Original article

The role of tonsillectomy in the initial diagnostic work-up of head and neck squamous cell carcinoma of unknown primary

E. Berta a,*, I. Atallah a, b, c, E. Rey a, b, E. Boyer a, A. Karkas a, b, C.-A. Righini a, b, c

a Pôle TCCR, clinique universitaire d’O.RL, CHU de Grenoble, 1, avenue des Maquis-du-Grésivaudan, 38330 Grenoble cedex 09, France
b Faculté de médecine, université Joseph-Fourier – Grenoble-I, domaine de la Merci, place du Commandant-Nal, 38706 La Tronche, France
c Centre de recherche Inserm-UJF U823, institut Albert-Bonniot, UJF site santé, BP 170, 38042 Grenoble-La Tronche cedex 9, France

Keywords:
Head and neck squamous cell carcinoma of unknown primary
Cystic adenopathy
18-FDG PET scan
Palatine tonsil
Squamous cell carcinoma

Abstract

Objective: The aim of the present study was to determine the value of tonsillectomy in the initial diagnostic work-up of head and neck squamous cell carcinoma of unknown primary (HNSCCUP).

Material and methods: A single-center retrospective study (1999–2012) included 45 patients. All cases underwent physical examination, panendoscopy and contrast-enhanced neck and chest CT scan; 27 (60%) also underwent 18-FDG PET scan. Imaging was systematically performed before panendoscopy. In 34 cases (75%), histologic tonsil samples ipsilateral to the HNSCCUP were collected (28 tonsillectomies and 6 biopsies) during panendoscopy. Categoric variables were compared on Chi-square test.

Results: Clinical examination and CT did not identify any primary tumor. In 13 cases (38%), invasive squamous cell carcinoma (SCC) was diagnosed on histological samples (12 tonsillectomies, 1 biopsy). For these 13 cases, lymph nodes were located in the upper or middle jugular group, and in 3 of these lymph nodes were cystic on CT scan. In 7 cases (26%), there was an abnormal tonsillar 18-FDG uptake ipsilateral to the cervical lymphadenopathy; tonsillectomy was performed, and SCC was found in 5 of these cases: i.e., 18-FDG PET showed sensitivity and specificity of respectively 55.5 and 88.8%.

Conclusion: Tonsillectomy has a role in the initial diagnostic work-up of HNSCCUP. It is especially useful when lymph nodes are located in the upper and/or middle jugular group with a cystic aspect on CT.

© 2014 Elsevier Masson SAS. All rights reserved.

1. Introduction

Exploration for the primary tumor is fundamental to the management of head and neck squamous cell carcinoma of unknown primary (HNSCCUP), enabling targeted therapy, thus reducing the morbidity incurred by systemic irradiation of 2 or even 3 levels of the pharynx, while also minimizing the risk of subsequent manifestation of the primary, which is a factor of poor prognosis [1–3]. Initial diagnostic work-up, however, is a matter of debate, especially as regards the contribution of associating systematic palatine tonsil biopsy and/or tonsillectomy ipsilateral to the HNSCCUP to panendoscopy to explore the primary tumor. Most reports find primary tonsillar tumor in 18 to 39% of histologic specimens collected ipsilaterally to the HNSCCUP as part of the diagnostic work-up [4–6]. Two types of sampling are involved: tonsillectomy or multiple non-targeted tonsil biopsy. 18-FDG PET scan allows sampling to be targeted, revealing primary cancer in 25% of HNSCCUP work-ups, with sensitivity and specificity of respectively 88 and 75% [7]. The present study sought to determine the percentage of palatine tonsil squamous cell carcinoma (SCC) found in tonsil samples from initial HNSCCUP work-up, and to compare the relative contributiveness of tonsillectomy versus 18-FDG PET.

2. Material and method

A single-center retrospective study included 45 HNSCCUP patients between January 1999 and December 2012. All underwent complete head and neck examination including fiberoptic nasopharyngoscopy, which was systematically normal. Palpation of the palatine tonsils and the tongue base was systematically normal. All underwent contrast-enhanced morphologic neck and chest CT scan. Twenty-seven (60%) underwent 18-FDG PET scan, performed prior to panendoscopy. In 34 cases (75%), a tonsillar biopsy was performed ipsilaterally to the HNSCCUP during panendoscopy (28 tonsillectomies, 6 multiple palatine tonsil biopsies), since endoscopic exploration failed to find any suspicious mucosal lesion. One patient underwent multiple biopsies during initial endoscopy followed by a tonsillectomy during cervicotomy, which was performed for the treatment of the HNSCCUP. Two patients showed
bilateral cervical lymphadenopathies; multiple bilateral tonsillar biopsies were performed in 1, with no tonsillar sampling in the other. Categoric variables were compared on Chi-square test.

