

**Thyroid carcinomas incidentally found in the cervical lymph nodes- Did they arise from the heterotopic thyroid tissues?**

**Tetsuya Yamamoto, DDS, PhD, Yukihiro Tatemoto, DDS, PhD, Yukiko Hibi, DDS, Akihiko Ohno, DDS, PhD, and Tokio Osaki, DDS, PhD**

Department of Oral and Maxillofacial Surgery,

Kochi Medical School, Kochi University

Kohasu, Oko-cho, Nankoku-city, Kochi, 783-8505, Japan

**Corresponding author:** T. Yamamoto,

Department of Oral and Maxillofacial Surgery,

Kochi Medical School, Kochi University

Kohasu, Oko-cho, Nankoku-city, Kochi 783-8505, Japan

TEL: +81-088-880-2423, FAX: +81-088-880-2424

E-mail address: [yamamott@kochi-u.ac.jp](mailto:yamamott@kochi-u.ac.jp)

## **ABSTRACT**

**Purpose:** Thyroid carcinomas have been incidentally found in the cervical lymph nodes during operation of head and neck squamous cell carcinoma (SCC) and such carcinomas have been considered metastatic.

**Patients and Methods:** We encountered 3 cases of incidental papillary carcinoma in the neck of patients with oral SCC and reviewed 75 cases previously reported.

**Results:** Papillary carcinomas were found in 3, 10 and 3 lymph nodes in cases 1, 2 and 3, respectively. CT examination revealed 2 tumor-like shadows and 1 calcified mass in the cases 2 and 3, respectively. These shadows did not enlarge during the 3 to 5 years of observation and all patients have been alive without any event at the neck and thyroid gland. In reviewed cases, approximately two-fifths were histopathologically or clinically free from thyroid carcinoma.

**Conclusion:** We proposed a possibility that occult thyroid carcinoma is not necessarily metastatic but occasionally arises from the heterotopic thyroid tissues.

## **Introduction**

Cervical lymph nodes often represent numerous malformative inflammation and neoplastic tumor. The lymph nodes resected by elective and therapeutic surgery in patients with head and neck squamous cell carcinoma (SCC) incidentally manifest histopathological evidences of thyroid carcinoma, which differ from the characteristics of SCC. The most frequent tumor that is incidentally associated with head and neck SCC is papillary carcinoma, and such carcinoma without clinical abnormalities of the thyroid gland is called an occult (incidental) thyroid carcinoma or an occult metastasis from the thyroid gland carcinoma.

A variety of incidental (occult) thyroid carcinomas of the cervical lymph nodes has been reported in patients with SCC of the head and neck regions.<sup>1-10</sup> Most authors of these reports insisted that thyroid carcinomas of the lymph nodes were metastatic. In fact, small thyroid carcinomas (occult carcinomas) were detected not only in cervical lymph nodes but also in the thyroid glands obtained from surgically removed tissues and autopsied bodies.<sup>11-15</sup> Do these reports, however, support a hypothesis that incidental thyroid carcinomas found in the lymph nodes are fully indicative of the occult metastasis of the thyroid carcinoma without any exception?

The existence of heterotopic thyroid tissues and salivary gland tissues in the cervical lymph nodes and parotid gland lymph nodes has been reported by many investigators.<sup>16-20</sup> This existence has been proved by the fact that epithelial protein markers such as keratins were detected in the cervical lymph nodes that were dissected in patients with oral SCC.<sup>20</sup> Thyroid papillary carcinoma was reported to be found in a heterotopic thyroid tissue within a branchial cleft cyst.<sup>16</sup> In addition,

no any primary thyroid carcinomas could be found in patients with “occult lymph node metastasis”.<sup>1-8</sup> These facts and case reports appear to support a possibility that occult thyroid carcinoma found in the cervical lymph nodes is not only metastatic (that is, occult metastasis) but also “primary” arising from heterotopic thyroid tissues in the lymph nodes.

