

Follicular Neoplasms Cytohistomorphological Aspects: A Case Study of 50 Cases

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Abstract

Background: Thyroid nodules are common clinically (prevalence about 5%) and even more common on ultrasound examination (about 25%). Most of the thyroid nodules are follicular neoplasms cytologically. Follicular neoplasms of the thyroid gland include benign follicular adenomas (FAs) and follicular carcinoma (FC).

Objectives: The objective of our study was to assess the histomorphological aspects of follicular neoplasms. The incidence of FAs and FCs was evaluated with respect to age, clinical presentation, and thyroid status. Our study also focuses on histopathology of the spectrum of follicular neoplasms.

Materials and Methods: This prospective study of 1 year included (June 2015-June 2016) 50 cases of thyroidectomy specimen received in the department of pathology. A careful sampling and multiple sections were taken to assess the histological aspects for differentiating between FAs and FCs. Clinical data, thyroid status, and fine needle aspiration (FNA) reports were retrieved from hospital records.

Results: About 50 thyroidectomy specimens studied showed 28 cases of follicular neoplasms, an incidence of 56% of which 25 were FAs and 3 diagnosed as carcinoma. The mean age of presentation was 41.5 years. The incidence of carcinoma in our study was 10.7%. Only one case had lymphnode metastasis.

Conclusion: FNA plays a significant role in thyroid nodules, but resection of the lobe is a definitive treatment as well as for the diagnosis between adenoma and carcinoma. Immunohistochemistry and molecular markers play a very small role in the diagnosis of follicular neoplasms.

Key words: Adenoma, Carcinoma, Histopathology, Thyroid nodule

INTRODUCTION

Follicular adenoma (FA) and follicular carcinoma (FC) of the thyroid gland are tumors of follicular cell differentiation that consists of a microfollicular architecture with follicles lined by cuboidal epithelial cells. A FA is a benign encapsulated tumor of the thyroid gland. About 5% of the thyroid nodules are malignant.¹ Most patients with a FA are clinically and biochemically euthyroid. Approximately, 1% of FAs are “toxic adenomas.”²

Adults who initially present with a thyroid lump, which on scan is usually “cold,” sometimes “warm” and only rarely “hot.” However, the large majority of “hot” nodules are benign.³

A FC cannot be distinguished from a FA based on cytologic features alone. It is distinguished from a FA based on capsular invasion, vascular invasion extrathyroidal tumor invasion, lymph node metastasis, systemic metastasis. Follicular neoplasm with tumor invasion into but not through the entire capsule is considered a FA. Occasionally FA will contain bizarre cells sometimes multinuclear cells may be seen. These lesions are benign. Vascular invasion is defined as tumor penetration into a large caliber vessel within or outside the capsule. Vascular invasion is the most valuable sign of malignancy.⁴

The incidence of thyroid cancers has steadily increased in most countries over the past two decades, predominantly

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attributed to increased detection of small tumors by imaging techniques.⁵

FC accounts for 10% of all cases of thyroid malignancy in iodine sufficient areas and 25-40% of thyroid malignancies in areas of iodine deficiency.^{2,6} Most follicular cancers are nonfunctional. FC is usually unifocal and <10% have lymph node metastasis. The most patients with follicular neoplasms present with a solitary thyroid nodule. The diagnostic evaluation of a patient who presents with a thyroid nodule consists of routine fine needle aspiration cytology (FNAC), ultrasound examination of neck, and serum thyroid-stimulating hormone level.

FNAC of follicular neoplasms is characterized by abundant follicular epithelial sheets with crowding, overlapping and microfollicular formation with scant or no colloid.

According to Bethesda system of reporting thyroid cytopathology, this cytological appearance is classified as follicular neoplasms or suspicious for follicular neoplasms. FNAC specimen consistent with a follicular neoplasm accounts for 20% of all fine needle aspiration FNA biopsy results and has a 15-30% risk of malignancy.⁷

The differential diagnosis for a patient with a thyroid nodule and FNAC result consistent with a follicular neoplasm is a FA, adenomatous hyperplasia, FC, follicular variant of papillary carcinoma, and classic papillary carcinoma. Cytomorphologic criteria alone cannot distinguish a FA from a FC.^{8,9}

MATERIALS AND METHODS

Surgically treated patients between June 2015 and June 2016 were prospectively analyzed. The study included 50 cases of thyroidectomy specimens. Histopathological analysis was performed. Clinical details and thyroid profiles were noted for available cases. Most of the patients had undergone an FNAC and those diagnosed as follicular neoplasms were correlated with histopathology analysis.