3. Results

Tables 1 and 2 present patient data, work-up, and cTNM (UICC 2002) staging following clinical and imaging work-up and before 18-FDG PET. There were no complications related to sampling. In 13 cases (38%), invasive SCC was detected in the tonsillar sample (12 tonsillectomy specimens and 1 from multiple biopsies). In the patient in whom biopsy was followed by tonsillectomy, biopsy samples were normal whereas SCC was found in the tonsilllectomy specimen. There was no significant difference between the rates of palatine tonsil cancer detected on biopsy versus tonsillectomy (P=0.23). Tonsil tumor size was systematically ≤8 mm. Seven of the 27 patients with 18-FDG PET scan showed palatine tonsil uptake despite normal CT scan. All underwent tonsillectomy; pathological examination found SCC in 5 cases and healthy palatine tonsil in 2 cases: i.e., 18-FDG PET sensitivity and specificity of respectively 55.5 and 88.8%. Two patients showed pulmonary uptake, corresponding to small non-specific nodules, on contrast-enhanced neck and chest CT scan; pulmonary metastasis was confirmed by transparietal fine-needle aspiration of a nodule in 1 case and by pulmonary segmentectomy with mini-thoracotomy in the other case. Two patients showed suspicious mediastinal lymph node with no pulmonary parenchymatous lesion on the chest CT scan. A multidisciplinary team meeting decided against further investigation, so as not to delay initiation of treatment; 1 of the patients died from metastasis with mediastinal lymph node progression associated with bilateral pulmonary cannon ball metastasis during the first year of follow-up. Finally, 1 patient showed bone and adrenal gland involvement. In the 2 patients with isolated mediastinal lymph node involvement, work-up was incomplete; otherwise, diagnostic 18-FDG PET showed metastasis in 3 cases, whereas neck and chest CT scan alone failed to detect any lesion or was inconclusive. Table 2 shows cTNM (UICC 2002) staging following clinical and radiological work-up including 18-FDG PET and following panendoscopy with tonsillar sampling.

In the 13 cases of tonsillar SCC, cervical lymphadenopathy was located in the upper (n = 9) or middle (n = 4) jugular groups patients. In 3 cases, CT morphology suggested second branchial arch cyst, with a lesion of liquid-like density surrounded by a thin regular wall without peripheral contrast uptake, 2 in the upper and 1 in the middle jugular group. These patients underwent ipsilateral tonsillectomy, and all 3 specimens revealed intraclinal tonsillar SCC. No cystic adenopathies were found in the sub-population with HNSCCUP without a tonsillar primary. There was a significant correlation (P = 0.005) between malignant cystic adenopathy and ipsilateral tonsillar primary. Partially necrotic adenopathies were not counted as cystic.

4. Discussion

In the present series, 7 patients (26%) showed tonsillar uptake on 18-FDG PET. All underwent tonsillectomy, revealing invasive SCC in 5 cases. Four patients (44% of those with tonsillar SCC who underwent 18-FDG PET) had tonsillar SCC without palatine tonsil uptake (Table 2). The sensitivity and specificity of 18-FDG PET were thus respectively 55 and 88%. In a meta-analysis of 16 studies, Rusthoven et al. [7] found that 18-FDG PET detected primary pharyngeal locations in 25% of HNSCCUP, with sensitivity and specificity of respectively 88 and 75%. The sensitivity and specificity of 18-FDG PET thus seem insufficient for an isolated means of detecting infraclinal tumors in initial HNSCCUP work-up [1,7]. Sensitivity in the present series was poorer than in Rusthoven et al.’s, probably due to the small size of the present cohort. Even so, 18-FDG PET seems to be essential in initial HNSCCUP work-up: leaving aside 2 cases of isolated mediastinal lymph node involvement in which work-up was incomplete, it was able to confirm 2 cases of pulmonary metastasis and 1 of diffuse metastatic extension which neck and chest CT alone failed to diagnose. It also enables targeted sampling, especially when contrast uptake is extra-pharyngeal. 18-FDG PET should precede panendoscopy, to target lesions for endoscopic biopsy and avoid artificial uptake caused by mucosal trauma, especially at the biopsy site.
Lymph node metastasis in the form of cystic adenopathy has been widely reported since the 1970s [2,8–10]. Gourin and Johnson [11], in a series of 121 patients with cervical cystic adenopathy, found a 23.5% rate of metastatic adenopathy in over 40-year-olds. Cystic adenopathy without known primary used wrongly to be considered to be of branchial origin [12–14]. Thompson and Heffner [12], in a retrospective study performed between 1971 and 1991, found 136 HNSCCUP patients with cervical cystic metastasis; initial work-up or clinical follow-up found 87 lingual or palatine tonsillar primaries (64%) and 11 nasopharyngeal primaries (8%), suggesting that most primary tumors in HNSCCUP are oropharyngeal and, more particularly, located in the palatine tonsils; the authors strongly recommended panendoscopy with biopsy of any suspect pharyngeal mucosal region, with ipsilateral tonsillectomy if no mucosal lesions are found, regardless of smoking or alcohol status, as part of initial work-up for any cervical cystic mass found in over 40-year-olds [11,14]. In this particular context, any metastatic adenopathy with primary located in the palatine tonsils should be considered suspect by default.

