Case Report

Aggressive cribriform-morular variant of papillary thyroid carcinoma: Report of an unusual case with pulmonary metastasis displaying poorly differentiated features

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The cribriform-morular variant of papillary thyroid carcinoma (CMV-PTC) is a rare variant of PTC, accounting for 0.16% of PTC cases, and is a representative subtype of inherited thyroid cancers.1–3 CMV-PTC is common in young females less than 30 years of age.1,4 Although sporadic forms of CMV-PTC appear as isolated tumors, cases associated with familial adenomatous polyposis (FAP), which make up about 1–2% of patients with FAP, develop CMV-PTC as an extracolonic manifestation that is often multifocal.4 The histology of CMV-PTC shows a combination of distinctive follicular, cribriform, papillary, and trabecular patterns, and squamous metaplasia. The follicles do not contain colloid, and carcinoma cells can exhibit the nuclear features of PTC in some tissue areas. An immunohistochemical characteristic of CMV-PTC is cytoplasmic and nuclear positivity for β-catenin. Although capsular and vascular invasion are usually present, the presence of regional or distant metastases is extremely rare. The clinical outcome of CMV-PTC is generally favorable, with few cancer-related deaths.1,2,5 To our knowledge, only three cases of metastasis by CMV-PTC, such as to the lung, bone, brain, and regional lymph nodes, have been reported.6–8 We describe here a rare sporadic case of CMV-PTC with multiple lung metastases in a 28-year-old female, 3 years after total thyroidectomy.

Key words: cribriform-morular variant of papillary thyroid carcinoma, immunohistochemistry, lung, metastasis, β-catenin

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CLINICAL SUMMARY

A 28-year-old woman without a history of FAP presented with a neck mass and underwent a total thyroidectomy with cervical lymph node dissection at Kuma Hospital (Japan). In preoperative computed tomography (CT), distant metastases were not observed. After surgery, the patient underwent thyrotropin suppression therapy. Three years later, the patient complained of chest pain, and a thoracic CT scan showed multiple bilateral masses in the lungs. Because a
metastatic tumor was suspected, the patient underwent colonoscopy but no tumor was identified. The decision was made to undertake a right partial lobectomy to obtain a definitive pathological diagnosis of a lung tumor. The patient subsequently underwent radioactive iodine remnant ablation and sorafenib therapies. Informed consent was obtained from the patient for this case study.

**PATHOLOGICAL FINDINGS**

Immunohistochemical stains were performed on formalin-fixed and paraffin-embedded tissues. Four-micrometer thick sections were stained with antibodies against estrogen receptor (ER; pre-diluted; Ventana, Tucson, AZ, USA), progestosterone receptor (PgR; pre-diluted; Dako, Glostrup, Denmark), β-catenin (BD Bioscience, Franklin Lakes, NJ, USA), Ki-67 (Dako), thyroglobulin (Dako), thyroid transcription factor 1 (TTF-1; pre-diluted; Ventana), paired-box gene 8 (PAX-8; Proteintech, Rosemont, IL, USA), adenomatous polyposis coli (APC; Millipore, Temecula, CA, USA), p53 (MBL, Nagoya, Japan), and homeobox protein CDX-2 (pre-diluted; Ventana). Immunohistochemical staining was performed with an automated staining system (BenchMark ULTRA; Ventana) as previously described.9,10 Primary antibodies were incubated for 30 min at a dilution of 1:1000 for anti-β-catenin, 1:25 for anti-APC, 1:50 for anti-p53, 1:50 for anti–Ki-67, 1:3000 for anti-thyroglobulin, and 1:300 for anti–PAX-8, respectively, at 37°C.

The DNA extraction and mutation analysis of the BRAF gene was conducted by LSI Medience Corporation (Tokyo, Japan) as previously described.10 Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue. Serial slices, at a 5 mm thickness, were made from a block for tumor cell dissection. After deparaffinization with xylene, tissue sections were stained with hematoxylin and eosin. Target tumor lesions were macroscopically dissected to minimize contamination with normal tissue. Real-time polymerase chain reactions with a THxID BRAF Kit (bioMérieux, Marcy-l’Étoile, France) were performed for BRAF V600E mutation analysis.

The thyroid tumor in the right lobe, measuring 9.1 cm in diameter, was found to be encapsulated and showed a cystic change. Microscopically, carcinoma cells showed a combination of cribriform and papillary patterns of growth (Fig. 1a). Very little colloid was found within the tumor; carcinoma cells were columnar with nuclei lacking the features of PTC, and with small foci of squamous metaplasia (Fig. 1b). Mitotic figures (5–6/10 high-power field) were observed. Carcinoma cells were positive for ER, PgR, and p53 (focally), and showed positive nuclear and cytoplasmic staining for β-catenin (Fig. 1c, d). Carcinoma cells also showed positive cytoplasmic staining for APC (Fig. 1e).

Carcinoma cells stained negatively for thyroglobulin, and the Ki-67 labeling index was 40.2%. The tumor was diagnosed as CMV-PTC. Lymph node metastasis was not observed.

