Thyroid Papillary Carcinoma of Columnar Cell Type

A Clinicopathologic Study of 16 Cases

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BACKGROUND. Thyroid papillary carcinoma of columnar cell type is considered an uncommon histologic subtype of papillary carcinoma characterized by its morphologic features and purportedly aggressive biologic course.

METHODS. Sixteen cases of thyroid papillary carcinoma of columnar cell type were identified from the Endocrine Tumor Registry at the Armed Forces Institute of Pathology and the Washington Hospital Center. Clinical records and follow-up were available in all cases. Paraffin blocks were available for histochemical and immunohistochemical studies in 15 of the 16 cases.

RESULTS. Of the 16 cases reported, 13 patients were female and 3 were male. The ages ranged from 16–76 years (average, 47 years; median, 40 years). An asymptomatic neck mass was the most common clinical presenting symptom. Macroscopically, the tumors varied from circumscribed or encapsulated to infiltrative, ranging in size from 1.5–6.5 cm. Histologically, the tumors had diverse growth patterns, including papillary, solid, microfollicular, and cribriform. A common pattern was the presence of markedly elongated follicles arranged in parallel cords. Colloid-filled follicles could be found, at least focally, in all cases. The characteristic histologic appearance included the presence of elongated cells showing nuclear stratification. Other features included the presence of vacuolated-appearing cells, spindle-shaped cells, and squamoid nests. Limited areas in the tumors showed morphologic features typical of thyroid papillary carcinoma. In 14 of the cases, the tumor was encapsulated, showed limited invasive growth, or was a microscopic tumor. In two of the cases, there was extrathyroidal invasion. Immunohistochemical studies showed consistent reactivity with cytokeratin and vimentin; varied reactivity with thyroglobulin, epithelial membrane antigen, carcinoembryonic antigen, and LeuM1; and no reactivity with calcitonin or chromogranin. Treatment was by surgical resection; supplemental radioactive iodine therapy was administered in eight patients. Follow-up was available for all patients, 13 of whom (81%) were alive and free of disease or had died of unrelated causes over periods ranging from 2–11 years (average, 5.8 years). All 13 of these patients had tumor confined completely to the thyroid gland. One patient died 4 months after diagnosis secondary to sepsis. Two patients (17%) had aggressive biologic courses. In both patients there was extrathyroidal invasion. One of these patients died of metastatic disease to the lungs 3 years after diagnosis; the other was alive with bilateral pulmonary metastases 9 years after the diagnosis.

CONCLUSIONS. The findings of the current study indicate that thyroid papillary carcinoma of columnar cell type is a distinct morphologic type but not a distinct clinical type of thyroid papillary carcinoma. The biologic behavior of this tumor is predicated on clinical stage, with the presence or absence of extrathyroidal invasion being the single most important parameter. Treatment of patients with these tumors should be based on the clinical stage and not on the morphologic appearance. ***Cancer* 1998;82:740–53.** © *1998 American Cancer Society.*

KEYWORDS: thyroid, papillary carcinoma, columnar cell type, prognostic features.

Thyroid papillary carcinoma generally is considered an indolent malignant tumor with an overall mortality rate of <1% per year.[1] Adverse prognostic factors that have been associated with all types of papillary carcinoma include men age > 40 years, women age > 50 years, the presence of metastatic disease, extrathyroidal extension of the tumor, size of the tumor, and tumor histology.[1] Arguably, the most important of these factors is the clinical stage of the tumor.

The World Health Organization classification of thyroid tumors recognizes a subcategory of thyroid papillary carcinoma termed the biologically aggressive variants that includes the diffuse sclerosing variant, the tall cell variant, and the columnar cell variant.[2] Until recently, the literature supported the concept that the columnar cell type of thyroid papillary carcinoma was a tumor that occurred primarily in men and behaved in an aggressive manner with early dissemination and short survival periods.[1,3] However, Gaertner et al.[4] and Wenig et al.[5] reported that the morphologic designation of thyroid papillary carcinoma of columnar cell type was not predictive of its biologic behavior but that clinical staging was the key feature in predicting the aggressiveness of this tumor. Subsequently, Evans[6] and Ferreiro et al.[7] reported cases of the thyroid papillary carcinoma of columnar cell type that behaved in an indolent manner. To better define the histologic spectrum of this tumor and to resolve conflicting issues relative to its biologic behavior and treatment, we undertook this study that, to the best of our knowledge, represents the single largest series reported on the thyroid papillary carcinoma of columnar cell type. Furthermore, we discuss whether the presence of ''tall'' cells or insular growth, as observed in other types of thyroid lesions, merit designating these lesions as ''aggressive'' on the basis of cell type or pattern of growth.

MATERIALS AND METHODS

Fifteen cases of thyroid papillary carcinoma of columnar cell type from the files of the Endocrine Tumor Registry at the Armed Forces Institute of Pathology (AFIP) and 1 case from the Department of Pathology at the Washington Hospital Center (WHC) were identified. The 15 cases from the AFIP represent 0.15% (15 of 9756) of the thyroid papillary carcinomas coded in the Endocrine Tumor Registry from 1917 to the current time; the case from the WHC represents 0.4% (1 of 255) of the thyroid papillary carcinomas coded in the WHC Tumor Registry from 1981–1996. Tumors classified as thyroid papillary carcinoma of columnar cell type showed the presence of columnar-appearing cells with the height of the cells being at least twice the width, and the presence of elongated nuclei with nuclear stratification. These cytomorphologic features had to be present in the majority of the tumor to merit inclusion in this category. Furthermore, there were no cytomorphologic features associated with thyroid papillary carcinoma of tall cell type, nor did the majority of the tumor show cytomorphologic features of the usual type of thyroid papillary carcinoma. Histochemical staining included periodic acid–Schiff (PAS) with and without diastase digestion, and Mayer's mucicarmine. Clinical records and follow-up data were available in all cases.

Paraffin blocks were available for immunohistochemistry in 15 of the 16 cases. Five-micra sections from paraffin embedded tissue blocks were prepared for immunohistochemical analysis according to the standardized avidin-biotin complex method of Hsu et al.[8] The basic commercially prepared antibody panel for each case included cytokeratin cocktail (AE1/AE3 & CK1) (mouse monoclonal, 1:400, AE1/AE3 from Dako, Carpinteria, CA; CK1 from Boehringer-Mannheim, Indianapolis, IN), thyroglobulin (rabbit polyclonal, 1:800; Dako), calcitonin (mouse monoclonal, 1:1600; Biogenex, San Ramon, CA), chromogranin (mouse monoclonal, 1:1000; Enzo Diagnostic, Syosset, NY), S-100 protein (rabbit polyclonal, 1:800; Dako), vimentin (rabbit polyclonal, 1:800; Dako), carcinoembryonic antigen (CEA) (mouse monoclonal, 1:4000; Sigma, St. Louis, MO), epithelial membrane antigen (EMA) (mouse monoclonal, 1:800; Dako), and LeuM1 (CD15) (mouse monoclonal, 1:40; Bectin Dickinson, Mountain View, CA). Of these antibodies, cytokeratin and EMA required predigestion for 3 minutes with 0.05% protease VIII (Sigma Chemical Co.) in 0.1 M phosphate buffer at a pH of 7.6 at 37 °C. Positive and negative controls were used.

