Does lymph node morphology using ultrasound reflect aetiology? 
A pictorial essay, part I

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Introduction

Transcutaneous ultrasound (US) is the primary imaging technique in the evaluation of peripherally located lymph nodes (LNs) [1-3]. In the abdomen and chest, computed tomography (CT) is usually the standard imaging method for staging purposes according to oncological guidelines [4-12]. In the mediastinum, endoscopic ultrasound (EUS) techniques are often necessary for biopsy and cytological and/or histological evaluation [13-21]. However, the knowledge of the clinical background is important for correct staging and determining the aetiology. The identical morphological patterns of LN imaging should be interpreted differently according to the underlying clinical symptoms and diseases. In combination with characteristic clinical symptoms, ultrasound LN morphology is often diagnostically decisive.

In the case of lymphadenopathy of unknown significance, US examination can be used within staging procedures, evaluation of the treatment response, characterisation of residual lymphomas and performing follow-up examinations.

Conventional B-mode ultrasound, elastography, Doppler and contrast enhanced ultrasound (CEUS) features...
are described in the literature for LN characterisation [2,10,11,13,14,18-21,30,31].

CEUS may be better than conventional colour Doppler techniques to evaluate vascular characteristics and the perfusion pattern [32,33] and can help to guide the needle to viable tissue.

Elastography is based on the principle that circumscribed malignant infiltration and malignancy in general tend to be stiffer than the surrounding non-malignant parenchyma or tissue (e.g., muscle-to-lymph node strain ratio).

US is useful for the monitoring of tumour therapy, evaluating the change in number, size and vascularity of involved LNs.

For more details we refer to the already published and underlying publications [1,2,11,13,16,20,21,25,34], which are illustrated. Recently the value of US for the diagnosis and differential diagnosis of haematological and oncological disorders has also been summarised [10].

Table I. Rules and recommendations for lymph node evaluation.

| In primary suspected LN pathology, it has to be clarified by US whether the observed visible or palpable tumour represents a LN. |
| It must be assessed whether the LN has criteria for a benign (inflammatory) or malignant aetiology and whether an ultrasound-guided biopsy is necessary for final diagnosis |
| Clinical and imaging criteria for the evaluation of the aetiology are the age of patient, sex, past medical history, LN localization (LN regions), B-mode morphologic parameters (size, shape, pattern of involvement, delineation) and structural parameters (hilar sign, echogenicity, homogeneity) |
| Vascularisation parameters such as colour Doppler sonography, spectral curve analysis [22-24], contrast enhanced ultrasound [25] together with elastography [19,25] can be used |
| The US guided core needle biopsy should be performed in any unexplained lymphadenopathy, especially in cases with therapeutic consequences and plays a decisive role in the evaluation of an enlarged LN of unknown cause [26-29]. |

The following criteria are discussed for the five distinct categories as follows: 1) have the appearance of LN but there are other structures; 2) normal LN; 3) inflammation; 4) carcinoma; 5) lymphoma.

The widely recognised features for LN characterisation are detailed in Table II.

Indications for US examination (mainly conventional B-mode) include techniques [1] for

- characterising palpable LNs
- characterising peri-intestinal and mediastinal LNs (EUS)
- detection of suspicious LNs
- staging (aiming the typical localisation of metastatic LNs)
- guidance for LN puncture.

The evaluation of suspicious LN requires a high level of clinical and US competence. This “pictorial essay” is intended to illustrate eye-catching examples of relevant “clinical-ultrasound visual diagnoses” of suspected LNs. The first part includes “important differential diagnoses of eye-catching features of suspected lymphadenopathy” and “benign lymphadenopathy”. The second part will include “Eye-catching features of malignant lymphadenopathy, both carcinoma and lymphoma”.

**“Important differential diagnoses of eye-catching features of suspected lymphadenopathy”**

In cases of palpable or visible lesions, it has to be clarified whether the observed pathology represents a LN at all. Non-lymphatic masses like lipoma (fig 1), cervical cyst (fig 2), abscess (fig 3), atheroma (fig 4), glomus tumour (fig 5), inguinal hernia (fig 6), schwannoma (fig 7) or accessory spleen (fig 8) are well known pitfalls for suspected LNs.
**Fig 1.** Patient presents with palpable tumour in the left groin, suspected as enlarged LN. B-mode imaging shows a fat-like oval soft mass (a). In colour Doppler sonography (CDS) the lesion shows no flow signals (b). According to the featured ultrasound criteria, the lesion is a lipoma. *Take home message: A ‘fat-like oval soft mass’ with no colour flow signals is an eye-catching feature for lipoma.*

**Fig 2.** Patient presents with palpable tumour on the left side of the neck, suspected to be an enlarged LN. B-mode imaging shows a homogeneous hypoechoic round elastic lesion at the front edge of the sternocleidomastoid muscle with swirling echoes on real time examination (a). In CEUS the lesion has no enhancement (b). According to ultrasound criteria, the lesion is a branchial cleft cyst (confirmed by surgery). *Take home message: In cases of typical localisation and corresponding clinical history or symptoms, a homogeneous hypoechoic round fluid lesion with no enhancement on CEUS is an eye catching feature for a branchial cleft cyst.*

