case report

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

Ann Saudi Med 2011; 31(6): 644-647

DOI: 10.4103/0256-4947.87104

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 macrofollicular 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.

Papillary thyroid carcinoma (PTC) has many histological variants. The macrofollicular variant of papillary thyroid carcinoma (MFPTC) is a rare entity, first described by Albores-Saavedra and colleagues in 1991.[1] These authors reported 17 cases of a distinct variant of encapsulated papillary carcinoma, which could be confused with macrofollicular adenoma or a hyperplastic macrofollicular nodule in a nodular goiter.

This variant is a well-differentiated carcinoma with a predominance of macrofollicles (>50% of a cross-sectional area); the cells lining the follicles have nuclear features characteristic of PTC (enlarged ground glass clear nuclei and nuclear grooves). Fine needle aspiration (FNA) is not helpful in reaching the diagnosis in most of the cases, as the cytological features may be difficult to distinguish from those of adenomatous goiter and macrofollicular adenoma.[2] The MFPTC is characterized clinically by non-aggressive biological behavior, with a low incidence of metastases. We present three cases of this rare entity encountered in our institution between 2002 and 2009, identified from 29 histologically proven follicular variants of PTC, along with a brief review of the literature.

CASE 1

A 34-year-old woman presented with an asymptomatic enlarging nodule of the right thyroid lobe. Ultrasonography revealed a diffusely enlarged right thyroid lobe with three hypoechogenic 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

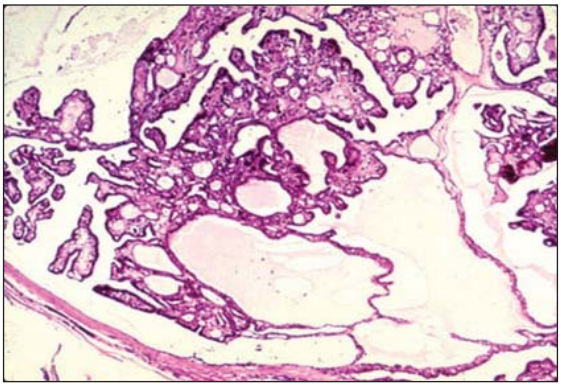

Figure 1. Low power view showing a macrofollicular patterned lesion. At this magnification, the tumor could be confused with amacrofollicular adenoma or multinodular goiter. (Hematoxylin & eosin, original magnification ×50).

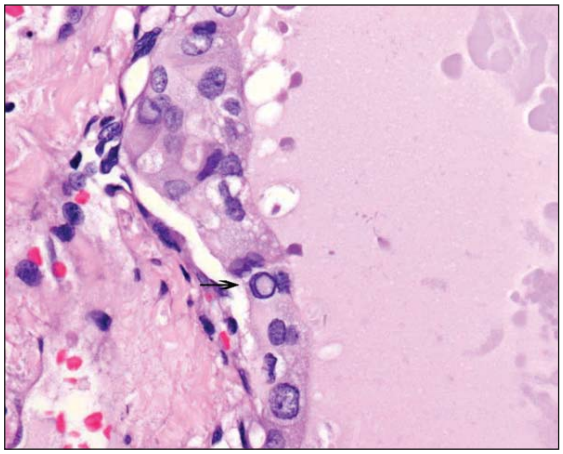

Figure 2. High power view showing follicles lined by cells with nuclear characteristics of papillary carcinoma, with prominent intra nuclear inclusions (Hematoxylin & eosin, original magnification ×250).

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.,[4] 1996	12+17	NR	NR	NR	2/29	6/29	0/29	2/29
Gamboa-Dominguez et al.,[12] 1996	6	5-F/1-M	38	3.2	0/6	0/6	0/6	0/6
Hirokawa et al.,[2] 1998	1	1-F	59	4.5	0/1	1/1	0/1	0/1
Mesonero et al.,[7] 1998	7	6-F/1-M	35	2.3	NR	0/7	0/7	0/7
Woyke et al.,[13] 1998	1	1-F	41	8	0/1	0/1	0/1	0/1
Nakamura et al.,[14] 1998	1	1-M	18	5.5	1/1	1/1	NR	NR
Fadda et al.,[15] 2002	3	NR	25	2.1	0/3	NR	NR	NR
Lugli et al.,[5] 2004	3	2-F/1-M	51	2.8	1/3	1/3	0/3	0/3
Ravindra et al.,[16] 2006	1	1-F	22	2	1/1	0/1	0/1	0/1
Cardenas et al.,[10] 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 μm[4,5] 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 al[7] 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 al[4] in 1996, two patients with a large-sized tumor, insular component and blood vessel invasion developed lung metastasis. In 2009, Cardenas et al[10] 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.

