Papillary Thyroid Carcinoma Cervical Lymph Node Metastasis with Cystic Change Differentiated from Congenital Cystic Lesions with the Assistance of Immunohistochemistry: A Case Study

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Abstract Diagnosis of cystic papillary thyroid carcinoma (PTC) lymph node metastasis at head neck region can be a challenge in the absence of known PTC history. The congenital cystic lesions of head neck, especially thyroglossal duct cyst (TGDC) and branchial cleft cyst (BCC), are major differential diagnoses in this clinicopathological scenario. The location of cyst and morphology of lining epithelium are critical clues for reaching correct diagnosis. However it is not uncommon that the flattened bland epithelial lining can be seen in both cystic metastases and congenital cystic lesions. Given that Pax8 and TTF-1 are common markers in thyroid follicular epithelium; we applied immunohistochemical stains of those two markers on aforementioned cystic lesions. Here we reported a case of cystic PTC metastasis to lymph node without prior malignancy history and cases of TGDC and BCC. Both Pax8 and TTF-1 stainings highlighted the cyst lining in PTC metastatic lymph node, while they were negative in the lining of TGDC and BCC. Collectively, Pax8 and TTF-1 immunohistochemical studies are very helpful tools for making correct diagnosis of head neck cystic lesions in the challenging clinical cases.

Keywords Papillary thyroid carcinoma · Lymph node metastasis · Congenital cystic lesions · Pax8 · TTF-1

Introduction

Thyroid cancer is among the 10 most common malignancies in the population and 80 % of thyroid cancers are papillary thyroid carcinoma (PTC) [1]. Although the most common clinical presentation of thyroid cancer is a thyroid mass or nodule in the central neck region, it has been reported that 11 % of patients harboring occult PTC can be only presented as lateral neck cysts [2]. Based on the 2015 American Thyroid Association guidelines, regional lymph node metastases are present at the time of diagnosis in the majority of patients with PTC [3]. Primary PTC was often found to metastasize to central, ipsilateral, and even contralateral lymph nodes [4, 5]. Landry et al. [6] found that among ultrasound detected head neck cystic lymph node lesions, the 93 % of them are due to cystic lymph node metastases. Since American Thyroid Association guidelines recommended a near-total or total thyroidectomy surgical procedure for apparent metastatic PTC to lymph nodes (clinical N1) [3]; the diagnosis of occult PTC lymph node metastasis is crucial for patient management.

Diagnosis of cystic PTC cervical lymph node metastases can be a challenge in the absence of known PTC history; because they can mimic congenital cystic lesions of head neck region, especially thyroglossal duct cyst (TGDC) and branchial cleft cyst (BCC) [7]. It is not uncommon that the lymph node metastases might not be apparent on preoperative radiologic evaluation [8]. Pathologically, PTC metastatic to lymph node can be distinguished with congenital cystic lesions by its cystic lining epithelium. In the common occurrence, cystic PTC metastasis can be easily recognized by morphologic characteristics of PTC, however, the absence of residual lymph node and flattened bland epithelial lining can be seen in both cystic metastases and congenital cystic lesions, such as the first case showed

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in this paper (Fig. 1a, d, g). In these difficult situations, immunohistochemistry is required to assist the morphologic diagnosis. Pax8 and TTF-1 are key transcription factors in thyroid organogenesis and differentiation [9]. They are expressed in normal thyroid and PTC follicular epithelium [10], but there is no report on the utility of immunohistochemistry for Pax8 in distinguishing metastatic lymph node with cystic changes from BCCs or TGDC.

In this study, pax8 and TTF-1 immunohistochemical stains were used in conjunction with morphology to make the diagnosis of cystic PTC lymph node metastases. We also tested the Pax8 and TTF-1 expression on the BCC and TGDC and summarized an algorithm to differentiate PTC

metastatic lymph node with cystic changes from the congenital cystic lesions in the challenging cases.

