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Case Report

Benign epithelial inclusion consisting of squamous metaplasia and small glandular elements in regional lymph node of a patient with tongue cancer: a case report and literature review

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Abstract: There are occasional reports of unexpected pathological findings during neck dissection, including benign inclusions (BIs) in cervical lymph nodes, comprising squamous epithelial, glandular, thyroid, neval and mesothelial cells. BIs can mimic regional lymph node metastases, therefore, pathological diagnosis is important. However, criteria for immunohistochemical diagnosis of BIs are not established. We report a 73-year-old woman with tongue cancer with squamous metaplasia and a glandular BI in a regional lymph node. Clinical and radiographic assessment of the lesion led to diagnosis of tongue squamous cell carcinoma (T3N2bM0, Stage IVa). The patient underwent right-side total neck dissection with wide local excision of the tongue tumor. All the lymph nodes in the dissection specimen were pathologically negative. In contrast, one BI in a level III lymph node was found incidentally. We could not diagnose this lesion clearly by routine pathological examination because of the lack of criteria for immunohistochemical diagnosis of BIs. To the best of our knowledge, BIs comprising squamous metaplasia and small glandular elements in the regional lymph nodes of patients with head and neck cancer have not been reported. We histologically predicted the lesion as BI, which was confirmed by additional immunohistochemical staining for cytokeratin 13 and 17. Clinicians should avoid misdiagnosis of metastases, which could lead to incorrect tumor staging and inadequate adjuvant therapy for patients with lymph node BIs. To distinguish BIs from metastases clearly, we recommend additional immunohistochemical staining for cytokeratin 13 and 17 in routinely stained sections of regional lymph nodes in patients with squamous cell carcinoma.

Keywords: Tongue cancer, benign inclusions, lymph node, metastasis, cytokeratin 13, cytokeratin 17

Introduction

Benign inclusions (BIs) of lymph nodes were first described in 1897 by Ries [1] in a case of gynecological malignancy. Since then, BIs have been reported in lymph nodes in various regions of the body [2-6] (**Table 1**). The presence of five cell types has been demonstrated in cervical lymph nodes, that is, benign squamous cell, salivary gland tissue, thyroid tissue, neval cell, and mesothelial cell inclusions (**Table 1**). In cervical lymph nodes, salivary gland tissue and thyroid follicles have been widely reported [2, 7-15]. In contrast, there are few case reports of squamous-cell type BIs in cervical lymph nodes. BIs can mimic regional lymph node metastases [6, 16, 17], therefore, pathological diagnosis is important to avoid misdiagnosis of metastases, which could lead to incorrect tumor staging and inadequate adjuvant therapy.

Here, we report the case of a 73-year-old woman with tongue cancer with BI consisting of squamous metaplasia and small glandular element in a regional lymph node. It was not pos-

Table 1. Benign inclusions in lymph nodes

Type	Common site of nodes
Squamous epithelium	Cervical [26], Axillary [28] and peripancreatic [24]
Salivary gland tissue	Cervical [13] and Mediastinal [5]
Thyroid follicles	Cervical [7]
Nevus cell	Cervical [3], Axillary [2] and inguinal [41]
Mesothelial cells	Cervical [4], Mediastinal [13], Pelvic [6] and retroperitoneal [26]
Breast tissue	Axillary [36]
Renal tubular epithelium	Perinephric hilar [42]
Decidual tissue	Pelvic [43]
Müllerian-type epithelium	Pelvic [44] and paraaortic [44]
Gland tissue	Pelvic [45]
Colonic glands	Mesenteric [13]

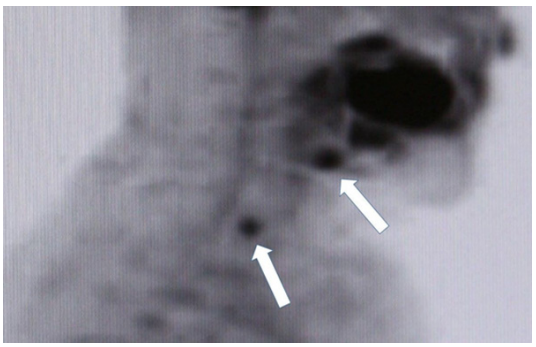

Figure 1. Fluorine-18 2-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET)/computed tomography revealed positive lymph nodes at levels I and IV (arrows). In contrast, the level III lymph node was negative on FDG-PET.

