Clinical Medicine Insights: Case Reports

CASE REPORT

Follicular Adenoma with Extensive Extracellular Mucin Deposition: Report on Two Cases

Na Rae Kim[1], Hyun Yee Cho[1], Sergio Piña-Oviedo[2], Gustavo De La Roza[2], Young Don Lee[3] and Jae Y. Ro[2]

[1]Department of Pathology, Gachon University Gil Medical Center, Incheon, Korea. [2]Department of Pathology and Genomic Medicine, The Methodist Hospital, Weill Medical College of Cornell University, Houston, Texas, USA. [3]Department of General Surgery, Gachon University Gil Medical Center, Incheon, Korea.
Corresponding author email: jaero@tmhs.org

Abstract: We report two cases of follicular adenoma of the thyroid with extensive extracellular mucin deposition. Fine needle aspiration in Case 1 showed singly discohesive polygonal cells in a granular mucinous background. They contained abundant eosinophilic cytoplasm, nuclear irregularities, and frequent nuclear inclusions with occasional bizarre mitoses. A right lobectomy was done. In Case 2, a 47-year-old Caucasian woman with multinodular goiter had total thyroidectomy and a yellow-tan nodule was found within the right lobe. Both tumors were well-encapsulated masses with thick capsules. Each was characterized by microfollicles without papillae in a mucinous stroma. Tumor cells were positive for thyroglobulin and negative for calcitonin, CEA, galectin-3, HBME-1, and CK19. The extracellular mucin stained with Alcian-blue and colloidal iron but not with mucicarmine and D-PAS. No *BRAF* gene mutation was detected. Because there were neither capsular nor vascular invasions, both cases were diagnosed as follicular adenomas of the thyroid with extensive extracellular mucin deposition, which as proposed by the WHO classification can be categorized as a mucinous variant of follicular adenoma. Retrospectively, frequent nuclear inclusions and the absence of nuclear grooves in the mucin-containing background of cytologic smears and histologic sections were shared by those of mucin-producing papillary carcinoma. It is unclear whether it belongs to an existing category of thyroid neoplasm with mucin production or whether it is truly a new tumor variant. Furthermore, pathologists should pay attention to avoid misdiagnosis of this variant of follicular neoplasm that shows an overlapping cytology with that of papillary carcinoma.

Keywords: thyroid, mucin, follicular adenoma, aspiration, fine needle

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Introduction

Mucin is a high molecular weight glycoprotein that is secreted by epithelia. In contrast to the common finding of mucin production in non-endocrine epithelial tumors or mucinous metaplasia, in endocrine tumors it is an unexpected rare finding.[1] Mucin is rarely encountered in the primary thyroid neoplasm and only occasionally has mucin production been reported in medullary carcinoma or poorly differentiated carcinoma of the thyroid, which subsequently may lead to diagnostic difficulties, especially in cytologic specimens.[2–5] Most of these tumors produce variable amounts of intracytoplasmic mucin similar to epithelial tumors.[6,7] Several cases of stromal mucin-producing thyroid neoplasms have also been reported.[8–16]

We report here on two additional cases of follicular adenoma with thick capsule and extensive stromal mucin deposits. Importantly, this is the first time that *BRAF* gene mutation analysis is performed in these types of lesions.

Case Reports

Case 1 is a 58-year-old Korean man who had undergone radioactive iodine therapy at another hospital for thyrotoxicosis twelve years prior to analysis. The neck ultrasound scan taken at the health care center revealed a small nodule (0.6 cm) at the lower pole of the right lobe near the isthmus. At that time, the free T4 level was within normal limits (1.15 ng/dL) and there was a slightly elevated TSH level (5.98 McIU/mL). Fine needle aspiration (FNA) was done only in Case 1. FNA smears were stained with both Papanicolaou and hematoxylin and eosin stains. The FNA taken from the right lobe showed many singly scattered discohesive cells and occasional clusters had scanty to abundant granular cytoplasm in a mixed sticky mucin and colloidal background (Fig. 1A). Frequent nuclear inclusions and rare mitoses with atypical forms were found (Fig. 1B and C). Rare intracytoplasmic vacuoles were also found (Fig. 1D). Although nuclear grooves were not found, the cytologic diagnosis was a thyroid neoplasm with a possibility of papillary carcinoma. Surgical removal was recommended. The tissue specimen was fixed in 10% formalin and embedded in paraffin. Paraffin sections were stained with hematoxylin and eosin. The excised right lobe measured 5.0 × 2.7 × 0.8 cm and weighed 7.5 grams. The external surface was smooth tan and the cut surface showed a well-circumscribed

