

## Case Report

# Foci of spindle cell proliferation in multinodular goiter of thyroid: epithelial-mesenchymal transformation or embryonic remnants?

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**Abstract:** Foci of spindle cell proliferation of the thyroid gland have been documented in adenoma and carcinoma, but not much in multinodular goiter. We report a case of spindle cell proliferation detected in multinodular goiter in a 61-year-old female. Histological examination revealed foci of solid area around the normal thyroid follicles. There were two components in this solid area; the first one was composed of epithelial cells with small bland ovoid nuclei and the second one with spindle cells with short spindle-shaped nuclei. Immunohistochemical analysis revealed that the spindle cells were positive for thyroid transcription factor (TTF)-1, Vimentin, CK (AE1/AE3), and negative for p63, etc. The cells with ovoid nuclei had more abundant CK (AE1/AE3) immunoreactivity than those with short spindle-shaped nuclei. In addition, the transition between these two cell types was clearly identified. We hypothesized that this area represented embryonic remnant of developing thyroid gland and therefore evaluated histological features of developing fetal thyroid but this lesion by no means simulated histological features of any developing stages of fetal thyroid gland. The spindle cell foci of thyroid gland could possibly arise from epithelial-mesenchymal transformation of thyroid follicular epithelium in this thyroid gland but it awaits further investigations for clarification.

**Keywords:** Spindle cells, multinodular goiter, epithelial-mesenchymal transformation, embryonic remnants

## Introduction

Spindle cell foci of the thyroid gland are quite rare and have been reported to be detected in reactive processes, benign or malignant tumors, including post-fine-needle aspiration spindle cell nodules of the thyroid [1], papillary carcinoma, follicular adenoma [2-4], multinodular goiter [5], and medullary carcinoma [6]. The diagnosis of spindle cell foci therefore could sometimes present challenges to surgical pathologists because it could affect the therapy of the patients if diagnosis undefined. In this study, we report a case of spindle cell lesion arising in the multinodular goiter of the thyroid and reviewed the literature. We discussed the morphologic features and immunohistochemical profiles of this case in order to further characterize this interesting spindle cell lesion of the thyroid in this case of multigoiter.

## Clinical summary

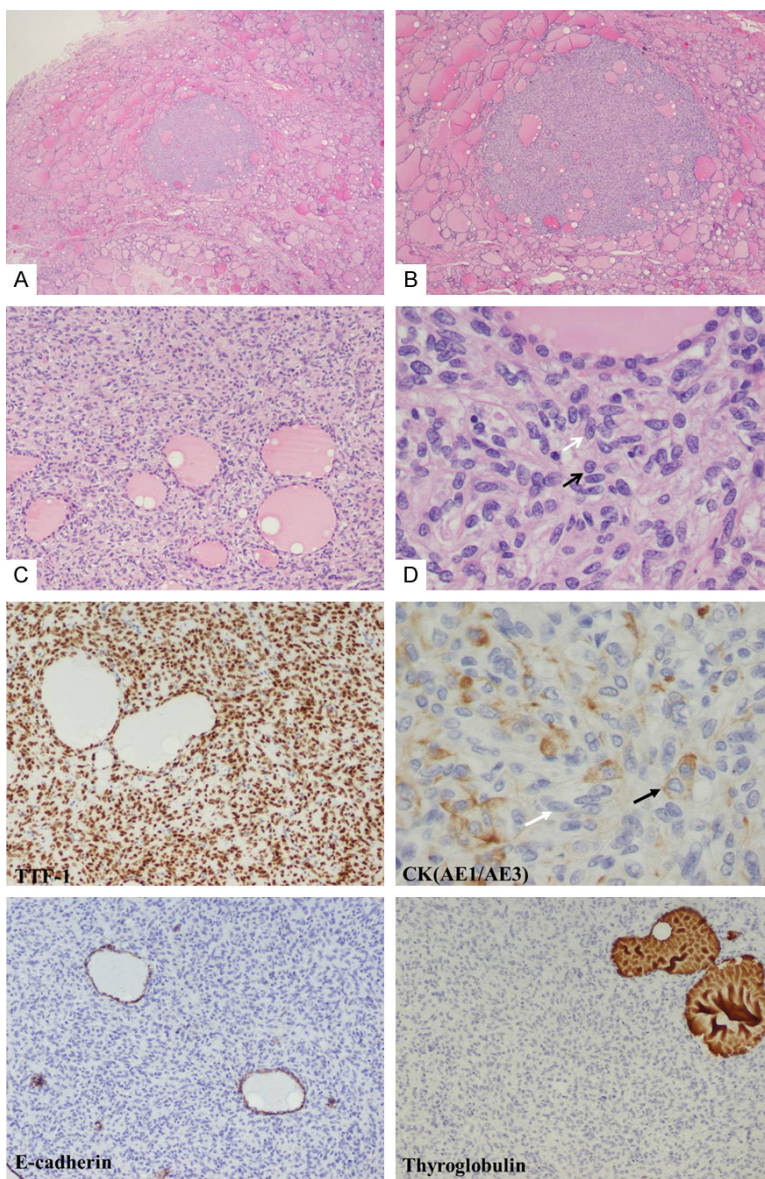
In 2014, a 61-year-old woman was admitted to The Second Hospital of Jilin University, China with multiple nodules in the thyroid gland detected at 3 days before admission. She had past history of hypertension. Her thyroid function was within normal limits. She did not manifest any fever, pain, dysphagia, dyspnea and other symptom and underwent bilateral subtotal thyroidectomy. Post-operative course was uneventful for 30 months after surgery.