**Fig 3.** Patient presents with palpable painful tumour in the left axillary region, suspected to be an enlarged LN (a). B-mode imaging shows a hypoechoic subcutaneous lesion with irregular margins, fluctuating in the real-time examination. According to ultrasound criteria, an abscess was suspected (confirmed by surgery). *Take home message: In case of corresponding clinical symptoms or patient’s history inhomogeneous fluid collection is an eye catching feature for axillary abscess.*
Fig 4. Patient presents with a painful tumour in the left axillary region, suspected to be an enlarged LN. B-mode imaging shows a hypoechoic subcutaneous inhomogeneous non-elastic oval lesion (a). In CDS the lesion had no signals (b). According to ultrasound criteria an atheroma was suspected (confirmed by surgery). Take home message: A heterogenous hypoechoic lesion with no blood signals is an eye catching feature for subcutaneous atheroma.

Fig 5. Patient presents with a palpable pulsating lesion on the right side of the neck suspected to be an enlarged LN. B-mode imaging shows a hypoechoic node (arrow) in the carotid bifurcation (a). In CEUS the lesion shows a strong enhancement. According to ultrasound criteria a glomus tumour was suspected (confirmed by surgery) (b). Take home message: A vascularised lesion on CDS or CEUS in continuity with the vagus nerve is an eye catching feature for glomus tumour.

Fig 6. Patient presents with a palpable painful tumour in the left groin, suspected to be an enlarged LN. B-mode imaging presents an echocomplex round mass atypical for a LN (a). In CEUS the lesion shows no enhancement (b). According to ultrasound criteria, an incarcerated omental hernia was suspected (confirmed by surgery). Take home message: An echocomplex round mass with non-enhancement on CEUS is an eye catching feature for an omental hernia. The localisation of the mass and the corresponding clinical symptoms are decisive.
The anatomy of LNs is roughly summarised by dividing a lymph node into multiple functional areas. LNs are formed by capsule, the often echo poor cortex (representing B-cell activity with lymphoid follicles containing germinal centre), paracortex (T-zone with interactive dendritic cells and endothelial venules) and medulla (containing plasma cells and lymphocytes). The vessels supplying the LN enter the hilum and form regular, tree-like branching vessels entering the medulla, paracortex and cortex. Accessory arteries and veins may enter and leave the LN through the cortex. Predominant penetrating cortical vessels are often seen in association with malignant infiltration.

"Eye-catching features of benign lymphadenopathy"

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Follicular (most commonly, autoimmune, infectious), paracortical (e.g., virus-related) and sinus hyperplasia (e.g., sinus histiocytosis) are the three morphological signs of pathophysiological inflammatory reactive lymphadenopathy (rLAP). rLAP is a non-specific and non-neoplastic response to immunological stimuli. Such lymph nodes are often but not always enlarged, soft, tender and mobile. Most viral infections present with diffusely enlarged LN with preserved vessel architecture.

Focal cortical thickening with localised hypervascularisation is mainly caused by local infection explained by segmentally involved afferent lymphatic vessels (e.g., erysipelas) but neoplastic infiltration must be ruled out. Necrotic LNs are mainly observed in tuberculosis (TB) and severely immune incompetent patients.
Anatomical localisation of LNs plays an important role in the diagnosis. Cervical lymph nodes are classified into several regions. One classification divides them into submental (region 1), sub-mandibular (region 2), parotid (region 3), upper, middle and lower cervical (regions 4-6), the supraclavicular fossa (region 7) and the posterior triangle (region 8). Each region has a particular probability of certain disease manifestations. The same is true for the entire body and the respective LN regions.

Peripheral benign LNs present an elongated configuration and a variably pronounced echogenic central hilum [1] (fig 9). In the case of erysipelas, LNs may be very large and painful when pressure is applied (so-called bell-shaped signal) (fig 10). Reverberation artefacts may be seen in axillary LNs after rupture of silicone implants (fig 11). Liver hilum LNs are usually associated with hepatitis [5,11,35-39] or portal hypertension in end stage disease (fig 12). LNs in mesenteric lymphadenitis [40], which are often grape-like, are localised around the mesenteric vessels and painful when compressed (fig 13). The clinical presentation of yersiniosis is characterized by an ileitis with a pronounced regional lymphadenopathy [41-43] (fig 14). A diffuse increase of the LN echogenicity can be observed in Whipple’s disease [44,45] (fig 15).
Large LNs, often considered to be malignant, are seen in mononucleosis (fig 16), sarcoidosis [9,13,14,16,46,47] (fig 17), in autoimmune diseases in general (fig 18) and in TB [48-50] (fig 19, fig 20). Large abscessing LN infections are seen in tularemia (rabbit plague) (fig 21, fig 22). The correct diagnosis is only possible from the knowledge of the clinical laboratory chemistry, further imaging and particularly histological examination.

