

EXPERIMENTAL / LABORATORY STUDIES

Problems Encountered in the Diagnosis of Encapsulated Follicular Variant of Papillary Thyroid Carcinoma and the Morphological Diagnostic Criteria

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Abstract: The encapsulated follicular variant of papillary thyroid carcinoma constitutes the most common source of consultation material in thyroid pathology. We present our five consecutive cases to illustrate this issue.

The diagnosis of the encapsulated follicular variant of papillary thyroid carcinoma is considerably controversial. These tumors are encapsulated neoplasms and have the nuclear features of papillary thyroid carcinoma. Although the criteria were described for the diagnosis, a considerable subjectivity is present among the pathologists. Therefore, the categories of "well differentiated carcinoma" and "well differentiated tumor of uncertain malignant potential" were included in the diagnostic spectrum of these neoplasms.

Five consecutive cases with encapsulated and follicular growth pattern showing nodular thyroid lesion were included in the study. Morphological and clinical features of the cases were evaluated on the basis of preoperative cytology, postoperative pathology and clinical data. The age of the cases ranged from 34 to 55 years. Three of the cases were female, two cases were man. The size of the dominant tumoral nodules ranged from 1.5 to 4 cm. Three cases were diagnosed as encapsulated follicular variant of papillary thyroid carcinoma, while two cases were evaluated as well differentiated unknown malignant potential in the postoperative histopathologic study.

We discuss the criteria of diagnosis, histological features and the diagnostic difficulties of these encapsulated and follicular growth pattern showing thyroid lesions with the accompanying literature.

Key Words: Papillary thyroid carcinoma, encapsulated follicular variant, clinical features

Introduction

The follicular variant of papillary thyroid carcinoma (FVPTC) is the most frequent variant of papillary thyroid carcinoma (PTC) after the classic type PTC (1). Encapsulated FVPTC (EFVPTC) is a subvariant of FVPTC and shows distinctive problems in the differential diagnosis. EFVPTC was first described in 1960 by Lindsay (2). Therefore, it is also called as "Lindsay's tumor" by some authors. These neoplasms were further characterized by Chen and Rosai in 1977 (3). Many problems are encountered in the cytological and histological diagnosis of these tumors. Preoperative cytological examination and intraoperative pathology

consultation have little value (1,4,5). The alternative terminology was suggested by Chernobyl Pathologists due to limited diagnostic criteria and very little information about the biological behavior of these tumors (6-8).

We present five cases including three cases of EFVPTC and two cases of well differentiated tumor-undetermined malignant potential. Our aim is to discuss the histological and cytological diagnostic characteristics of these lesions and to emphasize the difficulties encountered in preoperative and postoperative diagnosis of these lesions.

Material and Methods

Three of the cases were female, while two cases were male. The ages of the cases ranged from 34 to 55 years. All cases applied to Gaziosmanpasa University Hospital because of thyroid enlargement and thyroid hyperfunction findings. Three cases were evaluated by preoperative FNA biopsy. Intraoperative pathology consultation was required in only one case. Preoperative FNA biopsy diagnoses, intraoperative pathology consultation results and postoperative macroscopic-microscopic features of the all cases are summarized in the Table.

Cases 1 and 2 were treated by subtotal thyroidectomy first and they underwent completion thyroidectomy after the postoperative histopathological diagnosis. The other three patients were treated by total thyroidectomy. No postoperative complication was seen in any of the

patients. Completion thyroidectomy was performed in cases 1 and 2. The second postoperative pathological examination in both cases did not reveal any tumoral condition. These cases did not have any complaint in postoperative period. The cases reported as EFVPTC on postoperative pathological examination were directed for radioactive iodine therapy. The other two cases reported as “well differentiated tumor-undetermined malignant potential” are followed-up at the present time.

Microscopical findings

Case 1, 2 and 3 had similar histological findings in the sections stained with haematoxylin-eosin. Low power magnification revealed tumoral lesions that showed a predominantly follicular growth pattern surrounded by a fibrous capsule (Figure 1B). In all three cases nodular lesions were circumscribed with a complete or nearly complete fibrous capsule. The extensive fibrosis (Figure