RESULTS

The clinical features are detailed in Table 1. In brief, there were 13 women and 3 men ranging in age from 16–76 years (average, 47 years; median, 40 years). The most common presenting symptom was that of an asymptomatic or enlarging neck mass (n = 15). One patient (Case 3) presented with dysphagia. There were no distinct clinical features observed in association with this tumor type. The tumors were located in the left thyroid lobe in eight patients, in the right thyroid lobe in seven patients, and was bilateral in one patient (Case 2). The tumors appeared as ''cold'' nodules on thyroid scanning. None of the patients had a history of a preexisting thyroid pathologic process nor any prior history of irradiation to the neck region.

In all the patients, surgery was the treatment of choice. Often, the initial surgical procedure was conservative, including a lobectomy or subtotal thyroidec-

TABLE 1
Clinicopathologic Features of Thyroid Papillary Carcinoma of Columnar Cell Type

Case no./ age/gender	Clinical	Gross	Histology	Therapy	Follow-up
1/70/F	Asymptomatic L neck mass	Needle biopsies	Extent of invasion not determined due to limited sampling	External irradiation (4500 cGy)	Dead 4 months after diagnosis secondary to sepsis; uncertain whether residual tumor was present
2/16/F	Asymptomatic enlarged thyroid gland	Circumscribed tumors measuring 1.5 cm in greatest dimension	Bilateral tumors with limited invasive growth	Total thyroidectomy	ANED × 11 yrs
3/70/F	Dysphagia × 1 yr	Multinodular goitrous thyroid	Microscopic focus of columnar cell carcinoma measuring 0.9 cm in L lobe; ANs	Total thyroidectomy	ANED × 8 yrs
4/38/F	Asymptomatic L neck mass	Circumscribed 1.5-cm nodule	Limited invasion	Lobectomy	ANED × 7 yrs
5/59/M	Asymptomatic L neck mass	Large infiltrating tumor	Extensive intrathyroidal invasion and extrathyroidal extension	Total thyroidectomy plus RAI; chemotherapy	DWD × 3 yrs (lung metastasis)
6/23/F	Asymptomatic L neck mass	Circumscribed 2.5-cm mass	Encapsulated with limited invasion; opposite lobe with separate ''conventional'' microscopic TPC	Subtotal thyroidectomy plus RAI	DNED × 5 yrs secondary to metastatic melanoma
7/32/F	Asymptomatic R neck mass	Ovoid, firm 2.1-cm mass with a fish-flesh appearance	Encapsulated with limited invasion; same lobe with separate ''conventional'' microscopic TPC; AN	Total thyroidectomy plus RAI	ANED × 5 yrs
8/31/F	Asymptomatic R neck mass	3.8-cm tan-appearing mass	Encapsulated	Total thyroidectomy	ANED × 4 yrs
9/50/F	Asymptomatic L neck mass	Circumscribed 4.5-cm mass	Encapsulated with intrathyroidal invasion	Left thyroid lobectomy, right subtotal thyroidectomy plus RAI	ANED × 4 yrs
10/31/M	Enlarging R neck mass	Delineated 6.5-cm tan-pink mass	Encapsulated with limited invasion; AN	Total thyroidectomy plus RAI	AWD (cervical lymph node metastasis) × 4 yrs
11/39/F	Enlarging R neck mass	Circumscribed 6-cm mass	Encapsulated	Total thyroidectomy plus RAI	ANED × 3 yrs
12/26/F	Asymptomatic R neck mass	Circumscribed 5-cm mass, R lobe	Encapsulated with limited invasion	Near total thyroidectomy plus RAI	ANED × 3 yrs
13/67/M	Enlarging L neck mass	Circumscribed 6.5-cm mass, L lobe	Encapsulated with limited invasion; TMC, microscopic, same lobe; opposite lobe with separate ''conventional'' foci of TPC (encapsulated & microscopic)	Total thyroidectomy	ANED × 2 yrs
14/70/F	Enlarging R neck mass	Solid and cystic 8-cm mass, R lobe	Locally invasive tumor but no evidence of extrathyroidal invasion; lymph node metastasis at diagnosis	Total thyroidectomy plus RAI	AWD × 2 yrs (elevated serum thyroglobulin indicative of residual/ recurrent disease)
15/57/F	Asymptomatic ''cold'' R thyroid nodule	Well circumscribed 3 cm × 5-cm mass, R lobe	Encapsulated with limited invasive growth; separate ipsilateral microscopic focus of conventional TPC; ANs	Total thyroidectomy plus RAI	ANED × 2 years
16/76/F	Enlarging L neck mass	Infiltrative 6.5 × 5.5 cm × 2 cm, firm mass primarily within the L thyroid lobe with extension into the isthmus and R lobe	Extrathyroidal invasion	Total thyroidectomy plus RAI	AWD × 9 yrs after initial diagnosis; lung metastasis at 6 yrs after initial diagnosis; currently with numerous bilateral pulmonary metastases

F: female; M: male; L: left; R: right; RAI: radioactive iodine; TPC: thyroid papillary carcinoma; AN(s): adenomatoid nodule(s); TMC: thyroid medullary carcinoma; ANED: alive with no evidence of disease; AWD: alive with disease; DWD: dead with disease; DNED: dead no evidence of disease; cGy: centigray.

tomy followed by a completion (total) thyroidectomy after the diagnosis of papillary carcinoma. Postoperative radioactive iodine administration was utilized in ten patients (Cases 5–7, 9–12, and 14–16). One patient (Case 1) received external irradiation (4500 centigray). Follow-up was available for all patients. The follow-up periods ranged from 4 months to 11 years (average, 5.8 years). At last follow-up, approximately 81% (13 of 16) of the patients were alive with no evidence of disease (n = 10), alive with a recently diagnosed cervical lymph node metastasis (n = 1), alive with recurrent or persistent disease on the basis of elevated serum thyroglobulin levels (n = 1), or had died of unrelated causes (n = 1). All 13 of these patients had tumor confined to the thyroid gland. The patient with the lymph node metastasis (Case 10) underwent cervical

