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= **Abstract** =

Macrofollicular Variant of Papillary Thyroid Carcinoma with Extensive Hemorrhage
-Report of A Case-

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Background: The macrofollicular variant of papillary thyroid carcinoma (MVPC) is characterized by macrofollicles occupying more than half of the tumor and demonstrating nuclear features of classic papillary carcinoma. It is difficult to recognize on fine needle aspiration (FNA) cytology due to the paucity of aspirated neoplastic cell clusters, especially when the tumor is associated with extensive areas of hemorrhage. **Case**: A 34-year-old female presented with a well-demarcated nodule in the thyroid gland, diagnosed as a benign nodule on ultrasonography and computed tomography. FNA cytology smear revealed a few small aggregates of follicular cells with morphological features suspicious for papillary carcinoma, set in a background of hemorrhage, inflammatory cells, and hemosiderin-laden macrophages. Intraoperative frozen section revealed macrofollicular nests filled with hemorrhage and composed of follicular cells demonstrating nuclear clearing and grooves. **Conclusion**: MVPC is a rare but distinctive variant of papillary carcinoma, which is easily mistaken for adenomatous goiter or benign macrofollicular neoplasm on radiologic findings. The cytopathologist should alert oneself on encountering benign radiologic findings and any smear composed of scant numbers of follicular cells with nuclear features suspicious for papillary carcinoma despite the bland-looking background of hemorrhage and hemosiderin-laden macrophages, and recommend intraoperative frozen sections for a definite diagnosis.

Key words: Thyroid, Neoplasm Fine needle, aspiration cytology, Macrofollicular variant of papillary carcinoma

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INTRODUCTION

Papillary carcinoma of the thyroid gland has for long been traditionally diagnosed on the basis of the characteristic papillary structures,[1] and nuclear features, i.e. enlarged, clear ground-glass nuclei with nuclear grooves and pseudoinclusions. However, Chen and Rosai[1] in their description of the follicular variant of papillary carcinoma, emphasized the importance of the nuclear features in making the diagnosis of papillary carcinoma, rather than the papillary structures,[1] and the follicular variant of papillary carcinoma is being diagnosed on fine needle aspiration cytology with increasing frequency based on the nuclear features.[2] Moreover, a few cases of the macrofollicular variant of papillary carcinoma (MVPC) have been reported, described as an encapsulated variant with an architectural pattern predominantly composed of large follicles.[3-8] Most of the previously reported cases of this particular variant have been misdiagnosed as a follicular neoplasm or adenomatous nodule on cytology and even on histological examinations.[3-5]

We report a case of MVPC recently diagnosed at our institution, which showed extensive areas of hemorrhage, with focus on the cytologic features.

CASE

A 34-year-old female presented with a recently discovered neck swelling. On physical examination, a palpable soft mass, measuring 3.4cm, was noted at the left anterior cervical region, which was mobile on swallowing. Thyroid function tests were within normal limits. Ultrasound studies and computed tomography demonstrated a 2.6×1.6×2.4cm-sized well-demarcated nodule with mixed echogenicity and radiodensity on the left lobe of the thyroid, suggesting a benign lesion showing cystic change(Fig. 1). A fine needle aspiration biopsy was performed, guided by ultrasound. A preoperative cytological diagnosis of "suspicious of papillary carcinoma arising in a background of adenomatous hyperplasia" was rendered and she subsequently underwent a left total and right subtotal thyroidectomy with central compartment neck node dissection.

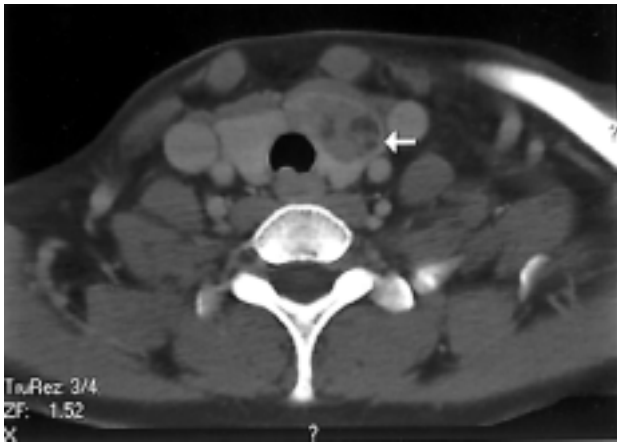

Fig. 1. Radiographic finding. Computed tomography demonstrates a 2.6x1.6x2.4cm-sized well-demarcated nodule with mixed radiodensity on the left lobe of the thyroid (white arrow).