We experienced 3 cases of so-called occult thyroid carcinoma of the cervical lymph nodes. No carcinoma could be directly detected in the thyroid glands. We present a report of these cases with a review of literatures and a discussion on the possibility of the development of thyroid carcinoma in the cervical lymph nodes.

## **Case reports**

### ***Case 1***

A 39-year-old man was referred to our department for treatment of T4N1M0 SCC of the lower gingiva (Fig. 1A and 1B). He underwent inductive chemo-radio-immunotherapy consisting of 5-fluorouracil (3250 mg), peplomycin (a bleomycin derivative, 30 mg), OK-432 (a streptococcal preparation, 35 KE) and  $\gamma$ -rays (30 Gy). Subsequently, mandibulectomy with cervical lymph node dissection and reconstruction of the resected mandible were performed. The histopathological examination of the extirpated lymph nodes revealed no metastasis of the gingival SCC but 3 lymph nodes at the level IV presented a papillary thyroid carcinoma (Fig. 1C and 1D, Table 1). Computed tomography (CT) examination of the thyroid gland was carried out with a suspicion of occult thyroid carcinoma but no abnormal shadows were detected and the patient has been

periodically observed without thyroidectomy. He has been alive without any adverse event for 11 years.

### ***Case 2***

A 67-year-old man was referred to our clinic for treatment of T4N2bM0 SCC of the tongue. He underwent partial glossectomy and cervical neck dissection. The histological examination revealed metastasis of the tongue SCC to 2 lymph nodes at level I (Table 1). Besides the metastatic foci of SCC, papillary carcinoma was incidentally found in 3 and 7 lymph nodes at levels II and III, respectively (Fig. 2A and 2B). The degree of development of the papillary carcinomas differed among the involved lymph nodes. Two tumor-like foci with a diameter of approximately 5 mm in the thyroid gland were detected on CT examination. Thyroidectomy was however not performed because of the patient's unwilling. The tumor-like shadows have been static during 5 years after the surgery.

### ***Case 3***

A 54-year-old man visited our clinic for the examination and treatment of tongue tumor. For the treatment of the tongue SCC (T4N2M0), he underwent chemo-radio-immunotherapy as did in case 1. After remission of the tumor, partial glossectomy and bilateral neck dissection were performed. Metastasis of the glossal carcinoma to multiple lymph nodes at bilateral levels I and IV and contralateral level III was observed histopathologically (Table 1). Papillary carcinomas were also detected at levels III and IV, in a total of 3 lymph nodes (Fig. 3A). A CT examination of the thyroid gland was carried out within 10 days after the surgery and a small calcified mass with a

diameter of approximately 5 mm was found (Fig. 3B). We decided to periodically observe the head and neck without application of thyroidectomy. Fortunately, no particular event has been induced during the 3 years following the treatment.

## **Patients and Methods**

### ***Immunohistochemistry***

To confirm the characteristics of the incidental papillary carcinomas, immunostainings were performed for the detection of thyroglobulin and cytokeratins. The extirpated tissues were fixed with buffered formalin and embedded in paraffin. The embedded tissues were sliced into thin sections and stained with hematoxylin-eosin. To retrieve the antigens, the paraffin sections were heated (121°C) in a 10-mM citrate buffer solution (pH 6.0) for 15 min. After cooling to room temperature, they were washed in phosphate-buffered saline (PBS) for 5 min. Thyroglobulin and cytokeratins were detected using a HISTOFINE SAB-PO (Multi) kit (Nichirei Co. Ltd., Tokyo, Japan) and the streptavidin-biotinyl immunoperoxidase method. The sections were reacted with monoclonal mouse antibodies (primary antibodies) against thyroglobulin, cytokeratin 13, cytokeratin 18 and total keratin (DAKO Japan Co., Ltd., Kyoto, Japan) for 1 h respectively. For the negative control, PBS or normal mouse serum (DAKO Japan Co., Ltd.) was used instead of the primary antibody. Counterstaining was performed with Mayer's hematoxylin.