Most of the cases were found in the age group of 41-50 years with female preponderance (Figure 1 and Table 1). Out of the 28 cases, only 2 cases were male and rest was females. All the cases presented with thyromegaly, only 9 presented a solitary nodule. Out of the 28 cases, 9 cases were unifocal and rest was multifocal. The thyroid profile tests for most of the patients were retrieved. Most of them were found to be euthyroid.

Out of the 50 cases, histopathological study revealed 28 cases were diagnosed as follicular neoplasms (25 - FAs and 3 - FCs). An incidence of 56% of all thyroidectomy specimens received in our institution (Figure 2).

The cytological reports were analyzed retrospectively for the 28 cases along with clinical information. 19 of the 28 cases were reported as follicular neoplasms, 5 as adenomatoid nodule and 4 as goiter with papillary hyperplasia cytologically.

Out of the 28 cases, 13 cases presented as a solitary nodule, 9 as multiple nodules, 4 were with diffuse swelling, and 2 of them had no swelling and were diagnosed having a nodule only on ultrasound examination (Figure 3). All the patients were euthyroid except for one who showed toxic features.

FC was diagnosed in 3 cases (2 females and 1 male) wherein there was a capsular and vascular invasion. One of the

Table 1: Age wise distribution of SNG diagnosed as follicular neoplasms

Age distribution (in years)	Number of cases
20-30	5
31-40	7
41-50	11
51-60	4
61-70	1
Total	28

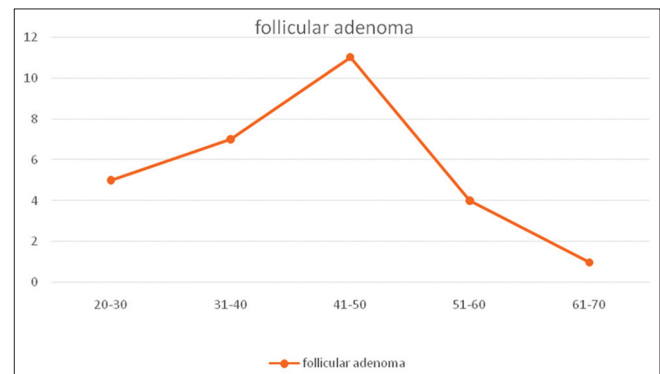


Figure 1: Line diagram depicting the incidence of follicular adenomas in various age groups

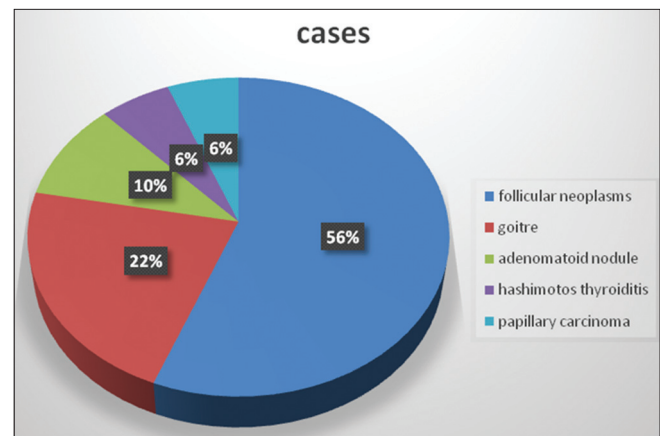


Figure 2: Incidence of cytological diagnosis of thyroid nodules (50 cases)

cases showed focal poorly differentiated carcinoma with lymph node metastasis. The incidence of FC was 10.7% in our institution. One case of Hurthle cell adenoma was diagnosed in a young female patient who had presented clinically as a colloid goiter.