The lung tumor was not encapsulated but well-circumscribed (Fig. 2a, b), showing a mixture of cribriform, glandular, and solid patterns of growth with necrosis (Fig. 2c, d). The carcinoma cells were tall columnar, with nuclei lacking the features of PTC. Mitotic figures (3–4/10 high-power field) were observed. Carcinoma cells were positive for TTF-1, PAX-8, ER, PgR, and p53 (focally) (Fig. 3a–c), and showed positive nuclear and cytoplasmic staining for β-catenin (Fig. 3d). Carcinoma cells also showed positive cytoplasmic staining for APC (Fig. 3e). Carcinoma cells were negative for thyroglobulin and CDX-2, and the Ki-67 labeling index was 22.1%. This immunoprofile suggested a pathological diagnosis of metastasis by a CMV-PTC displaying poorly differentiated features.

DNA was extracted from both primary and metastatic tumors, and mutation analysis for the BRAF gene was performed as described above. Both components showed no BRAF V600E missense mutation.

**DISCUSSION**

In general, patients with CMV-PTC follow an indolent clinical course with a favorable outcome.5,11 CMV-PTC has rarely showed regional or distant metastasis, and, until now, only three cases of metastasis by CMV-PTC have been reported, as shown in Table 1.6–8 The value of the Ki-67 labeling index in CMV-PTC cases is usually low,12,13 less than 6%; however, two of three cases of metastatic CMV-PTC showed a high Ki-67 labeling index. Previous reports indicated that a high Ki-67 labeling index correlated with distant metastasis and an unfavorable prognosis.14 In our case, the Ki-67 labeling indexes of thyroid (primary) and lung (metastasis) tumors were 40.2% and 22.1%, respectively; notably, the thyroid tumor in this study led to multiple lung metastases. Therefore, an assessment of the Ki-67 labeling index in CMV-PTC cases may be useful in predicting metastatic potential and for highlighting the need for careful follow-up. The Ki-67 labeling index is higher in metastatic cancer than in primary cancer in general; however, in our case the Ki-67 labeling index was higher in the primary thyroid cancer (40.2%) than in the metastatic lung cancer (22.1%). Previous reports indicated a decrease of Ki-67 immunoreactive cells in lymph nodes compared with the primary breast cancer was observed in 16% of cases; this could be related to the heterogeneity of the neoplastic cells, as different clone metastases are present in the primary cancer.15 A sub-population with a relatively lower growth
fraction and metastatic potential of the primary thyroid cancer may have metastasized to the lung in our case; however, this needs to be assessed in further studies.

To date, only three cases of metastasis by CMV-PTC have been reported as shown in Table 1; however, reports outlining the histological features of any visceral metastatic site are lacking. In the present case, the patient underwent a right lung partial lobectomy to obtain a definitive pathological diagnosis. Occasionally, differentiated carcinoma dedifferentiates to become an anaplastic thyroid carcinoma (ATC) during the metastatic process. In our case, the carcinoma cells in the lung were found to show a mixture of cribriform, glandular, and solid patterns of growth with necrosis; the lung carcinoma cells were tall columnar, although carcinoma cells in the thyroid showed columnar features without necrosis. As the tall cell variant of PTC is considered a more aggressive variant than conventional PTC, a histological change of carcinoma cells from columnar to tall columnar may suggest a dedifferentiation of carcinoma cells during the metastatic process. Furthermore, because a necrotic area existed in the lung but not thyroid tumor, poorly differentiated thyroid carcinoma (PDTC) may be considered as a differential diagnosis in our case. In fact, lymph node or visceral metastasis are frequent in PDTC; however, metastasis is very rare in CMV-PTC clinically. Nakazawa et al. reported a CMV-PTC case that transformed into PDTC within a thyroid tumor. Although a histological assessment of a metastatic site such as in the

![Figure 1](image_url)  

**Figure 1** Microscopic appearance of a nodule in the thyroid gland. (a) Carcinoma cells were arranged in a cribriform and papillary pattern. (b) Carcinoma cells were columnar with nuclei but lacked the features of papillary thyroid carcinoma; small foci of squamous metaplasia were present. (c) Carcinoma cells were positive for estrogen receptor, and (d) showed positive nuclear and cytoplasmic staining for β-catenin. (e) Carcinoma cells also showed positive cytoplasmic staining for adenomatous polyposis coli (APC). (a, b, hematoxylin and eosin; a, ×4; b, ×10; c, estrogen receptor immunostain, ×10; d, β-catenin immunostain, ×10; e, APC immunostain, ×10).  

