Three cases of macrofollicular variant of papillary thyroid carcinoma

Raddaoui Emad, Arafah Maha, Hala K. Kfoury, Abdul Malik Al-Sheikh, Shaesta N. Zaidi

From the Department of Histopathology, King Saud University, King Khalid University Hospital, Riyadh, Saudi Arabia

Correspondence: Dr. Emad Raddaoui, MD, FCAP, FASC · Department of Pathology, King Khalid University Hospital, King Saud University, PO Box 2925/32 Riyadh 11461, Saudi Arabia · T: 9661-467-1064, F: 9661-467-2462 · eraddaoui@yahoo.com · Accepted: November 2010

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The macrofollicular variant of papillary thyroid carcinoma (MFPTC) is a well-established entity with characteristic large follicles containing pale colloid and lined by cells with nuclear features of papillary thyroid carcinoma (PTC). In this study, we present three cases of MFPTC, along with a brief review of the literature. For all three of our cases, the histology of the resected specimen showed predominantly macrol follicular structures lined by cells with nuclear characteristics of PTC. Immunohistochemically, the three cases show positivity for galactin-3, cytokeratin-19, and HBME-1. These cases will help us in understanding the distinction from other benign and malignant follicular lesions of the thyroid, which is of utmost importance. The key to diagnosis is a high-power examination of any macrofollicular lesion of the thyroid.

**CASE 1**

A 34-year-old woman presented with an asymptomatic enlarging nodule of the right thyroid lobe. Ultrasoundography revealed a diffusely enlarged right thyroid lobe with three hypoechoigenic lesions, the largest of which measured 5 cm in maximum dimension. FNA biopsy was performed, which showed follicular epithelial cells, with optically clear nuclei and nuclear grooves, suggestive of a diagnosis of PTC. Total thyroidectomy was performed. Macroscopically, the sections revealed three partially encapsulated tan-white nodules in the right lobe. In addition, the largest nodule had diffuse microcystic changes, filled with colloid material. Histologically, each nodule was characterized by a well-encapsulated macrofollicular growth pattern, lined by large cuboidal cells, with optically clear, ground-glass, focally overlapping nuclei with nuclear grooves, pseudo-inclusions, and occasional prominent nucleoli (Figures 1 and 2). The macrofollicles were filled with dense eosinophilic colloid. The left lobe showed no evidence of carcinoma.

**CASE 2**

A 35-year-old man presented to our Surgical Outpatient Department with an asymptomatic swelling on the left side of the neck. The ultrasonographic study showed a heterogeneous nodule, 2.8 cm in maximum dimension, in the left lobe of the thyroid. FNA biopsy of the nodule revealed a few atypical cells, suspicious for PTC. A total thyroidectomy was performed. Microscopically, the nodule was completely encapsulated, and, on low
Figure 1. Low power view showing a macrofollicular patterned lesion. At this magnification, the tumor could be confused with an amacrofollicular adenoma or multinodular goiter. (Hematoxylin & eosin, original magnification ×50).

Figure 2. High power view showing follicles lined by cells with nuclear characteristics of papillary carcinoma, with prominent intra nuclear inclusions (Hematoxylin & eosin, original magnification ×250).

Table 1. Summary of the cases of macrofollicular variant of papillary thyroid carcinoma reported in the literature.

| Reference/year          | Total no. of cases | Sex | Average age (years) | Average size of tumor (cm) | Capsular invasion (%) | Lymph node invasion (%) | Bone metastasis | Lung metastasis |
|-------------------------|--------------------|-----|---------------------|----------------------------|-----------------------|------------------------|----------------|----------------|
| Albores-Saavedra et al., 1996 | 12+17              | NR  | NR                  | NR                         | 2/29                  | 6/29                   | 0/29          | 0/29          |
| Gamboa-Dominguez et al., 1996 | 6                  | 5-F/1-M | 38                | 3.2                        | 0/6                   | 0/6                    | 0/6           | 0/6           |
| Hirokawa et al., 1998    | 1                  | 1-F  | 59                  | 4.5                        | 0/1                   | 1/1                    | 0/1           | 0/1           |
| Mesonero et al., 1998    | 7                  | 6-F/1-M | 35                | 2.3                        | NR                    | 0/7                    | 0/7           | 0/7           |
| Woyke et al., 1999       | 1                  | 1-F  | 41                  | 8                          | 0/1                   | 0/1                    | 0/1           | 0/1           |
| Nakamura et al., 1998    | 1                  | 1-M  | 18                  | 5.5                        | 1/1                   | 1/1                    | NR            | NR            |
| Fadda et al., 2002       | 3                  | NR   | 25                  | 2.1                        | 0/3                   | NR                    | NR            | NR            |
| Lugli et al., 2004       | 3                  | 2-F/1-M | 51                | 2.8                        | 1/3                   | 1/3                    | 0/3           | 0/3           |
| Ravindra et al., 2006    | 1                  | 1-F  | 22                  | 2                          | 1/1                   | 0/1                    | 0/1           | 0/1           |
| Cardenas et al., 2009    | 2                  | 1-F/1-M | 69                | 3                          | 1/2                   | 1/2                    | 2/2           | 1/2           |
| Present study            | 3                  | 1-F/2-M | 30.3              | 2.3                        | 0/3                   | 0/3                    | 0/3           | 0/3           |

F-Female, M-Male, NR-Not reported
power, a macrofollicular growth pattern was noted. The non-neoplastic thyroid showed features of a nodular goiter with degenerative changes composed of fibrosis and calcification.