Currently, a FC cannot be distinguished from an FA based on cytologic, sonographic or clinical features alone. The patients diagnosed as follicular neoplasms cytologically should undergo a diagnostic thyroid lobectomy which is a definitive treatment for a benign FA or a minimal invasive follicular cancer. Our study included 50 cases of thyroid swelling wherein clinical examination, ultrasound findings and FNAC was done to diagnose follicular neoplasms. Grossly, all the specimens diagnosed as follicular neoplasms clinically and cytologically were subjected to careful capsule inspection. All the lesions were encapsulated with a well-defined capsule (Figure 4). Two of the 28 specimens showed a very thick capsule and one among the two showed a capsular breach clearly.

Our study showed various morphological patterns among the adenomas. 8 cases showed a fetal pattern, 3 an embryonal pattern and the most common being a combination of one or two patterns - 12 cases (42.8%) (Table 2).

DISCUSSION

Thyroid nodules showing follicular morphological features include adenomatous, nodule, FA, FC, and follicular variant of papillary thyroid carcinoma.⁸ Cytologic features are known to overlap among these tumors and definitive diagnosis is mostly obtained by pathologic examination followed by complete excision of the lesion. The diagnosis of a solitary encapsulated nodule with follicular histology features is frequently problematic since a broad range of benign to malignant subtypes of follicular tumors (FT) need to be differentiated.³ Differential diagnosis of FC from FA is based on the presence of capsular, vascular, extrathyroidal tissue invasion, and nodal or distal metastasis.¹⁰

FC used to comprise 10-20% of all primary thyroid cancers but its frequency has dropped to <5-10% in the recent years attributable to increased detection of early papillary carcinoma and adoption of a more liberal approach in the diagnosis of follicular variant of papillary carcinoma. The incidence of FC is high in areas of endemic goiter; iodine deficiency appears to be the main contributing factor because addition of iodine supplement to the diet has been associated with a decline in the incidence of FCs in these geographic areas. Rarely FC may arise in a pre-existing FA

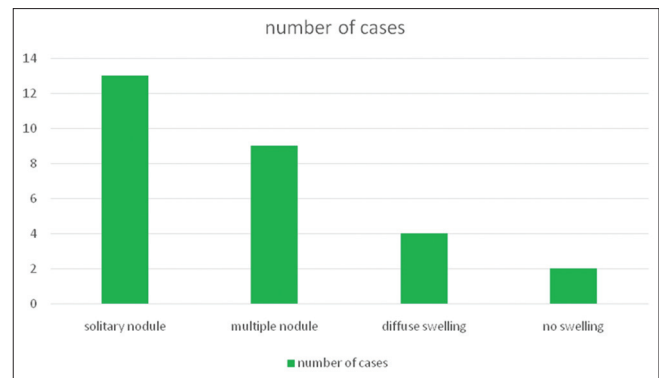


Figure 3: Clinical presentation of follicular neoplasms (28 cases)

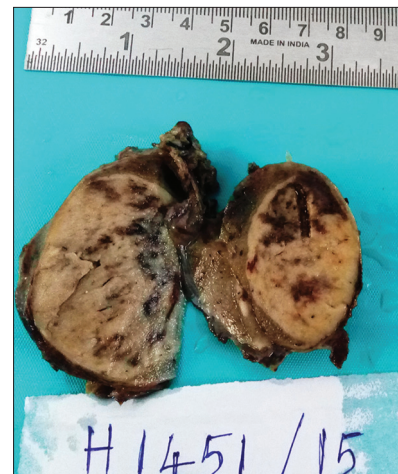


Figure 4: Gross specimen of follicular adenoma showing a tan brown circumscribed nodule

Table 2: Morphological patterns of adenomas

Patterns	Number of cases
Normofollicular (simple)	2
Macrofollicular (colloid)	3
Microfollicular (fetal)	8
Trabecular/solid (embryonal)	3
Combination	12
Total cases	28

dysmorphogenesis and irradiation predisposed to the development of FC.⁵ Rare cases of follicular neoplasms occur as part of hereditary nonmedullary thyroid cancer syndromes.