## **Results**

All foci of the papillary carcinoma in a total of 16 lymph nodes were positive for thyroglobulin but the SCCs (examined as the control for the papillary carcinomas) were fully negative for thyroglobulin (Table 2, Figure 4). Of the keratins examined, cytokeratin 13 (a ubiquitous cytokeratin) and total keratin (AE1/AE3) were observed in all carcinomas (Figure 5) and cytokeratin 18, which is expressed particularly in gland tissues and columnar cells, was expressed in 15 of the 16 papillary carcinomas in the lymph nodes and 1 of the 8 metastatic SCCs (Figure 6) but oral SCCs were fully negative for cytokeratin 18. These immunohistochemical results indicated that the papillary carcinomas possessed proteins characteristic of thyroid carcinoma and that the existence of cytokeratin 18 was indicative of the gland tissue origin.

### **Review of literatures**

We reviewed 10 articles on occult thyroid carcinoma that was incidentally found in the cervical lymph nodes of patients with the head and neck SCC.<sup>1-10</sup> The primary SCCs were located with equal frequency in the oral cavity (including the lips) and larynx but rarely located in the pharynx and other sites (Table 3). Of the incidental thyroid carcinomas, 49 were papillary type and 26 were follicular type (mixed type was observed in 12 cases), and solid type was found in 2 cases (the histological type was not shown in 6 cases). Thyroidectomy including lobectomy was performed in 48 glands and 26 glands of these glands revealed carcinoma on their histopathological examination but the remaining 22 glands were negative for carcinoma. Fourteen patients who did not undergo thyroidectomy were fully negative for thyroid carcinoma clinically during the

observation periods. In 13 patients, their thyroid status was not noted.

The levels and number of lymph nodes with occult thyroid carcinoma are insufficiently described in literatures (the description of the levels and number are limited to a few literatures)<sup>4,5,7,10</sup> (Table 4). In the 16 cases with a sufficient description, occult thyroid carcinoma was observed in 42 lymph nodes (mean number = 2.5 lymph nodes/case). Among the levels, level III was most commonly involved (19 lymph nodes), followed by level IV (14 lymph nodes) and level II (9 lymph nodes). Three cases revealed an involvement of level II with no carcinoma at other levels of lymph nodes.<sup>4,7,10</sup>

## **Discussion**

Cervical lymph nodes are frequently involved in both inflammatory and neoplastic diseases. In malignant tumors, the involved lymph nodes become usually enlarged to be detected clinically, but asymptomatic metastasis to the cervical lymph nodes (occult metastasis) is occasionally found in the lymph nodes that are dissected in treatment of head and neck carcinomas. However, incidental thyroid carcinoma is very rare in the cervical lymph nodes. Cervical occult thyroid carcinoma is generally regarded as a metastatic lesion from the thyroid gland. However, it is questionable whether all occult thyroid carcinomas found in the cervical lymph nodes are metastasized from the thyroid carcinomas. The existence of heterotopic thyroid tissues and salivary gland tissues in the cervical and parotid lymph nodes is well known and a possibility of the formation of thyroid and salivary carcinomas arising from these ectopic tissues has been



reported<sup>16-20</sup> although Maceri DR et al.<sup>13</sup> and Attie JN et al.<sup>12</sup> have reported the existence of thyroid gland carcinoma in patients with thyroid carcinoma in the cervical lymph nodes.