Cytologic findings

The smears, stained with Papanicolaou and Giemsa stains, demonstrated scanty irregular fragments of fibrous stroma set in a bloody background with some inflammatory cells and abundantly scattered hemosiderin-laden macrophages (Fig. 2A). A moderate amount of thick colloid material was seen. Small aggregates of follicular cells were occasionally noted, in monolayer or focally overlapping arrangements (Fig. 2B). The follicular cells showed enlarged nucleus, relatively monotonous nuclear size and shape with cloudy nuclei, moderate pleomorphism and high nuclear/cytoplasmic ratios. A few nuclear grooves were seen, being more easily appreciated on Papanicolaou-stained smears. The cytoplasm was moderate in amount without demonstrable oncocytic change, and the cytoplasmic borders were indistinct. Nucleoli were infrequently seen, and there were occasional intranuclear pseudoinclusions (Fig. 2C). No psammoma bodies were noted.

Gross findings

The left lobe, submitted for frozen section diagnosis,

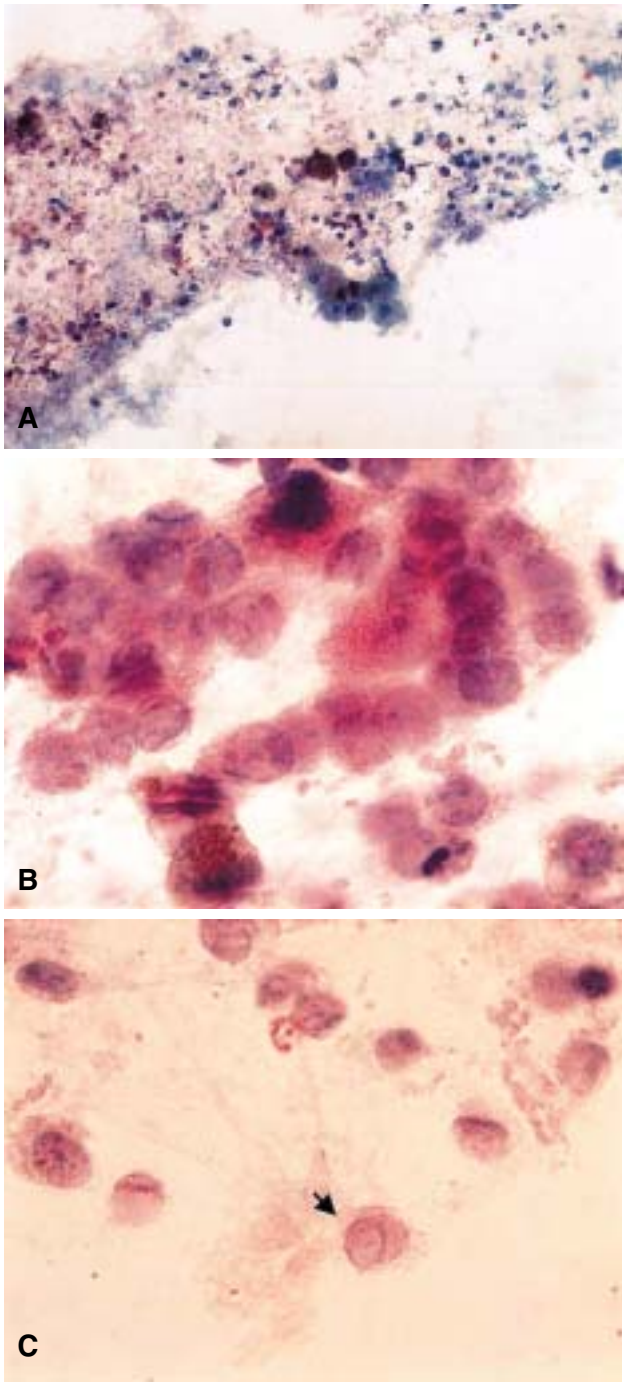

Fig. 2. Fine needle aspiration cytology findings. (A) The smear is predominantly composed of a mixture of hemosiderin-laden macrophages and inflammatory cells, with scant numbers of interspersed follicular cells. (B) A small loose cluster of follicular cells is noted, a few cells showing nuclear clearing and grooves. (C) A follicular cell with intranuclear pseudoinclusion is noted among scattered follicular cells and hemosiderin-laden macrophages. (Papanicolaou stain)

weighed 10.9g and measured 3.5×2.5×2cm. On cross-section, it revealed a well-defined, encapsulated, tan solid mass measuring 3×2×2cm, which showed areas of hemorrhage. The remaining thyroid tissue was grossly unremarkable. A portion of the opposite lobe was submitted separately for routine pathologic examination, and there were no grossly remarkable findings.

