Case report: exceptionally rapid growth character of hobnail variant of papillary thyroid carcinoma: a report of four cases

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Abstract. The newest WHO classification adopts hobnail variant as an aggressive variant of papillary thyroid carcinoma (PTC). We here report four cases (ages 70–76 years, all females) with hobnail variant PTC treated at Kuma Hospital. Their lesions were cytologically diagnosed as PTC before surgery, but not as hobnail variant. All patients underwent a total thyroidectomy with central node dissection, and two patients also underwent therapeutic lateral node dissection. The clinical courses of three of the patients were very eventful. One patient showed recurrence to lymph nodes in the lateral compartment only 5 months after the initial surgery. In the initial surgery, one patient had a 36-mm lymph node metastasis in the lateral compartment, which was diagnosed as hobnail variant on pathology; 9 months post-surgery, metastases to the ipsilateral lateral lymph node, lung, and bone were newly detected. Her lung metastasis grew rapidly; its tumor volume-doubling time was 0.15 years and its tumor-doubling rate was 6.67/year. One patient underwent annual ultrasound examinations as postoperative follow-up after hemithyroidectomy for a benign nodule, but a 35-mm nodule diagnosed as PTC on cytology and lateral node metastases appeared within a short period, and she underwent a second surgery. Both the primary lesion and lymph nodes were diagnosed as hobnail variant by postoperative pathology. Three of the four patients showed exceptionally rapid growth of primary and/or metastatic/recurred lesions, indicating that patients with the hobnail variant should undergo very close and careful post-operative observation.

Key words: Hobnail variant, Papillary thyroid carcinoma, Rapid growth, Recurrence
variant by our pathologists (M.H. and T.H.). For this study, one pathologist (M.H.) reviewed the pathology records again.

For the patients’ ultrasound (US) examinations, an Aplio 500 system (Canon Medical Systems, Tochigi, Japan) was used with a linear-type probe PLT-1005BT (Canon Medical Systems, Tochigi, Japan). For the evaluations of the ultrasound findings, we used the ultrasound classification (USC) system established in 1996 by Kuma Hospital [14]. Briefly, nodules were classified into the following five categories. USC1: A round and anechoic area (a cyst or adenomatous nodule). USC2: A round and cystic nodule (single or multiple) or isoechic solid nodule (adenomatous nodule, or follicular adenoma). USC3: A round and hypoechoic solid nodule (adenomatous nodule, follicular adenoma, or well-differentiated carcinoma). USC4: A solid nodule with an irregular border or the presence of psammoma calcification (carcinoma). USC5: A solid nodule with an irregular border and extrathyroidal invasion (carcinoma). Between USC2 and USC5, for nodules with ultrasound findings corresponding to two classes, we set intermediate classes: USC2.5, 3.5, and 4.5. Nodules in classes USC ≥3.5, USC3, and USC ≤2.5 were diagnosed as malignant, borderline, and benign, respectively. We also investigated these nodules based on the diagnostic criteria conducted by The Japan Society of Ultrasonics in Medicine, and we evaluated the nodules’ shapes, internal echoes, strong echoes, and boundary zones [15].

For the assessments of thyroglobulin antibody (TgAb) and thyroglobulin (Tg), we performed an electrochemiluminescence immunoassay (ECLIA; Roche Diagnostic, Tokyo).

Results

Four of the 1,675 patients (0.2%) who underwent an initial surgery for PTC in 2018 or 2019 at Kuma Hospital were pathologically diagnosed as having hobnail-variant PTC. We present the clinical courses of these four patients.

Case 1

A 76-year-old female was referred to our hospital because of a palpable and well-movable thyroid nodule. On ultrasound, a solitary 21-mm nodule was detected in the left lobe (USC4, irregular shape, hypoechoic internal echoes, coarse strong echoes, and slightly ill-defined boundary zone) as shown in Fig. 1a. No lymph nodes suspected of metastasis were detected. The cytological examination indicated Bethesda category (Be-) VI (Malignant: Papillary carcinoma) suggesting tall-cell variant because of the presence of carcinoma cells with elongated cytoplasm (Fig. 1b). The preoperative chest computed tomography (CT) scan showed a solitary nodule in the patient’s left lung, which had been followed at another hospital as a benign lesion. No suspicious lesions for metastasis were observed in the lung.