In our own experience, the rate of tonsillar SCC diagnosed during initial HNSCCUP work-up is independent of the type of sampling (tonsillectomy or multiple biopsies), although this finding is to be taken with caution due to the small size of the present series. According to the literature, tonsillectomy is more effective than untargeted biopsy in diagnosing infraclinical cancer: e.g., Randall et al. [15] and McQuone et al. [16]. In the present study, 39% of tonsillar SCCs were diagnosed on tonsillectomy, compared to 13% on multiple biopsies. Untargeted tonsillar biopsy may miss and overlook an invasive SCC site. Tonsillectomy is therefore to be preferred in HNSCCUP work-up.

Some teams [4,17–19] recommend systematic bilateral tonsillectomy in HNSCCUP work-up. In a series of 22 patients, Kothari et al. [18] reported 5 cases (23%) of bilateral tonsillar SCC, although cTNM stage was not reported and, in particular, the rate of bilateral cervical lymphadenopathy (cN2c) was not specified. Most cases in the literature are either isolated [19] or from very small retrospective series [17,18]. The contribution of systematic bilateral tonsillectomy in HNSCCUP work-up thus remains to be demonstrated, as the level of evidence of the published studies allows no definitive conclusion to be drawn. The attitude seems worthwhile to us only in work-up for apparently primary malignant adenopathy with bilateral lymph node involvement (cN2c). Only a prospective study with systematic bilateral tonsillectomy as part of HNSCCUP work-up, regardless of cN staging, could determine its diagnostic contribution.

An interesting new means of exploring for primary tumor in initial HNSCCUP work-up has emerged since the turn of the century with the demonstration that HPV-16 is often associated with SCC of the oropharynx, and in particular of the palatine tonsils and, less frequently, of the base of the tongue. Epidemiology differs from that of head and neck cancer in general: patients are often young, with only slight if any implication of smoking or alcohol abuse [20]. HPV-16 is rarely (<10%) found in fragments of macroscopically healthy mucosa sampled outside tumors overexpressing p16 protein [21,22]. It is confirmed by PCR detection of viral DNA or indirectly by immunohistochemical findings of overexpression of p16 protein. p16 overexpression in healthy tissue, however, should not, taken in isolation, be interpreted as indicating presence of HPV, as other poorly understood factors may also induce overexpression; it is, however, a reliable marker of HPV within head and neck SCC [22]. Weiss et al. [23], in a retrospective study of 131 patients, reported significant correlation between HPV-16+ viral DNA findings (P < 0.0001) and/or p16 overexpression (P = 0.001), on the one hand, and histologic findings of malignant cervical lymphadenopathy in neck dissection fragments and of oropharyngeal (tongue base or palatine tonsil) SCC, on the other hand. They therefore recommend systematic exploration for HPV-16 in lymph node fragments as part of etiological analysis in HNSCCUP, with multiple oropharyngeal biopsy or tonsillectomy ipsilateral to the lymph node involvement in case of HPV-16+ adenopathy. This attitude, however, entails a second general anesthesia, for oropharyngeal sampling in case of one or more HPV-16+ adenopathies. In current practice, in case of HNSCCUP, fine-needle aspiration is frequently included in the initial work-up to determine the malignancy of lymphadenopathies. There are reports of screening for HPV-16 by in situ hybridization and for p16 by immunohistochemistry on
fine-needle aspiration lymph node samples [24,25]; the techniques are experimental and not recommended for routine clinical practice, but early results have been encouraging and fine-needle aspiration may yet be included in initial work-up in HNSCCUP to select patients for multiple oropharyngeal (tongue base or palate tonsil) histology sampling during panendoscopy.

In the light of our own experience and an analysis of the literature, Fig. 1 presents a diagnostic algorithm for initial HNSCCUP work-up.

5. Conclusion

In the present state of knowledge, we suggest that initial work-up in HNSCCUP should, after classical contrast-enhanced neck and chest CT scan imaging, include systematic 18-FDG PET scan ahead of panendoscopy, to explore for the primary tumor and remote metastases. Taken alone, however, diagnostic imaging cannot rule out pharyngeal, and notably tonsillar primaries, due to the lack of sensitivity and specificity. We therefore recommend, given the low associated morbidity, systematic tonsillar sampling, preferably by tonsillectomy ipsilateral to the suspicious lymphadenopathy. This exploration is particularly effective when the adenopathy lies in the upper or middle jugular groups or when it shows a cystic aspect.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References