Histologic findings

At low power examination, the left thyroid showed a well-defined mass surrounded by a thick fibrous capsule, which compressed the adjacent thyroid parenchyma (Fig. 3A). The entire mass was composed mainly of macrofollicular nests of follicular cells, which were separated by irregular thin septa and mostly filled with lakes of blood and hemosiderin-laden macrophages (Fig. 3B). The follicles varied in size and shape, and were lined by a single layer of follicular cells. Scattered areas composed of microfollicular structures were seen, filled with thick inspissated colloid material, and occasional psammoma bodies were noted (Fig. 3C). No papillary structures with demonstrable fibrovascular cores were present. A few broader fibrous bands were noted traversing the mass with focal areas of calcification. On high power examination, the follicular cells demonstrated frequent nuclear clearing and nuclear grooves, especially in the microfollicular areas. A significant proportion of the follicular cells lining the macrofollicular structures were flattened or cuboidal with hyperchromatic nuclei, although some demonstrated the characteristic nuclear features of papillary carcinoma (Fig. 3D). There was no demonstrable invasion of the blood vessels or the surrounding fibrous capsule.

The right lobe of thyroid gland demonstrated normal thyroid follicles without evidence of tumor, and there was no metastatic tumor in the dissected central compartment lymph nodes.

DISCUSSION

First described in the literature by Albores-Saavedra et al. in 1991, the macrofollicular variant of papillary thyroid