REFERENCES

1. Albores-Saavedra J, Gould E, Vardaman C, Vuitch F. The macrofollicular variant of papillary thyroid carcinoma: A study of 17 cases. Hum Pathol 1991;22:1195-205.
2. Hirokawa M, Shimizu M, Terayama K, Kanahara T, Sonoo H, Manabe T. Macrofollicular variant of papillary thyroid carcinoma: Report of a case with fine needle aspiration findings. Acta Cytol 1998;42:1441-3.
3. LiVolsi VA, Albores-Saavedra J, Asa SL. Papillary carcinoma. In: De Lellis, Lloyd R, Heitz PU, Eng C, editors. Pathology and Genetics of Tumours of Endocrine Organs. Lyon, France: IARC Press; 2004. p. 57-66.
4. Albores-Saavedra J, Housini I, Vuitch F, Snyder WH. Macrofollicular variant of papillary thyroid carcinoma with minor insular component. Cancer 1997;80:1110-6.
5. Lugli A, Terracciano LM, Oberholzer M, Bubendorf L, Tornillo L. Macrofollicular variant of papillary carcinoma of the thyroid. Arch Pathol Lab Med 2004;128:54-8.
6. Bongiovanni M, Gremaud M, Moulin CS, Scheidegger C, Biton C, Clément S. Macrofollicular variant of follicular thyroid carcinoma: A clinical, cytologic, morphologic, and image analysis study of a unique case. Ann Diagn Pathol 2009;13:101-5.
7. Mesonero CE, Jugle JE, Wilbur DC, Nayar R. Fine needle aspiration of the macrofollicular and microfollicular subtypes of the follicular variant of papillary carcinoma of the thyroid. Cancer 1998;84:235-44.
8. Carcangiu ML, Zampi G, Pupi A, Castagnoli A, Rosai J. Papillary carcinoma of the thyroid: A clinicopathology study of 241 cases treated at the University of Florence, Italy. Cancer 1985;55:805-28.
9. Gaertner EM, Davidson M, Wenig BM. The columnar cell variant of thyroid papillary carcinoma: Case report and discussion of an unusually aggressive thyroid papillary carcinoma. Am J Surg Pathol 1995;19:940-7.
10. Cardenas MG, Kini S, Wisgerhof M. Two patients with highly aggressive macrofollicular variant of papillary thyroid carcinoma. Thyroid 2009;19;413-6.
11. Loru TR. Therapeutic implications of prognostic factors in differentiated carcinoma of the thyroid gland. Semin Surg Oncol 1995;11:246-55.
12. Gamboa-Dominguez A, Vieitez-Martinez I, Barredo-Prieto BA, Richaud-Patin Y, Herrera ME, Angeles-Angeles A. Macrofollicular variant of papillary thyroid carcinoma: A case and control analysis. Endocr Pathol 1996;7:303-8.
13. Woyke S, Al-Jassar AK, Al-Jazzar H. Macrofollicular variant of papillary thyroid carcinoma diagnosed by fine needle aspiration biopsy: A case report. Acta Cytol 1998;42:1184-8.
14. Nakamura T, Moriyama S, Nariya S, Sano K, Shirota H, Kato R. Macrofollicular variant of papillary thyroid carcinoma. Pathol Int 1998;48:467-70.
15. Fadda G, Fiorino MC, Mule A, LiVolsi V. Macrofollicular encapsulated variant of papillary thyroid carcinoma as a potential pitfall in histologic and cytologic diagnosis: A report of 3 cases. Acta Cytol 2002;46:555-9.
16. Ravindra S, Niveditha SR, Geethamani V, Rangaswamy R. Macrofollicular encapsulated papillary thyroid carcinoma: A case report. Indian J Pathol Microbiol 2006;49:24-6.