## Pathological finding

### *Ethics statement*

This study was approved by the ethics committee of The Second Hospital of Jilin University, (China). Thyroid gland was obtained from abort-

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**Figure 1.** HE and immunohistochemistry results of spindle cells foci. A, B: Spindle cells lesion in multinodular goiter shows a nodular pattern. C: The cells grow around the thyroid follicular. D: Higher magnification shows two kinds of cells which have eosinophilic cytoplasm and subtle nucleoli. The cells were positive for TTF-1 and CK (AE1/AE3) (weakly), whereas were negative for E-cadherin and thyroglobulin.

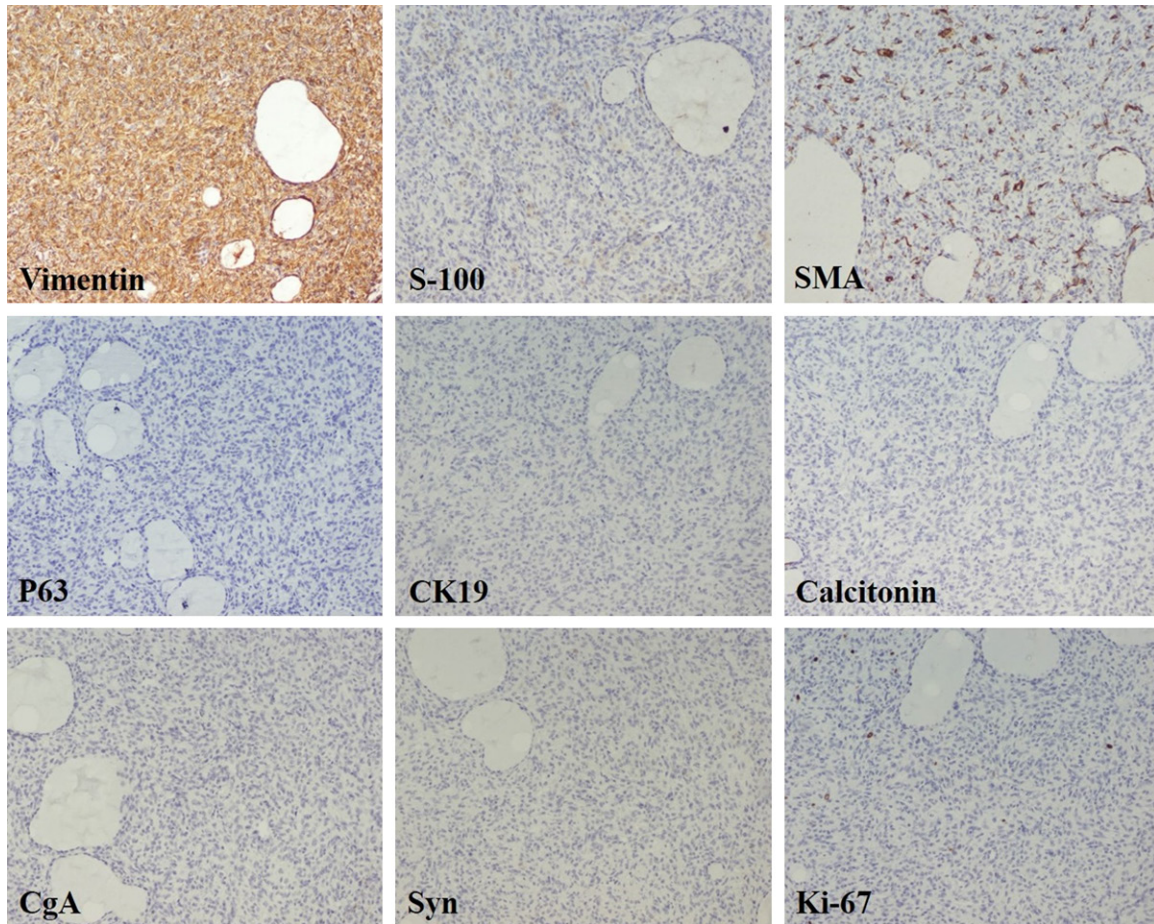
ed fetuses, after written informed consent, from The Second Hospital of Jilin University.

Gross examination revealed that the bilateral lobes of the thyroid measured  $5 \times 3 \times 1.5$  cm and  $4 \times 3 \times 1$  cm respectively. Multiple nodules ranging from 0.6 to 1.5 cm at maximum diameter were detected on the cut surface. The cut-surface of these nodules appeared grey-red and partly encapsulated, and cyst formation

was seen. The histopathology diagnosis was multinodular goiter (Supplementary Figure 1), but a nodule measuring 0.3 mm in diameter was detected. The lesion was well circumscribed (Figure 1A, 1B). The cells histologically different from thyroid follicular cells were detected adjacent to the thyroid follicles (Figure 1C). This lesion was composed of two different cell types. One had small bland ovoid nuclei (black arrow); the