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Cystic masses of the lateral neck – Proposition of an algorithm for increased treatment efficiency^{*}

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ABSTRACT

Preoperative discrimination of solitary cervical branchial cleft cysts from cystic lymph node metastasis often is challenging. Surgical excision of the cystic formation and consecutive histopathological examination of tissue specimens are the only means resulting in the correct diagnosis. However, in case of malignancies surgery on the lateral neck prior to the definitive treatment is considered to negatively influence the patients' outcome. The rate of cystic lymph node metastasis in patients presenting with a lateral branchial cleft cyst, localization of the primary tumour and oncological outcome were investigated. Retrospective chart review of 131 patients presenting clinically with solitary lateral cervical cysts between. A malignant tumour was detected in 12 patients (9.2%). Malignant tumours were significantly more frequent in patients older than 40 years of age (22.0%; $p = 0.0001$). In patients older than 40 years of age with solitary lateral cervical cysts a malignancy should be presumed.

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1. Introduction

Solitary cystic masses of the lateral neck usually develop in young adults, often as an inflammation of the cyst. The incidence of squamous cell carcinoma metastases in cystic cervical masses initially diagnosed as branchial cleft cysts range from 4 to 22% (Sheahan et al., 2002) and increases with patients' age. In patients older than 40 years of age the incidence is reported to range from 11 to 30% (Gourin and Johnson, 2000; Sira and Makura, 2011).

Isolated cervical cystic lymph node metastases, however, might be caused by metastatic squamous cell carcinoma (SCC) arising from lymphoepithelial tissue of the oro- or nasopharynx, specifically when the primary tumour was attributed to an infection with human papillomaviruses (HPV) (Regauer et al., 1999; Goldenberg et al., 2008; Schroeder et al., 2017). Solitary clinically detectable cystic lymph node metastases of SCC arising from the Waldeyer's tonsillar ring are described in 3.3%–7.3% of patients (Flanagan et al., 1994; Regauer et al., 1999).

To distinguish a branchial cleft cyst from a cystic lymph node metastasis just by history-taking and physical examination can be challenging, even despite computed tomography scan (CT), magnet

resonance imaging (MRI), or ultrasound examination of the lateral neck including fine-needle aspiration cytology (FNAC). The differentiation between a brachial cleft cyst and a metastatic squamous cell carcinoma with cystic appearance might even be ambitious for an experienced cytopathologist since rather well-differentiated squamous cells might have been aspirated not indicating the presence of malignancy. Therefore and because FNAC suspicious for the presence of lymph node metastasis must be confirmed by histopathology, especially in adults, the surgical excision of the cyst is recommended by some authors (Stanley, 2002).

Thus, patients with a cystic neck mass are frequently referred to a tertiary referral centre (McHugh, 2009) and the start of the oncologic treatment may be delayed, supposedly resulting in worse patient outcome. The influence of cervical lymph node biopsies prior to definitive treatment has been discussed controversially over the last decades: An increased rate of local recurrence, worse healing, and decreased survival as a consequence of neck violation prior to definitive treatment has been reported (McGuirt and McCabe, 1978). This notion was supported by Jones and co-workers fifteen years later (Jones et al., 1993). However, several other authors describe neither increase of complications (Parsons et al., 1985) nor poorer prognosis of patients (Robbins et al., 1986; Ellis et al., 1991; Mack et al., 1993) after cervical lymph node biopsies followed by definite neck treatment. In the lack of any clinical studies further addressing this issue, prospectively, due to

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ethical reasons a negative influence of neck violations prior to definite surgical treatment should be assumed.

Today, ultrasound examination of the neck and FNAC is a standard procedure in the diagnosis of neck masses (Stanley, 2002; Ahn et al., 2016). For FNAC, high accuracy of results with high sensitivity and specificity with low complication rates are established in literature (Shah and Ethunandan, 2016). Lately, core-needle biopsy (CNB) has been recommended by several authors for diagnosis resulting in tissue samples suitable for histopathological examination. In comparison to FNAC, the latter technique hardly is more invasive but is associated with a small risk of seeding (Shah and Ethunandan, 2016). CNB is recommended for the diagnosis of lymphomas. Applying modern immunohistochemical and molecular techniques when analysing such rather small tissue specimens, hematopathologists regularly achieve the correct diagnosis (Allin et al., 2017). Concerning squamous cell carcinomas, however, the question remains whether or not an open surgery approach resecting a whole lymph node is superior to CNB in terms of sensitivity and specificity of histopathology and oncological safety (Ahn et al., 2016).

Here, in a retrospective chart review, i) the rate of cystic lymph node metastasis in patients initially presenting with a lateral branchial cleft cyst and ii) the value of fine-needle-aspiration cytology for preoperative diagnostic were investigated. Additionally, iii) in 65 cases the cyst tissue were analysed for the presence of HPV16-DNA- and/or p16^{INK4A}-overexpression, and results were correlated to the presence of primary SCC of the oropharynx or lymph node metastasis detected later in the course of disease.