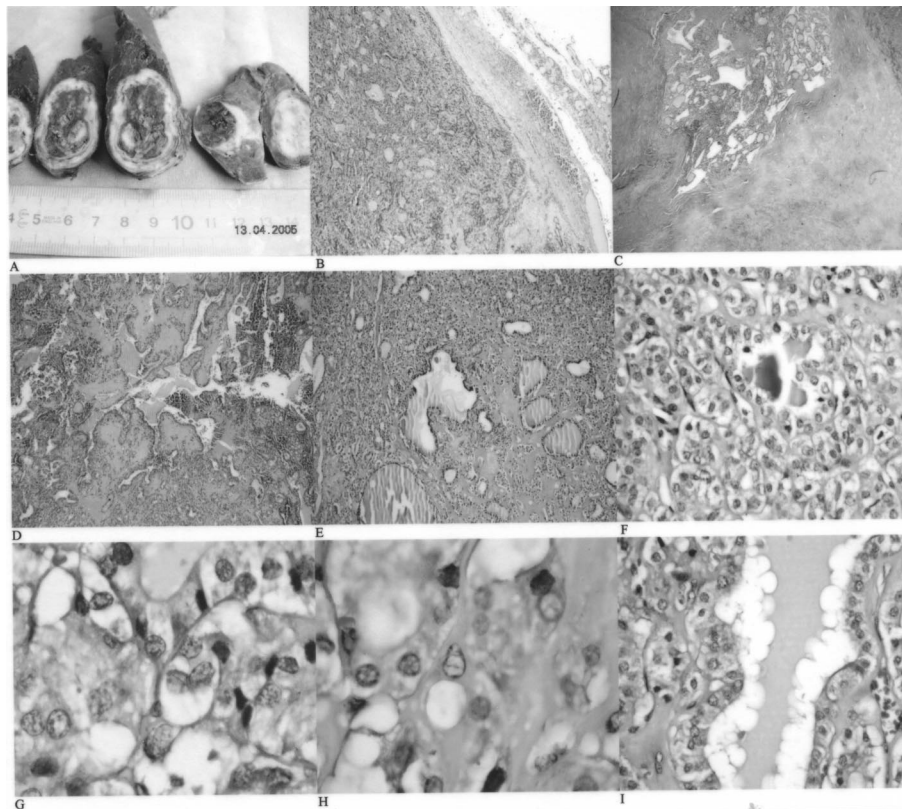


Figure (A); Macroscopic appearance of encapsulated tumoral lesion.(B); Low power appearance of tumoral lesion (HE, x5). (C); Extensive fibrosis areas in tumor centre (HE, x5). (D); Abortive papillae formations (HE, x10). (E); Elongated follicles and fibrohyaline band formation in the tumor (HE, x10). (F); Nuclear features reminiscent of PTC and dark colloid material (HE, x20). (G); High power appearance of characteristic nuclear features (HE, x40). (H); Intranuclear inclusion in the nucleus (HE, x40). (I); Luminal colloid showing scalloped edges (HE, x30).

Table: Clinical, pathological and cytological features of five cases.

Cases	Age	Sex	FNA diag.	FNA findings	IP diag.	Tumor location	Tumor size (cm)	Macros. features	Micros. features	Postop. Pathology	Treatment
1	55	F	No	No	Benign	Left lobe	2.5	Encapsulated nodule, heterogeneous appearance, focal grey-white colored solid areas.	Follicular pattern, focal complete nuclear cytological features	EFVPTC	First; subtotal thyroidectomy Second; completion thyroidectomy
2	50	F	Non-diagnostic	Follicular cell absent, watery colloid	No	Left lobe	3	Circumscribed nodule with a thin capsule, focal hemorrhagic, solid whitish areas (Fig 1A).	Follicular pattern, focal complete nuclear cytological features	EFVPTC	First; subtotal thyroidectomy Second; completion thyroidectomy
3	40	M	No	No	No	Left lobe	4	Encapsulated, solid, yellow-brownish nodule, focal hemorrhagic areas	Follicular pattern, focal complete nuclear cytological features	EFVPTC	Total thyroidectomy
4	38	M	Colloidal goiter	Watery colloid and thick colloid droplets, monolayer follicular cells, focal cellular groups	No	Right lobe	2	Encapsulated, solid, gray-whitish, nodule	Follicular pattern, incomplete nuclear cytological features	WDT-UMP	Total thyroidectomy
5	34	F	Colloidal goiter	Watery colloid and thick colloid droplets, monolayer follicular cells, focal cellular groups	No	Right lobe	1.5	Encapsulated, solid, gray- brownish nodule with focal central hemorrhagic area.	Follicular pattern, incomplete nuclear cytological features	WDT-UMP	Total thyroidectomy

Abbreviations: FNA; fine needle aspiration, diag.; diagnosis, IP; intraoperative pathology consultation,

Macros; macroscopic, micros; microscopic, Postop; postoperative, F; female, M; male, EFVPTC; encapsulated follicular variant of papillary thyroid carcinoma, WDT-UMP; well differentiated thyroid tumor-unknown malignant potential