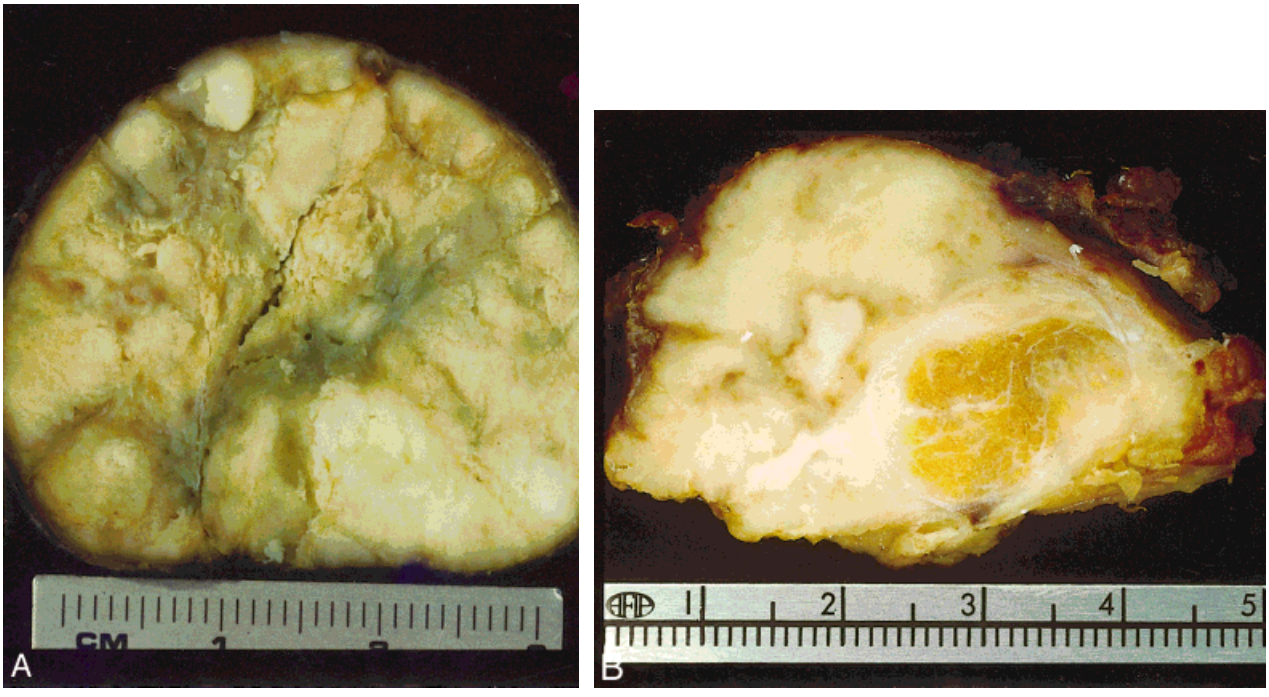

FIGURE 1. Gross appearance of thyroid papillary carcinoma of columnar cell type. (A) As depicted in this example (Case 13), the majority of the tumors were delineated or encapsulated with limited invasive growth but without extension beyond the thyroid capsule. (B) This tumor (Case 5) replaced most of the thyroid lobe and had associated extrathyroidal invasion.

lymph node dissection. The follow-up on this patient was too short (1 month) to be of any significance. One patient (Case 6) died of unrelated causes secondary to widespread malignant melanoma. At the time of death (5 years from the diagnosis of thyroid carcinoma), there was no evidence of thyroid papillary carcinoma of columnar cell type. One patient (Case 1) died 4 months after diagnosis secondary to sepsis. At the time of death, it was not known whether there was persistent thyroid disease. The two remaining patients had aggressive biologic courses. In both of these patients, the primary thyroid tumor invaded through the thyroid capsule into extrathyroidal soft tissues. In one patient (Case 16), metastatic tumor was identified in both lungs. At last follow-up, this patient was alive at 9 years from the time of the diagnosis. The other patient (Case 5) died of metastatic disease to the lungs 3 years after the diagnosis.

Pathology

The macroscopic appearance of the tumors could be separated into two categories. In 13 of the cases, the tumors were described as circumscribed or encapsulated, ranging in size from 1.5–6.5 cm (Fig. 1). In two of the cases (Cases 5 and 16), the tumors were diffusely invasive (Fig. 1).

Histologically, the tumors were characterized by a variety of growth patterns, including papillary, follicular, solid, cribriform, and fascicular, as well as markedly elongated follicles arranged in parallel cords (Fig. 2). Colloid-filled follicles were identifiable in all cases. The colloid was not distributed uniformly and was absent in any given location of any tumor. The neoplastic cells were columnar-appearing with elongated nuclei and amphophilic to clear-appearing cytoplasm. The nuclear chromatin varied from finely granular and evenly distributed to more coarse granularity to uneven distribution with chromatin clearing. Optically clear nuclei were not found in association with the columnar cells. Nuclear grooves could be found but were not identified prominently. Nucleoli were present variably and when found appeared small. There was no specific localization of the nucleoli to any portion of the cell. Intranuclear cytoplasmic invaginations (pseudoinclusions) were not found. Psammoma bodies were present in four of the cases (Cases 5, 8, 11, and 14).

Irrespective of the growth pattern, all of the tumors were characterized by the presence of nuclear stratification that comprised >70% of each tumor (Fig. 3). The cytoplasmic borders generally were not well delineated but, in any given tumor, delicate cell mem-

