Macrofollicular Variant of Papillary Thyroid Carcinoma: Its Clinicopathological Features and Long-Term Prognosis

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Abstract. Macrofollicular variant is a rare entity of papillary carcinoma. We previously demonstrated that this variant accounts for 0.3% of papillary carcinoma in Japan. In this study, we investigated the biological characteristics of 5 cases of macrofollicular variant. We reviewed the diagnosis and clinical course of 5 patients with macrofollicular variant. On preoperative ultrasonographic study, 2 cases were diagnosed as having benign nodule and the remaining 3 suspected of having papillary carcinoma, although they lacked typical ultrasonographic findings of papillary carcinoma. Cytological findings suggested papillary carcinoma for 3 cases and the remaining 2 were diagnosed as indeterminate. Based on both examinations, 4 of 5 patients were diagnosed as having or suspected of having papillary carcinoma. All patients underwent thyroidectomy with lymph node dissection. Three patients underwent central node dissection and the remaining 2 underwent modified radical neck dissection. None of these patients showed clinically apparent node metastasis or massive extrathyroid extension, although 3 of these patients had latent node metastasis confirmed by pathological examination. All patients survived with no evidence of carcinoma recurrence during follow-up (145-235 months). It is therefore suggested that patients with macrofollicular variant can be diagnosed as having or suspected of having papillary carcinoma if ultrasonographic and cytological examinations are appropriately performed and show an excellent prognosis possibly because this variant lacks the aggressive characteristics of papillary carcinoma.

Key words: Macrofollicular variant, Papillary carcinoma, Thyroid, Diagnosis, Prognosis

(PAPILLARY carcinoma, the most common malignant tumor originating from thyroid follicular cells, demonstrates numerous variants. On pathological examination, not only the diagnosis of papillary carcinoma but also classification of the variant is important because patient outcomes of some variants differ from conventional papillary carcinoma [1]. The macrofollicular variant is one of these variants, which was first reported by Albores-Saavedra et al. in 1991 [2] and was adopted as a specific variant in the WHO classification [3]. This variant is defined as a form composed predominantly or exclusively of macrofollicles (>50% of a cross-sectional area) larger than 200μm that morphologically resembles benign nodular goiter [1, 3]. Although some studies, including case reports, describing the pathological characteristics of macrofollicular variant have been published to date [2, 4-8], its prevalence and clinical outcomes on long-term follow-up have not been studied in depth. We previously reported that 5 (0.3%) of 1521 papillary carcinoma were diagnosed as the macrofollicular variant [1]. In this study, we investigated their preoperative findings and biological characteristics, including their clinical outcomes, in detail.)
Patients and Methods

Between 1987 and 1995, 1707 patients underwent an initial surgical treatment of papillary carcinoma. All these specimens were re-reviewed by a coauthor (M.H.) and after excluding 186 cases of poorly differentiated carcinoma, 5 (0.3%) of 1521 papillary carcinoma were diagnosed as the macrofollicular variant according to the WHO classification as described previously [1]. These 5 patients were enrolled in this study. They consisted of 4 females and 1 male and patient ages ranged from 31 to 78 years. All these patients underwent ultrasonography preoperatively to examine the size and location of primary tumors and determine whether they had clinically apparent node metastasis. Fine needle aspiration biopsy (FNAB) by palpation or guided by ultrasonography was performed for all patients. Patients who had been diagnosed as having or suspected of having papillary carcinoma also underwent chest CT scan preoperatively and there were no lung metastases detected in those patients.

We normally follow patients by ultrasonography with chest roentgenography and/or CT scan once or twice per year. The average follow-up period was 190.2 months. Serum thyroglobulin was also examined as a marker of recurrence or persistent disease in patients who had undergone total thyroidectomy. Radioiodine ablation therapy was not performed for any patient in this series.