As a matter of course, an occult metastatic thyroid carcinoma requires for primary carcinoma(s) in the thyroid gland. We reviewed the incidental thyroid carcinomas formed in the cervical lymph nodes and added the frequency of the existence of primary occult carcinomas in the thyroid glands (Table 3). Of the 75 patients associated with thyroid carcinoma that was incidentally found in the cervical lymph nodes, 48 patients underwent thyroidectomy and 26 patients revealed either foci of thyroid papillary or follicular carcinoma but no carcinoma was found in the thyroid glands in the remaining 22 patients. No occurrence of thyroid carcinoma had been ascertained in the clinical follow-up of the patients who did not undergo thyroidectomy. This result appears to indicate that nearly two-fifths of the patients with incidental thyroid carcinoma in the cervical lymph nodes were free from carcinoma of their thyroid glands. Coskun H, et al.<sup>5</sup> reported 3 cases of the incidental association of thyroid gland carcinoma with SCC of head and neck, and they developed an opinion that incidental thyroid carcinomas in the cervical lymph nodes were metastatic, additionally quoting the report of Attie JN et al. that<sup>12</sup> the histological examination of clinically normal thyroids in patients with occult metastatic thyroid carcinoma revealed thyroid cancer in all patients who underwent thyroidectomy. Pacheco-Ojeda L et al.<sup>8</sup> also reported 6 suspicious cases of occult metastasis and they ascertained the existence of thyroid gland carcinomas in 5 of these cases. In addition, some autopsy reports showed occult thyroid gland carcinomas,<sup>14,15)</sup> which indicated a high percentage of occult carcinomas. However, as we have

described above, nearly two-fifths of patients with incidental thyroid carcinoma in the cervical lymph nodes, including the cases of Attie JN et al.<sup>12</sup> did not have thyroid gland carcinoma. The result of this review of literatures is contradictory to the opinion of Attie JN et al.<sup>12</sup>

A large series of case studies is necessary for the discussion on this matter. According to the reports, the frequency of occult thyroid gland carcinoma differs largely. Our large series of studies indicate that incidental thyroid carcinoma of the lymph nodes does not appear to be necessarily associated with thyroid gland carcinoma, that is, it is not always metastatic. The ratio of papillary and follicular carcinoma among the incidental lymph node carcinomas was approximately 1 to 2, which was largely different from the ratio in thyroid gland carcinomas (approximately 90% of these are papillary type).<sup>21,22</sup> This relatively high incidence of papillary carcinoma compared with its incidence in the thyroid gland is suggestive of a non-metastatic origin of thyroid carcinoma in the lymph nodes.

Papillary and follicular carcinomas are not highly malignant. Therefore, it appears strange for small-sized foci of these types of carcinomas in the thyroid gland to metastasized to the cervical lymph nodes. In the cases reported, multiple lymph node involvements were observed in the “occult metastasis” despite the absence of primary thyroid carcinoma.<sup>6</sup> Our cases revealed multiple foci of papillary carcinoma in lymph nodes at the levels II to IV. In case 2, papillary carcinoma was found in 3 and 7 lymph nodes at the levels II and III, respectively, although the small tumor-like shadows did not enlarge during 5 years after their detection. In addition, thyroid carcinoma was not detected by CT examination in case 1 and no clinical evidence of thyroid gland

carcinoma has been detected for more than 10 years. If the thyroid carcinomas were metastatic, the “primary carcinoma” of the thyroid gland should naturally enlarge even if the growth speed is very slow. Another reason for the controversy against “occult metastasis” is that according to some reports, occult thyroid carcinoma was found only in the level II lymph node without any cancerous lesions in the lower levels.<sup>4,7,10</sup> When a thyroid gland carcinoma metastasizes through the lymph vessels, the metastasis appears to firstly occur in the level III or IV lymph nodes.

The existence of heterotopic thyroid gland tissues in the cervical lymph nodes was reported a few decades ago.<sup>23</sup> Recently, RT-PCR and immunohistology have revealed unexpectedly high frequencies of the existence of the ectopic epithelial tissues in the cervical lymph nodes.<sup>22</sup> Shinohara M et al.<sup>20</sup> reported that heterotopic salivary gland tissues in the cervical lymph nodes were found in 12.1% of the examined patients. A salivary gland tumor and Kimura’s disease arised in the cervical and intraparotid lymph nodes have been recently reported.<sup>18,19</sup> In addition, Fliegelman LJ et al.<sup>4</sup> reported a case of a benign follicular tumor that was incidentally found in a cervical lymph node dissected for the treatment of cervical metastasis of larynx carcinoma. Similarly, Ansari-Lari and Westra.<sup>11)</sup> found benign thyroid inclusions in cases among 1337 patients who underwent cervical lymphadenectomy (0.8%). Furthermore, a case of thyroid papillary carcinoma arising in ectopic thyroid tissue within a branchial cleft cyst was also reported recently.<sup>17</sup> A similar report has been published on a salivary carcinoma in the parotid gland lymph node.<sup>19</sup> The existence of the heterotopic thyroid tissues and the occurrence of carcinoma in the cervical lymph nodes appear to support the development of thyroid carcinoma from the ectopic tissues. In

conclusion, we insist that incidental thyroid carcinoma in the cervical lymph nodes (occult thyroid carcinoma) is not always metastatic but occasionally primary arising from the heterotopic thyroid tissues.

