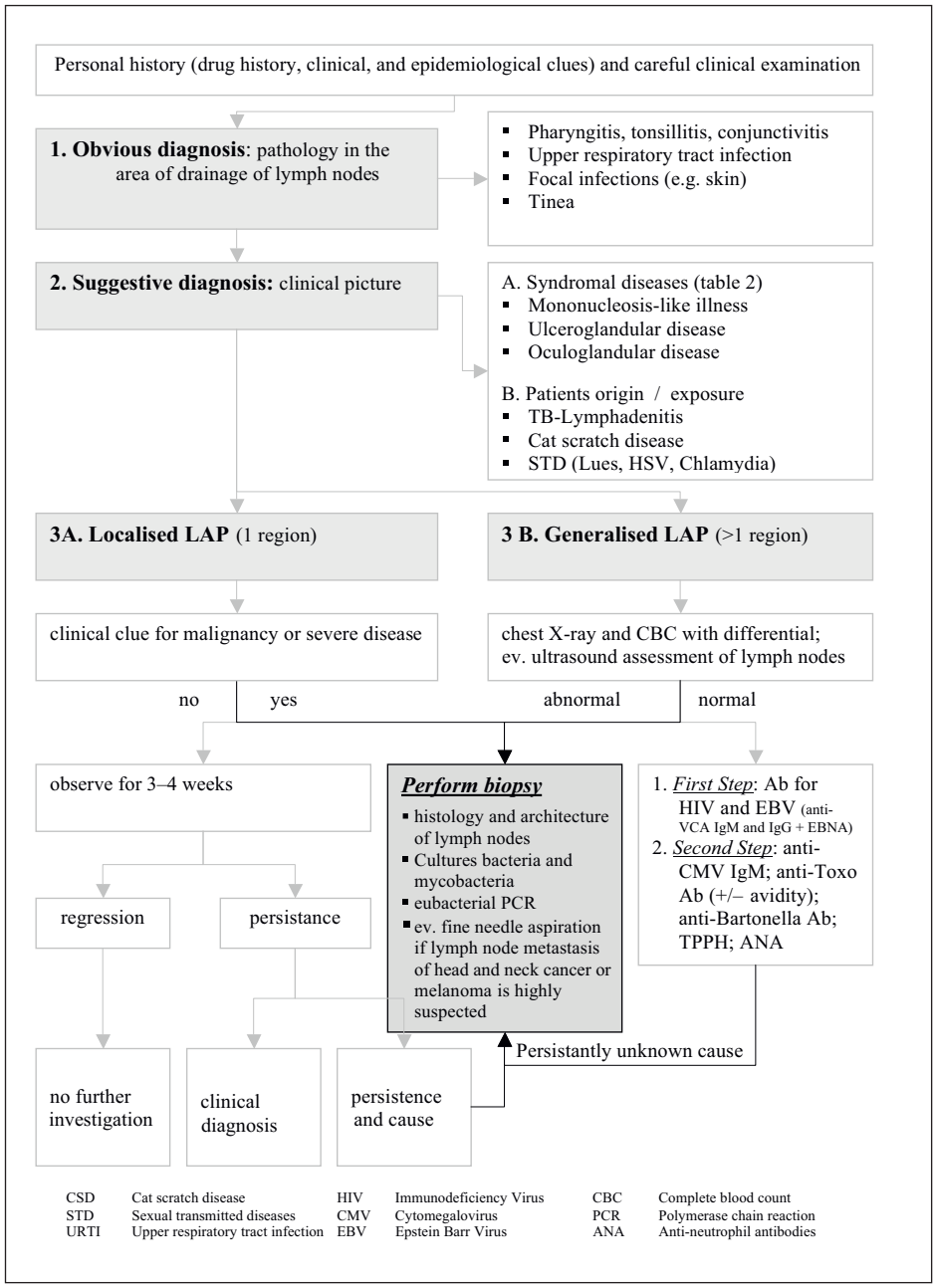

Figure 1

Diagnostic algorithm for the evaluation of patients with unexplained lymphadenopathy (adapted from [5] and [10]).