Results

In our series, 5 cases were diagnosed as having macrofollicular variant. Table 1 summarizes their backgrounds and clinicopathological features. On preoperative ultrasonographic examination, 2 patients (patients 1 and 2) were diagnosed as having benign nodule because tumors had a regular shape with well-defined and smooth border and their internal echoes were isodense and homogenous (Fig. 1-a). The remaining three were suspected of papillary carcinoma, because they showed slightly rough border and/or a small amount of fine strong echoes [9], but were not clearly diagnosed as papillary carcinoma (Fig. 1-b). None of the patients showed clinically apparent lymph node metastasis (N1b or N1a on UICC/TNM classification [10]) on ultrasonography. On cytological find-
Patient 1 underwent lobectomy based on preoperative diagnosis as follicular tumor, but the central compartment was also dissected because swollen lymph nodes in this compartment were detected during surgery. Patient 3 also underwent lobectomy but the central compartment was prophylactically dissected based on preoperative ultrasonographic findings suggesting papillary carcinoma. Patients 2 and 4 underwent total thyroidectomy with modified radical neck dissection (MND) based on cytological findings of papillary carcinoma. Patient 5 underwent only lobectomy and central node dissection because maximal tumor diameter was only 10 mm, although this patient was also cytologically diagnosed as having papillary carcinoma.

Figure 2 shows the macroscopic finding of the tumor. As shown in Figure 2, cut sections of the tumor appeared solid and succulent, implying abundant colloid. The cytological specimen of patient 1 showed only a small number of cells having enlarged nuclei with mild atypia, and that of patient 3 showed nuclear grooves in some cells but lacked inclusion bodies and papillary structures. The remaining 3 patients were diagnosed as having papillary carcinoma. Therefore, although only one patient (patient 1) was diagnosed as having follicular tumor, the remaining 4 patients were diagnosed as having or suspected of papillary carcinoma, by preoperative imaging and cytological studies.

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Figure 1. Ultrasonographic profile of macrofollicular variant. (Arrows: outline of tumor, TR: trachea).
1-a Ultrasonographic appearance of the tumor presents a regular shape with well-defined and a smooth border, and the internal echo is isodense and homogenous. (Patient No.1)
1-b Ultrasonographic appearance of the tumor presents a regular shape and a slightly rough border, and the internal echo is isodense with a few strong echoes. (Patient No.3)

Figure 2. Macroscopic profile of macrofollicular variant. Tumor is solid and succulent, implying abundant colloid. (Patient No.4) (Arrows: outline of tumor)
regarding this variant showed that it is often misdiagnosed as benign nodules [2]. Indeed, surgical specimens from patients that had previously been diagnosed as having adenoma or nodular goiter diagnosed 6 of 17 cases in that series. This is probably because most of their cases were treated before the era of routine ultrasonography and only 6 cases underwent FNAb. On ultrasonography, 3 of 5 cases were suspected of papillary carcinoma. In addition, on cytological examination, 3 of these patients were diagnosed as having papillary carcinoma. In total, 4 (80%) of 5 cases were diagnosed as or suspected of papillary carcinoma based on the findings of imaging and cytological studies. There is only one patient that failed to be preoperatively diagnosed as papillary carcinoma (patient 1), which is because the FNAB specimen was poor for diagnosis. It is possible that some macrofollicular variant cases have been followed-up based on the misdiagnosis as benign nodules. However, FNAB should be able to improve the ability for diagnosis of macrofollicular variant dramatically if properly performed, because the nuclei of the macrofollicular variant usually show typical findings of nuclei in papillary carcinoma. It is therefore suggested that a high percentage of the macrofollicular variant can be diagnosed as or, at least, suspected of papillary carcinoma, if ultrasonography and FNAB are appropriately performed and evaluated. On pathological examination, all cases in our series showed typical nuclear characteristics of papillary carcinoma, although they did not show papillary growth pattern. Therefore, pathologists should based on these findings.

None of these patients showed massive extrathyroid extension, although the tumor of patient 4 showed capsular invasion and minimal extrathyroid extension to the anterior connective tissue beyond the capsule. (Fig. 4) Lymph node metastasis was observed in 3 patients (patients 1, 2 and 4) on postoperative pathological examination. A macrofollicular variant structure was seen also in the metastatic nodes in patients 1 and 2, but in those in patient 4, only the structure of conventional papillary carcinoma was observed. Although swollen lymph nodes in the central compartment were perioperatively detected in patient 1, this patient involved only one metastasis in the delphian node. Patient 2 had 4 metastatic nodes, 3 in the central and 1 in the lateral compartment. Patient 4 had 4 metastatic nodes only in the lateral compartment.

Serum thyroglobulin decreased to below the measurement sensitivity and was not elevated during follow-up for two patients who underwent total thyroidectomy. All patients survived with no evidence of carcinoma recurrence for 145 to 235 months (average 190.2 months).