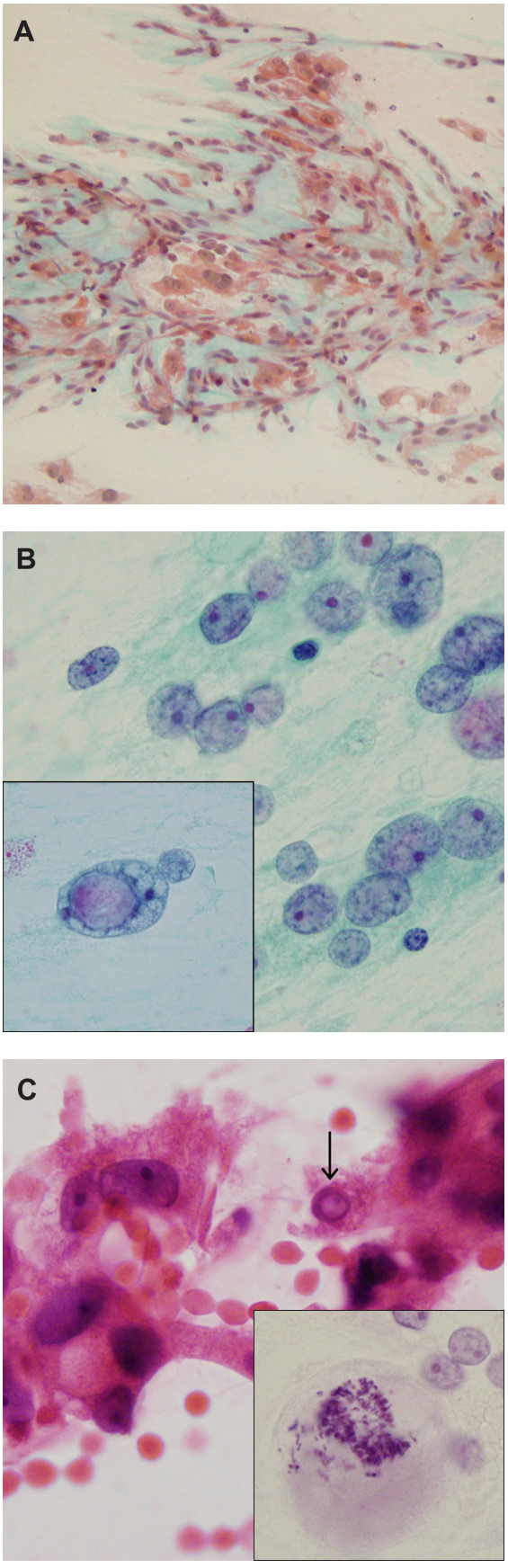

Figure 1. (*Continued*)

