Encapsulated Follicular Variant of Papillary Thyroid Carcinoma Arising in a Follicular Adenoma: a Diagnostic Dilemma

Kanika Singh¹ · Mukta Pujani¹ · Varsha Chauhan¹ · Charu Agarwal¹ · Shruti Dhingra²

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Abstract

Papillary thyroid carcinoma (PTC) arising within follicular adenoma is a rare histological subset of papillary carcinoma. A 24-year-old female (euthyroid and asymptomatic) presented with a solitary mass in the right lobe of thyroid for 2 years. Fine-needle aspiration cytology (FNAC) suggested features of hyperplasia of thyroid. Hemithyroidectomy was performed. Histopathological examination revealed two distinct areas and was reported as encapsulated variant of papillary carcinoma along with follicular adenoma. Papillary carcinoma was confirmed by positive immunohistochemistry for HBME-1. CT head and neck region ruled out metastasis and the patient was kept on follow-up. There have been reports of medullary and papillary carcinomas occurring together; however, there is a paucity of literature on co-existing follicular neoplasm and papillary carcinoma. We hereby report a rare case of follicular variant of papillary carcinoma arising within follicular adenoma of the thyroid.

Keywords Papillary thyroid carcinoma · Follicular adenoma · Immunohistochemistry

Introduction

Papillary thyroid carcinoma (PTC) arising within a follicular adenoma is a very rare histological subset of papillary carcinoma [1, 2]. The follicular variant is the most common variant of PTC and the encapsulated forms have been proposed to be termed as noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) [3]. The encapsulated tumor without invasion and follicular architecture along with the presence of nuclear features like enlarged, elongated, and overlapping nuclei, membrane irregularities (grooves and pseudoinclusions), chromatin clearing, margination, and glassy nuclei is the defining criteria [4]. The diagnosis can be missed in cases owing to the presence of minimal nuclear features of PTC; therefore, it can be misdiagnosed as follicular adenoma. The cytological interpretation may also be difficult in such cases and can be mistaken for a hyperplastic nodule [5]. There have been reports of medullary and papillary

carcinomas occurring together; however, there is paucity of literature on co-existing follicular neoplasm and papillary carcinoma [6]. We hereby report a case of multiple foci of follicular variant of papillary carcinoma arising within follicular adenoma of the thyroid.

Case Presentation

A 24-year-old female presented with a solitary mass in the right lobe of thyroid measuring 4 × 4 cm for 2 years with no cervical lymphadenopathy. The patient was euthyroid with no clinical symptoms. Ultrasonography (USG) findings revealed a hypoechoic lesion in the right lobe measuring 3.6 cm × 3.8 cm × 1 cm with well-defined margins and no microcalcifications. Fine-needle aspiration cytology (FNAC) suggested features of hyperplasia of thyroid showing hypercellularity along with fire flares in a background of colloid. In view of increased cellularity, a follow-up was advised.

A repeat FNA done 6 months later showed similar cytological features. The patient opted for surgery and right hemithyroidectomy was done. The cut section of the gross specimen showed a well-encapsulated grayish solid lesion along with few whitish areas of hemorrhage. The normal thyroid was compressed at the periphery. The isthmus was completely unremarkable (Figs. 1, 2, 3, 4 and 5).

✉ Varsha Chauhan
varsha.chauhan3@gmail.com

¹ Department of Pathology, ESIC Medical College, Faridabad, Haryana, India

² Department of ENT, ESIC Medical College, Faridabad, Haryana, India

Fig. 1 Cut section of thyroid showing well-encapsulated solid grayish mass (marked with blue arrows) and few whitish areas with areas of hemorrhage and the normal thyroid is compressed at the periphery

Histopathological examination revealed encapsulated mass with cells arranged in follicular pattern. However, there were multiple foci showing cells with nuclear features of papillary thyroid carcinoma (crowding, ground glass chromatin, and nuclear grooves), without any evidence of capsular or vascular invasion thus suggesting noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) along with adjacent areas with histological features corresponding to follicular adenoma. Papillary carcinoma was confirmed by immunohistochemistry for HBME-1 and CK-19 showing cytoplasmic positivity. However, the immunohistochemistry for RET oncoprotein

Fig. 2 Smear shows moderate cellularity with follicular epithelial cells in clusters in a blood mixed colloid background. Few follicular cells show acinar pattern (Giemsa, $\times 100$). Inset showing fire flares (Giemsa $\times 200$)

Fig. 3 sSection from follicular adenoma shows variable-sized follicles lined by low columnar cells and filled with colloid (hematoxylin and eosin, $\times 40$)

was negative. Retrospectively, the cytological smears were examined again to look for features of either PTC or follicular neoplasm. The smears showed few areas with follicular pattern; however, the nuclear features of PTC were still not prominent.