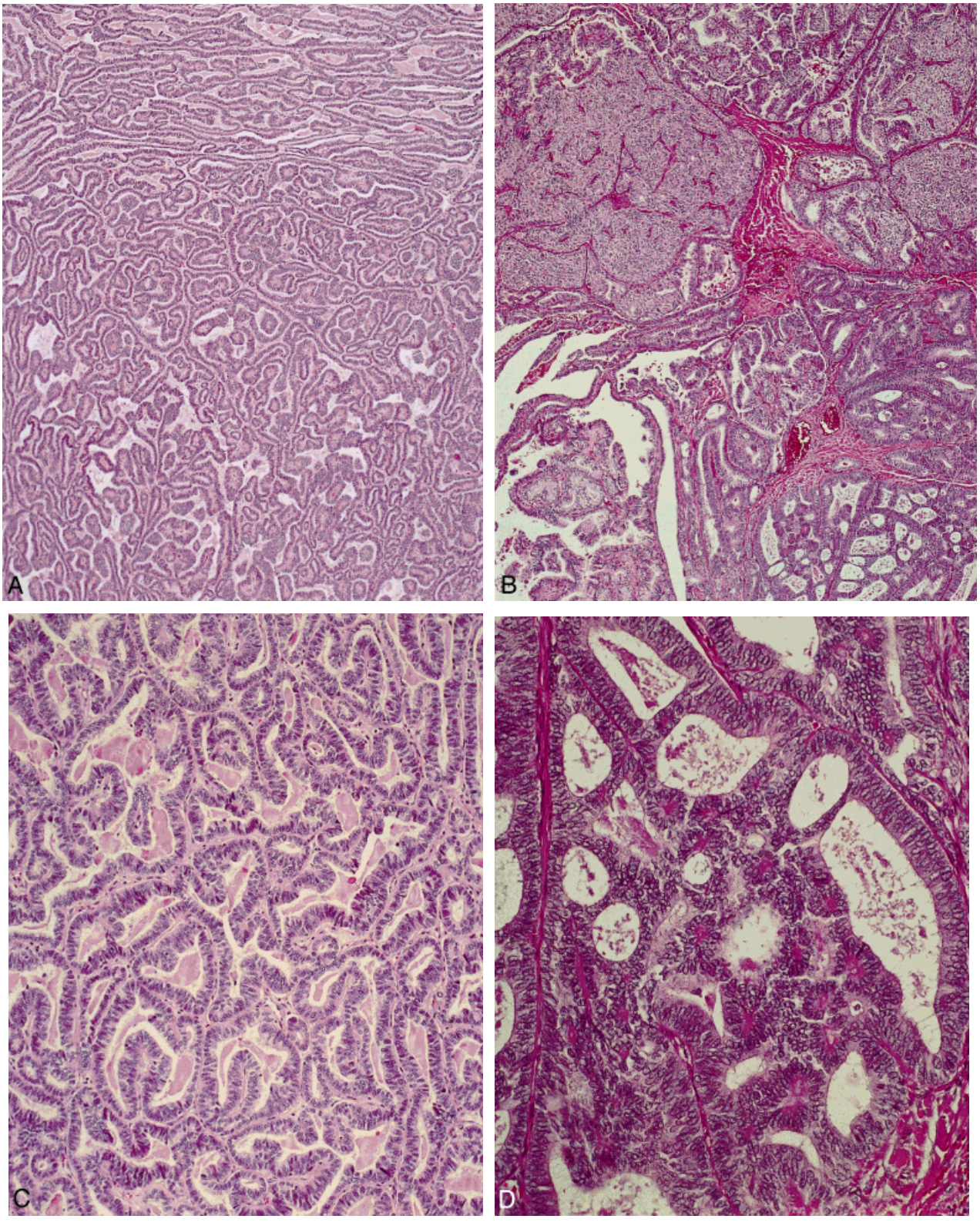

FIGURE 2. Thyroid papillary carcinoma of columnar cell type showing multiple growth patterns within a single tumor, including (A) papillary and follicular with elongated follicles arranged in parallel cords (Case 6) and (B) cribriform and solid growth patterns (Case 5). Higher magnification of the previous illustrations show (C) papillary growth with obvious colloid production and (D) cribriform and microfollicular growth patterns with less apparent but identifiable colloid.

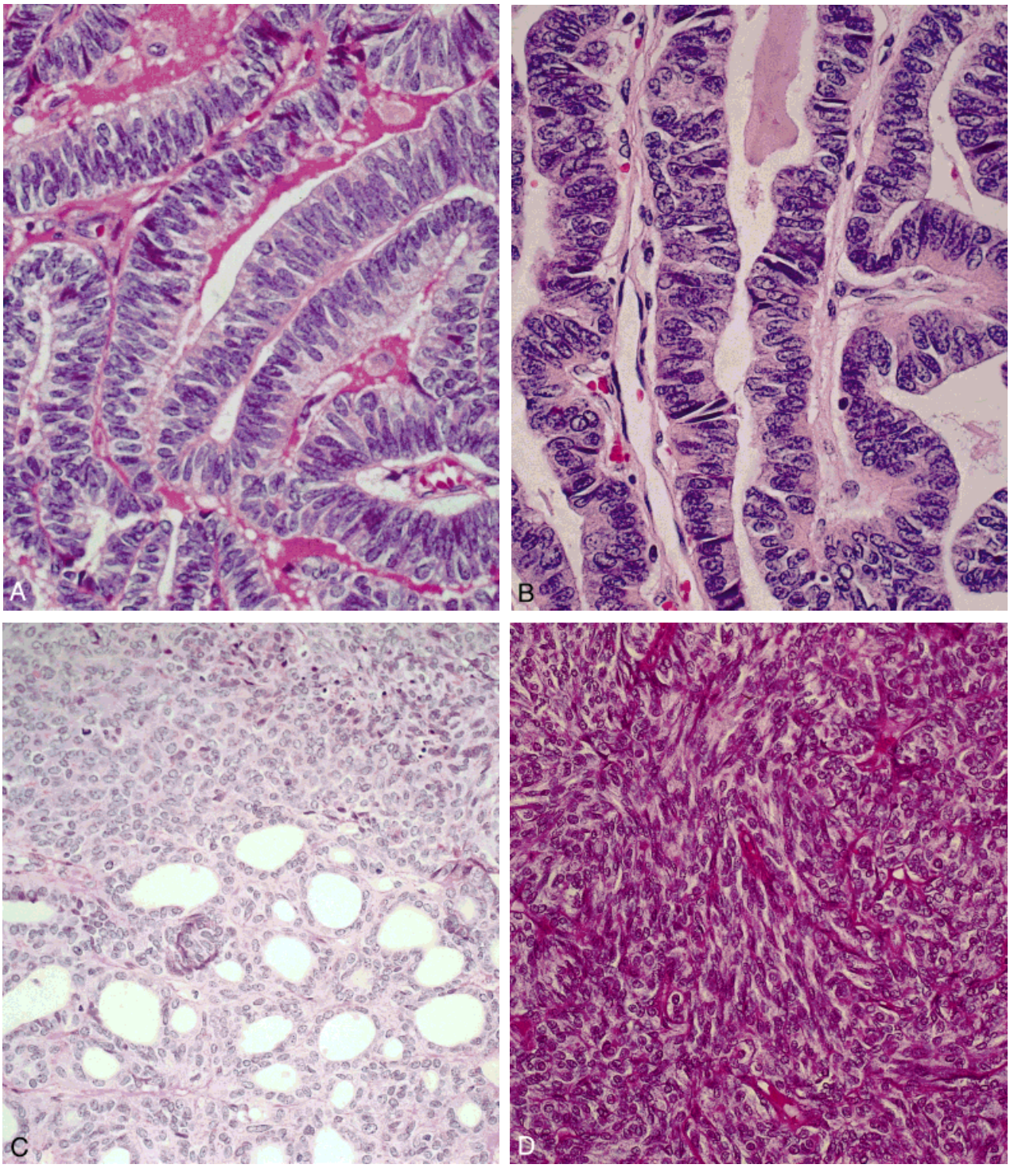

FIGURE 3. (A) and (B) The cytomorphologic characteristics of thyroid papillary carcinoma of columnar cell type include columnar-appearing cells with elongated nuclei showing nuclear stratification (Cases 11 and 6, respectively). In (B), there are hyperchromatic nuclei lying in between the columnar cells. (C) Less commonly, foci of cribriform (follicular) and solid growth could be seen (Case 4). (D) An uncommon finding was the presence of fascicular growth comprised of spindle-shaped cells (Case 5). This less differentiated component was a limited finding in a tumor that had predominant features of thyroid papillary carcinoma of columnar cell type.