Look for obvious causes of lymphadenopathy

Often there will be an obvious cause after examination of the drainage area of the affected lymph nodes. The most common cause of a *cervical lymphadenopathy* is a self-limiting viral infection. In case of an ill patient with fever and odynophagia, acute bacterial tonsillitis (most often due to group A streptococci) is the most likely diagnosis. More rarely pathogens include staphylococci, haemophilus influenzae, anaerobes like fusobacterium spp. or sexually transmitted pathogens (syphilis, gonorrhoea). Localised infections in the area of the teeth, ear, nose, throat or larynx must always be considered. In certain cases a more detailed examination by a dentist or ENT specialist (including endoscopy) is required. In particular a hard consistency of the lymph node in an elderly patient or a smoker must raise the suspicion of carcinoma. Other diagnoses include upper respiratory tract infections, conjunctivitis, skin infections, lymphoma or metastases. Lymphadenitis due to tuberculosis must be considered in every patient originating from an endemic area. Tuberculous lymphadenitis is the most frequent manifestation of extrapulmonary tuberculosis, accounting for 40% of cases [7]. The typical presentation is a slowly progressive, single, painless lymph node without prominent systemic signs of tuberculosis. Sixty percent will present as cervical lymphadenopathy. Patients with tuberculous lymphadenitis are typically younger than patients with extrapulmonary tuberculosis involving other sites [7]. HIV testing is strongly recommended in every patient with a diagnosis of tuberculosis.

Supraclavicular lymph nodes drain the gastrointestinal and urogenital tract as well as parts of the lungs. These lymph nodes are always suspicious of

malignancy. The prevalence of malignancy in biopsy studies ranges from 25% in patients <40 years up to 90% in patients >40 years [1, 3]. Right-sided supraclavicular lymphadenopathy is associated with carcinomas of the lung, oesophagus or mediastinum, whereas left-sided lymph nodes ("Virchow nodes") are suspicious of carcinomas of the stomach, gallbladder, pancreas, kidney, testicles, ovaries or prostate. *Infraclavicular lymph* nodes are rare and suspicious of a non-Hodgkin-lymphoma. An excisional biopsy without delay is recommended in this situation.

Axillary lymph nodes often result from focal skin lesions of the upper extremities or ulceroglandular disease (s. below). If no skin lesions are found, carcinoma of the breast must be considered, since breast carcinoma often metastasizes early into the anterior axillary region.

Epitrochlear lymph nodes are always pathological and most often due to skin infections or ulceroglandular disease, rarely due to secondary syphilis.

Inguinal lymph nodes up to 1 cm are frequently palpable and most often represent a benign reactive lymphadenopathy. Pathological enlargement is most commonly due to skin infections or sexually transmitted diseases (syphilis, HSV, chlamydia). Malignancies such as squamous cell carcinomas of the penis, vulva or anus, melanomas or sarcomas are rare.

Syndromes suggesting the cause of lymphadenopathy

If no obvious cause can be found as described above, the clinical picture may correspond to syndromal disorders such as mononucleosis-like illnesses or ulceroglandular and oculoglandular syndromes. Additional tests (serology, if necessary biopsy) to identify the specific cause are indicated (fig. 1). Beside syndromal diseases, epidemiological clues (e.g., patients' origin in case of a tuberculous lymphadenitis) or exposure (e.g., cat-scratch disease, tick bites) could lead to a specific diagnosis.

Mononucleosis-like illnesses

Epstein-Barr virus (EBV) accounts for the majority of mononucleosis-like illnesses. More than 90% of adults worldwide have a positive serology and shed the virus intermittently into the saliva – the most common source of transmission [8]. Approximately 25–30% of adolescents and adults up to the age of 30 with primary EBV infection will become ill [9]. Infections in childhood are more frequent but generally subclinical. Adolescents and adults present with the trias of fever, pharyngitis and a typically symmetrical, moderately tender lymphadenopathy, which tends to peak during the first week of symptoms and predominantly involves the posterior cervical lymph nodes [10]. A marked lymphocytosis (>50% of leukocytes) with atypical cells comprising >10% of all leukocytes constitute Hoagland's criteria for atypical lymphocytosis [11]. Enlargement of the liver and the spleen is common, and a rubeola-like exanthema is present in approximately 10%. Rare manifestations (<1%) include meningoencephalitis, Guillain-Barré syndrome, myocarditis, aplastic anaemia, and splenic rupture [12]. No specific therapy is recommended. Acyclovir does not influence the course of the disease, since most of the symptoms are mediated by the immune system. Corticosteroids may shorten the duration of symptoms but are not recommended unless there are complications such as upper airway obstruction, haemolytic anaemia, myocarditis, or neurological involvement. Diagnosis is made by serology. Though heterophile antibodies remain an excellent test for adolescents and adults with a capability to detect 70–90% of cases [13], there are reports of EBV-negative, heterophile-positive patients with acute HIV-infection [14].