**Fig 12.** Patient with liver cirrhosis. B-mode imaging shows multiple hypoechoic LNs (L) (arrow) in the liver hilum. VP = vena porta; VC = vena cave. According to clinical ultrasound criteria, the LNs are consistent with benign lymphadenopathy. *Take home message: Multiple hypoechoic LNs within the hepatoduodenal ligament is an eye catching feature for benign lymphadenopathy.* Further reading: [11].

**Fig 13.** Patient with abdominal pain before and after appendectomy (bladder vermiform appendix) coming postoperatively for ultrasound examination (a). B-mode imaging shows multiple painful LNs (during compression) which were located around the mesenteric vessels (c). According to clinical ultrasound criteria this case is a mesenteric lymphadenitis. *Take home message: Multiple painful LNs around the mesenteric vessels is an eye catching feature for mesenteric lymphadenitis.*

**Fig 14.** Patient with pain in the right lower abdomen and mild diarrhoea. B-mode imaging shows appearances in the terminal ileum suggestive of mild ileitis (a). The regional LNs (L) are significantly increased (b). The finding was suspected to be a Yersinia infection (confirmed serologically). *Take home message: Multiple painful LNs around the terminal ileum is an eye catching feature for ileocecal lymphadenitis.*

**Fig 15.** A 45 y/o male patient with Whipple’s disease with severe weight loss and polyarthritis. In Whipple’s disease, echo-rich LNs and the so called white bowel [44] can be identified [12,16,42]. *Take home message: Abdominal echo-rich LNs and the “white bowel” are eye catching features for Whipple disease.*
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Fig 16. Young patient with fever, sore throat, and enlarged neck LNs (a). B-mode imaging shows multiple enlarged neck LNs (b,c), splenomegaly and in the peripheral blood smear a large number of lymphomonocytoid cells were observed (d). The results suggested Epstein Barr infection which was confirmed by serological tests. Take home message: Multiple neck LNs and splenomegaly are eye catching features for Epstein Barr virus infection.

Fig 17. Young patient presents with large palpable LNs on both sides of the neck suspected to be malignant lymphoma. B-mode imaging shows multiple hypoechoic LNs in the cervical region (a) as well as in the abdomen (b). Chest X-ray examination revealed hilar lymphadenopathy (c). According to clinical and ultrasound criteria, the findings were suspected to be sarcoidosis, which was histologically confirmed by LN biopsy (d). Take home message: The presence of hypoechoic enlarged LNs in the mediastinum and neck is an eye catching features for sarcoidosis. The abdomen can be involved as well (d).

Fig 18. Patient with a “butterfly”- like exanthema and confirmed lupus erythematosus (a). Clinical examination shows a hypoechoic mass in the left infraclavicular region (b). B-mode imaging shows multiple hypoechoic LNs (c). A LN extirpation was performed with the diagnosis of an inflammatory pseudotumour. Take home message: The presence of multiple hypoechoic enlarged LNs is an eye catching features for inflammatory pseudotumour in the neck. However, histological proof always is necessary.

Fig 19. Young immigrant patient presents with a palpable LN in the region of the neck. B-mode imaging shows a LN with anechoic areas (a). In CEUS the anechoic areas have no enhancement (b). According to ultrasound criteria the necrotic LN was suspected to be caused by TB, which was clinically confirmed. Take home message: The presence of an anechoic area on B mode ultrasound and non-enhancement area on CEUS are eye catching features for TB.
Fig 20. Young migrant patient comes with palpable fluctuating LN supraclavicular left seen on computed tomography (a). B-mode imaging presents a completely liquified LN (b). US guided biopsy was performed (c). Only necrotic material could be obtained. TB was suspected and clinically confirmed. Take home message: The presence of a completely anechoic area within an enlarged LN on B mode ultrasound is an eye catching feature for necrotic TB.

Fig 21. A young poacher comes with chronic painful mass in the area of the left axilla (arrow) (a). B-mode ultrasound imaging showed a hypoechoic fluctuating mass (b). CEUS shows an edge enhancement, and a LN abscess was suspected (c). The diagnosis of a rabbit’s parasite (Tularemia) was clinically suspected and microbiologically confirmed (Francisella tularensis). Take home message: Given an indicative patients history the presence of a hypoechoic fluctuating lesion on B mode ultrasound and edge enhancement on CEUS are eye catching features for a LN abscess.

Fig 22. A patient presents with palpable LNs on the right side of the neck due to tularemia (a). B-mode imaging shows a markedly hypoechoic enlarged LN (b). Colour Doppler imaging shows the hypervascularity, and the hilar vascularity is maintained (c). Suppuration (necrosis) of affected lymph nodes is a relatively common complication and may occur despite antibiotic therapy (d). Take home message: the presence of markedly hypoechoic enlarged lymph nodes with rich vascularity, or an enlarged lymph node with inside suppuration (necrosis), located in cervical or occipital regions, are eye catching features for tularemia.

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