other had short spindle-shaped nuclei (white arrow). Both of these cells had eosinophilic cytoplasm and nucleoli. Mitoses were rare and apoptosis was absent (Figure 1D). The antibodies were summarized in Supplementary Table 1. Thyroglobulin was negative in these cells above. Of particular interest, these cells were weakly positive for CK (AE1/AE3) and negative for E-cadherin whereas positive for TTF-1 (Figure 1). The cells with ovoid nuclei (black arrow) had more abundant CK (AE1/AE3) immunoreactivity than those with short spindle-shaped nuclei (white arrow). In addition, a transition from the cells with ovoid to those with short spindle-shaped nuclei was clearly identified. In order to further explore whether these spindle cells acquired a phenotype of stromal cells, we performed immunohistochemistry of Vimentin, SMA, and S-100 and others. All the spindle cells in the lesion were markedly positive for Vimentin and negative for SMA and S-100 (Figure 2). Other markers including high molecular weight CK19 were uniformly negative in this lesion. In addition, all of these spindle cell lesions had a relatively low Ki67 labeling index with  $<1\%$  (Figure 2). We retrieved fetal thyroid gland from autopsy files of the second Jilin University Hospital in order to study wheth-



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**Figure 2.** Immunohistochemistry results of spindle cells foci. The cells were positive for Vimentin, whereas were negative for SMA, S-100, P63, CK19, Calcitonin, CgA and Syn. Ki-67 label index was less than 1%.