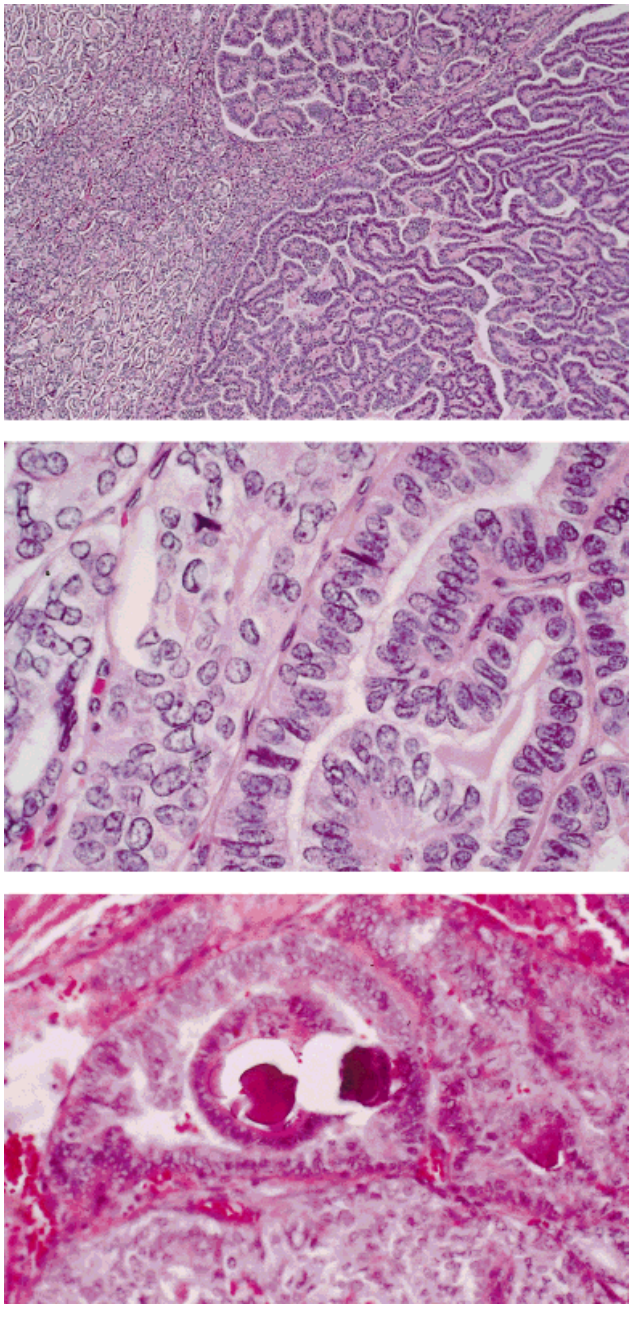

FIGURE 4. In three cases, cytomorphologic characteristics of the usual thyroid papillary carcinoma could be found admixed with the thyroid papillary carcinoma of columnar cell type. (Top) The right portion of this figure shows a thyroid papillary carcinoma of columnar cell type with papillary growth. The left portion of the figure depicts a component of the tumor with a different morphologic appearance (Case 7). (Middle) Higher magnification of the previous illustration shows the right half with features of thyroid papillary carcinoma of columnar cell type juxtaposed with the left showing classic nuclear features of the usual thyroid papillary carcinoma. (Bottom) Psammoma bodies were identified in association with the neoplastic proliferation (Case 5).

branes separating one cell from another could be identified focally. Lying between the stratified nuclei, scattered smaller darker staining elongated nuclei could be seen (Fig. 3). Subnuclear vacuolization similar in appearance to secretory type endometrium was the predominant finding in two of the cases (Cases 3 and 16) (Fig. 3). In two other cases (10 and 11), subnuclear vacuolization was found focally in tumors that otherwise were typical for thyroid papillary carcinoma of columnar cell type.

Foci in which the cytomorphologic features were those of the usual type of papillary carcinoma were present in three cases (Cases 5, 7, and 14) (Fig. 4). This component never represented >20–25% of the neoplasm. Foci of squamoid whorls were found in association with neoplastic proliferation in five cases (Cases 1, 4, 5, 10, and 14) (Fig. 5). In Case 9, there was marked nuclear pleomorphism but this tumor lacked evidence of aggressive growth, necrosis, or increased mitotic activity. Mitotic figures were identifiable but were not excessive in number and atypical mitoses were not present. Necrosis was identified very focally in two of the cases (Cases 4 and 14) and was localized to the center of the neoplastic lobules. A lymphocytic cell infiltrate in association with the neoplastic proliferation was not present. Histologic features described in association with the tall cell type of thyroid papillary carcinoma, including cytoplasmic eosinophilia (pink cell) nuclei located in the central or basal portions of the cell, demarcated cell borders, or prominent intranuclear inclusions were not present in any of the tumors.

The microscopic appearance of the 13 cases that were considered macroscopically to be delineated or encapsulated showed the tumors to be encapsulated completely by a thick fibrous capsule (Fig. 6). Limited invasive growth, including capsular or small caliber vascular space invasion, was present (Fig. 6). However, in all these cases, the tumors were confined entirely to within the thyroid gland without evidence of extrathyroidal (thyroid capsular) extension. In the one patient (Case 2) with bilateral tumors, the histology of the separate lesions was identical and both tumors had limited invasive growth. In one patient (Case 3), the carcinoma was not appreciated macroscopically but represented an incidental microscopic focus measuring 0.9 cm, occurring in the setting of a multinodular goitrous thyroid gland (Fig. 6). In two of the patients (Cases 5 and 16), the carcinoma spread beyond the thyroid capsule with evidence of extrathyroidal invasion into perithyroidal soft tissues. In both of these patients, the tumors eventually metastasized to the lungs. Histologic slides were available for only one of

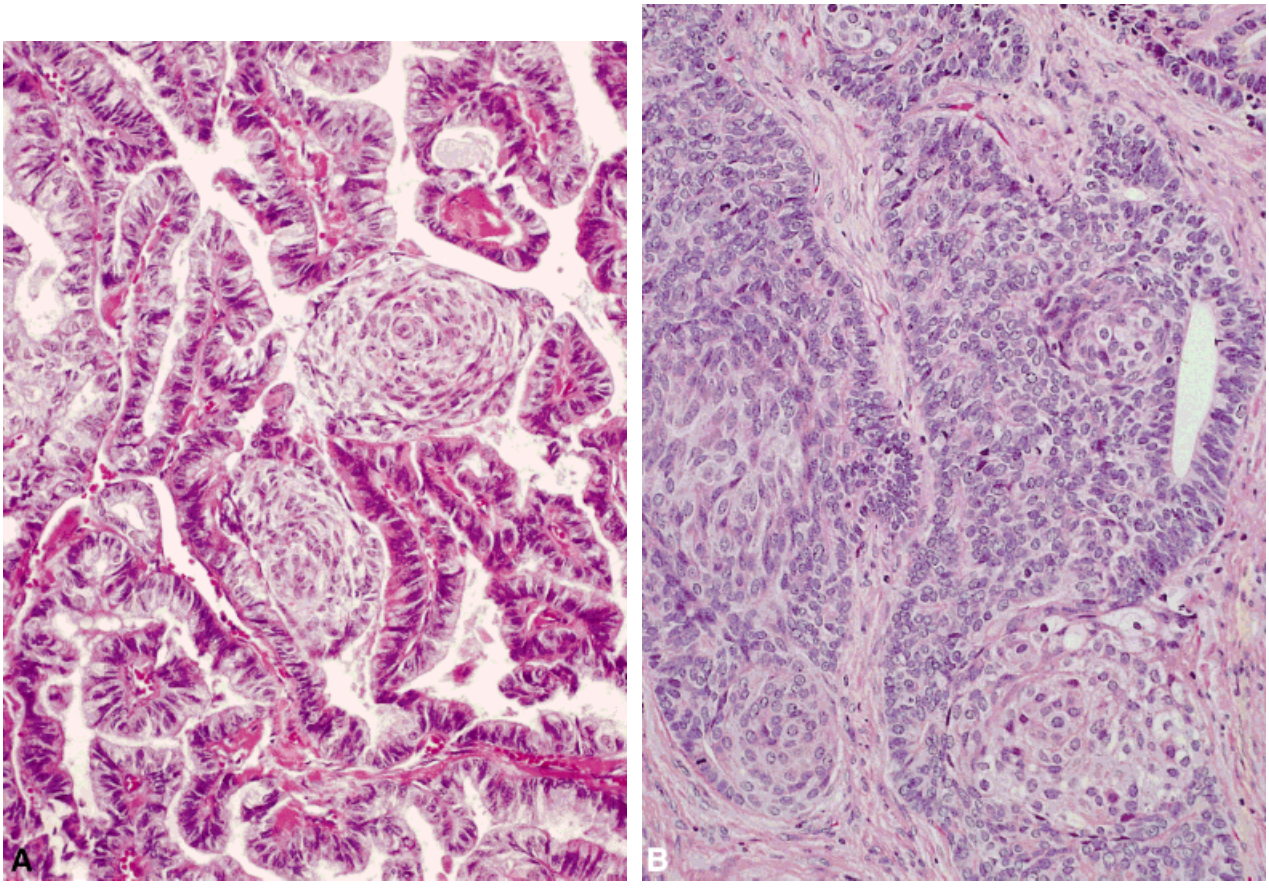

FIGURE 5. (A) and (B) Squamoid whorls or morules intimately associated with the thyroid papillary carcinoma of columnar cell type (Cases 10 and 4, respectively).

the patients (Case 16) and the metastatic foci were identical to the primary tumor.

