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SFORL Guidelines

Cystic form of cervical lymphadenopathy in adults. Guidelines of the French Society of Otorhinolaryngology (short version). Part 2–etiological diagnosis procedure: Clinical and imaging assessment

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ABSTRACT

Introduction: The authors present the guidelines of the French Society of Otorhinolaryngology (SFORL) for clinical and radiological assessment of cystic neck lymphadenopathy of unknown primary in adults. Most cases concern head and neck carcinoma metastasis, often in the oropharyngeal area, or less frequently differentiated thyroid carcinoma or non-keratinizing nasopharyngeal carcinoma.
Methods: A multidisciplinary task force was commissioned to carry out a review of the literature on the etiological work-up in cystic neck lymphadenopathy in adults: clinical examination, conventional imaging (ultrasound, CT, MRI) and metabolic imaging. Guidelines were drafted based on the articles retrieved, and graded A, B, C or expert opinion according to decreasing level of evidence.
Results: Oriented clinical examination, cervical and thyroid ultrasound scan and contrast-enhanced neck and chest CT scan are recommended in the assessment of cystic neck lymphadenopathy of unknown primary in adult patients. PET-CT is recommended prior to panendoscopy, to identify the primary tumor.
Conclusion: Clinical and radiological assessment is fundamental for etiologic diagnosis of cystic neck lymphadenopathy in adult patients, and should be completed by cytological examination before in initiating treatment.

1. Introduction

In case of cervical mass with cystic aspect, the clinical and paraclinical elements suggestive of metastatic neck lymphadenopathy were presented in "Cystic form of cervical lymphadenopathy. Guidelines of the French Society of Otorhinolaryngology. Part 1: diagnostic procedures for lymphadenopathy in case of cervical mass with cystic aspect". Once this initial distinction has been made, the type of lymphadenopathy and the primary tumor need to be determined. In a large majority of cases, such lymphadenopathies with a cystic aspect are metastases of head and neck squamous cell carcinomas, notably in oropharyngeal locations, predominantly implicating human papilloma virus (HPV+) [1] [Gourin CG 2000] (level of evidence, 4) [2] (sharma 2016) (level of evidence, 4). More rarely, they are related to thyroid papillary carcinoma or non-keratinizing nasopharyngeal squamous cell carcinoma implicating Epstein Barr virus (EBV) [2–4] [Pazaitou-Panayiotou K 2008] [Thompson LD 1998] (sharma 2016) (level of evidence, 4). Clinical and imaging data contribute to the diagnostic procedure, and are the topic of the present article. Cytology and histology examination and results are the topic of a further article.

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2. Clinical data

Interview should determine the date and circumstances of onset of the cervical mass and its progression [5] [Mackenzie K 2016] (Expert opinion) [6] [Vergez S 2013] (Expert opinion). It should screen for suggestions of primary tumoral origin (notably, alcohol abuse and smoking), functional signs of head and neck cancer (dysphagia, odynophagia, dysphonia, inspiratory dyspnea, recent-onset unilateral nasal obstruction and epistaxis, unilateral hearing loss, etc.), and history of cancer, especially in the head and neck region (thyroid, skin, as a resection scar after cutaneous squamous cell carcinoma may not be highly visible and the operation may have been deemed "minor" enough to be overlooked by the patient) [5–7] [Strojan P 2013, Mackenzie K 2016, Vergez S 2013] (Expert opinion).

Clinical examination seeks to locate the primary among all the various possible sites, by nasal endoscopy, head and neck tegument examination (to screen for in-situ tumor or scar), and painstaking scalp examination. All cervical lymph-node areas are examined, as well as other areas accessible to palpation (axillary and inguinal hollows), and the liver and spleen to screen for hepatosplenomegaly in a context of possible lymphoma, with palpation of the thyroid and salivary glands (parotid and submandibular) [5–8] [Galloway TJ 2015, Strojan P 2013, Mackenzie K 2016, Vergez S 2013] (Expert opinion).

1. Guideline

In case of lateral cervical mass with cystic aspect in an adult, it is recommended to perform clinical examination with inspection of head and neck teguments, otoscopy, head and neck mucosal examination with pharyngolaryngeal flexible endoscopy, and palpation of the tongue base and tonsils, thyroid and salivary glands and lateral and central cervical lymph-node areas (Expert opinion).