Table 2. Panel of antibodies with benign inclusion and SCC

Antigen	BI	SCC
CK17	(-)	(+)
CK10	(-)	(-)
CK10/13	(+)	(-)
Ki-67	2%-3%	20%-30%
CAM 5.2	(+)	(-)
p63	(+)	(+)

sible to evaluate and diagnose this lesion clearly by routine pathological examination, because criteria for immunohistochemical diagnosis of BI have not yet been established.

Case report

Written informed consent was obtained from the patient for publication of this case report.

A 73-year-old woman was referred to our hospital for further evaluation of a tongue mass. She had a 1-month history of pain involving the right lateral edge of the tongue. Physical examination revealed an elastic, hard, 46 × 22-mm mass of the right tongue. There was some palpable lymphadenopathy at levels I, III and IV of the head and neck area. Her past medical history was unremarkable.

She had no history of smoking and alcohol consumption. Physical examination, ultrasonography (US), and contrast-enhanced computed tomography (CT) showed three enlarged, mobile and non-tender right cervical lymph nodes at levels I, III and IV, with a 42 × 28-mm enhancing mass in the right edge of the tongue. Whole-body fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was positive for metastatic lesions at levels I and IV in the right cervical lymph nodes. In contrast, the level III lymph node was negative on FDG-PET (**Figure 1**). Biopsy of the lateral edge of the tongue showed squamous cell carcinoma (SCC). According to radiographic and clinical assessment, we diagnosed tongue SCC (T3N-2aM0, Stage IVa) (UICC TNM classification 7th edition, 2009).

The patient underwent right-side total neck dissection with wide local excision of the tongue tumor, and reconstruction with a rectus abdominis musculocutaneous flap. All 54 excised lymph nodes were numbered at each level on the anatomical map of the neck to coincide with the original position on contrast-enhanced CT, US, and FDG-PET/CT according to the method of Matsubara et al. [18]. All of the lymph

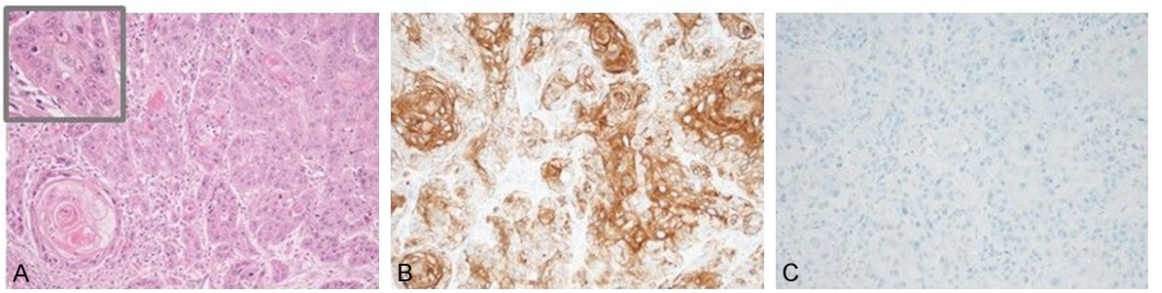

Figure 2. Histopathological examination of the tongue SCC. (A) H&E staining (original magnification, × 200, inset × 400); (B) CK17 staining (original magnification, × 200); (C) CK10/13 staining (original magnification, × 200). Inserted large magnification in (A) indicates the tumor cells have large nuclei with prominent nucleoli. The specimen of tongue SCC was stained strongly positive for CK17, and negative for CK10/13 and CK10.

