Papillary Thyroid Microcarcinoma with Lung Metastases: A Case Report and Review of the Literature

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Case report

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Abstract

Introduction: Distant metastasis from papillary thyroid microcarcinoma (PTMC) is rare. Here we report a case of PTMC with multiple lung metastases.

Case Presentation: A 64-year-old man presented to our hospital with abdominal pain. Computed tomography incidentally revealed multiple lung nodules. The lung tumor was histologically diagnosed as metastasis of papillary thyroid carcinoma (PTC) by core needle biopsy via thoracoscopy. The patient was referred to our department for further examination. Neck ultrasonography revealed a 0.8 cm hypoechoic mass in the right lobe of the thyroid gland, diagnosed as PTC by fine-needle aspiration cytology. Subsequently, total thyroidectomy was performed, followed by radioiodine therapy. Iodine-131 (131-I) scintigraphy showed a strong accumulation in the lung metastasis. The patient presented no evidence of progression of lung metastasis for 25 months after the operation.

Discussion/Conclusions: Although there are few published cases of metastatic PTMC, lymph node metastasis or extraglandular extension was observed in most patients, including the present case, and the average age of these cases was 58.8 ± 12.0 years. Although active surveillance without surgical resection is expected to remain standard of care for PTMC, this case indicates that a subset of PTMC patients with risk factors may develop distant metastases. Careful preoperative screening is required to avoid complications associated with reoperation of the remnant thyroid gland.

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinoma (PTC) measuring less than or equal to 1.0 cm in diameter. PTC generally grows slowly, and recent clinical studies have demonstrated that most PTMCs do not increase in size over long-term observation [1–4]. Given the indolent nature of PTC, distant metastasis from PTMC has been considered very rare [3–5].

Although tumor size, multifocal cancers, extrathyroidal extension, and lymph node metastasis have been suggested as prognostic factors for PTMC recurrence [6–9], the risk factors for distant metastasis remain unclear. We report a case of PTMC with multiple lung metastases and review similar cases in the literature to explore the risk factors for distant metastases from PTMC.

Case Report/case Presentation

A 64-year-old man was diagnosed with multiple nodules in the lungs on a computed tomography (CT) scan to investigate the cause of abdominal pain. He had no history of malignant tumors. Thoracoabdominal CT revealed a solid tumor in the middle lobe of the right lung measuring 30 mm in diameter (Fig. 1A) and multiple bilateral lung nodules less than 5 mm in size (Fig. 1B). Primary lung cancer or multiple lung metastases from a malignant tumor originating in another organ were suspected. Because the lesions were difficult to access via a transbranchoval approach, core needle biopsy of the tumor in the middle lobe of the right lung was performed via thoracoscopy. Histopathological examination revealed atypical cells with intranuclear cytoplasmic inclusions that formed papillary structures (Fig. 2A). In addition, immunohistochemical examination showed
positive staining for thyroglobulin (Tg), thyroid transcription factor-1 (TTF-1), and PAX8, but negative staining for Napsin A (Fig. 2B–E). Based on these findings, the tumor was diagnosed as a metastasis of PTC.

Subsequently, the patient was closely examined for a primary lesion in the thyroid gland. Physical examination showed no palpable mass on the neck. Both Tg antibody and thyroid peroxidase antibody were negative [53.9 IU/mL (≥40.6) and 2.1 IU/mL (≥5.2)], and the serum Tg level (31.0 ng/mL) was within normal limits (≤33.7) (Table 1). Ultrasonography revealed a hypoechoic nodule with an indistinct border measuring 8.6 x 4.6 mm in the right lobe of the thyroid gland (Fig. 1C). Multiple lung nodules showed strong uptake on $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET), but no uptake was detected in the thyroid gland tumor (Fig. 1D). As fine needle aspiration cytology from the thyroid nodule demonstrated atypical cells with intranuclear cytoplasmic inclusions and grooved nuclei, the nodule was diagnosed as PTC. Consequently, the patient was diagnosed with PTMC with multiple lung metastases and underwent total thyroidectomy with central neck lymph node dissection.

Histopathological examination of the resected specimen revealed that the thyroid tumor in the right lobe was 0.7 x 0.3 cm in size, and metastasis to the paratracheal lymph nodes and histopathological findings of the tumor were consistent with those observed in the lung tumor (Fig. 2F). Extrathyroid extension to the perithyroid soft tissue was also detected. Subsequently, radioactive iodine (RAI) therapy was administered to treat the multiple lung metastases. In 131-I scintigraphy following the first RAI therapy, an accumulation of 131-I was observed in the thyroid bed alone. Later, 131-I accumulation was observed in the metastatic lesion in the right lung on scintigraphy following the second and third RAI therapies (Fig. 1E). The patient has received RAI therapy three times to date and has been well with no signs of progression in the lung and other organs for 25 months after the operation.