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## Figure legends

**Figure 1.** Case 1. (A) A panoramic radiograph showing diffuse absorption of the retromolar region of the mandible. (B) The histopathological view of SCC of the gingival (H-E,  $\times 15$ ). (C and D) The extirpated lymph node at level IV histopathologically presents a papillary thyroid carcinoma (H-E, C:  $\times 15$ , D:  $\times 200$ ).

**Figure 2.** Case 2. Papillary carcinoma in the extirpated lymph nodes at level II (A) and III (B) (H-E,  $\times 8$ ,  $\times 150$ ).

**Figure 3.** Case 3. (A) A histopathological view of papillary carcinoma in the lymph node at level III (H-E,  $\times 150$ ). (B) The CT finding of the thyroid gland: A small mass approximately 5 mm in diameter is visible in the right side of the thyroid.

**Figure 4.** Immunohistochemical expression of cytokeratin 13. (A) Negative control (Case 1, Level III lymph node without papillary carcinoma), (B) Papillary carcinoma (Case 1, Level III lymph node), (C) Metastatic SCC (Case 3, Level I lymph node). Original magnifications:  $\times 100$  in all.

**Figure 5.** Immunohistochemical expression of cytokeratin 18. (A) Negative control for papillary carcinoma (Case 1, Level III lymph node), (B) Papillary carcinoma (Case 1, Level III lymph node), (C) SCC (Case 2, Level I lymph node). Original magnifications:  $\times 100$  in all.

**Figure 6.** Immunohistochemical expression of thyroglobulin. (A) Papillary carcinoma (Case 1, Level III lymph node), (B) Papillary carcinoma (Case 2, Level II lymph node), (C) Metastatic SCC (Case 2, Level I lymph node). Original magnifications:  $\times 100$  in all.



Table 1. Summary of patients, oral tumors, occult carcinomas and followings

Case	Oral carcinoma (T-stage)	Metastasis of oral SCC	Occult carcinoma in the nodes	CT findings in the thyroid gland	Followings
Patient 1, 39/M	Lower gingiva (T4)	–	Papillary Level IV (3)	Nothing special	No sequence for 11 years
Patient 2, 67/M	Tongue (T4)	Level I (2 <sup>a</sup> /0 <sup>b</sup> )	Papillary Level II (3) Level III (7)	Tumor-like shadow (ø5mm) in each lobe	No change of the size for 5 years
Patient 3, 54/M	Tongue (T4)	Level I (1/1) Level III (0/1) Level IV (2/1)	Papillary Level III (1) Level IV (2)	Calcified small mass (ø5mm)	No change of the size for 3 years

( ): number of the involved nodes. a / b: ipsilateral / contralateral lymph nodes

Table 2. Expression of thyroglobulin and cytokeratin

Tumor	Thyroglobulin		Cytokeratin 13		Cytokeratin 18		Total keratin AE1/AE3	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Oral SCC (n=3)	3	0	0	3	3	0	0	3
Metastatic SCC (n=8)	8	0	0	8	7	1	0	8
Papillary carcinoma (n=16)	0	16	0	16	1	15	0	16

Table 3. Thyroid carcinomas incidentally found in the cervical lymph nodes associated with SCC of the head and neck