Symptoms of acute *human immunodeficiency virus (HIV)* infection develop in the second week after infection starting with a generalised lymphadenopathy (cervical, axillary, inguinal, and occipital) [15]. Other symptoms include fever, pharyngitis, myalgias, arthralgias, headache, malaise, a non pruritic maculopapular rash, and mucocutaneous ulcerations. The level of viraemia is high in acute HIV infection and the patients are highly infectious for their sexual partners. Not every patient is sick enough to seek medical attention, hence it is important to remember that enlarged lymph nodes – at more than one site over a period of 2–3 months – are always suspicious of HIV infection and must be detected for epidemiological reasons and treatment consequences. Diagnosis is made by combined antibody and antigen testing. Typically, anti-HIV antibodies do not reach detectable levels for about two weeks after infection, so the test must be repeated in case of suspicion, or a test for HIV plasma viral load (PCR) should be performed if the disease is severe.

Cytomegalovirus (CMV) primary infection is usually asymptomatic but can produce a mononucleosis-like illness with fever, sore throat, malaise and lymphadenopathy. Transaminases are moderately elevated in 90% of the patients but rarely exceed 5-fold above the normal values. Diagnosis can be made either by demonstration of anti-CMV IgM antibodies or by measuring the antigen (pp65-antigen or quantitative PCR).

Human herpes virus 6 (HHV-6) – responsible for exanthema subitum or "sixth disease" in childhood – rarely cause a mild but prolonged febrile mononucleosis-like illness with a typically non-tender cervical lymph node enlargement.

Primary *herpes simplex virus (HSV) type I* infec-

tion causes fever, odynophagia with pharyngitis, and tonsillar exudates. The symptoms are self-limiting but cervical lymphadenopathy may persist for several weeks. The diagnosis is made by viral cultures from a pharyngeal swab or by PCR-testing.

Primary *Toxoplasma gondii* infection in immunocompetent adults is often asymptomatic but may present as lymphadenopathy, typically with a single lymph node most often located in the posterior cervical triangle associated with mild constitutional symptoms. A maculopapular rash, pharyngitis, or hepatosplenomegaly are less frequent. The clinical course is benign and self-limiting without need for a specific treatment. Diagnosis of acute infection in pregnancy is important as toxoplasmosis may cause damage to the developing foetal nervous system. Anti-toxoplasmosis IgM antibodies are not reliable in the diagnose of an acute infection since they may persist for years after infection. Avidity testing of IgG antibodies in two consecutive blood samples is often needed to confirm the diagnosis.

Bacterial infections like group A streptococcal disease rarely mimic mononucleosis-like illnesses (<5%). Abrupt onset of fever and odynophagia with enlarged anterior cervical lymph nodes are the main symptoms. Rapid antigen detection tests or a throat culture confirm the diagnosis.

Ulceroglandular syndromes

Cat-scratch disease is a rare subacute granulomatous lymphadenitis caused by Bartonella henselae. The lymphadenopathy appears two weeks after a cat scratch with a localised skin lesion. In general only one lymph node is enlarged and rarely progresses to a fluctuating lymph mass or generalised lymphadenopathy. The pathogen is difficult to culture, hence diagnosis relies on either serology or Whartin-Starry-Silver staining (suppurative lymphadenitis with giant cell granulomas) and PCR testing in case of a biopsy. Specific treatment of immunocompetent patients is not necessary. In case of painful fluctuant lymph nodes, aspiration or drainage is indicated for pain relief.

Ulceroglandular tularaemia due to Francisella tularensis is a febrile infectious disease transmitted by rodents or ticks. In Europe the disease is endemic in the northern countries (Sweden, Finland), but reports in Central Europe are emerging. Clinical manifestations include a skin ulcer with a sharp border ("eschar", fig. 2) at the portal of entry together with a regional lymphadenopathy. Diagnosis is made by culture of a tissue specimen or by serology.

Lyme disease can rarely manifest as an ulceroglandular syndrome. Although it may present with fever and rash, lymphadenopathy is not a particularly characteristic feature of the disease [16]. In the absence of a classical erythema migrans, the diagnosis of Lyme disease is not straight forward since approximately 10% of the population in Central Europe will have a positive serology and even IgM antibodies can persist for many years.

