

## Two Patients with Metastasis of Cancer to Other Neoplasm: A Thyroid Carcinoma Metastatic to a Lung Carcinoma and a Gastric Carcinoma Metastatic to a Thyroid Adenoma

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### Abstract

Two patients with rare cancer-to-neoplasm metastasis are presented. One patient was a 69-year-old woman who had undergone gastrectomy for gastric cancer 10 months previously and died of generalized metastases. An autopsy revealed generalized metastases of the gastric carcinoma, together with a cystic, hemorrhagic thyroid tumor measuring 2.0 cm in diameter. Histologically, the thyroid tumor was an oxyphilic adenoma with multiple metastatic foci of gastric adenocarcinoma. Because no metastasis was found in the background thyroid tissue, this metastasis might have developed specifically and not by chance, most likely due to the rich vascularity and good circulation of the thyroid adenoma. The other patient was an 82-year-old man who had undergone total thyroidectomy for thyroid cancer 6 years previously. An abnormal lung shadow was found on a chest radiograph during postoperative follow-up. Transbronchial biopsy of the lung tumor revealed a squamous-cell carcinoma. The resected lung tumor measured 2.7 cm in diameter, with small foci of metastatic papillary carcinoma of the thyroid gland and multiple small metastases in the background lung tissue, indicating that the metastases to lung cancer had occurred by chance. Metastasis of cancer to other neoplasms is discussed, and a review of the literature is presented. **Endocr Pathol** 5:233-239, 1994.

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Because of the apparent rarity of metastatic cancer to other neoplasms, we present 2 patients, 1 of whom had gastric cancer metastatic to a thyroid adenoma, and the other had thyroid carcinoma metastatic to a lung carcinoma. Because it remains controversial whether neoplasm-to-neoplasm metastasis is merely a chance occurrence or is due to selective lodging, survival, and growth within the recipient tumor, an additional purpose of this report is to contribute to the body of knowledge regarding whether the metastatic pattern has certain features other than those associated with chance occurrence. In addition, to

gain more knowledge of this rare metastatic phenomenon, we review previously reported cases and discuss the features of metastasis of cancer to another neoplasm.

The occurrence of various malignant donor tumors metastasizing to different recipient tumors is extremely rare, despite the relatively high incidence, reported to range from 4.2 to 8% [13,21], of multiple neoplasms in the same individual. To our knowledge, fewer than 200 cases of neoplasm-to-neoplasm metastasis have been reported in the English and Japanese literature [1,14,17,18,25]. The lungs are the most frequent site of metastatic growth

from malignant neoplasms of almost all classes [23]. However, metastasis of cancer to a coexisting lung carcinoma is extremely rare. To our knowledge, only one case of this combination has previously been reported [4]. Although less frequent than metastatic lung carcinomas, metastases of carcinoma to the thyroid gland are also not uncommon [8,16,24]; the reported incidence ranges from 3 to 5% with routine autopsy examination, and from 20 to 24% with meticulous examination [8,16,20]. However, the incidence of carcinoma metastasis to thyroid adenomas is far less frequent than the expected percentage of thyroid metastasis, and only a few cases have been reported [9,11,25].

### Materials and Methods

The tissues obtained at autopsy in Patient 1 and surgically resected specimens from Patient 2 were fixed in 10% formalin, and multiple tissue specimens were obtained and embedded in paraffin. For microscopic examination, sections (5 $\mu$ m thick) were stained with hematoxylin and eosin (H & E), periodic acid-Schiff (PAS), alcian blue (pH, 2.5), and silver impregnation for

reticulin. For immunohistochemical examination, tissues were stained with the avidin-biotin-peroxidase complex (ABC) method using antihuman thyroglobulin antibodies (Dako Corp., Carpinteria, CA; 1:400) and antihuman carcinoembryonic antigen (CEA) (Dako; 1:400) as previously described [10]. In both patients, previously resected surgical specimens were also examined.