Authors	Year	No. of cases	Accompanied head and neck carcinoma	Histology of thyroid carcinoma (P <sup>a</sup> /F <sup>b</sup> /M <sup>c</sup> /S <sup>d</sup> )	Carcinoma in the thyroid			
					c(-) <sup>e</sup>	p(-) <sup>f</sup>	p(+) <sup>f</sup>	? <sup>g</sup>
Clark RL et al.	1966	12	Oral cavity:6, Larynx:5, Pharynx:1	F:5, M:6, S:1		2	7	3
Butler JJ et al.	1967	13	Oral cavity:7, Larynx:5, Pharynx:1	F:6, M:6, S:1	3	2	7	1
Pacheco-Ojeda L et al.	1991	6	Oral cavity:3, Pharynx:2, Larynx:1	Not noted			5	1
Vassilopoulou-Sellin et al.	1992	8	Oral cavity:8	P:4, F:4	4	1	3	
Pitman KT et al.	1996	7	Larynx:4, Oral cavity:2, Pharynx:1	P:7				7
Lopez-Escamez JA et al.	1999	1	Larynx:1	P:1		1		
Fliegelman LJ et al.	2001	4	Oral cavity:4	P:4		2	2	
Coskun H et al.	2002	3	Larynx:3	P:3	1	1	1	
Ansari-Lari SM, et al.	2003	10	Head and neck:10	P:10		10		
Resta L et al.	2004	8	Larynx:7, Oral cavity:1	P:7, F:1	4	3	1	
Ours	2006	3	Oral cavity:3	P:3	2			1
Total		75		P:49, F:26, M:12, S:2	14	22	26	13

a: P=papillary, b: F=follicular, c: M=mixed, d: S=solid, e: clinically, f: histopathologically, g: unknown

Table 4. The levels and number of lymph nodes with occult thyroid carcinoma

Authors	Case No.	No. of lymph nodes				Total
		Level II	Level III	Level IV	Level VI	
Pitman KT et al.	1	1	0	0	0	1
Fliegelman LJ et al.	2	3	1	0	0	4
Coskun H et al.	3	0	8	2	1	11
Resta L et al.	7	2	2	6	1	11
Ours	3	3	8	5	0	16
Total	16	9	19	13	2	43

The cases of Pitman KT et al.<sup>10)</sup>, Fliegelman LJ et al.<sup>4)</sup>, Coskun H et al.<sup>5)</sup>, Resta L et al.<sup>7)</sup> and ours were added.

Figure 1 (Case 1)