The findings in the nonneoplastic thyroid gland showed a variety of alterations, including lymphocytic thyroiditis, adenomatoid nodules, and separate foci of the usual type of thyroid papillary carcinoma in the same or opposite thyroid lobe to the thyroid papillary carcinoma of columnar cell type. In one patient (Case 5) an intrathyroidal metastasis of the thyroid papillary carcinoma of columnar cell type in the same thyroid lobe was found. Although we can not exclude completely the presence of multicentric disease, this focus was believed to represent intrathyroidal spread rather than multifocal tumor based on its similar histology to the main tumor, its extreme small size (1 mm), and the absence of associated tumoral fibrosis.

Histochemistry and Immunohistochemistry

Colloid-filled follicles were identifiable readily by light microscopy in all cases but for completion PAS without diastase digestion was performed that enhanced the appearance of the colloid. In those cases that showed vacuolated, clear-appearing cells, intracytoplasmic granular PAS positive, diastase sensitive material was present. The tumor cells without the clear cell changes had focal PAS positive, diastase sensitive intracytoplasmic material. The mucicarmine stains were negative.

Cytokeratin immunoreactivity was diffusely and intensely positive in all cases. The squamoid areas of individual cases showed limited cytokeratin staining. Thyroglobulin reactivity was present in all cases. The reactivity was variable from case to case and even within a given case, including diffuse and intense to focal and weak to absent staining (Fig. 7) Within individual cells, there was no specific localization of the staining and the thyroglobulin reactivity included diffuse cytoplasmic staining, as well as staining along the apical portion of the cells. The squamoid areas of individual cases showed limited thyroglobulin staining. Focal EMA reactivity was found in 7 of 15 cases (Cases 1, 3, 5, 11, 13, 14, and 16) and focal LeuM1

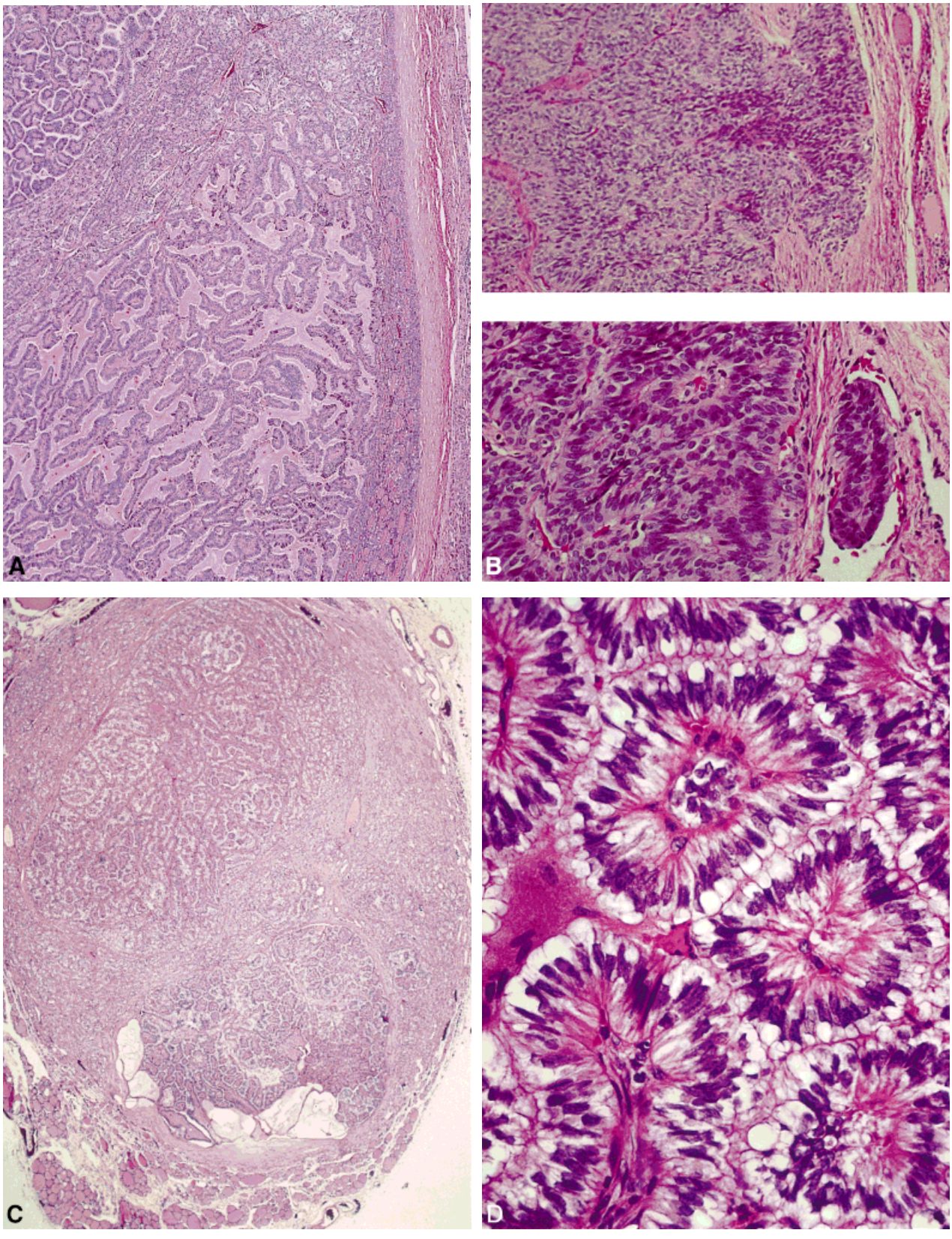

FIGURE 6. The majority of the thyroid papillary carcinomas of columnar cell type were (A) encapsulated (Case 7) or (B) had limited invasive growth with capsular (top) or small vascular space (bottom) invasion (Case 12). The solid growth pattern seen in (B) occurred in a tumor that had predominant features of thyroid papillary carcinoma of columnar cell type. (C) A microscopic focus of thyroid papillary carcinoma of columnar cell type was found incidentally in a gland removed for adenomatoid nodules (Case 3). (D) This tumor was comprised exclusively of cells with clear cytoplasm.