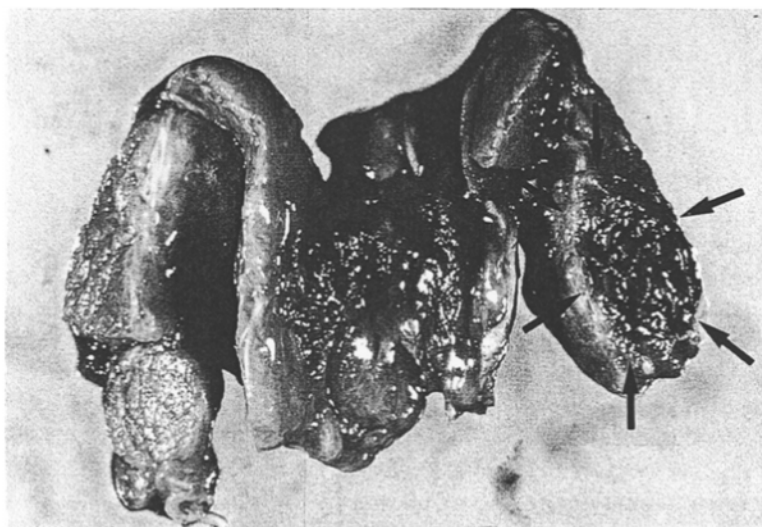
### Case Reports

#### Patient 1

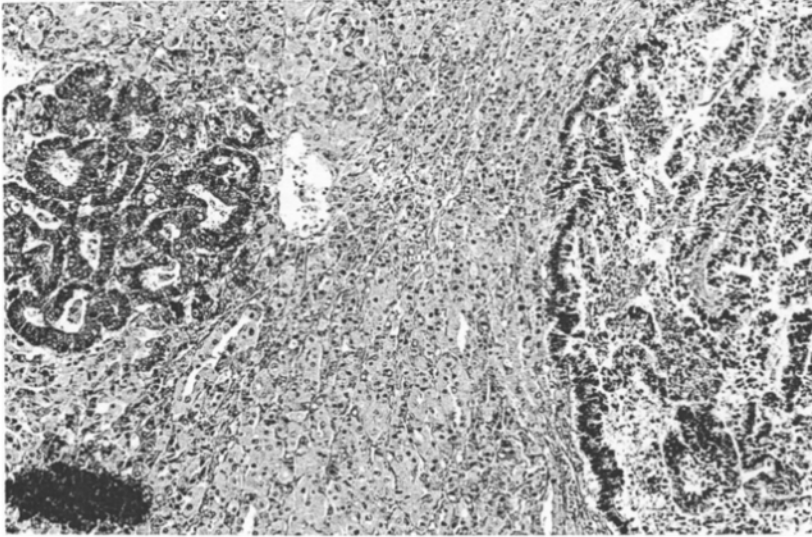
A 69-year-old woman presented at a hospital with the complaints of appetite loss, weight loss, and dull epigastric pain of 5 months' duration. Gastric cancer was found at gastroscopy and radiographic examination, and she underwent partial gastrectomy for advanced gastric cancer. Pathological examination revealed a moderately differentiated adenocarcinoma of the stomach, with multiple liver and lymph node metastases (stage IV). After surgery, she received combined chemotherapy (mitomycin C and OK432) for cancer, but she died of generalized metastases 10 months later. An autopsy was performed 90 minutes after her death.

**Pathological Findings** The autopsy revealed generalized cancer metastases to the abdominal, thoracic, and cervical lymph nodes; liver; bilateral lungs and ovaries; peritoneum; pancreas; spleen; diaphragm; uterus; and retroperitoneum. In addition, there was a multicystic, hemorrhagic tumor, which measured 2.0 cm in diameter, in the left lobe of the thyroid gland (Fig. 1). The background thyroid tissue showed some nodular configurations with a pale-tan cut surface.

Histologically, the thyroid tumor was an oxyphilic adenoma within which multiple foci of adenocarcinoma were found (Fig 2). The tumor was entirely composed of large cells with granular acidophilic cytoplasm, and the character of the oxyphilic tumor cells was clearly distinct from that of the adenocarcinoma cells (Fig. 3). No transition between the oxyphilic tumor cells and the adenocarcinoma cells was found. In the background thyroid tissue, chronic diffuse