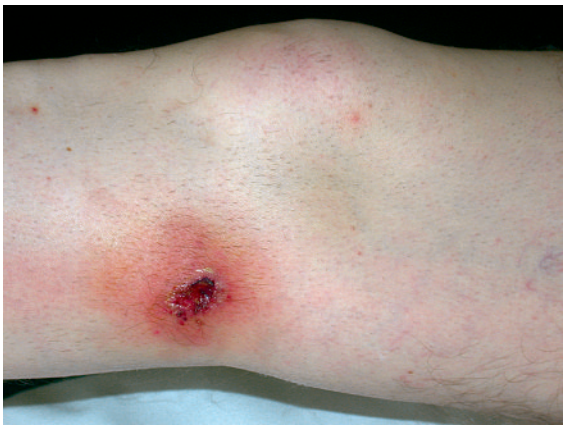

Figure 2

"Eschar" at the inner side of the right knee due to ulceroglandular tularaemia in a young man after a tick bite (Zurich, Switzerland).

Oculoglandular syndromes

Oculoglandular syndromes are rare diseases characterised by conjunctivitis and associated preauricular lymph nodes most often due to a viral ceratoconjunctivitis. Adenovirus infection, a common cause of self-limiting childhood respiratory tract infection, rarely causes illness with fever, pharyngitis, tracheobronchitis, cervical lymphadenopathy, and conjunctivitis in adults. Outbreaks of pharyngoconjunctival fever have been associated with public swimming pools. Other rare causes of oculoglandular syndromes include ocular cat-scratch disease or sarcoidosis.

Unexplained localised lymphadenopathy

Many inflammatory lymph nodes resolve without specific treatment. If a localised lymphadenopathy remains unclear with no clinical suspicion of malignancy or severe acute disease, it is prudent to wait for three to four weeks and to observe the clinical course. Fixed, firm or mattered lymph nodes and persistent nodes larger than 1.5 cm require further evaluation. Excisional biopsy should be performed without delay in case of severe acute disease, strong suspicion of lymphoma or other malignancies (e.g., location within the supraclavicular fossa), progressive growth or lymph node size exceeding 3 cm. Again, empirical treatments either with antibiotics or steroids are not recommended.

Kikuchi lymphadenitis is a rare, benign and self-limiting disease of unknown origin most often found in young women from Asia. Fluctuating symptoms such as fever, malaise, headache over a period of a few weeks are common, the diagnosis is made by the typical histological picture of a necrotising cervical lymphadenitis [17]. Occasionally histology can be confounded with lymphoma.

Unexplained generalised lymphadenopathy

Generalised lymphadenopathy rarely presents without concomitant symptoms and is frequently a clue to a significant systemic disease. The causes can be broadly divided into infectious (i.e, mononucleosis-like illnesses), autoimmune and neoplastic causes.

Drug reactions present as serum sickness with fever, arthralgia and rash. Allopurinol, atenolol and certain antibiotics such as penicillins and cotrimoxazol are the most common drugs involved. Plasmacytes in the peripheral blood smear may be a valuable sign of serum sickness. Phenytoin may cause a generalised lymphadenopathy without serum sickness.

Autoimmune conditions including systemic lupus erythematodes (SLE), rheumatoid arthritis, Sjögren's syndrome and sarcoidosis may present with lymphadenopathy, fever and rash. Histological findings on lymph node biopsy include non-specific findings such as reactive follicular and paracortical hyperplasia [18]. In SLE a typically soft, non tender, generalised lymphadenopathy is found in approximately 50% of patients, especially at the onset of the disease or in association with exacerbations. Splenomegaly is rare. A positive antinuclear antibody test is highly sensitive for SLE, although not specific. In rheumatoid arthritis, lymphadenopathy may precede joint pain. Adult-onset Still's disease predominantly presents as fever of unknown origin together with arthralgias, an evanescent salmon-coloured rash and lymphadenopathy.

Most *lymphomas* present subacutely over a period of weeks to months [19]. The majority of non-Hodgkin's lymphomas are of B-cell origin and the diagnosis is made with an excisional lymph node biopsy. Lymphomas that are more difficult to diagnose in biopsies include Hodgkin lymphomas, T-cell/histiocyte-rich large B-cell lymphomas and peripheral T-cell lymphomas. Angioimmunoblastic T-cell lymphomas account for nearly 30% of T-cell lymphomas in Europe [20] and characteristically present acutely with diffuse lymphadenopathy and fever, mimicking an infectious cause of the lymphadenopathy.