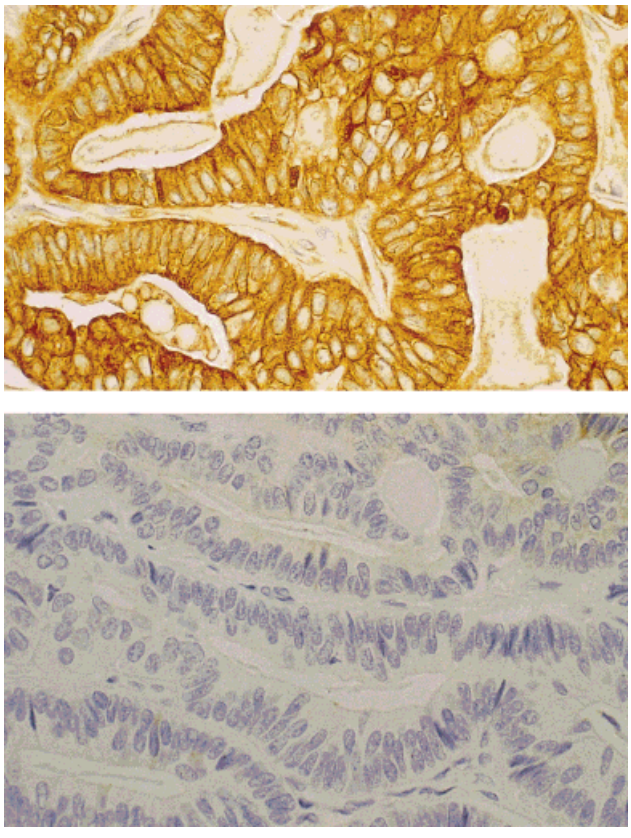

FIGURE 7. Thyroglobulin immunoreactivity varied from tumor to tumor and even within a single tumor. In this example (Case 8), intense thyroglobulin staining was present (top) adjacent to areas (bottom) with no staining.

reactivity was present in 6 of 15 cases (Cases 1, 4, 5, 13, 14, and 16). CEA was positive in only one case (Case 3). Vimentin reactivity was focal and of moderate intensity in 13 of 15 cases. There was no immunoreactivity identified with calcitonin, chromogranin, or S-100 protein.

DISCUSSION

Thyroid papillary carcinoma represents a heterogenous group of tumors that show marked variability in macroscopic and histologic appearance. A subset of thyroid papillary carcinoma is recognized and classified by the World Health Organization as the so-called aggressive variants,[2] including the diffuse sclerosing, tall cell, and columnar cell carcinomas. These tumors have been believed to represent distinct clinicopathologic entities that share aggressive biologic behavior.[1,3,9] The concept has been perpetuated that papillary carcinomas could be considered aggressive on the basis of growth characteristics, such as insular pattern[10] and cell type (i.e., tall and columnar cell).[9,11] In the current study, we dispel the notion that the behavior and treatment of papillary carcinoma is based specifically on either growth pattern or cell type. Our findings reaffirm those already documented in the literature by other authors.[4,5,12] The critical pathologic parameter in assessing behavior for papillary carcinomas is whether the tumor has extended beyond the thyroid capsule into extrathyroidal tissues. A thyroid papillary carcinoma, irrespective of cell type or growth pattern, that does not invade through the thyroid gland capsule generally will have an excellent prognosis. However, those thyroid papillary carcinomas with extrathyroidal spread are at greater risk for more aggressive biologic behavior. In our opinion, these behavior characteristics hold true for any differentiated thyroid papillary carcinoma irrespective of growth characteristics or cell type. Thus, tumors with insular growth patterns, tall cells, or columnar cells that are encapsulated or show limited invasion but are confined to the thyroid gland will have a better prognosis than any other type of papillary carcinoma, including the usual type that invades beyond the thyroid capsule into extrathyroidal tissues.

The clinical and histopathologic features that distinguish thyroid papillary carcinoma of columnar cell type from other types of papillary carcinoma initially were based on the details of three cases reported in two separate studies.[13,14] LiVolsi, citing these cases, generalized these features to include its prevalence in men and its uniformly aggressive behavior with distant metastasis and the rapid death of the patient irrespective of treatment.[3] After the reports by Evans[13] and Sobrinho-Simões et al.,[14] additional reports of the thyroid papillary carcinoma of columnar cell type further supported the contention that this type of papillary carcinoma was an aggressive neoplasm.[15–18] Similarly, the theme of aggressive behavior for thyroid papillary carcinoma of columnar cell type appears in the most recently published AFIP tumor fascicle on thyroid neoplasms.[1] As of 1995, there were nine reported cases of thyroid columnar cell carcinoma.[4,13–18] The patients included 5 men and 4 women ranging in age from 21–63 years with a median age of 46 years. The clinical follow-up of these patients indicates that the thyroid papillary carcinoma of columnar cell type had the potential for aggressive biologic behavior. Seven of the nine patients reported had a fatal outcome, with death from the time of initial surgery ranging from 7 months to 6 years.[4,13–15,17] Of the remaining two patients, one was alive but had extensive residual disease, including invasion into the trachea and pulmonary metastasis.[18] The other patient, reported by Hui et al.,[16] was alive without residual disease over a limited follow-up period. In the eight cases reported to be associated with aggressive behavior, the tumors were large and there

was extrathyroidal invasion.[4,13–15,17,18] In contrast, the case reported by Hui et al. was small (1.5 cm) and encapsulated, and confined to within the thyroid gland.[16]

The histopathologic features that are used to define the thyroid papillary carcinoma of columnar cell type include the presence of (tall) columnar-appearing cells with nuclear stratification.[1,3,4–7,13–18] ''Tall'' cells have been defined as cells that are twice as tall as they are wide.[11] LiVolsi expanded the histopathologic parameters of thyroid papillary carcinoma of columnar cell type to include tumors showing the presence of subnuclear vacuolization similar to that observed in secretory type endometrium.[3] The latter was confirmed by Rosai et al.[1] and also by Gaertner et al.[4] In the current study, we found that the morphologic spectrum of thyroid papillary carcinoma of columnar cell type includes tumors with diverse growth patterns, including papillary, solid, microfollicular, and cribriform patterns. Multiple growth patterns can be observed in a single tumor. A common feature of thyroid papillary carcinoma of columnar cell type is the presence of markedly elongated follicles arranged in parallel cords. Ultimately, the defining histologic criterion of thyroid papillary carcinoma of columnar cell type is the presence of nuclear stratification. Recently, Sweeney[19] described a cell that he termed a ''dormant'' cell in association with both tall cell and columnar cell carcinoma types of papillary carcinoma. According to Sweeney,[19] these ''dormant'' cells showed apical thyroglobulin staining and abundant cytoplasmic mitochondrial content by ultrastructural analysis. He indicated that these cells did not show the presence of internucleosomal double-stranded DNA breaks, a feature observed in apoptotic cells.[20] Although Sweeney was unsure of what these cells represented, he suggested the possibility that these were Hürthle cells. We identified these ''dormant'' cells in our cases but we do not believe that these are unique cells. Despite the apparent absence of internucleosomal double-stranded DNA breaks, we believe these cells represent neoplastic columnar cells with pyknotic nuclei. The illustrations depicted by Sweeney[19] do not demonstrate nuclear stratification and, in our opinion, show features of the tall cell type of papillary carcinoma accounting for the presence of increased cytoplasmic mitochondrial content reported in these two cases.[19]

In limited portions of three of our cases, there were typical nuclear changes associated with the usual type of thyroid papillary carcinoma. In addition, laminated calcified concretions (psammoma bodies) were present in association with the thyroid papillary carcinoma of columnar cell type in four of the cases. These findings support the concept that the columnar cell carcinoma is a morphologic type of the usual papillary carcinoma.