The patient underwent a total thyroidectomy with central node dissection. On pathological examination, her PTC exhibited hobnail structures in 30%–40% of the carcinoma cells (Fig. 1c), and the case was diagnosed as hobnail-variant PTC. The patient had two lymph node metastases on pathology. The Ki-67 labeling index at the hot spot was high at 5%–10%. At 1 month post-surgery, the patient’s TgAb level was negative (<28.0 IU/mL) and her Tg level had become low at 0.26 ng/mL under thyroid stimulating hormone (TSH) suppression. Eight months after the surgery, the patient underwent radioactive iodine (RAI) ablation (30 mCi) using rhTSH, but uptake only to the thyroid bed was detected. At 18 months post-surgery, the patient had no evidence of recurrence and her Tg level remained low.

Case 2

A 70-year-old female was referred to our hospital for a thyroid nodule suspected of malignancy. On ultrasound,
a USC4 nodule measuring 42 mm was detected in the right lobe of the thyroid (irregular shape, hypoechoic internal echoes, coarse strong echoes, and slightly ill-defined boundary zone) (Fig. 2a). Multinodular goiter in the left lobe was also present. The patient had no suspicious lymph nodes on ultrasound. On cytology, the right nodule was diagnosed as PTC (Be-VI). No metastasis was observed on chest CT scan. The patient underwent a total thyroideectomy with central node dissection. Her primary lesion significantly invaded the right recurrent laryngeal nerve and cricothyroid muscle. The recurrent laryngeal nerve was preserved by shaving the tumor off the nerve, but a minute carcinoma lesion might have remained around the nerve.

The pathological examination revealed no lymph node metastasis, but the primary lesion was diagnosed as hobnail-variant PTC because a hobnail-like structure was detected in 40% of her carcinoma lesion. The Ki-67 labeling index was >10% at the hot spot. The patient’s TgAb was weakly positive at 29.0–95.0 IU/mL throughout her course, and her postoperative Tg level remained low (up to 0.29 ng/mL) under TSH suppression. Since there was a possibility of non-curative surgery, the patient was administered adjuvant RAI therapy at 100 mCi at 3 months after the surgery, but no abnormal uptake was observed.

However, only 5 months after the initial surgery, a suspicious 12-mm node was detected in the right lateral compartment (Fig. 2b), and it was cytologically diagnosed as PTC. A right lateral node dissection was performed. On pathological examination, two metastatic nodes of PTC with the hobnail-variant structure (Ki-67 labeling index >10%) were identified. Close follow-up with ultrasound plus the monitoring of the patient’s Tg and TgAb levels under TSH suppression are being conducted.

**Case 3**

A 79-year old female was referred to our hospital for the treatment of PTC. She had a 19-mm nodule in her right lobe (USC4, slightly irregular shape, hypoechoic internal echoes, slightly coarse strong echoes, and slightly ill-defined boundary zone) and also showed a metastatic 36-mm node with intravenous tumor thrombus in the right lateral compartment (Fig. 3a, b). On cytology, both of these nodes were diagnosed as PTC (Be-VI). A preoperative chest CT scan showed no metastasis to the lung (Fig. 3c). Her preoperative TgAb level was very high (＞4,000 IU/mL).

She underwent a total thyroideectomy with central node dissection and right lateral node dissection. Although her primary lesion had no invasion, the lateral metastatic node significantly invaded the internal jugular vein, requiring resection of the vein with the metastatic node. On pathology, the primary lesion was diagnosed as conventional PTC, but the metastatic node was diagnosed as the hobnail variant (30–40%), with a Ki-67 labeling index >40%.