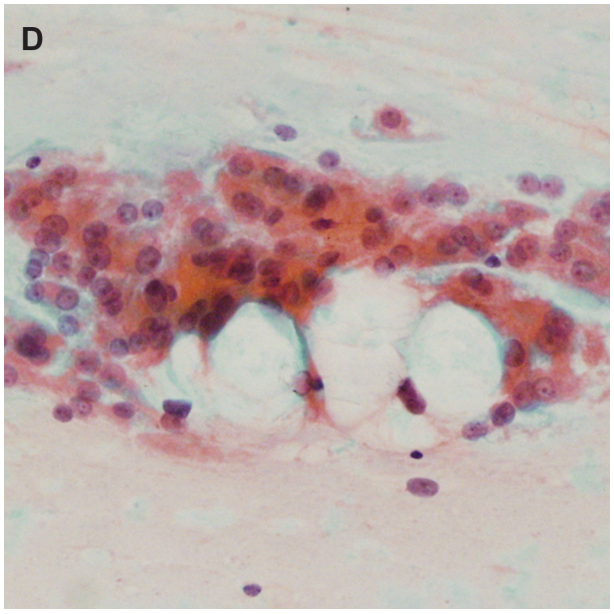

Figure 1. FNA cytology, Case 1. (**A**) Low magnification shows several sheets of follicular cells with some singly scattered oval-shaped tumor cells within a background of abundant bluish mucin (Papanicolaou stain). (**B**) High magnification shows the tumor cells having abundant cytoplasm and vesicular nuclei with nuclear inclusions (Papanicolaou stain). Inset indicates nuclear inclusions. (**C**) Microfollicles of tumor cells show irregular nuclei and rare mitotic figures. (**D**) Intracytoplasmic vacuoles compressing cell nuclei are rarely found (Papanicolaou stain).

dark brown, oval shaped, muddy, mucoid mass at the lower pole of the right lobe near the isthmus measuring 0.6 × 0.5 × 0.4 cm (Fig. 2A). On light microscopy, the mass was well delineated and had a thick capsule (Fig. 2B). The tumor was composed of microfollicles in the background of bluish mucin pools; no papillary structures were seen. There were rare follicular structures, and the microfollicles contained some colloid or mucin (Fig. 2C). The oval shaped tumor cells showed irregular nuclei with a prominent single nucleolus. The nuclei showed frequent nuclear inclusions and nuclear clearing (Fig. 2D).

Case 2 is a 47-year-old Caucasian American woman who had a previous history of slowly growing masses in the thyroid with clinical symptoms of hypothyroidism. She was later diagnosed with large multinodular goiter on the ultrasound scan. A total thyroidectomy was done. The specimen measured 10.0 × 3.5 × 3.0 cm and weighed 36.5 grams. A 1.5 cm mass with a cystic surface containing clear yellow fluid and slightly calcified areas and covered by a thick capsule was located in the right lobe. Microscopically, the tumor was composed of anastomosing cords and trabeculae of polygonal cells with intervening amyloid-like extracellular eosinophilic