So far significant differences have not been shown between FA and FC in terms of cytoarchitecture, histomorphometry, immunophenotypic profile, DNA ploidy, or molecular alterations. Up to 27% of adenomas may show aneuploidy and yet the patients remain well on follow of more than 5 years.⁵ Furthermore, the prevalence of RAS oncogene mutation is nearly as high in FA as in FC. Hence if one accepts that some FAs are in reality *in situ* carcinoma, the

above results make sense the attempt to derive clear cut discriminatory parameters will be futile when one has to compare FCs with a mixture of adenomas and *in situ* carcinomas. However, for management purposes, it is not important to identify these hidden *in situ* carcinomas which lack metastatic potential. Currently, histologic evaluation remains the gold standard in the distinction between FC and FA.

Our study of 50 thyroidectomy specimens revealed an incidence of 56% of follicular neoplasms of which an incidence of 10.7% of FC which is slightly higher in iodine sufficient areas where FC accounts for 10% of all cases of thyroid malignancy and 25-40% in areas of iodine deficiency. Female preponderance in the age group of 40-50 years was the presentation in our study consistent with other studies. The three cases diagnosed histopathologically as FC did not reveal much atypia cytologically.

FAs are characteristically surrounded by a generally thin capsule that is grossly and microscopically complete. Microscopically adenomas may exhibit a variety of patterns singly or in combination - normofollicular (simple), macrofollicular (colloid), microfollicular (fetal), and trabecular/solid (embryonal).³ The morphological differences among these various patterns may be striking. They have no apparent clinical significance but elicit different differential diagnosis. Thus, on a general rule the larger the follicles, the less likely that the lesion is a FA or a FC as opposed to a hyperplastic nodule or a follicular variant of papillary carcinoma. Instead a predominance of solid/nesting trabecular areas should alert one to the alternative possibilities of poorly differentiated or medullary carcinoma.²

Both iodine deficiency and irradiation have been implicated in the development of FC.¹¹ In contrast to the statement that FCs are common in iodine deficient areas we found that the incidence was equal to papillary carcinoma in spite of our area being an iodine sufficient one, 3 cases of papillary carcinoma thyroid was reported among the 50 thyroidectomy specimens.

FC should be defined in a generic sense as any malignant thyroid tumor exhibiting evidence of follicular differentiation. Grossly, follicular cancer varies in size has a yellow tan color and has a thick white fibrous capsule. Areas of hemorrhage and necrosis are not uncommon, as well as foci of cystic degeneration.¹⁰ Gross differential diagnosis between adenomas and carcinomas may sometimes be difficult except for the marked thickening of capsule seen in cancers. Depending on the degree of invasiveness FC has been subdivided into a minimally invasive and a widely invasive form. A sampling of encapsulated follicular lesions

is of paramount importance. Evans *et al.* have made the interesting observation that the capsule of FC tends to be thicker and more irregular than that of adenoma.

FCs present in elderly men carried worse prognosis.¹⁰ In our study, we had a case of FC in an elderly male in the fifth decade who had a focal poorly differentiated carcinoma histologically.

The frequency of ipsilateral lymphadenopathy is considerably less than that observed in patients with papillary carcinoma and has been reported to be <10%. Our study showed one case with lymph node metastasis. Distant metastasis has been reported in up to 20% of patients at presentation with the most common sites of involvement being lungs and bone.¹¹ We did not have any case with metastasis.

The cytopathologic pattern in a well differentiated FC is similar to that seen in a FA making the differentiation between the two difficult. There is considerable controversy over differentiating FAs and FCs based on differences in nuclear size and nuclear pleomorphism, and the literature is mixed on this issue.

The chernobyl group of thyroid pathologists mentioned in the preceding section recommended the adoption of the following terminology for this situation.

1. For tumors showing definite capsular invasion and no papillary thyroid carcinoma (PTC) type nuclear changes - FC (Figure 5)
2. For tumors showing questionable capsular invasion - FT of uncertain malignant potential (UMP).

If PTC type nuclear changes are absent and well-differentiated tumor of UMP, if those nuclear changes are questionable (incomplete).