3. Ultrasound exploration

Ultrasound scan is an inexpensive, non-irradiating and accessible examination, widely used in the work-up for cervical mass. The expression "cystic aspect" is used, partly because ultrasound imaging is not macroscopic histology, however close it may come, and because the corresponding ultrasound signal is not necessarily unambiguous: a strictly anechogenic avascular image clearly indicates a liquid component, but a hypoechogenic area may equally correspond to necrosis or even to certain solid pathologies such as lymphoma, which are strongly hypoechogenic. Moreover, many cervical masses with liquid component can mimic lymphadenopathy: e.g., certain second-cleft branchial cysts.

In superficial lesions, the equipment should include a high-frequency probe, to optimize spatial resolution. Brightness-mode imaging has to be coupled to either color or power Doppler mode, and possibly elastography.

Descriptively, ultrasound examination aims:

- to locate the lesion precisely, using a sector-based cartography as in the European Thyroid Association guidelines [9] [Russ G 2017] (level of evidence, 2);
- then to describe the shape, contours and contents, and notably any microcalcification, vascularization and elasticity [9] [Russ G 2017] (level of evidence, 2);
- to study the entire thyroid to screen for any suspect carcinoma nodule, to be mapped onto a diagram; and 4) to screen for other neck sectors showing lymphadenopathy.

Ultrasound can orient diagnosis. In head and neck squamous cell carcinoma metastasis, cyst-like areas in fact correspond mainly to tumoral necrosis [10] [Ghafoori M 2015] (level of evidence, 2), or more rarely to cystic serosity suggestive of HPV-related pathology (Fig. 1). Lymphadenopathy in level II and clinical context are the main elements orienting diagnosis. In metastasis from differentiated vesicular-layer thyroid carcinoma, the cystic component is colloid (Fig. 2) [11] [Leboulleux S 2007] (level of evidence, 2). Level III, IV or VI involvement indicates thyroid origin [12] [Eskander A 2013] (level of evidence, 1). Nodal semiology is suggestive when the cystic component is anechogenic and/or associated with microcalcification, tissue component mimicking thyroid tissue and anarchic vascularization [9] [Russ G 2017] (level of evidence, 2). Ultrasound screens for thyroid nodule, usually ipsilateral to the lymph node, especially with EU-TIRADS score 5, with strong signs of cancer. More rarely, the nodule is EU-TIRADS 4 [9] [Russ G 2017] (level of evidence, 1). Lymphoma is often highly hypoechogenic and pseudocystic, and Doppler mode corrects diagnosis by identifying richly vascularized tissue.

Ultrasound also guides fine-needle aspiration.

1. Guideline (Grade B)

In cystic neck lymphadenopathy without clear etiology, it is recommended to:

- perform first-line cervical and thyroid ultrasound scan;
- use a high-frequency probe coupled to B-mode and Doppler;
- perform ultrasound-guided fine-needle aspiration of the lymph node, and of any suspect thyroid nodule.

4. CT and MRI

Imaging exploration should always precede invasive exploration, to reduce the risk of false positive primary identification. Exploration, and biopsy even more, modifies inflammatory tissue, causing interpretation errors. Imaging results may moreover guide invasive exploration toward the most suspect sites.

In reporting the performance of the various imaging types, 2 factors are to be taken into consideration: detection rate (number of lesions found on imaging as a proportion of the number finally found), and false positive rate. In lymphadenopathy of unknown primary, exploration finds a primary in only 50% of cases [13] [Cianchetti M 2009] (level of evidence, 4), inevitably limiting sensitivity and specificity if the optimal standard would be to detect all underlying primaries. Technically, CT should follow the current CIREOL guidelines [14]. Exploration comprises staged slices from skull base to superior thoracic orifice. In the context of cervical neoplasia, lung CT scan should be associated, to explore for possible secondary locations [6] (Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part I: locoregional extension assessment: 2012 SFORL guidelines.). The rate of primary detection on CT in lymphadenopathy of unknown primary ranges between 9.6% and 23% [15] [Muraki AS 1984] (level of evidence, 2), [16,17] [Waltonen JD 2009, Freudenberg LS 2005] (level of evidence, 4). The false positive rate is around 14% [17] [Freudenberg LS 2005] (level of evidence, 4).