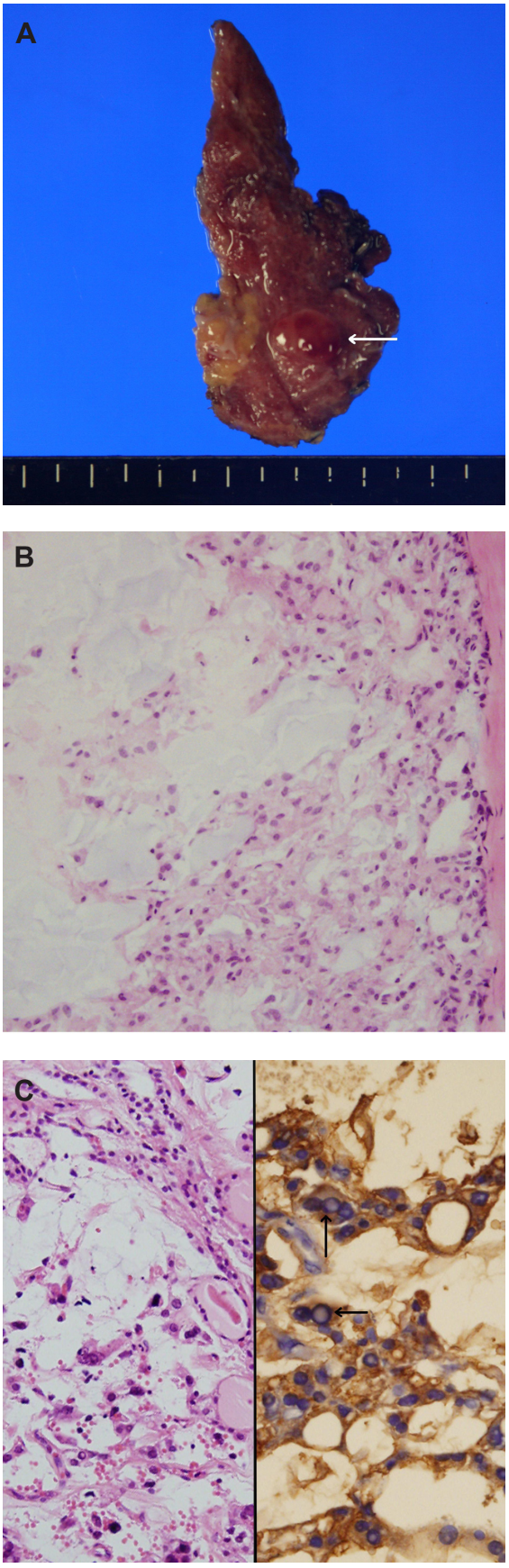

Figure 2. (*Continued*)

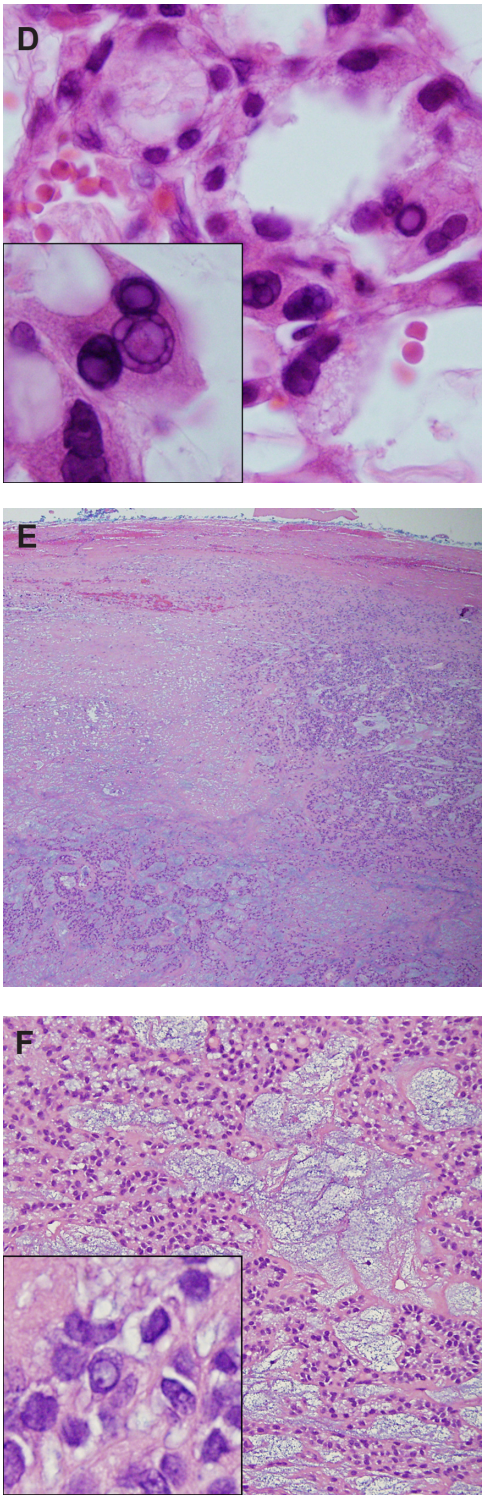

Figure 2. (**A**–**D**) Case 1. (**A**) Grossly, the thyroid nodule is ovoid and shows a greenish to brown-colored mucoid cut surface. (**B**) On light microscopy, the oval-shaped mass is encapsulated by a well-formed thick capsule and contains abundant extracellular mucin. (**C**) Some tumor cells of the microfollicles contain mucinous material. Arrow indicates nuclear clearing and inclusions (right: thyroglobulin immunostain). (**D**) Microfollicles of tumor cells show nuclear irregularities and nuclear inclusions (inset). (**E** and **F**) Case 2. (**E**) The thyroid nodule shows trabecular arrangements of oval shaped tumor cells in abundant myxoid stroma. (**F**) High magnification of this lesion shows spillage of extracellular mucin and irregular nuclei with nuclear inclusions (inset).