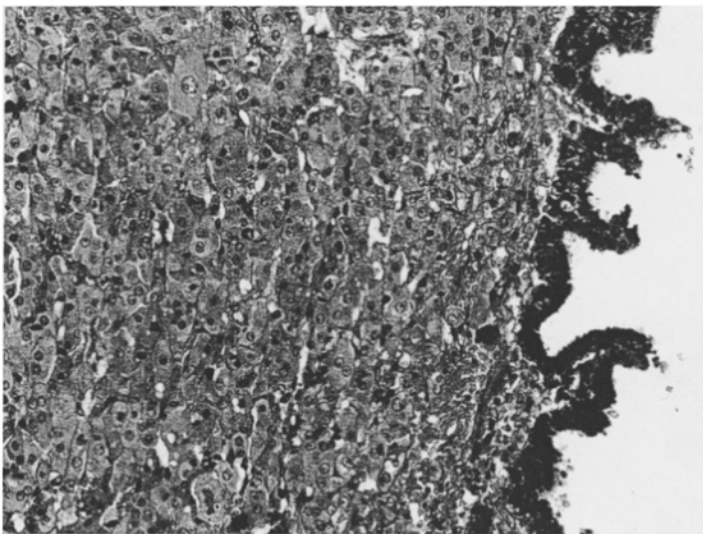
**Figure 1.** Patient 1. Macroscopic appearance of the thyroid tumor in the left lobe [arrows] of the thyroid gland, with nodular configuration in the background thyroid tissue. The cut surface of the right lobe is pale tan, with a nodular configuration.



**Figure 2.** Patient 1. The metastatic gastric adenocarcinoma within the oxyphilic adenoma of the thyroid. Multiple, small metastatic foci were found in the adenoma tissue (H & E stain, original magnification  $\times 125$ ).

thyroiditis with a nodular configuration of the parenchyma was found. The histologic appearance of the carcinoma was identical to that of the gastric carcinoma. No metastatic foci were observed in the surrounding thyroid tissue, even though multiple tissue sections were examined.

Immunohistochemically, the luminal



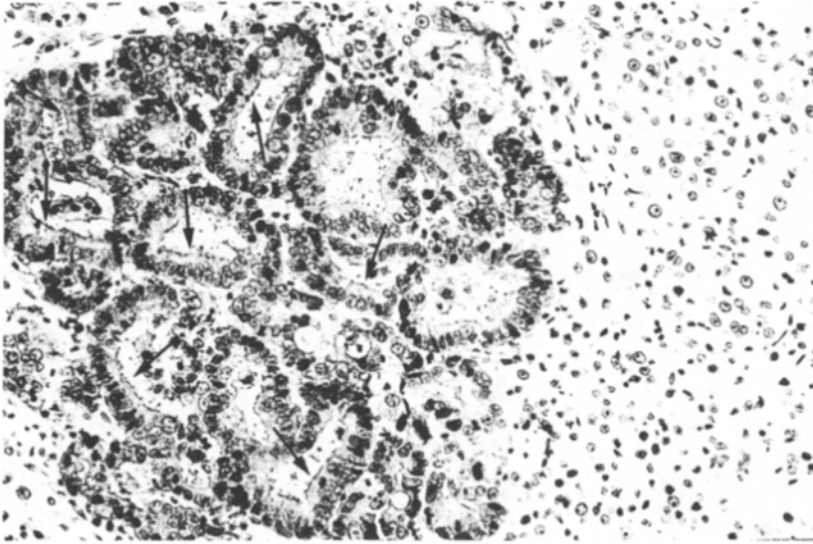
**Figure 3.** Patient 1. The thyroid adenoma was composed entirely of large cells with granular acidophilic cytoplasm (left), which are clearly distinct from the adenocarcinoma cells (right). No transition was found (H & E stain, original magnification  $\times 250$ ).

surfaces of the adenocarcinoma cell nests were clearly positive for CEA, whereas the cytoplasm of the cancer cells was weakly positive for CEA (Fig. 4), but both were negative for thyroglobulin. "Metastatic" gastric cancer to thyroid oxyphilic adenoma was diagnosed. The metastatic foci in the oxyphilic adenoma were clearly associated with hemorrhage.

#### Patient 2

An 82-year-old man who had undergone total thyroidectomy for papillary carcinoma of the thyroid gland 6 years previously and radical neck dissection for recurrent cancer 3 years previously was hospitalized for evaluation of an abnormal lung shadow. He had been treated with radioactive iodine and thyroid medication, and his condition was well controlled. On June 6, 1989, an abnormal shadow was noted on a chest radiograph, and uptake of radioactive iodine was observed in the left lung by scintiscan, although no abnormality had been observed at the follow-up examination on June 15, 1988. Laboratory data revealed a slightly hypothyroid and hypoparathyroid state, but other data, including tumor markers, were all within normal ranges. Examination of the transbronchial lung biopsy specimen revealed squamous-cell carcinoma. On July 17, 1989, under the preoperative diagnosis of squamous-cell carcinoma of the lung, segmentectomy of the lingula pulmonaris for lung tumor was performed, together with a resection of a palpable nodule, which was considered to be a metastatic lesion located in the left lower lobe.