CASE 3
A 22-year-old male presented with a progressively increasing right thyroid nodule. Ultrasonographic studies detected two solid cystic nodules in the right lobe of the thyroid, the largest measuring 1.7 cm at its greatest dimension. FNA showed benign follicular cells. Histologically, the nodules showed an encapsulated macrofollicular growth pattern. The remainder of the thyroid tissue showed features of a multinodular goiter.

In all three of our cases, there was an absence of capsular or vascular invasion, extra-thyroid extension, or lymph node involvement. Our immunohistochemical study revealed diffuse positive staining for cytokeratin 19 (Novocastra, Newcastle upon Tyne, UK); clone b-170, mouse monoclonal antibodies, dilution 1:100), galectin-3 (Novocastra; clone 9c4, lyophilized mouse monoclonal antibodies, dilution 1:100), and HBME-1 (Dako; clone HBME-1, mouse monoclonal antibodies, dilution 1:30), supporting the diagnosis of a MFPTC.

At the 3-year follow-up, all three patients were alive and well.

DISCUSSION
PTC is the most common malignant tumor of the thyroid gland, comprising an estimated 80% of all thyroid cancers.3 The macrofollicular variant is regarded as one of the rarest histological variants of PTC. It was first described by Albores-Saavedra et al in 1991.1 This variant is recognized as a well-differentiated carcinoma formed by large follicles and nuclei with all the nuclear characteristics of PTC. Women are affected more often than men. The presence of a number of macrofollicles in classical PTC or the conventional follicular variant of PTC is a common feature and can be seen both in the primary tumor and in the metastatic deposits. However, to pigeon hole the carcinoma as an MFPTC, more than 50% of the cross-sectional area of the tumor must be formed by macrofollicles, with a mean diameter of at least 200 μm4,5 and the lining cells of the follicles must show the nuclear features characteristics of PTC. The MFPTC is usually encapsulated, and the macrofollicles are lined by large cuboidal cells, with optically clear, focally overlapping nuclei, with pale, evenly distributed chromatin, nuclear grooves, pseudo-inclusions, and small eccentric nucleoli. The macrofollicles contain a dense and eosinophilic colloid, which is often scalloped or vacuolated. The first few studies of MFPTC have shown that it can be easily misdiagnosed as representing a benign lesion. Six of the 17 cases reported by Albores-Saavedra et al were initially considered as being benign. Cases of MFPTC reported in the literature are listed in Table 1.

Sometimes it is difficult to recognize MFPTC on FNA because the macrofollicles contain abundant colloid, and some are lined by a follicular type of epithelium. The differential diagnosis includes macrofollicular adenoma, a hyperplastic macrofollicular nodule in a nodular goiter, and a macrofollicular variant of follicular thyroid carcinoma.6 To discriminate MFPTC from these other entities on FNA cytology, the pathologist should recognize the nuclear features characteristics of PTC, which are typically seen in MFPTC. Mesonero et al7 have suggested that ovoid and pear-shaped nuclei, nuclear hypochromasia, and nuclear grooves all contribute to the cytological diagnosis of MFPTC on FNA biopsy.

The prognosis of MFPTC is reported to be excellent, with a low incidence of metastases compared with conventional PTC or the columnar cell variant.4,8,9 In a series reported by Albores-Saavedra et al9 in 1996, two patients with a large-sized tumor, insular component and blood vessel invasion developed lung metastasis. In 2009, Cardenas et al10 also reported two similar cases with aggressive behavior, represented by extra-thyroid extension, lymph node involvement, and bone and lung metastases. The aggressive behavior of these cases may be related to capsular and/or vascular invasion. The various factors that are considered to be of prognostic importance in a patient with well-differentiated PTC are young age, small tumor size, and an absence of extra-thyroid extension or blood vessel invasion.11

In conclusion, MFPTC is one of the rare histological subtypes of PTC. We have presented three additional cases of MFPTC, with favorable histological features. In all three cases, the carcinoma was completely encapsulated, and there was no evidence of extrathyroid and/or vascular invasion. We suggest that MFPTC is a well-differentiated variant of PTC, which should be distinguished from other follicular thyroid lesions on the basis of the nuclear characteristics of the follicular cells. Cells should be viewed at high magnification, in both FNA biopsy slides and histopathology sections.
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