**Discussion/conclusion**

The overall incidence of PTC continues to increase worldwide [10-13]. In addition, PTMC has increased due to the spread of health screening, technological progress in ultrasonography, and improved accuracy of ultrasonography-guided fine needle aspiration cytology [14-16]. Although PTCs generally grow slowly, lymph node metastases are known to occur even when the primary tumor is small. As for PTMC, Elliot et al. reported that 11.5% of PTMC had cervical lymph node metastases in a retrospective study of 112 resected cases [17]. However, two prospective observational studies from Japan demonstrated that the incidence of distant metastasis from PTMC is very rare [3, 4]. Ito et al reported that no patients developed distant metastasis for ten years after the diagnosis of PTMC in 1,235 patients observed without surgery [3]. Similarly, Sugitani et al reported that no distant metastasis occurred in 230 non-surgical PTMC patients observed for ten years [4].

On the other hand, in a large-scale retrospective analysis using the Surveillance, Epidemiology and End Results (SEER) Cancer Database (18,445 cases) in the United States, the incidence of distant metastasis from PTMC was reported to be 0.5% [18]. In a recent retrospective analysis of 8808 patients with PTMC in Korea, Jeon et al reported that 12 patients (0.1%) had distant metastases, and four patients died of the primary disease [19]. Thus, although distant metastases from PTMC rarely occur, PTMC should be included in the differential diagnosis list for the primary lesion when we find metastatic lesions from an unknown origin.
A literature search revealed that only 24 cases of distant metastases from PTMC, confirmed histopathologically or by uptake of radioactive iodine, have been reported in the last 20 years (Table 2) [5, 14, 19-28]. Other than tumor size, extraglandular extension of the primary tumor, extranodal extension of metastatic lymph nodes, size of metastatic lymph nodes, older age, and male sex have been indicated as possible risk factors for recurrence of PTC [29-32]. In addition, the recently revised TNM staging system defined a high risk for people aged 55 and over [33]. Jeon et al recently reported the association of disease-specific mortality with old age, large metastatic lymph nodes with extranodal extension, and a change to an aggressive pathologic subtype of metastatic lymph nodes by analyzing a large number of patients with PTMC [19]. Although detailed information on pathological diagnosis was unknown for several of the 24 cases found in the literature, either lymph node metastasis or extraglandular extension was observed in most patients, including the present case, and the average age of these cases was 58.8 ± 12.0 years. Thus, the possibility of distant metastases should be considered in PTMC cases with risk factors for PTC recurrence.

RAI therapy is the standard therapy for distant metastases from PTC, and patients must undergo total thyroid gland resection before treatment. However, it is known that resection of the remnant thyroid gland is associated with a higher incidence of surgical complications such as recurrent laryngeal nerve paralysis and permanent hypoparathyroidism compared with initial surgery.\(^{34}\) To avoid such complications due to re-operation, PTC patients should be carefully assessed for distant metastases by CT or other imaging modalities before surgery.

On the other hand, Kawano et al recently showed that routine chest CT at the time of PTMC diagnosis did not identify distant lung metastasis in 1,000 patients with low-risk PTMC and suggested that chest CT is not beneficial for PTMC patients with respect to cost, radiation exposure, and so on.\(^{35}\) Considering these findings, when cervical ultrasonography reveals the existence of extrathyroidal extension of the primary lesion, extranodal extension of the metastatic lymph nodes, or large metastatic lymph nodes in patients over 55 years of age, we should consider screening for distant metastases to avoid complications from reoperation and to facilitate subsequent RAI therapy.

In conclusion, PTMC with multiple lung metastases is rare. Although active surveillance of PTMC is expected to remain the standard for care, this case suggests that a subset of PTMC patients may develop distant metastases. In particular, screening for distant metastases should be considered in patients with risk factors for recurrence of PTC.

**Abbreviations**

PTMC: papillary thyroid microcarcinoma, PTC: papillary thyroid carcinoma, 131-I: Iodine-131, CT: computed tomography, Tg: thyroglobulin, TTF-1: thyroid transcription factor-1, FDG-PET: \(^{18}\)F-fluorodeoxyglucose positron emission tomography, RAI: radioactive iodine, SEER: Surveillance, Epidemiology and End Results

**Declarations**

Ethics approval and consent to participate
Written informed consent was obtained from the patient for publication of this case report and any
accompanying images.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials

The data supporting the findings of this work are available from the authors upon reasonable request.