**Pathological Findings** The resected lingula specimen, which measured 6 x 4.5 x 3.5 cm, contained a white-yellow, well-defined tumor measuring 2.7 x 2.5 x 2.5 cm (Fig. 5). Microscopically, the lung tumor was a moderately differentiated squamous-cell carcinoma. In addition, multiple small foci of a papillary carcinoma were found within the lung squamous-cell carcinoma (Fig. 6). Papillary carcinoma, however, was a minor component within the squamous-cell carcinoma, which formed small cell nests. These 2 types of carcinoma were mutually independent, and transition from one tumor type to another in the same cell nest



**Figure 4.** Patient 1. Immunohistochemical staining for carcinoembryonic antigen (CEA). The luminal surfaces of the adenocarcinoma cell nests are clearly positive for CEA (*arrows*), and the tumor cell cytoplasm is also weakly positive, whereas the tumor cells of the thyroid adenoma are totally negative for CEA (ABC immunoperoxidase stain counterstained with hematoxylin, original magnification  $\times 250$ ).

was not found (Fig. 7). The morphological pattern of the papillary carcinoma found in the lung was the same as that of the original thyroid carcinoma and of the recurrent papillary carcinoma of the neck.

Immunohistochemically, the cell surfaces in the papillary area and the luminal contents of the follicular area of the papil-



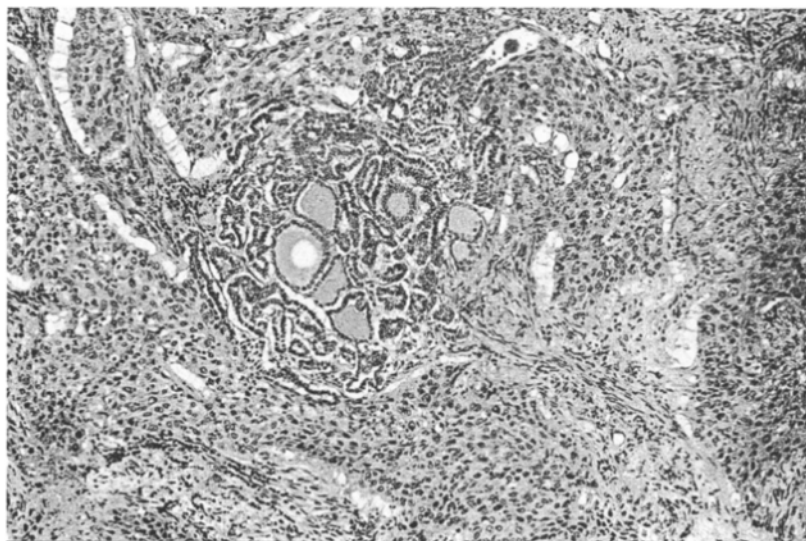
**Figure 5.** Macroscopic appearance of the lung tumor in Patient 2.

lary carcinoma were positive for thyroglobulin (Fig. 8). There were also multiple small metastatic foci of a papillary carcinoma in the surrounding lung tissue. The lung specimen obtained from the lower lobe of the left lung showed no carcinoma, but it did show scar-like fibrosis with ossification.