1C), calcification and cystic degeneration areas were noted in tumoral nodules. Abortive follicles and papillae formations (Figure 1D) were present. Some follicles showed elongation and distortion (Figure 1E). The cells lining the follicles had clear or ground glass nuclei, nuclear grooves, rare intranuclear pseudoinclusions especially in subcapsular areas (Figure 1F,G,H). Mitotic figures, calcification of psammomatous character were not seen in any of the cases. Nuclear overlapping was focally observed in all cases. The follicles lined with benign appearing follicular epithelium were present among the follicles lined with epithelium showed characteristic nuclear features of papillary thyroid carcinoma. Some benign follicles were of macrofollicular character and contained small papillary projections similar to those of diffuse hyperplastic goiter. However, some of these papillary projections were covered by cells with large ground-glass nuclei. Macrofollicles and some follicles contained denser, thicker, more eosinophilic stained colloid than that of adjacent normal follicles (Figure 1F). There were areas of hyalinization consisting of bands of eosinophilic fibrous tissue which were multifocally present throughout the lesions (Figure 1E). Some areas of this fibrous tissue seemed to envelop the individual follicles. Peripheral scalloping of the colloid was present in all three cases (Figure 1I). In these cases, capsular and vascular invasion were not determined.

The tumoral nodules of case 4 and 5 had histological features of the former three cases. However nuclear clearing or ground glass nuclei, nuclear grooves, pseudoinclusions and elongation of nuclei were not present in the tumoral nodules of the latter two cases. In both cases, the nodules had complete fibrous capsule. Capsule or vascular invasion was not present.

Discussion

The differential diagnosis of encapsulated follicular patterned lesions of the thyroid includes follicular adenoma, follicular carcinoma and a follicular variant of papillary thyroid carcinoma (FVPTC). All these lesions exhibit similar clinical presentation and gross morphology (9). The distinction between these tumors has important clinical implications. Therefore, if a preoperative or intraoperative diagnosis of FVPTC can be established, definitive surgical treatment may be provided (1). However, unfortunately, the diagnosis of FVPTC is

challenging because the classic nuclear features of PTC in cases of FVPTC may be subtle on fine needle aspiration (FNA) or may be obscured by freezing artifact on frozen section (FS) (1,5). However, the difficulty of diagnosis is mostly encountered on paraffin sections. The diagnostic problem is due to the morphological nature of FVPTC. FVPTC may show a pure follicular or predominantly follicular growth pattern. Papillary projections are rarely present. The most important diagnostic criterion is the characteristic nuclear cytological features of classic PTC, but, these nuclear features are seen focally or multi focally rather than diffusely and usually have a lesser diagnostic character compared to that of classic PTC. The characteristic nuclear features are usually localized in subcapsular areas of the nodule. Also, benign follicles mostly intersperse between the neoplastic follicles (1,4-9).

Little information about the biological behavior of these lesions is present. In the literature, cases which presented with distant metastasis 7-30 years after their initial operation were reported (7,9). Besides, review of the literature showed that lymph node metastasis developed in up to 25% of the patients (6). These cases had been reported as "follicular adenoma" or "atypical adenoma" after the initial operation (7,9). When pathology slides were retrieved and reviewed, it was determined that these neoplasms were a partially encapsulated and circumscribed follicular patterned nodular lesion and the nuclear cytology was concordant with that of papillary thyroid carcinoma. These lesions, diagnosed previously as atypical adenoma or follicular adenoma, were reclassified as EFVPTC. These neoplasms with indefinite biologic behavior gave rise to the creation of an alternative terminology because of the litigation climate. This terminology proposed by Chernobyl Pathologists suggests the diagnosis of "well differentiated thyroid tumor of uncertain malignant potential" when an encapsulated tumoral lesion of the thyroid did not show capsular or vascular invasion and the characteristic nuclear features of PTC were not present or not convincing. If such a lesion shows definite capsular or vascular invasion, the diagnostic term of "well differentiated thyroid carcinoma, not otherwise specified" are recommended by this pathologist group. One reason proposing this alternative terminology is also to prevent aggressive surgery (total thyroidectomy) and treatment (radioactive iodine) (6,8).

The age range of the cases presented in our report was between 34 to 55 years. Male/female ratio was 2/3. The sizes of tumors in our cases ranged to 4 from 1,5 cm. Tumoral lesions in all cases of EFVPTC were located in the left lobe. Two cases of EFVPTC were female. The longest diameter of tumoral nodules in EFVPTC cases were more than 2,5 cm and these cases were over 40 years. However, WDT-UMP cases were under 40 years and the diameter of tumoral nodules was lower than 2 cm. It is stated that the exclusive occurrence of these tumors in females might be a distinctive clinical feature (10,11,12). In addition, these tumors seem to occur more commonly in patients 40 years or over (9).