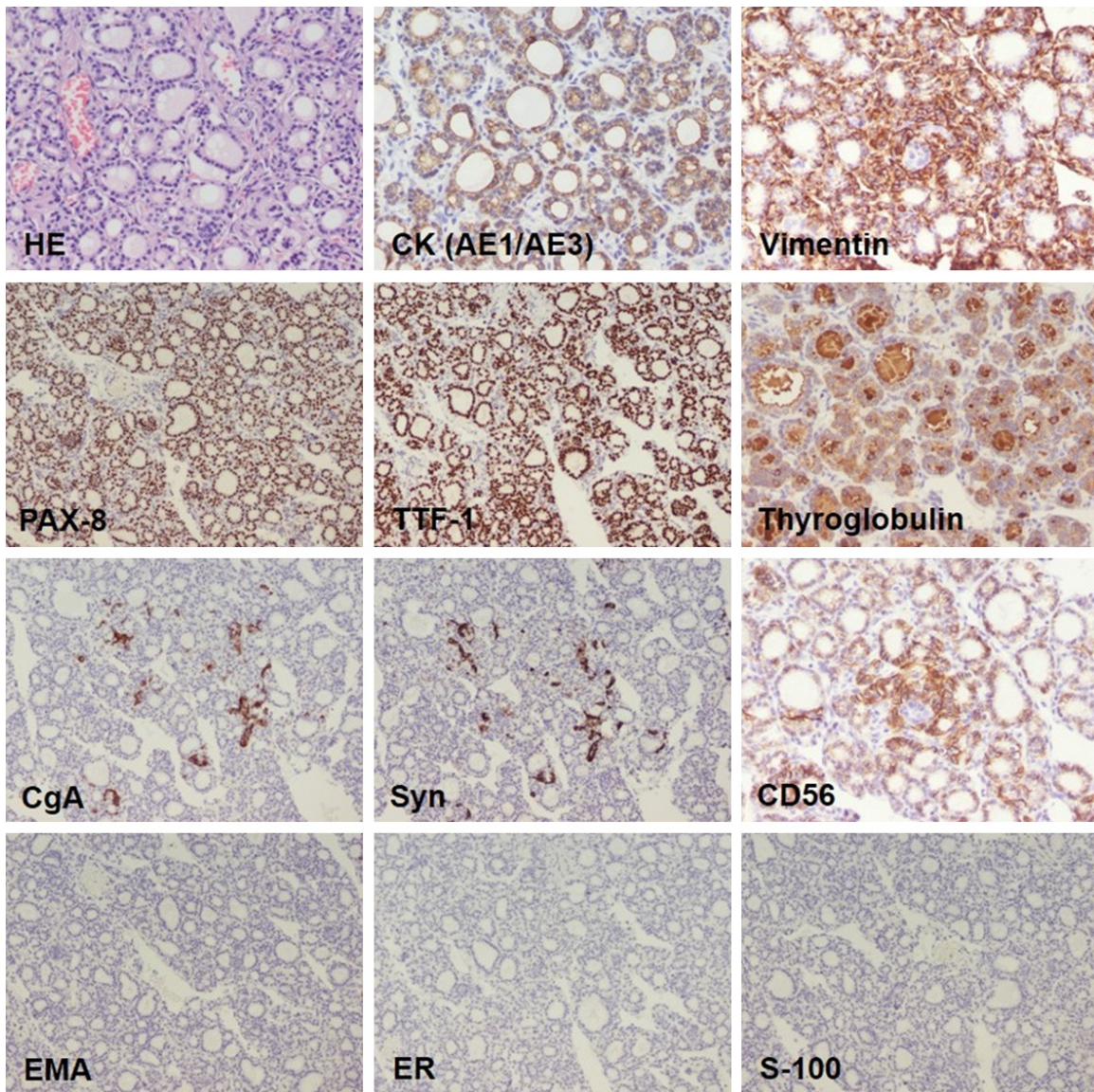
er these lesions had any similar histological features of developing fetal thyroid gland to prove the hypothesis above. Fetal thyroid glands which we studied were four cases from 22 to 26 gestational weeks. Results revealed that these cells were by no means detected in any of thyroid parenchymal cell components in developing fetal thyroid gland. We further evaluation immunoreactivity of TTF-1, CK (AE1/AE3), Vimentin, CD56, CgA, Syn, PAX-8, ER, PR, EMA, S-100 and thyroglobulin in this lesion and developing fetal thyroid glands. PAX-8, TTF-1, CK (AE1/AE3), thyroglobulin and Vimentin were all immunohistochemically positive in fetal thyroid gland. CK (AE1/AE3) was more abundant at luminal border and Vimentin more at basolateral (**Figure 3**) in fetal thyroids. C-cells positive for CD56, CgA and Syn. C-cells were scattered and ER, PR, EMA and S-100 were all negative in fetal thyroid glands (**Figure 3**).