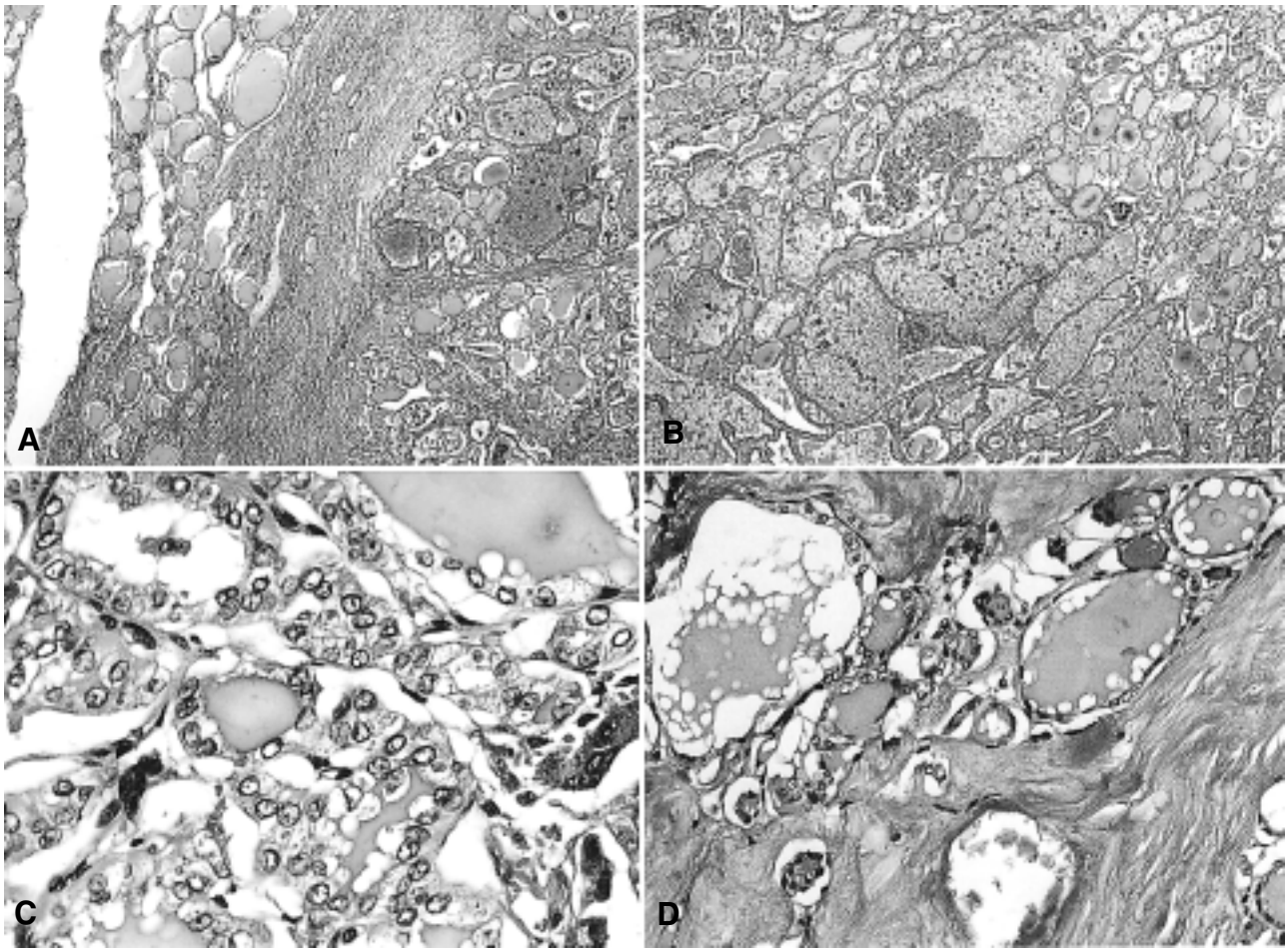

Fig. 3. Histologic findings of the tumor. The tumor is demarcated from the non-neoplastic thyroid by a thick, fibrous capsule (A), and is composed of numerous macrofollicles, which are filled with hemorrhage and hemosiderin-laden macrophages (B). The cells lining the macrofollicles show prominent nuclear clearing and grooves (C), and the smaller follicles, also demonstrating occasional nuclear grooves, contain thick inspissated colloid material (D).

carcinoma is a rare but distinctive variant, defined as papillary carcinoma composed predominantly of macrofollicles (follicles measuring more than 200 μm in diameter), occupying at least 50% of the tumor.[3] Due to the striking similarities in histological appearances at low power, careful examination at high power magnification is required for the differentiation of macrofollicular papillary carcinoma from benign thyroid lesions, such as macrofollicular adenoma, adenomatous goiter, and diffuse hyperplasia or Graves' disease, in surgically resected specimens. Rendering a diagnosis of macrofollicular papillary carcinoma on preoperative fine needle aspiration biopsy is even more demanding, as the classic cytological features of papillary carcinoma are unidentifiable in many cases.

The fine needle aspiration biopsy findings of macrofollicular papillary thyroid carcinoma have been described by a few authors,[4-8] and most have found that the procedure yields equivocal results due to the paucity of aspirated neoplastic cell clusters. The pathognomonic features of the typical papillary carcinoma, namely, nuclear clearing, grooves or pseudoinclusions, have been infrequently seen in this variant.[3] There have been suggestions that a cytologic picture of a follicular lesion with prominent nuclear pleomorphism, mostly with an absence of oxyphilic changes, should raise suspicion of MVPC, and that chromatin dispersion, elongation and irregularity of the nuclei, and an inflammatory background

provide important clues in making the diagnosis of MVPC, even in the absence of nuclear grooves and pseudoinclusions.[8] Another characteristic finding, which should alert the cytopathologist, may be the abundant colloid in the background, possibly obtained from the center of a macrofollicle.[4,6-8] This may obscure the small aggregates of neoplastic follicular cells, resulting in a faulty diagnosis of benign colloid nodule.