A CT of the head and neck region was done to rule out extension or metastasis to lymph nodes; therefore, total thyroidectomy or radio-iodine therapy was not advised and the patient was kept on close follow-up. On follow-up, the patient was healthy and no new complaints or lesion was noticed.

Discussion

The neoplasms of the thyroid gland are classified on the basis of the cells from which they originate and arise most commonly from the follicular cells.

Fig. 4 Section shows follicular variant of papillary carcinoma on one side (left) and follicular adenoma on other side (right) (hematoxylin and eosin, $\times 40$). Inset (right lower corner) showing cells arranged in follicular pattern with nuclear features of PTC—nuclear crowding, clearing, and intranuclear grooves (hematoxylin and eosin, $\times 400$)

Fig. 5 **a** IHC for HBME-1 shows cytoplasmic positivity in tumor cells ($\times 400$). **b** IHC for CK-19 shows cytoplasmic positivity in tumor cells ($\times 400$). **c** IHC for RET is negative in tumor cells ($\times 100$)

Papillary thyroid carcinoma is the most common histological type of thyroid carcinoma [7] with follicular variant of PTC (FVPTC) as the most common [3]. The presence of follicular architecture and nuclear features of papillary carcinoma, which include nuclear elongation, chromatin clearing, intranuclear grooves and inclusions, eccentric nucleoli, and irregular nuclear envelope, are the defining features of this tumor [3, 8]. FVPTC have fewer calcifications and psammoma bodies [9]. In our case, the follicular pattern and the presence of nuclear crowding, ground glass chromatin, and nuclear grooves were the morphological features, which led to the diagnosis of FVPTC.

The diagnosis of FVPTC by FNAC is difficult and unreliable with low sensitivity and due to paucity of nuclear features of PTC can be misdiagnosed as hyperplastic nodule [5, 10]. Similarly, in our case, the lesion was missed on cytology due to the absence of nuclear features and abundant colloid in the background.

The diagnostic difficulties arise in permanent sections also when the tumor is without typical nuclear features of PTC or features are present only focally within the lesion and also since majority of the tumors arise within a background of nodular goiter resembling an adenoma and are encapsulated without vascular or capsular invasion, the distinction from follicular adenoma/carcinoma is difficult [9, 10]. Similarly, in our case, the presence of nuclear features of PTC in the cells arranged in follicular pattern was seen focally admixed with areas of benign follicular adenoma and made it difficult for us to diagnose it as PTC with confidence.

The use of immunomarkers like galectin-3, cytokeratin-19 (CK-19), Ret oncoprotein (RET), and HBME-1 have been of great importance in differentiating FVPTC from other benign

conditions (9). HBME-1 and CK-19 were positive in our case in areas corresponding to FVPTC, which aided in the diagnosis.

FVPTC has a genetic profile, which is markedly different from classic PTC and includes high RAS mutations and PAX8/PPAR γ rearrangement and less common BRAF mutations and RET gene translocation. Thus, the genetic profile is intermediate between PTC and follicular carcinoma as PTC involves somatic rearrangements that have RET protooncogene and BRAF mutations and follicular carcinoma characterized by RAS mutations and PAX8/PPAR γ rearrangements [8, 11]. The immunohistochemistry for Ret oncoprotein, which is positive in classical PTC being negative in our case, can thus be explained on the basis of the above-mentioned findings in different studies.

The two main subtypes include infiltrative and encapsulated FVPTC which is now renamed as “noninvasive follicular thyroid neoplasm with papillary like nuclear features”. The presence of morphological features, i.e., follicular pattern with nuclear features of PTC, lack of invasion, clonal origin, and low risk of adverse outcome characterize this entity. NIFTP has an indolent behavior and has a low recurrence rate and thus an aggressive management is not required which will reduce the psychological burden and also in turn save expense on medical overtreatment [11]. Since there was no evidence of invasion in our case, the patient was advised a close follow-up without the need for total thyroidectomy or radioactive iodine therapy.

Thyroid follicular adenomas are encapsulated neoplasms without capsular, lymphatic, and vascular invasion and also the absence of characteristic nuclear features of PTC. However, few adenomas show atypical nuclear features and

are classified as atypical adenomas which are hypothesized to be precursor neoplasms of both follicular and papillary thyroid carcinomas. The atypical adenoma includes adenoma with unusual cellular density, mitosis, and less regular cytological pattern [12]. However, in our case, the atypical features as mentioned were not noted in the adenomatous areas.

In our case, we present multifocal areas of FVPTC arising within a follicular adenoma, which on review of literature have been found to be very rare, and only few cases have been reported so far.

Conclusion

Papillary thyroid carcinoma arising within a follicular adenoma is a rare entity and the subtle nuclear features of PTC in its follicular variant can be easily missed both in cytology and permanent sections. The absence of capsular and vascular invasion adds to the difficulty. Therefore, a careful examination for the atypical nuclear features should always be done along with the aid of immunohistochemistry in an adenoma to rule out a malignancy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

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