## Discussion

The foci of spindle cell have been reported in follicular adenoma, follicular and papillary carcinomas, and multinodular goiter (**Table 1**). Among these lesions, papillary carcinoma was most frequent (n=10), and followed by follicular adenoma (n=9), multinodular goiter (n=6) and follicular carcinoma (n=2). Only one case was reported in encapsulated follicular thyroid carcinoma. The mean age of spindle cell foci in multinodular goiter was 49 years old, which is younger than our present case. The reported lesions in multinodular goiter were all nodular or diffuse at low power magnification. The lesion contained spindle cells harboring thin, elongated, or plump nuclei with eosinophilic cytoplasm and subtle nucleoli at the high power magnification as in our present case. However, in our present case, some areas also harbored the epithelial cells with small bl-



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**Figure 3.** HE and immunohistochemistry results of fetus thyroid gland (22 weeks). The thyroid cells were positive for TTF-1, CK (AE1/AE3), PAX-8, thyroglobulin and Vimentin. ER, EMA and S-100 were negative. C-cells were positive for CD56, CgA and Syn.

and ovoid nuclei and others contained stromal cells with short spindle-shaped nuclei. Necrosis, inflammation, vascular and perineural invasion were absent in all the reported cases.

The differentiation of this lesion could include many tumors and tumor like lesions, such as medullary carcinoma and others. Histologically, medullary carcinoma is composed of round, oval, and spindle-shaped cells occurring in cords and nests. Immunohistochemically, medullary carcinoma is positive for calcitonin, carci-

noembryonic antigen, and neuroendocrine markers in the great majority of the cases. However, this case was positive for TTF-1 but negative for calcitonin and other neuroendocrine markers.

Solid cell nests of the thyroid are generally considered embryonic remnants of endodermal origin. The morphological features of these solid cell nests were lined by cuboidal-to-columnar cells with eosinophilic cytoplasm and round-to-oval nuclei [14]. In our present case, the spindle cells had small bland ovoid to short

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**Table 1.** Clinicopathological features of spindle cell foci of thyroid (n=29)

Author	Age	Histological Type (number)	Spindle cell pattern	TTF-1	TG	CK	Vimentin	Other diseases
Hutter et al [2]	50	Papillary carcinoma (1)	Nodular	+	+	+	ND	No follow-up
Vergilio et al [3]	33-71	Follicular Adenoma (3)/papillary carcinoma (7)	Diffuse	ND	+/ND (2)	ND (6)/-(3)/+(1)	ND	No follow-up
Matoso et al [5]	34-62	Follicular Adenoma (2)/multinodular goiter (2)/Follicular Carcinoma (2)	Nodular/Diffuse	+	+	-/+	+	No follow-up
Aker et al [7]	27	Follicular Adenoma (1)	Diffuse	ND	+	Focal+	+	Alive and well 15 months
Shikama et al [8]	60	Follicular Adenoma (1)	Nodular	+	+	-	+	No follow-up
Magro et al [9]	69	Multinodular goiter (1)	Nodular	+	+	Focal+	+	No follow-up
Yuji et al [10]	16	Encapsulated Follicular Thyroid Carcinoma (1)	Diffuse	ND	ND	+	-	Alive and well 5 years
Hirokawa et al [11]	50-65	Multinodular goiter (3)	Nodular/Diffuse	+	+	ND	ND	No follow-up
Abbas et al [12]	70/77	Follicular Adenoma (2)	Diffuse	+	+	ND	+	Alive and well 2 years/Autopsy case
Stefania et al [13]	56/53	Papillary carcinoma (2)	Nodular/Diffuse	+	+	+	ND	Alive and well 3/1 years
Our case	61	Multinodular goiter (1)	Nodular	+	-	+	+	Alive and well 30 months