In case of a generalised lymphadenopathy, a complete blood count (leukaemia, lymphoma, atypical lymphocytes) and a chest-x-ray (mediastinal or hilar lymphadenopathy; intrapulmonary lesions) are recommended. In case of any pathological findings, a lymph node biopsy should be performed without delay. Additionally, bone marrow aspiration and histology are important analytic tools for the diagnosis of a lymphoid neoplasia.

In all other patients it is advisable to serologically test for HIV, EBV, CMV, toxoplasmosis, Bartonella, and syphilis and to screen for autoimmune diseases with the determination of an antinuclear antigen antibody (fig. 1). Most experts would also recommend Mantoux-testing or an interferon-gamma release assay. Since these tests are not able to discriminate active tuberculosis from inactive disease, we do not recommend them in the setting of an unexplained lymphadenopathy.

If the diagnosis is not achieved, a diagnostic excisional biopsy should be performed. An *excisional biopsy* is generally regarded as the method of choice, since it allows an assessment of the lymph node architecture as well as histological, immunohistochemical, cytogenetic and molecular investigations. Cultures for bacteria and mycobacteria should be performed. In case of suspicion of an infectious disease without cultural growth, an eubacterial PCR may lead to the diagnosis. Again we do not suggest empirical treatment trials with antibiotics or steroids.

Half of all lymph node biopsies will show a non-specific lymphadenopathy not requiring further treatment [21]. Especially the management of enlarged neck lymph nodes show great variation in referral pattern and management [21]. If no single lymph node predominates, inguinal and axillary lymph nodes, though easy accessible, should preferably not be excised since they carry the greatest risk of an unspecific result. Clinical algorithms to guide the need for surgical biopsies have been developed [22] but are not generally accepted. There is a clear need to develop an algorithm to predict which patients will profit from biopsies.

Other diagnostic tests

A *core needle biopsy* provides tissue for immunohistological, genetic and molecular studies and is a relatively low-morbidity alternative to an excisional biopsy in patients with suspected lymphoma without easily accessible lymph nodes.

Though novel immunocytological methods have improved the diagnostic value of *fine needle aspirations*, this investigation is limited by a higher false negative rate as a result of sampling errors and the fact that no information about the nodal architecture is obtainable.

With cytology from fine needle aspirations, metastatic nodal disease [23] or a recurrence of a malignancy can be detected with a high sensitivity. If there is a high clinical suspicion for head and neck cancer or melanoma, a fine needle aspiration of a cervical or axillary lymph node can be performed in the first place. If a carcinoma can be detected, a lymph node extirpation or biopsy can be avoided. Unfortunately fine needle aspiration is not useful for diagnosing lymphoma or tuberculous lymphadenitis.

Drainage is not an efficient diagnostic approach but useful to relief pain when nodes are fluctuating (e.g., in cat-scratch disease).

Imaging studies: When there is clinical doubt as to the significance of a lymph node, ultrasound is a valuable tool [24]. Other imaging studies (computed tomography, MRI) are not particular helpful for the diagnosis of an unexplained lymphadenopathy, though the size and distribution of the lymph nodes can be better evaluated. Of course, CT and MRI are essential methods for the staging of tumours and are helpful in guiding biopsies. In case of a generalised lymphadenopathy they can provide additional information such as hepatosplenomegaly or a mediastinal or abdominal lymphadenopathy.

Conclusion

The differential diagnosis of an unexplained peripheral lymphadenopathy in an immunocompetent adult patient is broad. The challenge is to establish a clinical algorithm to diagnose severe and treatable diseases in a cost-effective and efficient way. The investigations should follow a multiple step approach and should focus on obvious diseases in the drainage area of the affected lymph nodes as well as the recognition of syndromal diseases such as mononucleosis-like illnesses. In case of a generalised lymphadenopathy or in substantially ill patients, the diagnosis of severe diseases (lymphoma, leukaemia) or diseases with substantial clinical or epidemiological consequences (HIV, tuberculosis) should not be delayed. The algorithm proposed in this review can help as a decision pathway to avoid unnecessary and expensive investigations but is not yet validated in prospective studies.

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