Competing interests.

The authors have no conflicts of interest to declare.

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Author's Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Tadafumi Shimizu, Takaaki Oba, Ken-ichi Ito. The first draft of the manuscript was written by Tadafumi Shimizu and all authors commented on the manuscript. Yoshinori Sato, Takeshi Uehara evaluated the pathological findings. All authors read and approved the final manuscript.

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Tables

Table 1 Preoperative blood test findings for a 64-year-old man with papillary thyroid microcarcinoma with lung metastases

| Parameter                  | Value               | Normal range       |
|----------------------------|---------------------|--------------------|
| Free T3                    | 3.10 pg/ml; normal  | 2.30–4.00 pg/ml    |
| Free T4                    | 1.36 pg/ml; normal  | 0.9–1.7 pg/ml      |
| Thyroid stimulating hormone| 2.27 μIU/ml; normal | 0.50–5.00 μIU/ml   |
| Thyroglobulin antibody     | 53.9 IU/ml; normal  | <40.6 IU/ml        |
| Thyroid peroxidase antibody| 2.1 IU/m; normal    | <5.2 IU/ml         |
| Thyroglobulin              | 31.0 ng/ml; normal  | <33.7 ng/ml        |

Table 2 Clinicopathological features of previously reported cases of papillary thyroid microcarcinoma with distant metastasis
| N  | Author et al. | Year | Age (years) | Sex | Reasons for detection | Diagnostic method for PTMC metastases | Surgery for thyroid | Tumor size (cm) | pN | Ex | Metastatic site | 131-I therapy | Prognosis |
|----|---------------|------|-------------|-----|-----------------------|--------------------------------------|-------------------|----------------|----|----|----------------|--------------|-----------|
| 1  | Murakami et al.[5], 2001 | 63 M | Abdominal tumor | Extirpation of abdominal tumor | Partial resection of L thyroid lobe and ND TT | 0.1 | + | N.A | Rectus muscle | - | 1 y 8 m, alive |
| 2  | Yamada et al. [14], 2001 | 68 M | Chest X ray | Fiberoptic bronchoscopic biopsy | TT | <1.0 | N.A | N.A | Lung | + | 1 y 10 m, alive |
| 3  | Erdem et al. [20], 2003 | 40 M | Dysphagia | Resection of a R parapharyngeal mass | TT and ND | 0.8 | - | N.A | Parapharyngea | + | 3 y, alive |
| 4  | Liou et al. [21], 2005 | 50 F | Right pelvic fracture | R hemipelvectomy and renal biopsy | TT | 1 | N.A | N.A | Kidney, pelvic bone, lung | + | about 3 y, alive |
| 5  | Itoh et al. [22], 2008 | 82 F | Cough, back pain | Fiberoptic bronchoscopic biopsy | None | 0.6 | - | N.A | Brain, liver, pancreas, kidney, ovary, bone, lung | - | 7 m, dead |
| 6  | Lecumberri et al.[23], 2010 | 65 F | Headache, tinnitus | Resection of a cerebellar mass | TT and ND | 0.2 | - | + | Brain | + | 7 y, dead |
| 7  | Xu et al. [24], 2011 | 46 F | Cervical mass | 131-I WBS and SPECT/CT | TT and ND | 0.3 | + | N.A | Brain, lung | + | 3 m, alive |
| 8  | Saito et al. [25], 2011 | 70 F | Cough | R lung lobectomy | Subtotal thyroidectomy and ND | 0.8 | - | N.A | Lung | - | 3 y 10 m, alive |
| 9  | Kozu et al. [26], 2014 | 70 M | Chest CT | L lung lobectomy | None | N.A | N.A | N.A | Lung | - | 4 m, alive |
| 10 | Kaseda et al. [27], 2016 | 66 F | Chest CT | Transbronchial biopsy and R lung lobectomy | None | N.A | N.A | N.A | Lung | - | N.A |
| 11 | Kawai et al. [28], 2016 | In70's M | Chest discomfort | R lung lobectomy | R thyroid lobectomy and ND | 1 | + | + | Lung | - | 11 y, alive |
| 12 | Jeon et al. [19], 2014 | 51 F | Neck US | 131-I WBS and SPECT/CT | TT and ND | 0.8 | + | - | Lung | + | 1.9 y, alive |
| 13 | Jeon et al. [19], 2016 | 31 F | Neck US | 131-I WBS and SPECT/CT | TT and ND | 0.9 | + | + | Lung, bone | + | 6.7 y, alive |
| 14 | Jeon et al. [19], 2016 | 55 F | Neck US | 131-I WBS and SPECT/CT | TT and ND | 0.9 | + | + | Lung, bone | + | 7.6 y, alive |
| 15 | Jeon et al. [19], 2016 | 59 F | Neck US | 131-I WBS and SPECT/CT | TT and ND | 1 | + | + | Lung | + | 2.1 y, alive |
| 16 | Jeon et al. [19], 2016 | 73 F | Neck US | 131-I WBS and SPECT/CT | TT and ND | 1 | + | + | Lung | + | 8.8 y, alive |
| 17 | Jeon et al. [19], 2016 | 54 F | Hoarseness | 131-I WBS and SPECT/CT | TT and ND | 0.8 | + | + | Lung | + | 10.7 y, alive |
| 18 | Jeon et al. [19], 2016 | 63 F | Neck mass | 131-I WBS and SPECT/CT | TT and ND | 0.8 | + | + | Lung | + | 11.4 y, dead |
| No. | Authors [Year], Reference | Age | Gender | Initial Symptom | Imaging Studies | TT and ND | Metastasis Sites | Survival | Status |
|-----|---------------------------|-----|--------|-----------------|----------------|-----------|-----------------|---------|--------|
| 19  | Jeon et al. [19], 2016    | 46  | F      | Chest CT        | 131-I WBS and SPECT/CT | TT and ND | 0.7 + + | Lung, bone | +       | 15 y, alive |
| 20  | Jeon et al. [19], 2016    | 65  | M      | Hoarseness      | 131-I WBS and SPECT/CT | TT and ND | 0.6 + - | Lung, bone | +       | 1 y, dead |
| 21  | Jeon et al. [19], 2016    | 58  | M      | Neck mass       | 131-I WBS and SPECT/CT | TT and ND | 1 + -  | Lung, brain | +       | 4.9 y, dead |
| 22  | Jeon et al. [19], 2016    | 60  | F      | Neck mass       | 131-I WBS and SPECT/CT | TT and ND | 0.8 + - | Lung, brain | +       | 10 y, dead |
| 23  | Jeon et al. [19], 2016    | 63  | F      | Neck mass       | 131-I WBS and SPECT/CT | TT and ND | 0.9 + + | Lung, bone | +       | 10.7 y, dead |
| 24  | Our case                  | 64  | M      | Chest CT        | Lung biopsy via VATS  | TT and ND | 0.7 + + | Lung       | +       | 2 y 1 m, alive |