## Discussion

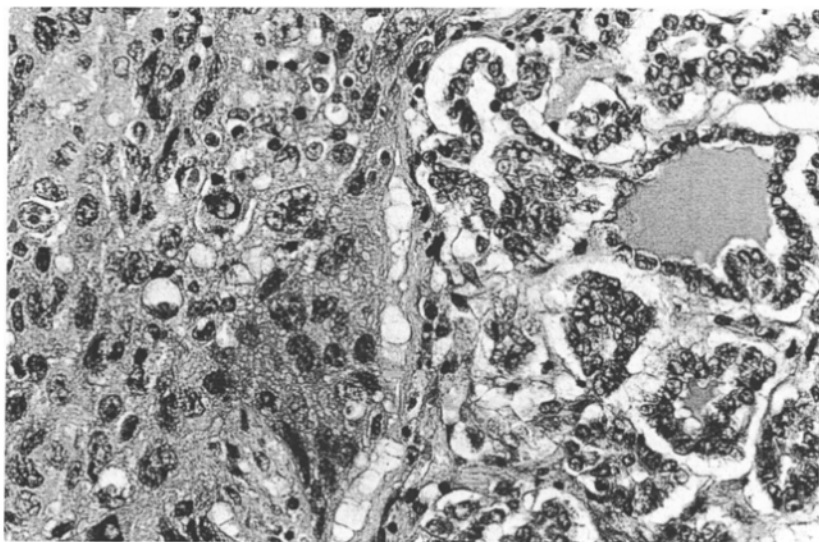
According to Campbell and associates [1], in the diagnosis of cancer-to-cancer metastasis, several criteria should be adopted. More than 1 primary tumor should be present, and the recipient tumor should be a true neoplasm. There should be evidence that the second malignant neoplasm is a true metastasis, with established growth or invasion in the host tumor, and not due to continuous growth or embolism of tumor cells. Finally, it should not pertain to tumors that have metastasized to lymphatic systems that are already the site of generalized lymphatic malignant disease, such as leukemic lymph nodes with metastatic carcinoma. All these criteria were met in our patients.

Previous reviews have revealed that the most common malignant and benign recipient host tumors are renal-cell carcinomas (RCC) and meningiomas or endocrine adenomas, such as thyroid adenomas or adrenocortical adenomas. Campbell and associates [1], in a review of 35 patients with cancer-to-cancer metastasis, reported that in 23 (65.7%) the recipient or the host neoplasm was primary RCC. Sella and Ro [18] evaluated 46 patients and reported that RCC was the recipient tumor in 33 (71.7%). In a study of 52 patients by Ichijima and colleagues [6], RCC was reported to be the recipient host tumor in 34 (65%). In a recent evaluation by Seitz and Schüder [17] of 80 patients, including 1 patient of their own, the recipient tumor was malignant in 46 and benign in the remaining 34. The most common malignant recipient neoplasm was RCC (29; 63%), followed by malignant lymphoma (4); the most common benign recipient neoplasm was meningioma (15; 44%), followed by neurinoma (4). Ortega and coworkers [11] reported that 8 of 11 (73%)



**Figure 6.** Patient 2. The metastatic papillary carcinoma within the squamous-cell carcinoma of the lung. The formation of follicular elements with colloid was also noted (H & E stain, original magnification  $\times 100$ ).

malignant recipient tumors were RCC, and that 15 (37%) and 10 (24%) of 41 benign recipient tumors were thyroid adenomas and adrenal adenomas, respectively. In Japan, Yamamoto and associates [25] reviewed 11 patients with cancer-to-cancer metastasis and 8 patients with cancer-to-benign tumor metastasis and reported that the most frequent malignant recipient tu-

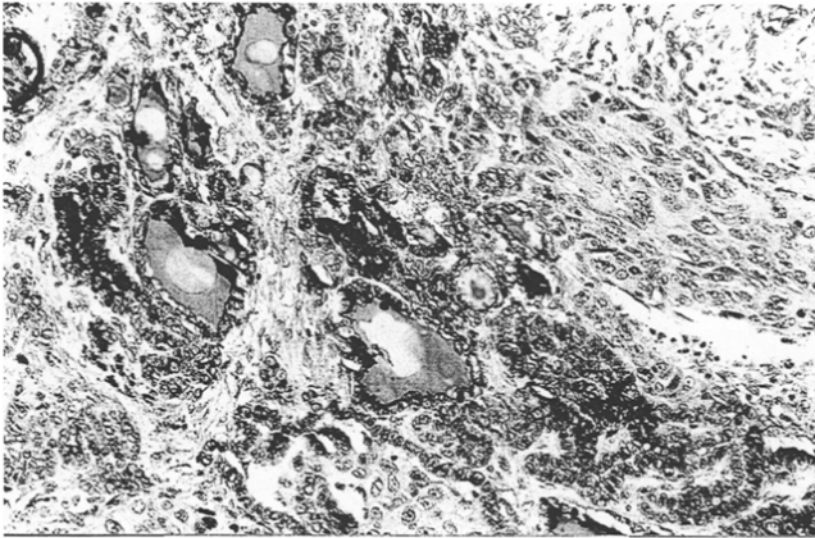


**Figure 7.** Patient 2. Higher magnification of the papillary carcinoma within the squamous-cell carcinoma. No transition between the tumor cell types was found (H & E stain; original magnification  $\times 400$ ).

mor was papillary carcinoma of the thyroid gland (5), followed by RCC (4). Of the 8 benign recipient tumors, 5 were thyroid adenomas and 2 were uterine leiomyomas.