stroma and bluish mucinous material (Fig. 2E). Some areas of the first case's lesion showed nuclear irregularities with frequent inclusions, whereas Case 2 showed nuclear irregularities with occasional intranuclear inclusions (Fig. 2F). All the tumor of both samples including the surrounding capsule were entirely submitted for histologic diagnosis. Neither case showed capsular or vascular invasion except for "mucin spillage". In addition to the abundant extracellular mucin pools, occasional intracytoplasmic mucin vacuoles were found. Dystrophic calcification was also found in case 2. Cases 1 and 2 were diagnosed as follicular adenoma with extensive extracellular mucin deposition.

Immunohistochemically, the tumor cells in both cases were positive for thyroglobulin (1D4; Dako, Glostrup, Denmark, prediluted) and thyroid transcription factor-1 (TTF-1) (8G7G3/1; Dako, 1:50 dilution), whereas they were negative for cyclin D-1 (SP4; Dako, prediluted), CAM5.2 (Dako, prediluted), CD56 (123C3; Dako, 1:100 dilution), p53 (DO-7; Dako, 1:100 dilution), calcitonin (Dako, 1:100 dilution), CK19 (RCK108; Dako, 1:200 dilution), galectin-3 (9C4; Novocastra, *Newcastle* Upon Tyne, UK, 1:100 dilution), HBME-1 (M3505; Dako, 1:50 dilution), synaptophysin (Dako, 1:200 dilution), chromogranin (Dako, 1:200 dilution), carcinoembryonic antigen (CEA) (Dako, prediluted), high molecular weight cytokeratin (34βE12; Dako, prediluted), and smooth muscle actin (1A4; Dako, prediluted).

Mutation status in the *BRAF* gene was tested in these two cases using two different methods: (1) allele-specific polymerase chain reaction (PCR) for V600E mutation, and (2) *BRAF* mutation targeted for exon 15 of the *BRAF* gene at the RNA and DNA levels. No mutation was detected in the tumor cells in our two cases.

Each case was diagnosed as a follicular adenoma due to a lack of capsular and vascular invasion. After the surgical procedures, the patients are alive and well after 28 months (Case 1) and 27 months (Case 2) of follow up.

Discussion

The most characteristic pathologic findings of our two cases were thick capsule, extracellular mucin deposition, and frequent nuclear inclusions. The main differential diagnosis included the mucin-producing papillary carcinoma, medullary carcinoma, and mucinous carcinoma.[8,12,17,18] Mucin-producing medullary carcinoma

can be distinguished from the present two cases based on the absence of amyloid, the positivity for thyroglobulin, and negativity for CEA and calcitonin. However, the cytological overlapping features such as abundant mucin, frequent nuclear inclusions, and intravacuolar globules with violaceous-colored magenta bodies of the target-like cytoplasmic vacuoles under Diff-Quik stain, prompted a differential diagnosis with mucin-producing papillary carcinoma.[2,19,20] Intranuclear inclusion is usually considered the most important feature and is a characteristic but not a specific cytologic finding of papillary carcinoma in up to 90% of cases. It can be observed in a variety of thyroid lesions such as follicular adenoma, hyalinizing trabecular adenoma, and even colloid goiter, as well as lesions mentioned above.[21] Cytology of Case 1 did not show nuclear grooves but frequent nuclear inclusions in mucinous background and the cytologic diagnosis was challenging. The possibility of papillary carcinoma in our cases was finally excluded based on the histological absence of papillae or nuclear grooves and a lack of the *BRAF* mutation, along with immunonegativity for galectin-3, CK19, and HBME-1.[22] On histologic slides, our cases were finally diagnosed as follicular adenomas with extensive extracellular mucin deposition, which according to the latest WHO classification can belong to the mucinous variant of follicular adenoma, albeit the term does not fully describe the pathologic characteristics of our two cases.[13,16.23] These atypical nuclear changes and extensive mucin spillage into the thick capsule may also be described as "follicular neoplasm of uncertain malignant potential or atypical follicular adenoma", although these terms are not fully accepted and they generally pursue benign courses contrary to follicular carcinoma.[24]