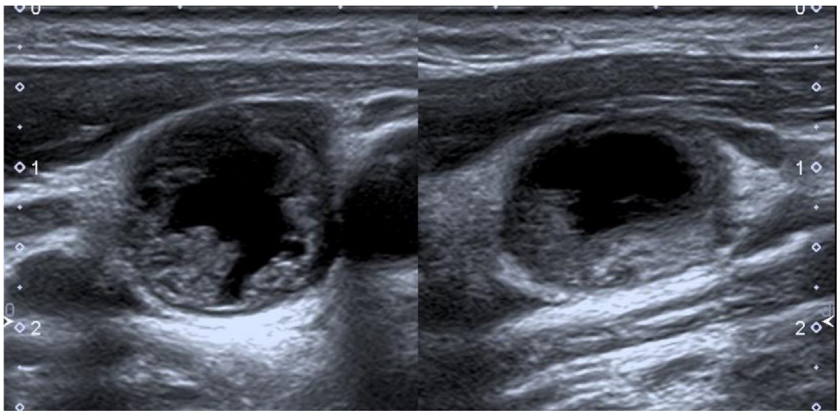

Fig. 1. Ultrasound aspect of cystic cervical metastasis at the sector II/III junction from an HPV+ squamous cell carcinoma: longitudinal (1a) and transverse sections (1b).

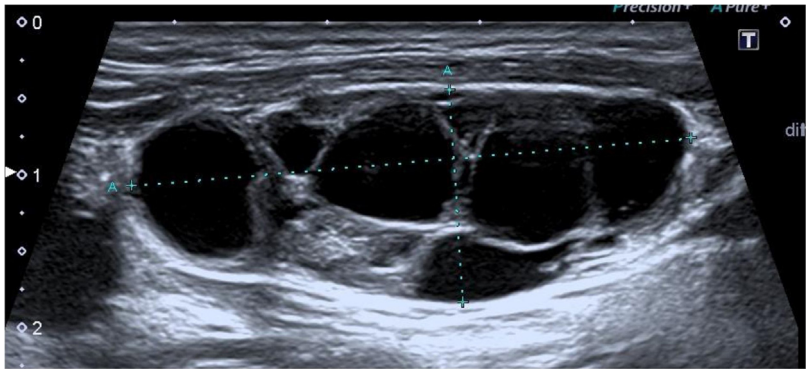

Fig. 2. Ultrasound aspect of cystic cervical metastasis of a right sector-III papillary thyroid carcinoma. The hilum is not visible, and the lymph node is largely occupied by anechogenic cystic pockets.

MRI has been little studied for the identification of head and neck primaries, but some recent reports showed it to be contributive [18,19] [Godeny M 2016, Choi YJ 2016] (level of evidence, 4). In one study, the detection rate was 39.5% when performing all of the following: axial T1 rapid spin echo, axial T2 rapid spin echo, axial diffusion-weighted and three T1-weighted gadolinium-enhanced fat-sat sequences [18] [Godeny M 2016] (level of evidence, 4). Analyzing the apparent diffusion coefficient histogram in the tonsils (which requires post-treatment not routinely used) showed a detection rate of 79% for occult tonsillar tumor in a series with histologically proven neoplasm [19] [Choi YJ 2016] (level of evidence, 4); this was a 52.6% gain in detection over morphologic sequences, and 15.8% over 18F-FDG PET-CT. The false positive rate was 21%.

1. Guidelines

- cross-sectional imaging is recommended before any invasive exploration (percutaneous biopsy or surgery) in cystic neck lymphadenopathy (Expert opinion);
- in cystic cervical neck lymphadenopathy of unknown primary in adults, contrast-enhanced head and neck and chest CT should be performed (Expert opinion);
- data are presently lacking to support first-line MRI in this situation (Expert opinion).