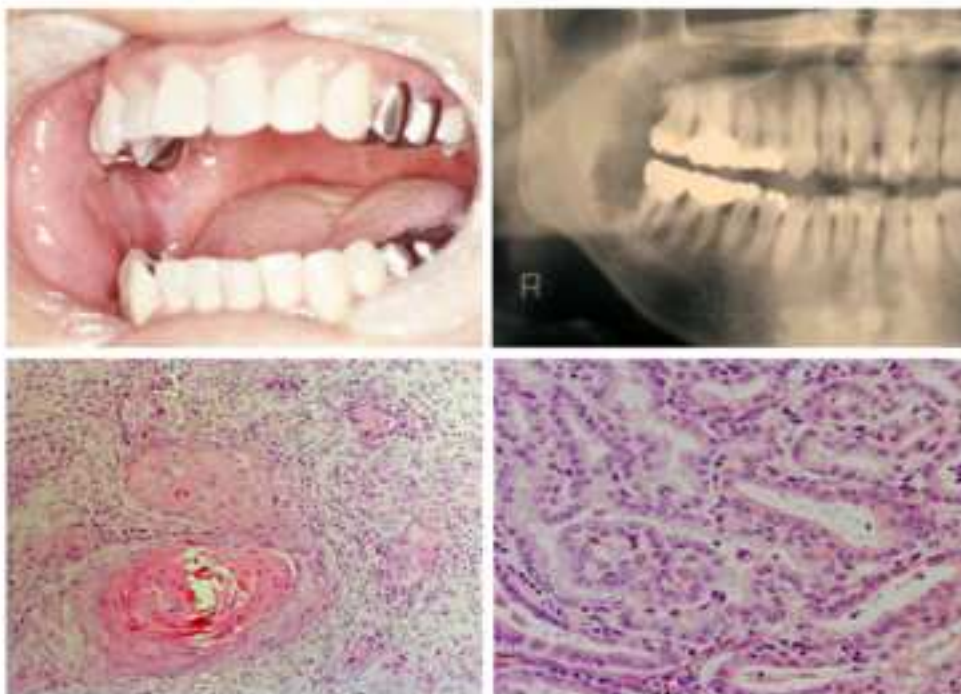
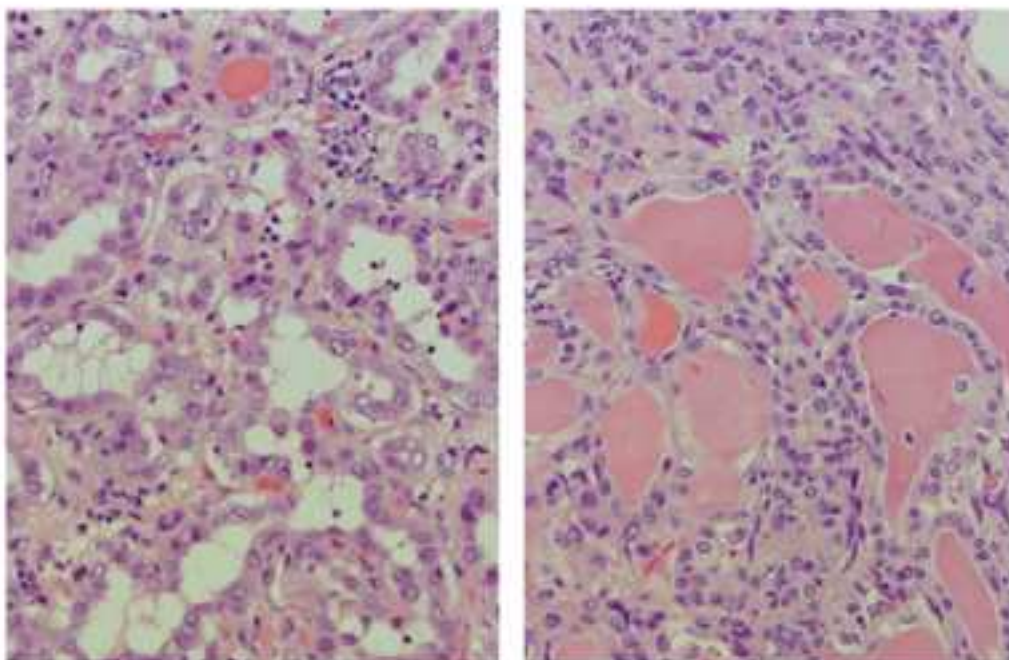


Figure 2  
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Figure 2 (Case 2)



**Figure 3**  
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Figure 3 (Case 3)

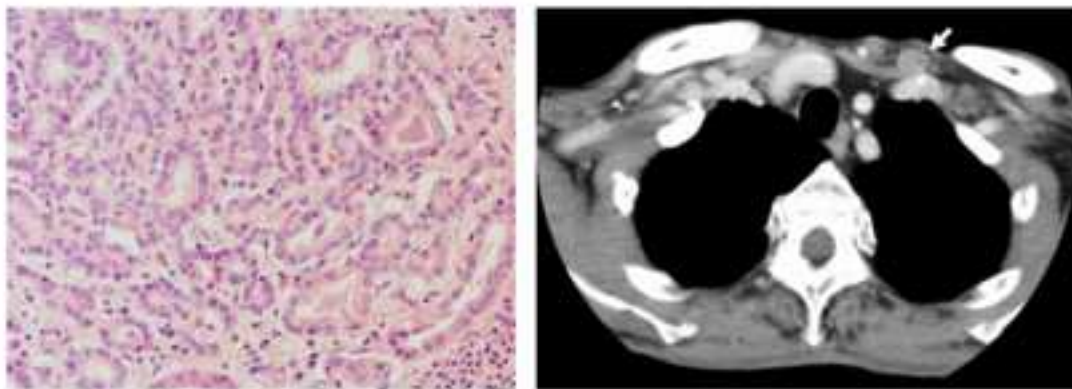


Figure 4 (CK13)