Widely invasive FC is the high-risk counterpart of the minimally invasive subtype. Recent classification of FC is done as:

1. Encapsulated
 - i. With capsular (but no vascular) invasion
 - ii. With limited (<4) vascular invasion (with or without capsular invasion).
With extensive (≥ 4) vascular invasion (with or without capsular invasion)
2. Widely invasive.

The morphological criteria for identifying for sure signs of vascular invasion have been thoroughly described by Rosai *et al.* as well as the WHO book (Figure 6).^{3,11} According to Mete and Asa about the ideal criteria for diagnosing vascular invasion (tumor cells invading the

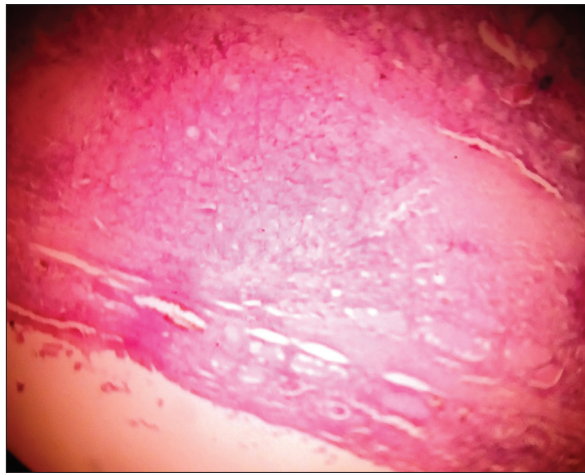


Figure 5: H and E section showing tumor cells mushrooming the capsule (x10)

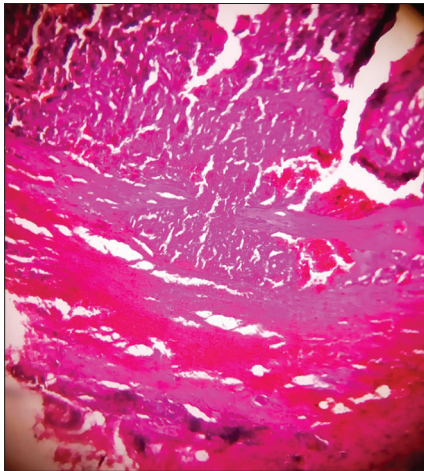


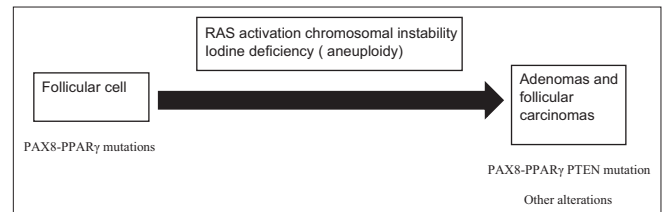
Figure 6: H and E section of follicular carcinoma showing definite vascular invasion (x40)

vessel wall associated with the thrombus adherent to intravascular tumor), we diagnose vascular invasion if we detect well preserved neoplastic tissue within a vein. Whenever facing the dilemma “vascular invasion or not,” we do not rely on any immunostaining of endothelial cells. We search the additional sections of the capsule and stick to the following rule. If we do not detect any unequivocal signs of venous permeation we diagnose the tumor as non angioinvasive.¹² The search for such signs was made for the 3 cases after multiple sampling of the capsule.

The prognosis of FC is directly related to the degree of encapsulation, hence the important distinction between minimally invasive and widely invasive types.

The most prominent molecular features of FC are the prominence of aneuploidy and the high prevalence of RAS mutations and of PAX8-peroxisome proliferator-activated

receptor γ (PPAR γ) rearrangements, the latter as a result of a 2;3 translocation.¹³



The prognosis of FC thyroid depends on several factors such as age of the patient, size and staging of the tumors, completeness of surgery and responsiveness to radioactive iodine. It also depends on the degree of invasiveness of tumors. Minimally invasive carcinomas carry a much better prognosis than do widely invasive carcinomas. The coexistence of less well-differentiated areas in some FCs raises the problem of differential diagnosis between FC and poorly differentiated carcinoma. In our study, we had one case with such diagnostic problems for which careful sampling was done and reported as FC with focal poorly differentiated carcinoma.