ND: not done.

spindle-shaped nuclei and eosinophilic cytoplasm, which is similar to histological features above. In addition, we immunolocalized p63 which was usually positive in solid cell nests but negative in our case (Supplementary Figure 2). In order to further explore the possibility of this particular nodule in our case as an embryonic remnant, we retrieved four fetal thyroid glands (22 weeks-26 weeks) but morphology of any components of fetal thyroid glands was by no means similar to the spindle cells detected in our present case. Therefore, in our case, it is considered unlikely that the lesion represented solid cell nests and embryonic remnant in our case.

Almost all these cells in previously reported studies were positive for thyroglobulin immunoreactivity, suggesting that these could possibly represent metaplastic transformation of thyroid follicular epithelium [10]. However, the spindle cells of the thyroid were negative for thyroglobulin in our case. Of particular interest, the cells were weakly positive for CK (AE1/AE3) but retained marked immunoreactivity of TTF-1. We then performed immunohistochemistry for Vimentin, SMA and S-100 in order to evaluate whether these cells acquired cellular features of stromal cells or not. Results revealed that these spindle cells were markedly positive for Vimentin and negative for SMA and S-100. Other epithelial markers including E-cadherin and CK19 were uniformly negative in this case. Among these two cell types, the cells with ovoid nuclei had more abundant CK (AE1/AE3) positive cells than those with short spindle-shaped nuclei. In addition, a transition from the cells with ovoid nuclei to those with short spindle-shaped nuclei areas was clearly identified. These results did indicate that the highly differentiated epithelium positive for cytokeratin could be transformed into vimentin positive and thyroglobulin negative cells. Therefore, spindle cells in our present case are reasonably postulated to arise from epithelial-mesenchymal transformation of thyroid follicular cells. Previous studies [15] also demonstrated that the cells isolated from both papillary carcinoma and follicular adenoma, when maintained in cell culture, underwent an epithelial-mesenchymal transformation but further investigations are required for clarification.

In summary, we demonstrated the morphologic features and immunohistochemical profile of spindle cell in multinodular goiter of the thyroid gland. Results of this study further indicated that the spindle cell foci of thyroid gland could possibly arise from epithelial-mesenchymal transformation of existing thyroid follicular epithelium.

### Disclosure of conflict of interest

None.