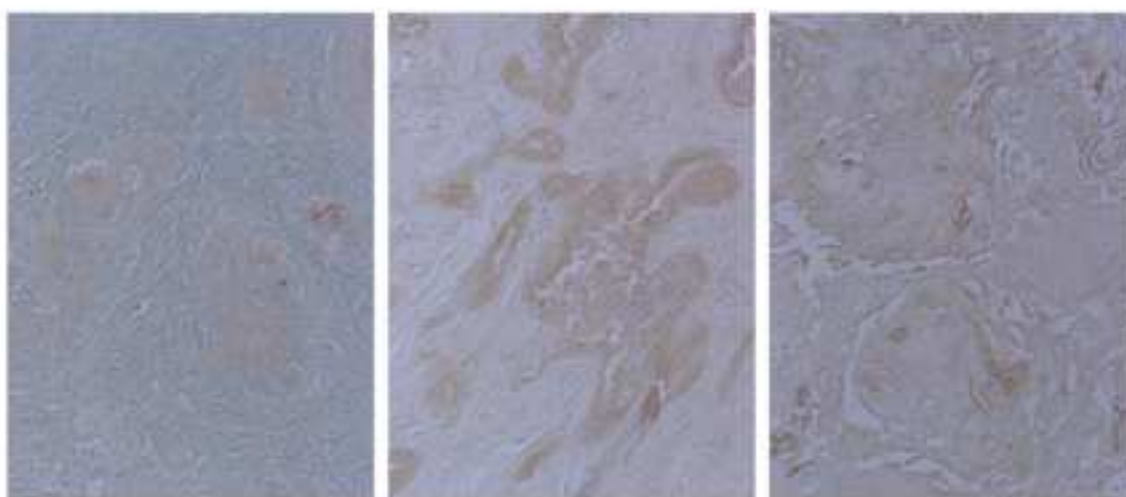




Figure 5 (CK18)

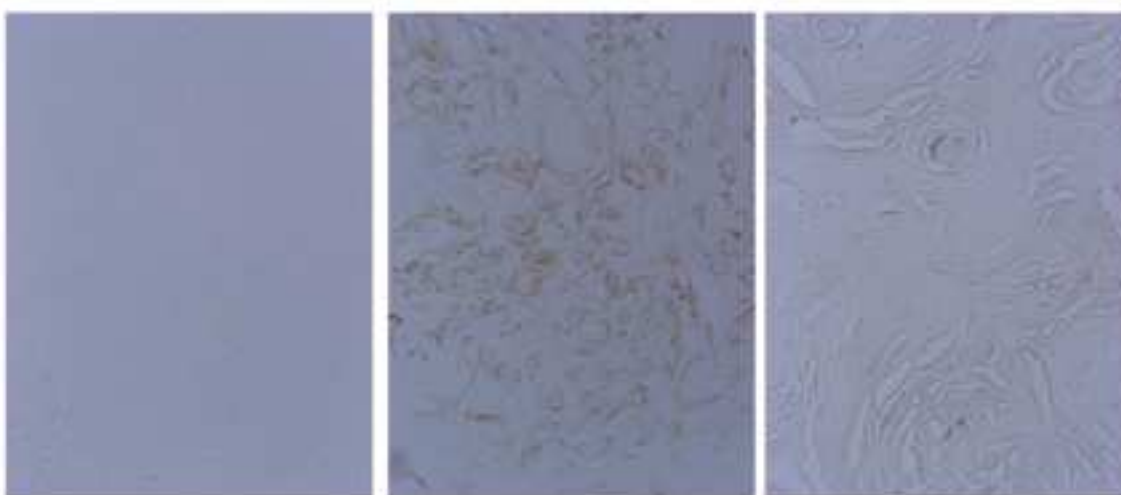


Figure 6 (Thyroglobulin)