**Discussion**

This is the first study investigating the prevalence, preoperative diagnosis and biological characteristics, including long-term prognosis, of macrofollicular variant at a single institute in Japan. The first study regarding this variant showed that it is often misdiagnosed as benign nodules [2]. Indeed, surgical specimens from patients that had previously been diagnosed as having adenoma or nodular goiter diagnosed 6 of 17 cases in that series. This is probably because most of their cases were treated before the era of routine ultrasonography and only 6 cases underwent FNAB. On ultrasonography, 3 of 5 cases were suspected of papillary carcinoma. In addition, on cytological examination, 3 of these patients were diagnosed as having papillary carcinoma. In total, 4 (80%) of 5 cases were diagnosed as or suspected of papillary carcinoma based on the findings of imaging and cytological studies. There is only one patient that failed to be preoperatively diagnosed as papillary carcinoma (patient 1), which is because the FNAB specimen was poor for diagnosis. It is possible that some macrofollicular variant cases have been followed-up based on the misdiagnosis as benign nodules. However, FNAB should be able to improve the ability for diagnosis of macrofollicular variant dramatically if properly performed, because the nuclei of the macrofollicular variant usually show typical findings of nuclei in papillary carcinoma. It is therefore suggested that a high percentage of the macrofollicular variant can be diagnosed as or, at least, suspected of papillary carcinoma, if ultrasonography and FNAB are appropriately performed and evaluated. On pathological examination, all cases in our series showed typical nuclear characteristics of papillary carcinoma, although they did not show papillary growth pattern. Therefore, pathologists should
take notice of the presence of the nuclear pattern of the papillary carcinoma when they examine thyroid nodules lacking papillary growth pattern in order to avoid misdiagnosis. Our institution encountered 5 cases that were diagnosed as benign goiter but showed metastasis to the lymph nodes and/or distant organs after initial surgery [11]. Those cases were diagnosed as benign goiter on pathological examination because, unlike the macrofollicular variant, they did not show any typical findings of nuclei in papillary carcinoma. Therefore, we can conclude that macrofollicular variant is an entirely different entity from those cases.

There are several prognostic factors related to papillary carcinoma. We demonstrated that, among these, massive extrathyroid extension (pT4 [10]) and clinically apparent lateral node metastasis (N1b [10]) independently affect both disease-free survival and cause-specific survival of patients [12-14]. The 5 cases in our series did not show either of these features. Three cases showed lymph node metastasis detected on pathological examination, but we have also shown that latent metastasis found only on pathological examination does not affect cause-specific survival of patients [14]. All 5 patients survived with no evidence of carcinoma recurrence on long-term follow-up (145-225 months), which is thought to be because this variant lacks the prominent clinicopathological features that adversely affect prognosis. Previous studies from Western countries have also shown a good prognosis for this variant [2, 4-8]. However, cases demonstrating palpable lymph node metastasis, recurrence to the lung and locoregional recurrence with anaplastic transformation have also been reported [2, 4, 5], indicating that the macrofollicular variant in Japan is possibly more indolent than that in Western countries.

Although 80% of cases in our series could be diagnosed as having or suspected of having papillary carcinoma, some patients with macrofollicular variant may undergo limited thyroidectomy without lymph node dissection after being preoperatively misdiagnosed as benign nodule or follicular tumor. We previously demonstrated that papillary carcinomas that had been resected as benign nodules showed an excellent prognosis even if they did not undergo immediate additional surgery such as completion total thyroidectomy and lymph node dissection after being preoperatively misdiagnosed as benign nodule or follicular tumor. We previously demonstrated that papillary carcinomas that had been resected as benign nodules showed an excellent prognosis even if they did not undergo immediate additional surgery such as completion total thyroidectomy and lymph node dissection, indicating that papillary carcinoma misdiagnosed as benign nodule even on imaging and cytological studies has a mild character [15]. Therefore, no additional surgery may be necessary if this variant is resected under the preoperative misdiagnosis as benign nodule. At present, it is difficult to diagnose macrofollicular variant on preoperative examinations, but if it becomes possible in the future, limited thyroidectomy and lymph node dissection could be considered because this variant shows a mild character.

In summary, patients with macrofollicular variant can be diagnosed as having or suspected of having papillary carcinoma in high incidence if ultrasonographic and cytological examinations are appropriately performed. This variant, at least in Japan, has a very mild character and long-term survival without recurrence can be expected.

References