Case Present

Case #1 A 35-year-old male who has no malignancy history presented with odontogenic infection and neck lymphadenopathy at level 4. The CT scan showed that enlarged lymph node has cystic change that could reflect cystic/necrotic lymph nodes due to patient's known dental infection (such as mycobacterial) and the possibility of metastatic lymph node was initially less favored. However, ultrasound-guided fine needle aspiration biopsy suspected

Fig. 1 Pathologic findings of PTC metastatic to lymph node with cystic change, TGDC and BCC. PTC metastatic to lymph node shows flattened bland cyst lining and adjacent PTC tissue (a, H&E stain); TGDC shows ciliated pseudostratified columnar cyst lining, focal flattened bland cyst lining and adjacent normal thyroid follicles (b, H&E stain); BCC shows ciliated pseudostratified columnar and squamous cyst lining without thyroid tissue (c, H&E stain). PTC metastatic lymph node demonstrates positive Pax8 and TTF-1 in the

cyst lining and adjacent PTC tissues (d, Pax8 and g, TTF-1); TGDC demonstrates negative Pax8 and TTF-1 in the cyst lining and positive Pax8 and TTF-1 in the adjacent thyroid tissue (e, Pax8 and h, TTF-1); BCC demonstrates negative Pax8 and TTF-1 in the cyst lining (f, Pax8 and i, TTF-1). (Insets of a–i at left lower quadrant show the cyst lining; insets of a, d and g at right upper quadrant show PTC tissue; insets of b, e and h at right upper quadrant show thyroid tissue; insets of c, f and i at upper quadrant show squamous cyst lining).

cystic carcinomatous metastasis. Neck dissection of level 4 was performed and specimen was sent for pathologic analysis. H&E stain showed a cyst lined by flattened, bland epithelial cells. Another region of the lymph node showed papillae lined by cubical cells with overlapping nuclei and finely dispersed optically clear chromatin. Immunohistochemistry for Pax8 and TTF-1 highlighted both the bland cyst lining and the papillae (Fig. 1a, d, g). The pathologic findings are consistent with PTC metastatic lymph node with cystic change. Thereafter, the patient received total thyroidectomy and neck dissection, PTC was also diagnosed in the thyroid specimen.

Case #2 A 32-year-old female presented for workup after a motor vehicle accident. MRI incidentally found a neck cyst suggestive of a TGDC. CT scan demonstrated a cystic lesion in the anterior neck that probably is a TGDC. The cyst was removed by Sistrunk procedure and sent for pathological analysis. H&E stain showed a cyst lined by ciliated pseudostratified columnar epithelium and focally flattened bland epithelial cells. There were normal thyroid follicles adjacent to the cyst. Immunohistochemistry for Pax8 and TTF-1 was negative in the cyst lining, but positive in the thyroid follicular epithelium (Fig. 1b, e, h). The histologic findings were consistent with TGDC. The patient was cured by the surgical treatment.

Case #3 A 58 year old female presented with a left neck mass. CT scan suggested that it could be either an enlarged lymph node or a neoplasm. The mass was removed surgically and sent for pathologic analysis. H&E stain revealed reactive lymph nodes with a cyst lined by ciliated pseudostratified columnar epithelium and squamous epithelium. No thyroid tissue was identified. Immunohistochemistry for Pax8 and TTF-1 was negative in the cyst lining (Fig. 1c, f, i). The pathologic findings were consistent with BCC. The patient was cured by the surgical treatment.

Collectively, PTC metastatic to lymph node with cystic change sometime can be presented as flattened bland epithelial lining in portions of tumor. On the other hand, benign TGDC and BCC could be lined by ciliated pseudostratified columnar epithelium, squamous epithelium or flattened bland epithelium. Normal thyroid tissue usually can be found in adjacent area to the TGDC. Pax8 and TTF-1 are positive in the cyst lining of metastatic lymph node; but negative in the lining of TGDC and BCC. The clinical information and pathologic findings are summarized in Table 1.