Mucin can be seen in a wide spectrum of primary thyroid tumors including follicular neoplasms, medullary carcinoma, poorly differentiated carcinoma, papillary and undifferentiated carcinomas, and mucoepidermoid and primary mucinous carcinomas.[1–16,19,25,26] A mucin-containing thyroglossal duct cyst in the thyroid has also been described in the literature.[27] Most of the mucin of these tumors are of intracellular location and a large amount of mucin can cause a signet-ring appearance in signet-ring cell adenoma of the thyroid gland.[6,28–31] The presence of mucosubstances in the normal thyroid gland is well known because the complex carbohydrate type of mucosubstances is essential for thyroglobulin metabolism. As a result, one of the possible pathogeneses of the mucin-materials present in a thyroid neoplasm is due to protein-degradation of thyroglobulin, suggesting that the mucin is originally produced in follicular cells. In recent years, mucin genes such as *MUC1* and *MUC4* have been detected in papillary carcinoma.[32,33] The epithelial mucin found in the mucinous change of papillary carcinoma can be explained by this theory. Dual differentiation of the tumor cells that allows a combination of mucin secretion and endocrine function may be another mechanism considered.[7] Other possible explanations of mucin production include an origin from the ultimobranchial gland,[34] solid cell nests,[35] intrathyroidal embryonal nests of salivary gland, or a thyroglossal duct cyst.[27] The presence of stromal mucin, like those found in the present cases, may be produced by stromal fibroblasts or myofibroblasts.[11] Extracellular mucin differs from epithelial mucin and is composed of uniformly sulphated acid mucin, which is stained with mucicarmine and Alcian blue but not with PAS, with or without diastase treatment.[36] We retrieved 9 cases of primary thyroid neoplasms with extensive extracellular mucin deposition found in the literature.[8–16] Of 11 cases of primary thyroid neoplasms with extensive extracellular mucin deposition, including our two cases, there were 3 cases of follicular carcinomas, 4 cases of mucinous carcinoma, 1 case of mucoepidermoid carcinoma and 3 cases of the mucinous variant of follicular adenoma. In only three previously reported cases, aspiration cytologic findings were described;[12,13,16] Case 1 of current cases and another case of follicular carcinoma reported by Kuma et al[12] described nuclear grooves (not in Case 1), inclusions, and pleomorphism, but no nuclear clearing, requiring the lesion to be distinguished from papillary carcinoma. Careful search for mucin in the background as well as the intracytoplasmic portion may be a clue to these uncommon thyroid neoplasm. To our knowledge, papillary carcinoma with extensive extracellular mucin deposition has not yet been reported. Despite these sharing FNA findings with those of papillary carcinomas, the possibility of papillary carcinoma could be excluded by lack of the *BRAF* mutation in the present cases. Papillary thyroid carcinomas harbor the *BRAF* mutation, whereas follicular carcinomas, medullary carcinomas, and benign neoplasm are hardly associated with the *BRAF* mutation.[23,37] These thyroid tumors with stromal mucin deposits are summarized in Table 1.

Table 1. Thyroid tumors showing extensive extracellular mucin deposition.

No. of cases	Authors	Age, gender	Histologic diagnosis	Cytology
1	Diaz-Perez et al[8]	44, M	Mucinous adenocarcinoma	ND
2	Deligdisch et al[9]	54, F	Mucinous adenocarcinoma	ND
3	Levine et al[10]	64, M	Follicular carcinoma with lymph node metastasis	ND
4	Minagawa et al[11]	52, M	Mucoepidermoid carcinoma	ND
5	Kuma et al[12]	63, M	Oncocytic carcinoma, minimally invasive	Nuclear grooves, inclusions, pleomorphism with no ground-glass appearance, suggestive of the follicular variant of papillary carcinoma or follicular carcinoma
6	Kondo et al[13]	82, M	Mucinous carcinoma	Single or weakly bound cells with no nuclear inclusions or grooves, a small amount of mucin
7	Cretney et al[14]	50, F	Minimally invasive follicular carcinoma	ND
8	Murakami et al[15]	63, M	Follicular adenoma	ND
9	D'Antonio et al[16]	62, F	Mucinous carcinoma	Moderately cellular, mucin producing cells with signet-ring cell features
10	Present case 1 (2012)	58, M	Follicular adenoma	Discohesive single cells with nuclear inclusions, nuclear pleomorphism with rare atypical mitoses in mucin
11	Present case 2 (2012)	47, F	Follicular adenoma	ND