Three months after the patient’s surgery, she underwent RAI ablation (30 mCi) using rhTSH, but no abnormal uptake was observed. Nine months post-surgery, the TgAb level had decreased to 116.0 IU/mL, but at that time, a 14-mm lymph node suspected of metastasis was detected on ultrasound, and it was cytologically diagnosed as PTC metastasis. We then performed a chest CT scan; it revealed a novel appearance of lung metastasis (Fig. 3d), which was not detected preoperatively (Fig. 3c). The patient underwent surgery for the metastatic node (diagnosed as PTC but dominantly granulation tissue) and immediately afterward, a positron emission tomography-computed tomography (PET-CT) scan revealed not only lung metastasis but also metastasis to the lumbar spine (Fig. 3e). We then referred the patient for the treatment of lung and bone metastases to a uni-
versity hospital. After extrabeam radiotherapy for the bone metastasis, the patient returned to our hospital and underwent a chest CT scan; the lung metastasis had significantly enlarged compared to the last examination 5 months earlier (Fig. 3f). The tumor volume-doubling time was 0.15 years and the tumor-doubling rate was 6.67/year, indicating very rapid growth. Tyrosine kinase inhibitor therapy at the university hospital is planned for the lung metastases.

Case 4

This patient had undergone a right lobectomy for a benign nodule (hyperfunctioning nodule diagnosed as adenomatous nodule on pathology) and was being followed by blood examinations and ultrasound once per year at our clinic. Six years after the initial surgery (at age 73), a minute 5-mm lesion was present, but the attending technician did not regard it as a significant finding (Fig. 4a). One year later (7 year after the initial surgery at age 74), the nodule very rapidly grew and measuring 35-mm (USC4, slightly irregular shape, isoechoic internal echoes, punctate strong echoes, and ill-defined boundary zone) (Fig. 4b). On cytology, the nodule was diagnosed as PTC (Be-VI).

A completion total thyroidectomy with central node dissection was planned for the patient, but an ultrasound examination performed the day before the surgery (at 3 months after the last ultrasound) revealed two lymph nodes suspected of metastasis (22 mm and 13 mm) (Fig. 4c). The completion total thyroidectomy with central node dissection was then performed along with therapeutic left lateral node dissection. On pathology, the primary

Fig. 3 Case 3. a: Primary lesion (arrowhead). This was pathologically diagnosed as conventional PTC. TR, trachea; CA, carotid artery. b: Lateral node metastasis, which invaded the internal jugular vein and was diagnosed as hobnail-variant PTC on pathology (arrowhead). JV, internal jugular vein. c: Chest CT scan before surgery. No metastatic lesion was detected. d: Chest CT scan 9 months after the initial surgery. Lung metastasis newly appeared (arrowhead). e: Lumbar spine metastasis detected by PET-CT scan. f: Chest CT scan 4 months after the last examination. The lung metastasis had enlarged and the tumor volume-doubling time was 0.15 years (arrowhead).

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lesion was diagnosed as the hobnail variant (30–40%) with a Ki-67 labeling index >10% (also with tall cell variant component (around 15%). There were 14 nodal metastases on pathology, some of which showed the hobnail-like structure. The patient was negative for TgAb, and after the surgery her Tg level became negative (<0.08 ng/mL). At 5 months after the surgery she underwent adjuvant RAI therapy (100 mCi) using rhTSH, but no abnormal uptake was detected. At her last visit to our clinic 10 months after the surgery, no evidence of recurrence could be found.

Table 1 summarizes the 4 cases of hobnail variant enrolled in this study.

Discussion

To date, several studies about hobnail variant have been published from other countries than Japan. However, very few studies presented each case from preoperative imaging studies to postoperative follow-up. We investigated the clinicopathological characteristics and clinical courses of four hobnail PTC patients treated in our hospital. Case 1 showed no special clinical course, but the clinical courses of the other three cases are very eventful. Case 2 showed a novel appearance of a metastatic node in the lateral compartment only 5 months after the initial surgery, and Case 3 showed node metastasis with intravenous tumor thrombus, resulting in an extremely rapid growth of lung metastasis as well as bone metastasis. Regarding Case 4, a primary lesion showed an extremely rapid growth from 5 mm to 35 mm only for 1 year, and clinical node metastasis newly appeared for a further 3 months.