Our three cases diagnosed as EFVPTC had focally characteristic nuclear changes and these nuclear changes were usually incomplete. Pseudoinclusion and groove formations were not evident in most area. The descriptive nuclear changes were noted in a few limited focal, especially subcapsular areas. However, the interspersed follicles of benign appearance were mostly observed. Although the architecture of the tumoral nodules was warning in some areas, areas simulating an adenomatous goiter were also present in the tumors. In the diagnosis of FVPTC, a single morphologic feature that could be pathognomonic has not been established. Furthermore, accepted minimal criteria are also not present. Therefore, a constellation of morphologic features have been suggested for the diagnosis. It has been proposed that these features can be divided as major and minor features. Major features; 1- Nuclei are ovoid rather than round. 2-Nuclei are crowded, often manifesting as lack of polarization in the cells that line a follicle. 3-Nuclei show a clear or pale chromatin pattern. 4-Psammoma bodies are found. If 1 of these 4 features is lacking, 4 or more of the following subsidiary features have to be present for a diagnosis of EFVPTC to be made; 1-Presence of abortive papillae, 2-Predominantly elongated or irregularly shaped follicles, 3-Dark-staining colloid, 4-Presence of rare nuclear pseudoinclusions, and 5-Multinucleated histiocytes in lumens of follicles (6,8). When we analyzed our cases according to this diagram, our three cases (case1,2,3) diagnosed as EFVPTC had the first three of the major criteria. No psammoma body was seen in any cases. All the minor criteria were also present in all cases diagnosed as EFVPTC. In the other two cases, the nuclear groove and pseudoinclusion formations were not seen, although the architectural histological features,

nuclear overlapping, powdery chromatin and nuclear elongation were present. These cases were interpreted as well differentiated thyroid tumor-uncertain malignant potential because satisfactory characteristic nuclear features of PTC and capsule/vascular invasion were not present.

The preoperative cytological examination of these lesions shows evident difficulties. The factor causing diagnostic difficulty is the extensive fibrosis seen especially in central areas. In addition, sampling errors may occur if PTC nuclear features are focal rather than diffuse, leading to false negative results (4). Most studies have found sensitivities ranging from 25% to 37% (4,13-15). Nuclear grooves, intranuclear cytoplasmic inclusions, and powdery chromatin were found to be the most consistent nuclear features characteristic of FVPTC. Other cytological features suggesting FVPTC by FNA are highly cellular monolayer sheets, eosinophilic cells with nuclear enlargement in a background of abundant watery, and thick eosinophilic colloid (4,5). Nevertheless, the diagnosis of FVPTC by FNA remains challenging in spite of these distinct nuclear features (1). Only three of our cases (case 2, case 4 and case 5) had preoperative cytological analysis. One of these was evaluated as non diagnostic, while other two cases were reported as colloidal goiter. When the cytology slides of all three cases were reevaluated, some cellular groups with mild elongated nuclei were noted in aspiration smears of the case (case 4) interpreted as colloidal goiter, nevertheless, cytological features were not definitive. The histology of all these cases showed extensive fibrotic areas at postoperative pathology.

The role of intraoperative pathology consultation (IP) in the evaluation of thyroid nodules is not as well defined as FNA (1). The main problem in IP is that characteristic nuclear features are obscured by a freezing artifact on FS (1,4). Intraoperative pathology consultation was required in only case 1. The nodule was interpreted as benign because it consisted mostly of macrofollicles filled with colloid. Cytological features were not clear. A further interpretation beyond nodular goiter was not made on frozen sections.

The preoperative and intraoperative examination of follicular neoplasms does not allow accurate definitive diagnosis, so the standard treatment for follicular neoplasms consists of unilateral thyroid lobectomy. If postoperative pathological examination of unilateral

thyroidectomy reveals malignancy, completion thyroidectomy should be performed. For these reasons, the preoperative or intraoperative diagnosis of EFVPTC creates a principal and exclusive matter (1).

The presented cases were diagnosed in 2004 and 2005 and the biological behavior and clinical course of these cases will become clear after a long time period. All cases underwent total thyroidectomy whether an primary surgery or completion surgery. This condition may affect the biological behavior and clinical course. We consider that these encapsulated follicular patterned thyroid lesions might be related to the Chernobyl accident as most authors do. The Middle and East Black Sea Regions were the more affected areas in Turkey during the Chernobyl nuclear accident. We consecutively

encountered these lesions at the end of 2004 and beginning of 2005 with short time intervals. We think that these thyroid lesions with the problems of preoperative and intraoperative diagnosis will increase further in the near future.

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