The most frequently reported donor tumors are of lung or breast origin. In Seitz and Schüder's [17] review of 80 patients with cancer-to-neoplasm metastasis, the most frequent donor tumors were lung and breast carcinomas, which were observed in 27 and 20 patients, respectively, followed by prostatic adenocarcinoma in 8. However, carcinomas originating from almost all parts of the body have been identified as donor tumors [11,17]. Furthermore, although a few exceptions have been reported, neoplasms that have metastasized to other tumors are also generally widely disseminated in other regions of the body, indicating that any widely disseminated tumor can lodge and grow in other tumors, although no specific type of tumor with a predilection to metastasize to other tumors has been identified [11,17]. Although there are several reported cases of gastric carcinoma as the donor tumor [9,11,17,25] and thyroid adenoma as the recipient tumor [11,25], only 1 case of gastric carcinoma metastatic to thyroid adenoma has been reported [25]. Similarly, although several cases of thyroid carcinoma as the donor tumor have been reported [4,17,25], there is only one such case in which lung carcinoma was reported as the recipient of the thyroid cancer [4]. Therefore, the combinations in our patients are extremely rare.

It is still unknown whether the metastasis of one neoplasm to another is incidental or due to specific conditions of the donor and recipient neoplasms, although several hypotheses have been proposed to account for this phenomenon. Regarding the high incidence of lung carcinomas as the donor in tumor-to-tumor metastasis, Horie and colleagues [5] proposed that the rich vascularity of lung carcinoma together with the probable shedding of tumor cells during respiratory lung movement might increase the frequency of invasion into the pulmonary vein and subsequently into the general circulation. The extremely high incidence of RCC as the recipient tumor in tumor-to-tumor metastasis could be accounted for by the rich vascularity and good circulation of this tumor, by which it may receive a large



**Figure 8.** Patient 2. Immunohistochemical staining for thyroglobulin. The follicular contents and the luminal surfaces of the tumor cell lining of the papillary carcinoma are strongly positive for thyroglobulin, whereas the squamous-cell carcinoma cells are completely negative for thyroglobulin (ABC immunoperoxidase stain counterstained with hematoxylin,  $\times 200$ ).

proportion of the tumor emboli from donor tumors [11], as well as by tumor cell factors, such as rich glycogen and lipid contents, which provide a suitable environment for the acceptance and growth of tumor metastasis [2]. The rich vascularity of endocrine tumors also accounts for the high incidence of metastasis in thyroid and adrenocortical adenomas [11].

The high lipid content of the adrenal cortex may also contribute to the high incidence of metastasis in adrenal adenomas. The aerobic metabolic state of RCC cells, as opposed to the anaerobic state of fully malignant cancer cells, may result in their weak nutritive competition with donor cancer cells, thus allowing the latter to survive [3,22]. Furthermore, a possible tumor angiogenesis factor released by RCCs may prevascularize the surrounding environment, creating a favorable target for the metastasizing primary tumor [12]. In addition, it has been suggested that tumors do not possess the immunological capacity to reject foreign bodies that the normal tissues from which they are derived possess [13,19]. Finally, the possibility that the phenomenon is entirely coincidental should not be overlooked.

The thyroid adenoma and the lung

carcinoma in our patients were sufficiently vascular that it would not be surprising to find metastatic deposits in them. However, reported cases of either gastric carcinomas metastatic to thyroid adenomas or thyroid papillary carcinomas metastatic to lung carcinomas are extremely rare, despite the pathological evidence that metastasis to the thyroid gland is not uncommon in cancer patients and, as described, is seen in up to 25% [15], or that the lung is the most frequent site of blood-borne metastases of thyroid papillary carcinoma, the occurrence of which is not uncommon [4,7,8].

In the second patient presented herein, multiple small metastatic foci were found in the background lung tissue, as well as within the lung carcinoma. Therefore, we speculate that the papillary carcinoma metastatic to the lung carcinoma occurred incidentally. In contrast, in the first patient, the metastatic foci in the thyroid gland were found exclusively within the thyroid adenoma and not in the surrounding thyroid tissue, although widely disseminated metastases were found outside the thyroid tissue. Therefore, we speculate that the rich vascularity and the good circulation of the thyroid adenoma might have been related to the metastasis in this patient.

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