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bone and lung was not made, their report described the
coeexistence of CMV-PTC and PDTC within the thyroid
tumor. They also showed that the tissue region with PDTC
maintained an ER, PgR and TTF-1 immunoprofile. The
case reported by Nakazawa et al. showed that the border
between CMV-PTC and PDTC components was relatively
well defined; however, the solid nests of cells observed
in the tumor of our case occasionally intermingled with glandu-
lar cells, so that there was no apparent border to suggest a
PDTC component. A PDTC case with a predominant
cribiform pattern within the thyroid tumor may be consid-
ered for a differential diagnosis. Because there was almost
no difference in mitotic activity or Ki-67 positivity between
solid cell nests and cribiform cells, the thyroid tumor in our
case was considered a CMV-PTC without a PDTC compo-
nent. Necrosis existed in the lung tumor of our case;
however, carcinoma cells were tall columnar with nuclei
lacking the features of PTC and showed a mixture of
cribiform, glandular, and solid patterns of growth. Dediffer-
entiation of carcinoma cells during the metastatic process
may occur and lead to a display of poorly differentiated
features. Genetically, mutations of the APC gene and/or
catenin beta 1 (CTNNB1), both of which are key regulators
of the Wnt signal transduction pathway, are often detected in
CMV-PTC. CTNNB1 gene mutations are also associ-
ated with high grade PDTC. In our case, positive APC
immunohistochemistry suggested the absence of APC
mutations. Furthermore, the focal positivity of p53 immuno-
histochemistry suggested the absence of p53 mutations,
which are often detected in PDTC. Because a previous
report showed a lack of mutations in CTNNB1 in both of
CMV-PTC and PDTC within a thyroid tumor, CTNNB1
mutations involving the Wnt signaling pathway may not be
essential for a differential diagnosis. However, CTNNB1 or
telomerase reverse transcriptase promoter mutations may
be related to the poorly differentiated features of the lung
tumor in our case.

In the present case, a low serum thyroglobulin level was
maintained during the 3 year follow-up period. Similarly, a
previously reported case showed serum thyroglobulin levels
remained undetectable, although structurally identifiable
bone metastases persisted. Thyroglobulin monitoring of
serum after total thyroidectomy and radioactive iodine
remnant ablation therapy are well known as useful predic-
tors of recurrence. A previous report revealed that
diagnostic accuracies in the measurement of serum thyro-
globulin for a tumor's presence during thyrotropin suppres-
sion therapy were very high (sensitivity 100%, specificity
93%). However, CMV-PTC showed characteristic histo-
logical features such as follicular structures devoid of colloid
and thyroglobulin immunostaining that is often focal and
weak. With regard to these characteristics, serum

Figure 2  Macroscopic and microscopic appearances of a lung tumor. (a, b) The lung tumor was not encapsulated but well-circumscribed
and showed a mixture of cribiform, glandular, and (c) solid patterns of growth with (d) necrosis (asterisk). (b–d, Victoria Blue–hematoxylin
and eosin; b, ×4; c, ×10; d, ×10).
thyroglobulin levels may not be useful for the monitoring of active CMV-PTC disease.

In conclusion, we report a quite unusual case of sporadic CMV-PTC metastasis to the lung. The carcinoma cells in the lung showed poorly differentiated features and the same immunohistological features as the primary thyroid tumor. Usually, CMV-PTC is a well-differentiated thyroid carcinoma that displays a favorable clinical outcome and rarely causes

Table 1 Profiles of metastatic cases of the cribriform-morular variant of papillary thyroid carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Metastasis</th>
<th>Age</th>
<th>Sex</th>
<th>FAP</th>
<th>Mutation</th>
<th>Ki-67 labeling index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameselle-Teijeiro et al. (8)</td>
<td>Lung</td>
<td>42</td>
<td>Male</td>
<td>+</td>
<td>APC and RET/PTC</td>
<td>Primary: 60%</td>
</tr>
<tr>
<td>Nakazawa et al. (9)</td>
<td>Brain</td>
<td>35</td>
<td>Female</td>
<td>–</td>
<td>Somatic APC</td>
<td>Primary:15–20%</td>
</tr>
<tr>
<td>Oh et al. (10)</td>
<td>Bone</td>
<td>45</td>
<td>Female</td>
<td>–</td>
<td>TERT promoter</td>
<td>Unknown</td>
</tr>
<tr>
<td>Present case</td>
<td>Lymph node</td>
<td>28</td>
<td>Female</td>
<td>–</td>
<td>Unknown</td>
<td>Primary: 40.2%</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metastasis: 22.1%</td>
</tr>
</tbody>
</table>

APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; PTC, papillary thyroid carcinoma; RET, rearranged during transfection; TERT, telomerase reverse transcriptase

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cancer-related death. The present case suggests that CMV-PTC with a high Ki-67 labeling index may cause visceral metastasis.

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DISCLOSURE STATEMENT

None declared.

Abbreviations. APC, adenomatous polyposis coli; ATC, anaplastic thyroid carcinoma; CT, computed tomography; CTNNB1, catenin beta 1; ER, estrogen receptor; FAP, familial adenomatous polyposis; PAX-8, paired-box gene 8; PDTC, poorly differentiated thyroid carcinoma; PgR, progesterone receptor; TTF-1, thyroid transcription factor 1.

REFERENCES