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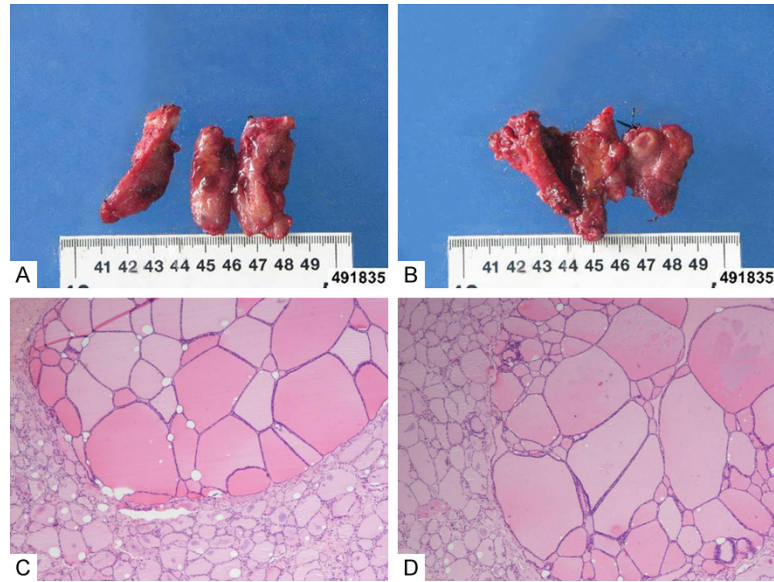
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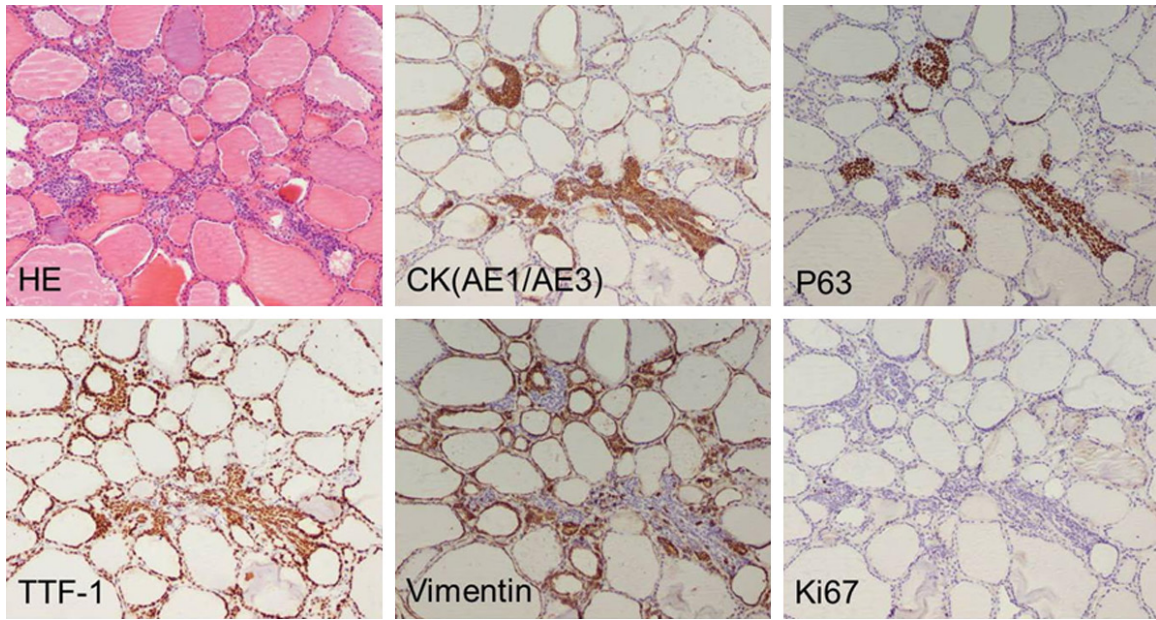
**Supplementary Figure 1.** The representative macroscopy and microscopic illustrations of bilateral thyroid. A and C: Left; B and D: Right.

**Supplementary Table 1.** All the information of antibodies used in this manuscript list in the table

Antibody	Antibody Clone	Company
CK(AE1/AE3)	(AE1/AE3)	DAKO
S-100	S100A1	DAKO
CK19	RCK108	DAKO
SMA	1A4	DAKO
Vimentin	V9	DAKO
CD34	QBEnd 10	DAKO
Chromogranin A	DAK-A3	DAKO
Ki67	MIB-1	DAKO
P63	7JUL	Zhongshan
Calcitonin	EP93	Zhongshan
E-cadherin	4A2C7	Zhongshan
CEA	ZC23	Zhongshan
thyroglobulin	2H11/6E1	Zhongshan
TTF-1	SP141	Roche



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**Supplementary Figure 2.** HE and immunohistochemistry pattern of solid cell nests. The cells were positive for TTF-1, p63 and CK (AE1/AE3), whereas were negative for Vimentin. Ki-67 label index was less than 1%.