2. Material and Methods

A retrospective chart review was performed to identify all patients with solitary lateral cervical cysts presenting to the Department of Otorhinolaryngology, Head and Neck Surgery, Christian-Albrechts-University Kiel, Germany from November 2003 to September 2011. Patients with a clinically apparent malignant primary tumour or a history of head and neck cancer were excluded. One hundred thirty-one patients were available for analysis. HPV-analysis was performed applying PCR-based methods and p16^{INK4A} expression was determined by immunohistochemistry as described previously (Hoffmann et al., 2010). The p16^{INK4A} antibody reactivity was scored on a semi quantitative scale, according to Klaes and colleagues as follows: 300 cells in at least five areas were analysed (200 × magnification) and cases were assigned to one of the following categories: negative <5%, weak 5–30%, moderate 31–75% and strong >75% (Klaes et al., 2001).

Statistical analysis was performed using Fisher's exact test.

3. Results

One hundred thirty-one patients (male, n = 69; female, n = 62) were identified. All patients presented with a solitary cervical cystic mass suspected to be a branchial cleft cyst. The mean age of patients was 38.8 years (range, 3–69 y).

Preoperative examination included anamnesis, complete head and neck examination and ultrasound examination of the neck. In 58 patients (44.3%) ultrasound-controlled fine-needle aspiration cytology (FNAC) was performed. In all 58 cases FNAC results were negative for malignancy and rather supported the notion of the presence of a cystic lesion.

Prior to the first visit at our department 11 patients (8.4%) had received computed tomography scan and 14 patients (10.7%) magnetic resonance imaging. None showed signs of malignancy. In addition, FNAC performed prior to surgery in 8 of those 12 patients with cystic metastasis did not detect any malignant cells.

All 131 patients underwent surgical excision of the cystic cervical mass assuming the presence of a branchial cleft cyst which was confirmed by histopathological work-up in 119/131 (90.8%) patients. In 12/131 (9.2%), however, a malignant tumour was detected. The exact histopathological findings of these 12 cases and further patient characteristics are given in Table 1.

In tissue specimens derived from 65 cysts, three cystic lymph node metastases and two carcinomas of the tonsil representing the corresponding primary tumour which was detected in the course of disease the HPV16-DNA- and p16^{INK4A}-status was analysed, additionally. HPV-DNA was detected in all examined cystic lymph node metastases (100%), the two carcinomas of the tonsils (100%) and in 9.2% (n = 6) of benign lateral cervical cysts. p16^{INK4A} was detected in all cystic lymph node metastases (n = 3), one tonsillar carcinoma (50%) and one cervical cyst (1.5%). HPV-DNA and p16^{INK4A} overexpression was detected in all cystic lymph node metastases (100%), in one tonsillar carcinoma (50%) but not in the lateral cervical cysts. Hence, all HPV-DNA positive cysts were p16^{INK4A} negative and the one p16^{INK4A} positive cyst was HPV-DNA negative.

Further statistical analysis was performed with respect to patients' age. Based on the findings by Gourin and Johnson (2000) and those by Sira and Makura (2011), the cohort was divided into two groups: patients < 40 years (n = 81); patients ≥ 40 years (n = 50). At time of diagnosis 11 (91.7%) patients with a malignant tumour were older than 40 years. Only one (8.3%) patient was younger than 40 years (Table 1, patient #11), namely 39 years of age. Thus, the incidence of a malignant tumour was 1.2% in patients younger than 40 years and 22.0% in patients aged 40 years and older (p = 0.0001).

In all patients with a malignant disease the diagnostic regimen was within short time extended to panendoscopy, bilateral tonsillectomy, biopsies of the nasopharynx, and CO₂-laser biopsies of the base of tongue as recommended in Germany for all cases of cervical metastases and clinically undetectable primary tumour, i.e. CUP-syndrome. Intriguingly, in 10 patients (83.3%) the primary tumour was detected, all being squamous cell carcinomas: six and two tumours were located in the ipsilateral palatine and lingual tonsil, respectively. In these cases, transoral CO₂-laser resection of the primary tumour was performed. In one patient suffering from a papillary thyroid carcinoma a total thyroidectomy was performed with adjuvant radioiodine therapy. The patient with a carcinoma in situ within a branchial cleft cyst received no further surgical treatment and was assigned for surveillance. In all 10 cases with cervical SCC metastasis a neck dissection was additionally performed. Nine patients with SCC received risk adapted postoperative radio (chemo)therapy. One further patient did not receive any further treatment and was assigned to surveillance with thorough clinical and ultrasound examination (Table 1).

The mean follow-up period of the cancer patients was 85.3 months (range 7–129 months). One patient (patient #6) showed early regional recurrence and finally was lost to follow-up after seven months; one patient (patient #10) presented after 5.5 years with a second malignant tumour of the epiglottis that could be successfully treated by transoral CO₂-laser surgery. One patient (patient #12) was lost to follow-up directly after treatment. All other patients did not suffer from recurrent disease (for details see Table 1).

4. Discussion

The results of this unique study clearly support the notion that in patients presenting with a cystic mass of the lateral neck and being older than 40 years of age a malignant disease has to be expected. Although in the present study the investigated cysts were predominantly (90.8%) benign, in patients 40 years of age and older

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