In our series, all patients were aged ≥70 years, which might be one of the clinical characteristics of hobnail variant (similar to other aggressive variants). In the WHO classification, a high Ki-67 labeling index was listed as a typical pathological characteristic of hobnail variant [1]. All four of our patients had a Ki-67 labeling index higher than 5%. Indeed, a high Ki-67 labeling index is a significant prognostic factor of PTC, and we previously demonstrated that it is an independent predictor of carcinoma death of PTC patients [16]. Several gene alterations (e.g., BRAF mutation and deleterious TP53 mutations) have also been reported in hobnail variant [11].

In our series, none of the four patients were cytologically diagnosed as or suspected of having the hobnail variant. It is thus difficult to diagnose this variant preoperatively. Two of the four patients showed significant extrathyroid extension or extranodal tumor extension, but the remaining two did not. Two patients were regarded as having clinical lateral node metastasis, but the remaining two were not. Therefore, the hobnail variant does not always present aggressive clinicopathological features at the initial surgery. Regardless of the stage at initial surgery, however, it is important for patients pathologically diagnosed as having the hobnail variant to undergo close and constant observation by blood examination (Tg and TgAb levels) and imaging studies such as ultrasound after surgery, considering the possibility of rapid growth of recurred lesions. Close observation enables the patients to undergo immediate therapies suitable for organs where PTC recurs.

In case 3, although primary lesion was conventional PTC, lymph node metastasis showing intravenous tumor thrombus was diagnosed as hobnail variant. It remains unknown whether and how hobnail variant arises, but this finding indicates the possibility that hobnail variant arises from conventional PTC due to some kind of genetic alterations. Further studies are needed to elucidate this point.

This study has a limitation. We could not present any genetic alterations in our series, which are important for diagnosis and predicting prognoses of patients.

In summary, primary and metastatic lesions of hobnail
| Case No. | Gender | Age at initial surgery | Tumor size (mm) | N factor | Largest size of N (mm) | Extent of surgery | Ex | LN-Ex | Percent-age of hobnail variant (%) | Ki-67 labeling index (%) | No. of pN | RAI administration (mCi) | Appreciable points |
|----------|--------|------------------------|----------------|----------|------------------------|------------------|----|-------|---------------------------------|------------------------|-----------|------------------------|-------------------|
| 1        | Female | 76                     | 21             | 0        | N/A                    | TT + CND         | No | N/A   | 30–40                           | 5–10                   | 2         | 30                     | Not in particular  |
| 2        | Female | 70                     | 42             | 0        | N/A                    | TT + CND         | Trachea cartilage | N/A | 30–40 | >10                             |                        | 2         | 100                    | Nodal metastasis appeared 5 months after surgery |
| 3*       | Female | 78                     | 19 (this was conventional PTC) | 1b | 36*                    | TT + MND         | No | Jugular vein | 40                  | >40                   | 3         | 30                     | Lung, bone and LN metastasis appeared and rapidly grew from 3 months after surgery |
| 4**      | Female | 74                     | 35             | 1b       | 22                     | CT + MND         | No | No    | 30–40                           | >10                   | 13        | 100                    | The primary lesion rapidly grew for about 1 year and lateral node metastases appeared only for 3 months. |

Abbreviations: N, clinical node metastasis; Ex, extrathyroid extension on surgical findings; LN-Ex, Extranodal tumor extension on surgical findings; RAI, radioactive iodine; TT, total thyroidectomy; CT, completion total thyroidectomy; CND, central node dissection; MND, central node dissection and modified radical neck dissection; pN, pathological node metastasis.

* Tall cell variant component was also detected in about 15% of carcinoma lesion (in the lymph node). The metastatic node measuring 36-mm was diagnosed as hobnail variant (not primary lesion).

** This case was postoperative status of hyperfunctioning nodule (adenomatous nodule).
PTC can show extremely rapid growth regardless of whether aggressive features such as clinical node metastasis and extrathyroid extension are present at the initial surgery. Very careful and close observation of these patients after surgery is required and when recurred lesions appear, immediate suitable therapies such as reoperation, RAI therapy, extrabeam radiotherapy, and tyrosine kinase inhibitor administration should be provided.

Disclosure
None of the authors have any potential conflicts of interest associated with this research.

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