Immunohistochemistry of endothelial cells of the capsular vessels does not provide useful diagnostic data. There is also no immunohistochemical or molecular feature that may be needed as a reliable marker of invasion.¹⁴ Hence, no immunohistochemistry was used in our study and only careful histopathological analysis of our specimens was done to categorize the broad spectrum of follicular neoplasms.

CONCLUSION

Thyroid nodules whose FNA is diagnosed as follicular neoplasms should be resect unless there are significant contradictions to the surgical procedures. Our study of 50 thyroidectomy specimens of FAs and FCs has showed a slight increase in incidence 10.7% despite being an iodine sufficient area. Most of the patients were euthyroid and had come to the outpatient department only for a palpable thyroid swelling noted clinically. FNA does play an important role in the diagnosis of follicular neoplasms, but only histopathological examination can give the conclusive diagnosis.

For most thyroid tumors a diagnosis can be reached by morphologic assessment alone as with tumors in other endocrine organs the presence of nuclear atypia in a thyroid tumor is not necessarily synonymous with a diagnosis of malignancy.

Careful sampling of the specimen should be done to differentiate adenomas and carcinomas. Microscopically there should be a definite capsular and vascular invasion for the conclusive diagnosis of carcinoma.

Immunohistochemistry and molecular markers play a very insignificant role in the categorization and diagnosis of follicular neoplasms.

REFERENCES

1. Mackenzie EJ, Mortimer RH. 6: Thyroid nodules and thyroid cancer. *Med J Aust* 2004;180:242-7.
2. Rosai J, Carcangiu ML, DeLellis RA. Tumours of thyroid gland. *Atlas of Tumour Pathology*. 3rd Series. Washington, DC: Armed Forces Institute of Pathology; 1992. p. 21-48.
3. Rosai J. Rosai and Ackerman's Surgical Pathology. 9th ed., Vol. 1. London: Mosby; 2004. p. 1482.
4. Mills SE, Baloch ZW. Sternberg's Diagnostic Surgical Pathology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010. p. 510-1.
5. Dei Tos AP, Seregard S, Calonje E, Chan JK, Fletcher CD. Giant cell angiofibroma. A distinctive orbital tumor in adults. *Am J Surg Pathol* 1995;19:1286-93.
6. Correa P, Chen VW. Endocrine gland cancer. *Cancer* 1995;75 1 Suppl:338-52.
7. Ali SZ, Cibas ES. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes. New York: Springer Science + Business Media; 2010.
8. Duggal R, Rajwanshi A, Gupta N, Vasishta RK. Interobserver variability amongst cytopathologists and histopathologists in the diagnosis of neoplastic follicular patterned lesions of thyroid. *Diagn Cytopathol* 2011;39:235-41.
9. Greaves TS, Olvera M, Florentine BD, Raza AS, Cobb CJ, Tsao-Wei DD, *et al.* Follicular lesions of thyroid: A 5-year fine-needle aspiration experience. *Cancer* 2000;90:335-41.
10. Silverberg SG, Deleius RA, Frable WJ. *Surgical Pathology and Cytopathology*. 3rd ed. New York: Churchill Livingstone; 1997. p. 2691.
11. Simoes MS, Asa SL, Kroll TG, Nifivorov Y, DeLellis R, Farid P, *et al.* Follicular Carcinoma WHO Classification of Tumours Pathology and Genetics. Tumours of Endocrine Glands. Lyon, France: IARC Press; 2004. p. 67-76.
12. Sobrinho-Simões M, Preto A, Rocha AS, Castro P, Máximo V, Fonseca E, *et al.* Molecular pathology of well-differentiated thyroid carcinomas. *Virchows Arch* 2005;447:787-93.
13. Nikiforova MN, Lynch RA, Biddinger PW, Alexander EK, Dorn GW 2nd, Tallini G, *et al.* RAS point mutations and PAX8-PPAR gamma rearrangement in thyroid tumors: Evidence for distinct molecular pathways in thyroid follicular carcinoma. *J Clin Endocrinol Metab* 2003;88:2318-26.
14. Prasad ML, Pellegata NS, Huang Y, Nagaraja HN, de la Chapelle A, Kloos RT. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. *Mod Pathol* 2005;18:48-57.

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