Given the rarity and uncertainty of these mucin-producing thyroid tumors, it is unknown whether extensive mucin production in benign and malignant thyroid neoplasms confers a different biologic behavior. Mucinous changes are one of several clear cell changes occurring in thyroid neoplasms of various microscopic types and as a consequence of variable mechanisms and subsequent accumulation of mucin, glycogen, lipid or thyroglobulin. In general, mucins have become molecules of interest as prognostic factors for various cancers. However, treatment and clinical prognosis of the thyroid neoplasm producing extracellular mucin deposits are not different to that of their non-mucinous counterparts. The clinical course and treatment of these tumors is determined by their basic nature rather than the presence of cytoplasmic clearing.[38,39] It is unclear whether it belongs to an existing category of thyroid neoplasm with mucin production or it is truly a new tumor variant. Furthermore, pathologists should pay attention to avoid misdiagnosis of this variant of follicular neoplasm that shows overlapping cytology with that of papillary carcinoma.

Table 1 (*Continued*)

No. of cases	Immunohistochemical results	Molecular analysis	Procedure	Prognosis
1	ND	ND	Total thyroidectomy, neck dissection	NR (8 years of follow up)
2	ND	ND	Partial thyroidectomy	Not described
3	CD56+ pancytokeratin+ CEA+ CK MNF116+ vimentin+ calcitonin–	ND	Total thyroidectomy, neck dissection, oral iodine, radiation	NR (14 months of follow up)
4	CEA+ Tg– chromograninA– calcitonin–	mRNA for TTF-1 + TTF-2+ PAX-8+ NIS+ TPO+ TSHR– Tg–	Radiotherapy, chemotherapy	Died
5	Tg + CK19+ HBME-1 + CEA– calcitonin–	ND	Total thyroidectomy	Not described
6	Tg+ TTF1+ CK19+ CAM5.2+ CEA– calcitonin– HMWCK- synaptophysin–	ND	Lobectomy with cervical lymph node excision	Died with multiple metastases (4 years)
7	TTF-1+ NSE+ weak, calcitonin- chromogranin- synaptophysin– CEA– S100 protein–	ND	Subtotal thyroidectomy	Not described
8	Tg + CK19– calcitonin–	ND	Hemi-thyroidectomy	Not described
9	TTF1+ Tg+ CK MNF116+ CK7+ calcitonin– CK20–	ND	Total thyroidectomy with lymph node dissection	Died after 6 months
10	TTF-1+ Tg+ cyclin D1– CD56– CAM5.2– galectin-3– HBME1-CK19– calcitonin– synaptophysin– CEA- SMA– HMWCK–	*BRAF* mutation (–)	Lobectomy	NR (28 months)
11	TTF-1+ Tg+ cyclin D1– CD56– CAM5.2– galectin-3– HBME1- CK19– calcitonin– synaptophysin- chromogranin– CEA– SMA- HMWCK–	*BRAF* mutation (–)	Total thyroidectomy	NR (27 months)

Abbreviations: CK, cytokeratin; NSE, neuron specific enolase; CAM5.2, cytokeratin clone CAM5.2; Tg, thyroglobulin; SMA, smooth muscle actin; CEA, carcinoembryonic antigen; TTF, thyroid transcription factor; TSHR, TSH receptor; TPO, thyroid peroxidase; NIS, Na-I symporter; HMWCK, high molecular weight cytokeratin; NR, No recurrence; ND, not done.

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Author Contributions

NRK drafted the manuscript while HYC and GR helped in the case summary. YDL is a surgeon who operated the first patient. SPO amended the English and JR proof read the manuscript. All authors reviewed and approved the final manuscript.

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