5. 18-Fluorodesoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)

5.1. Head and neck squamous cell carcinoma

5.1.1. Metastatic cystic lymphadenopathy of unknown primary

18F-FDG PET/CT is of proven contribution in detecting primary head and neck tumor in metastatic cystic lymphadenopathy of unknown primary. Detection rates range between 24.5% and 41%, with significantly lower risk of false positives with prior staged biopsy [20–22] (level of evidence, 2). Studies highlighted treatment modification in 12.2–34.7% of cases. In a meta-analysis of 7 studies for 243 patients, Zhu et al. reported 97% sensitivity and 68% specificity [23] (Zhu L 2013) (level of evidence, 1). Two comparative studies versus conventional imaging suggested superiority of 18F-FDG PET/CT in detecting primary tumor, with rates approaching 50%. Roh et al. reported significantly higher sensitivity than with CT: 87.5% versus 43.5% ($P < 0.001$) [24] (Roh JL 2009) (level of evidence, 4). More recently, Lee et al. reported superiority over CT ($P < 0.001$) or CT + MRI ($P = 0.039$) in terms of sensitivity in primary localization [25] (Lee JR 2015) (level of evidence, 3).

Based on this exhaustive literature, 18F-FDG PET/CT is recommended in various French and international guidelines [6,26] (Adelstein D 2017, Vergez S 2013). Although none of the above-cited studies focused on isolated metastatic cystic neck lymphadenopathy, the main primary site detected was the palatine tonsils in most series.

Only the recent retrospective study by Abadie et al. reported 14/20 (70%) primary detection in isolated cystic neck lesions, 7 of the 14 being tonsillar [27] (Abadie P 2017) (level of evidence, 4).

1. Guideline

18F-FDG PET/CT is recommended for primary detection in metastatic cystic lymphadenopathy of unknown primary, notably revealing oropharyngeal carcinoma (Grade B). Examination should preferably precede pharyngeal biopsy (Grade B). Contrast enhancement improves diagnostic performance, with around 50% primary detection (Grade C).

5.1.2. Cervical lymph-node staging

18F-FDG PET/CT is not currently recommended in first line [6,26] for cervical lymph-node staging, despite diagnostic performance equal to or better than conventional CT and/or MRI, according to a meta-analysis by Kyzas et al. with 32 studies for 1326 patients [28] (Kyzas PA 2008) (level of evidence, 1). For cystic lymph-node lesions, on the other hand, PET-CT was not superior to CT in Haerle et al.'s series assessing tonsillar tumor lymph-node staging. Contrast enhancement, however, significantly improved performance in staging pN0 versus pN+ ($P = 0.017$) [29] (Haerle SK 2011) (level of evidence, 4).

Recent progress in imaging with PET/CT opens up applications in head and neck oncology, notably for staging oropharyngeal and oral cavity tumors, combining functional and morphological information and avoiding certain drawbacks of CT in terms of radiation dose and contraindications to contrast agent. In a prospective study by Kuhn et al., with 150 head and neck cancer patients, diagnostic performance did not significantly differ between PET-Ct and 18F-FDG PET/MRI in assessing cervical lymph-node extension. On the other hand, 2 histologically proven metastatic cystic lymph-node lesions (2.4%) were FDG-negative but considered N+ on PET/MRI morphologic criteria [30] (Kuhn FP 2014) (level of evidence, 3).

1. Guideline

18F-FDG PET/CT is effective for metastatic cystic cervical lymph-node staging, but is not recommended in first line. Performance is improved by contrast injection during CT. 18F-FDG PET/MRI is not indicated outside research contexts (Grade C).

5.2. Differentiated thyroid carcinoma

5.2.1. Preoperative work-up

Preoperatively, 18F-FDG PET/CT is much less used than post-dose scintigraphy after radioactive iodine treatment, except in case of aggressive histology [31] (Leboulleux S 2012) (level of evidence, 4).

1. Guideline

18F-FDG PET/CT is not a first-line examination in the initial diagnostic work-up for metastatic cystic lymphadenopathy from well-differentiated thyroid carcinoma. It can be used for suspected distant metastasis in parallel to post-dose scintigraphy after iodine^{131} treatment, especially in case of suspected non-iodine-fixing disease or aggressive histology (Grade C).

6. Conclusion

This part of the guidelines reviewed the literature on diagnostic procedures in suspected cystic cervical lymphadenopathy in adults, and presented the recommended elements of clinical and imaging work-up. Assessment is completed by cytology and/or histology, dealt with in another article. Work-up results should enable treatment to be undertaken in the light of all necessary data.

Disclosure of interest

The authors declare that they have no competing interest.

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