In the present case, the cytologic findings almost match those previously described. However, the presence of a hemorrhagic background with abundant hemosiderin-laden macrophages, which presumably correspond to the lakes of blood in the center of the macrofollicles seen on histologic section, may mislead the cytopathologist into making a diagnosis of adenomatous goiter with cystic change, especially in the absence or rarity of the characteristic nuclear grooves or pseudoinclusions. Although the cytologic features of a hemorrhagic background with the scattered hemosiderin-laden macrophages in this case favored a benign hyperplastic lesion at first glance, careful search revealed rare small aggregates of follicular cells showing focal nuclear features suspicious for papillary carcinoma. Logani et al. suggested that cases characterized by monolayer sheets of follicular cells in a background of abundant colloid with focal nuclear features of typical papillary carcinomas be diagnosed as “follicular-derived neoplasms with nuclear features suspicious for the follicular variant of papillary carcinoma” with recommendations for intraoperative frozen section and touch preparation for definite diagnosis.[9] Likewise, we think it would be prudent to give warning to the surgeon and recommend intraoperative frozen sections upon encountering a case demonstrating scant numbers of follicular cells with cytologic features suspicious for papillary carcinoma despite the somewhat 'discordant' background suggestive of an adenomatous goiter with cystic change. Intraoperative frozen section was performed in this present case, and the typical nuclear features of papillary carcinoma were easily recognizable on histologic section.

Nuclear features, enlarged nucleus, and relatively monotonous nuclear size and shape including nuclear clearing, grooves, and pseudoinclusions are the most important criteria in considering papillary carcinoma, and the possibility of MVPC should be considered on cytology, when encountering smears showing small numbers of follicular cells demonstrating these nuclear features without discernible papillary structures or tight follicular clusters, set in a background of hemorrhage, inflammation, and hemosiderin-laden macrophages.

REFERENCES

1. Chen KTK, Rosai J. Follicular variant of thyroid papillary carcinoma. A clinicopathologic study of six cases. *Am J Surg Pathol* 1977;1:123-30.
2. Goodell WM, Saboorian MH, Ashfaq R. Fine-needle aspiration diagnosis of the follicular variant of papillary carcinoma. *Cancer* 1998;84:349-54.
3. 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.
4. Mesonero CE, Jugle JE, Wilbur DC, Nayar R. FNA of the macrofollicular and microfollicular subtypes of the follicular variant of papillary carcinoma of the thyroid. *Cancer* 1998;84:235-44.
5. Woyke S, Al-Jassar AK, Al-Jazzaf H. Macrofollicular variant of papillary thyroid carcinoma diagnosed by fine needle aspiration biopsy: A case report. *Acta Cytol* 1998;42: 1184-8.
6. Hirokawa M, Shimizu M, Terayama K, Kanahara T, Sonoo H, Manabe T. Macrofollicular variant of papillary carcinoma: Report of a case with fine needle aspiration biopsy findings. *Acta Cytol* 1998;42:1441-3.
7. Hernandez-Ortiz MJ, Amengual-Antich I, Canet-Ribas de Pina R. Fine needle aspiration cytology of macrofollicular variant of thyroid papillary carcinoma in a male. *Acta Cytol* 2001;45:483-6.
8. Fadda G, Fiorino MC, Mule A, LiVolsi VA. Macrofollicular encapsulated variant of papillary thyroid carcinoma as a potential pitfall in histologic and cytologic diagnosis: A report of three cases. *Acta Cytol* 2002;46:555-9.
9. Logani S, Gupta PK, LiVolsi VA, Mandel S, Baloch ZW. Thyroid nodules with FNA cytology suspicious for follicular variant of papillary thyroid carcinoma: follow-up and management. *Diagn Cytopathol* 2000;23:380-5.