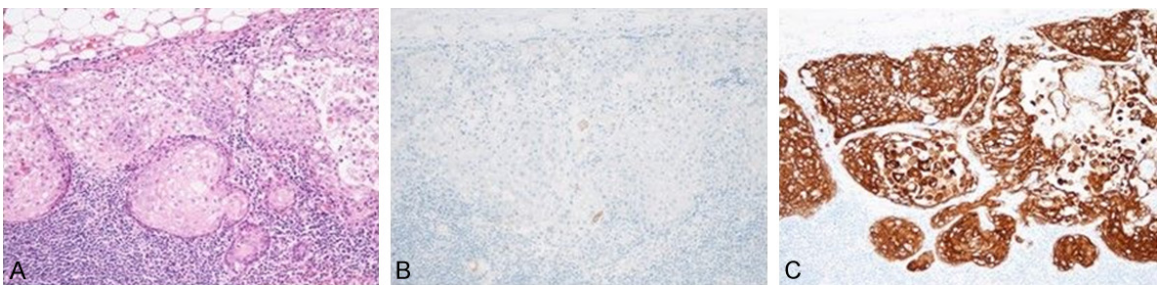

Figure 3. Histopathological examination of the level III lymph node showed a small epithelial lesion on the surface of the node. A. Hematoxylin and eosin staining (original magnification, × 200); B. CK17 staining (original magnification, × 200); C. CK10/13 staining (original magnification, × 200). The specimen of BI in the lymph node was stained positively for CK10/13, and negative for CK17. As a result of negative staining for CK10, positive CK10/13 staining suggested the expression of CK13.

nodes obtained from the dissection specimen were pathologically negative for metastasis, although one benign epithelial lesion was detected in a level III lymph node.

Macroscopically, a central part of the dissected tongue sample had a tumor component that showed invasive characteristics. Microscopically, the tongue lesion was composed of atypical squamous epithelium that showed nuclear enlargement and irregular nuclear morphology, as well as invasive characteristics. Therefore, the tumor was diagnosed as primary SCC of the tongue (Intermediate grade: refer to National Cancer Institute, "Tumor Grade", accessed 18 November, 2015). No invasion to adjacent structures was identified. The epithelial lesion in the level III lymph node was histologically different from the primary lesion because it showed neither strong nuclear atypia nor nuclear enlargement. Therefore, the lesion was suspected of being a BI. Immunohistochemical examination of the primary tumor tissue and the level III lymph node lesion is summarized in **Table 2**, and representative histological and immunohistological findings are shown in **Figures 2** and **3**. There was no significant difference in Ki67 index between the primary tumor and level III lymph node lesion (**Table 2**). The staining patterns of cytokeratin (CK) 10/13, which meant the antibody could react with both CK10 and CK13, and CK17 were inverted between the primary tumor and lymph node lesion (**Figures 2** and **3**), while the staining patterns of CK10 and p63 were the same. As a result of negative staining of CK10-specific antibody in the primary tumor and lymph node lesion, we concluded that the molecule stained by CK10/13 antibody would be CK13. Therefore, we finally diagnosed the lymph node lesion as a BI. As a result of partial staining of low molecular weight cytokeratin antibody CAM 5.2 and partial glandular pattern in the BI, as well as p63-positive squamous epithelium, we suggest that the BI was a glandular epithelial inclusion with squamous metaplasia.