Discussion

The differential diagnoses of cystic neck masses can be a perplexing and challenging. Cystic neck masses consist of a wide range of congenital and acquired lesions including

Table 1 Clinical information and pathologic findings of the patients

Pt	Age	Sex	Present	Radiology	Surgical procedure	Pathologic findings		Diagnosis	
						Cyst lining	Pax 8	TTF-1	Adjacent tissue
#1	35	M	Right neck mass	CT: cystic/necrotic lymph nodes due to infection or metastases; ultrasound FNA: suspecting cystic carcinomatous metastasis	Right level 4 neck dissection	Flattened bland epithelium	+	+	PTC
									PTC metastatic lymph node with cystic change
#2	32	F	Incidental finding of cyst in central neck	CT and MRI: possibility of TGDC	Sistrunk procedure	Ciliated pseudostratified columnar, squamous or flattened bland epithelium	-	-	Normal thyroid follicles
									TGDC
#3	58	F	Left neck mass	CT: reflecting a lymph node, not excluding neoplastic soft tissue tumor	Removal of left neck lymphadenopathy		-	-	N/A
									BCC

Fig. 2 Schematic diagram for neck cystic lesion pathologic diagnosis

various neoplastic diseases [11]. TGDC and BCC are the most common neck congenital cystic lesions. TGDC is usually located in midline and accounts for 70 % of congenital neck anomalies. It occurs along the residual tract left by the thyroid gland after descent from the foramen cecum at the tongue base to its final position [12]; therefore normal thyroid tissue can be seen adjacent to the cyst, which is consistent with what we found in Case #2. BCC usually located in the lateral neck [13]; thus thyroid tissue does not present as what we observed in Case #3. Metastatic lymph nodes from head-and-neck malignancy are the most common types of nodal metastases presenting as cystic masses in the neck. PTC accounts 80 % of cystic masses in patients over 40 years old [14]. The most common route of spread of PTC is to the cervical lymph nodes. A study of 553 PTC patients showed that central lymph node metastases were presented in 43.6 % of cases, while 11.6 % of them had lateral lymph node metastasis [2]. Radiology is frequently utilized for evaluating neck cystic lesions but the sensitivity to identify lymph node metastasis is only 77 % for CT and 62 % for ultrasound [3]. The definite diagnosis is usually provided by pathologic analysis.

Histologically, we could differentiate cystic metastatic lymph node from congenital cystic lesions by the cyst lining. The cyst lining of TGDC and BCC can be ciliated pseudostratified columnar or squamous epithelium; while cystic lining of metastatic lymph node can show flattened bland epithelium or the cytological features of PTC.

However, flattened bland epithelial lining can also be seen in TGDC and BCC, at least focally. Therefore the carefully sampling specimen is critical as the typical PTC lesion or pseudostratified/columnar/squamous lining from TGDC or BCC can be just located at adjacent tissue. However, in difficult cases, if the entire cystic lining shows attenuated epithelial cells; the immunostains for Pax8 and TTF-1 can be extremely helpful to reaching the correct diagnosis.

Pax8 and TTF-1 are expressed in normal thyroid and PTC follicular epithelium [17]. Pax8 is an important transcription factor involving development in many organ systems such as thyroid and genitourinary organs [15]. TTF-1 also plays biological function in multiple organs and activates the expression of selected genes in thyroid, lung and ventral forebrain [16]. Other than thyroid carcinomas of follicular origin, many malignancies are well known to be positive for either Pax8 or TTF1. Renal cell carcinoma, mullerian carcinomas, and most anaplastic thyroid carcinomas are positive for Pax8 immunostain [17, 18], while TTF1 is positive in lung adenocarcinoma, neuroendocrine tumors, small cell carcinomas and hepatic cell carcinoma [19]. It should be also aware that some mesonephric adenocarcinomas, thymic and pulmonary neuroendocrine carcinomas are positive for both Pax8 and TTF-1 [20, 21]. Therefore the careful correlation with patient's clinical history and presentation is necessary when such rare scenario is encountered.

In a summary, although PTC metastatic lymph node with cystic change can be differentiated with congenital cystic

lesions by location, cystic lining type and adjacent tissue morphology in most cases; Pax8 and TTF-1 immunohistochemistry can be helpful in the challenging cases. (Fig. 2).

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