pN: pathological cervical lymph node metastases, Ex: extrathyroid extension, 131-I: 131-iodine, WBS: whole body scan, SPECT/CT: single-photon emission computed tomography, CT: computed tomography, VATS: video-assisted thoracic surgery, TT: total thyroidectomy, ND: neck dissection, N.A: not available, y: years, m: months

**Figures**

**Figure 1**
A,B: Computed tomography findings in the lung. A solid 30 mm mass (arrow) in the middle lobe of the right lung (A) and several 5 mm nodules (arrowheads) (B) can be seen in both lungs. C: Ultrasonographic findings in the thyroid gland. A hypoechoic mass measuring 8.6 × 4.6 mm and showing an indistinct border can be seen in the right lobe of the thyroid gland (arrow). D: 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) findings. Strong FDG uptake is detected in the right lung tumor (arrow) and multiple tumors in the left lung (arrowhead). F: First 131-iodine scintigraphy findings. 131-iodine has accumulated in the tumor in the middle lobe of the right lung.

![Image of A, B, C, D, E](image)

**Figure 2**

A-E: Histopathological findings of the tumor in the middle lobe of the right lung. Atypical cells with intranuclear cytoplasmic inclusions have grown with papillary formations (A; HE, ×100). The tumor cells are positive for thyroglobulin (B; ×100), thyroid transcription factor-1 (C; ×100), and PAX8 (D; ×100) and negative for Napsin A (E; ×100). Scale bar: 100 μm  
F: Histopathological findings of the thyroid. The tumor in the right lobe of the thyroid is diagnosed as papillary thyroid cancer, consistent with the lung tumor. Firm infiltration into the surrounding fat tissue can be observed (×100). Scale bar: 100 μm