Discussion

This case illustrates two important clinical issues. First, BIs are rare. We searched PubMed and Google Scholar and found no reports between 1897 and 2015 of BIs comprising squamous metaplasia and small glandular elements in the regional lymph nodes of patients with head and neck cancer. Five types of BIs have been reported in the cervical region. Salivary and thyroid tissue inclusions have been widely reported [7, 19]. In contrast, there are few reports of squamous-type lesions in the cervical region. Among those, there are three reports of squamous metaplasia of glandular BIs [8, 20, 21]; however, the inclusions reported were not associated with head and neck cancer. Why are there so few case reports of squamous-type BIs? We believe that most of them were reported as lymphoepithelial cysts (LECs). Some authors have hypothesized that LECs may arise from BIs [22-27]. Furthermore, cases of pathological cystic lesions in BIs have been reported [16, 19, 20, 28-30]. The sites of LECs were similar to those of cervical lymph nodes [31]. Therefore, we speculate that, to date, LECs have been reported instead of squamous-type BIs. The origin of BIs is not well understood, although Ioachim and Ratech [32] have reported several proposed theories, including transportation to detached epithelial cells as a type of benign metastasis, developmental heterotopia, and metaplasia of local multipotential cells. We believe that the origin of BIs is associated with cancer metastasis, in accordance with the following three theories. (1) BIs tend to be concomitant with metastasis of the same lymph node area [16, 33-36], and two lesions, that is, BI and cancer can be found in one lymph node [16, 36]. (2) BIs may be more commonly encountered in sentinel lymph nodes than in the remaining nonsentinel nodes [36]. (3) No BIs were found in an autopsy study of 3,904 lymph nodes obtained from dissection of 160 axillary lymph nodes in 80 patients without breast cancer [37]. The aim of that study was to determine the incidence of BIs in axillary lymph nodes, because false-positive diagnosis of metastases leads to incorrect tumor staging and inadequate adjuvant therapy.

Second, we diagnosed the BI clearly by additional immunohistochemical staining for CK13 and CK17. The occurrence rate of BIs in the head and neck region varies in the different reports between 0.3% and 10% [11, 13, 15]. BIs are incidentally found during neck dissection, sentinel lymph node biopsy, or lymphoidectomy. Most cases of BIs were found in routine hematoxylin and eosin (H&E)-stained sections. Fellegara et al. suggest that the BI features revealed by H&E staining remain the most useful criteria by which to make this diagnosis [28], however it is important to distinguish BIs from macro- or micrometastasis [16, 17]. Immunohistochemical studies may be helpful in distinguishing metastases from BIs; however criteria for immunohistochemical diagnosis of BIs have not been established. Kitamura et al. [38] have reported that combined CK13/CK17 staining is a suitable marker of malignant transformation of oral disease. They reported that the percentage of CK17-positive cases increased gradually in accordance with dysplastic leukoplakia and oral SCC, while the percentage of CK13-positive cases declined gradually [38]. In our case, the BI in the lymph node was stained with a CK13-positive/CK17-negative pattern. In contrast, the tongue SCC was stained with a CK13-negative/CK17-positive pattern.

The clinical and radiological features of BIs are controversial. In our case, the BI showed lymphadenopathy suspicious of metastasis without hypermetabolic lesions on FDG-PET. BIs with lymphadenopathy have been described previously [9, 16, 20, 33, 39]; however, there are few reports of the radiological findings of BIs [4, 5]. BIs are often a potential pitfall for clinicians and pathologists. Misdiagnosis can result in inaccurate staging of a known tumor or excess searching for an occult primary tumor [14]. Polymerase chain reaction likely generates a positive signal and leads to a false-positive diagnosis of metastatic disease [37, 40].

In conclusion, when clinicians encounter suggestive BIs in regional lymph nodes in patients with SCC, the staining pattern of CK13 and CK17 is an effective tool to distinguish BIs from metastases. BIs can arise in the regional lymph nodes of patients with cancer, and in head and neck cancer they may be misdiagnosed as metastases. Further studies should establish a new protocol for histopathological staining for CK13 and CK17 in lymph nodes dissected from patients with cancer to detect hidden BIs,

which may be more frequent than previously thought.

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Disclosure of conflict of interest

None.

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