A key question is what percentage of columnar cells (as previously defined) are required to diagnose a given tumor as columnar cell carcinoma. Ferreiro et al.[7] state that >50% of the tumor should include characteristic columnar cells to be classified as this type of thyroid papillary carcinoma. In all our cases, >50% of each tumor was comprised of columnar cells. In fact, columnar cells, including tumors with vacuolated-appearing cells, comprised the cell population in >70% of each tumor. As such, a diagnosis of thyroid papillary carcinoma of columnar cell type can be considered as long as the majority of a given tumor (>50%) is comprised of this cell type. However, based on our cases, we have adopted 70% as the percentage required before we render this diagnosis.

Prognostic features observed in association with thyroid papillary carcinoma include gender, age, tumor size, the presence or absence of extrathyroidal extension, histology, and metastasis. For differentiated thyroid carcinomas, prognostic scoring systems[21] and risk group classifications[22,23] have been proposed. Our findings showed that in thyroid papillary carcinoma of columnar cell type there were no differences in biologic behavior based on gender, age, tumor size, or histology. However, our findings show that the single most useful prospective parameter in these tumors was the presence or absence of extrathyroidal extension. In 14 of our cases, the tumor was either encapsulated or showed limited invasive growth (capsular or small caliber-sized vascular space) whereas in 2 of the cases (Cases 5 and 16), there was extensive intrathyroidal invasion with extension beyond the thyroid capsule into perithyroidal soft tissue. The patients whose tumors were confined to the thyroid gland had a good prognosis whereas both patients with extrathyroidal invasion (Cases 5 and 16) fared less favorably. Similar findings are documented in the literature. Those patients with thyroid papillary carcinomas of columnar cell type that were confined to within the thyroid gland (encapsulated, limited invasion) had a favorable prognosis.[6,7,16] In contrast, those patients reported with extrathyroidal extension of their tumors had visceral (lung) metastases and a poor clinical outcome.[4,7,13–15,17,18]

We do not believe that the cell type or growth pattern represent defining prognostic findings in thyroid papillary carcinoma. Furthermore, we do not believe that either the columnar cell type or so-called tall cell type are distinct clinical and pathologic entities. The exceptions to these statements among the differentiated thyroid papillary carcinomas would be

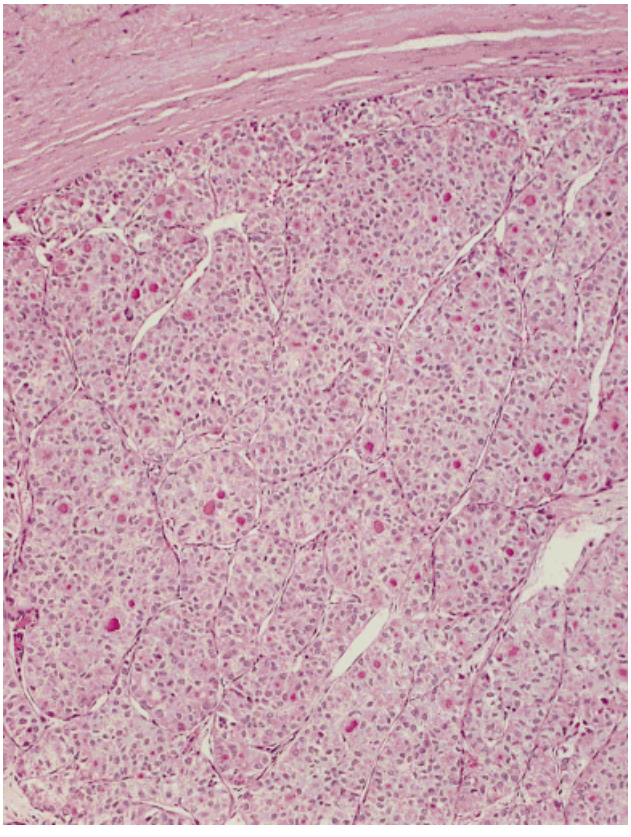

FIGURE 8. Follicular adenoma with insular growth.

the diffuse sclerosing type, which does represent a distinct entity with unique clinicopathologic parameters.[24–26] Pilotti et al. designated both the columnar cell and tall cell types of thyroid papillary carcinomas as poorly differentiated tumors.[9] However, both of these tumor types readily are identifiable as being of thyroid follicular epithelial origin on the basis of colloid production, as well as the presence of thyroglobulin immunoreactivity. In our opinion, these are differentiated thyroid follicular epithelial cell neoplasms. A poorly differentiated thyroid carcinoma should be a tumor that has evidence of epithelial differentiation (cytokeratin reactivity) but is not recognizable as being of follicular epithelial origin by light microscopic appearance or immunohistochemical findings. The only thyroid tumor type that qualifies under this definition would be the undifferentiated or anaplastic carcinoma. Pilotti et al.[9] also attempted to justify designating columnar cell and tall cell types of papillary carcinoma as both distinct clinical and pathologic entities. We agree that these tumors have distinct histologic features but, as previously detailed, we do not believe that these tumors are distinct clinically from other types of papillary carcinoma (i.e., usual types or follicular types of papillary carcinoma). Pilotti et al.[9] attempted to justify their conclusions by showing a difference between the behavior characteristics of the ''poorly differentiated'' columnar and tall cell carcinomas from more usual types of papillary carcinoma. However, these authors do not match tumors for size or growth characteristics. Rather, the group of usual papillary carcinomas used for comparison included microscopic and encapsulated tumors, tumor types that are known to have an indolent biologic behavior. As such, the study by Pilotti et al.[9] is flawed. This fact is substantiated by the findings in the current study as well as the findings by Evans,[6] Ferreiro et al.,[7] and Kaleem and Dehner.[27] Kaleem and Dehner[27] reported 118 cases of incidental (microscopic) thyroid papillary carcinoma of all histologic subtypes, including pink cell (i.e., tall cell); all these cases were reported to have had an excellent prognosis. As such, the cell type (unless poorly differentiated) should not be used as a defining parameter in predicting the behavior of thyroid papillary carcinoma. Furthermore, neither columnar cell nor tall cell papillary carcinomas should be considered poorly differentiated neoplasms.

In addition to cell type, the growth pattern has been implicated in defining an aggressive type of thyroid carcinoma. Carcangiu et al.[10] reported that thyroid tumors demonstrating an insular growth pattern should be considered as poorly differentiated tumors with aggressive behavior. Similar findings have been reported by other authors.[28–30] Although there are thyroid tumors with insular growth that are aggressive neoplasms, we have observed thyroid papillary carcinomas with insular growth that were neither poorly differentiated nor aggressive tumors, and we have identified insular growth patterns in nonneoplastic lesions such as dyshormonogenetic goiters and follicular adenoma (Fig. 8). The presence of cell islands (insulae) represents a growth pattern and, similar to cell type, does not in and of itself justify designating a tumor as poorly differentiated or an aggressive neoplasm. This issue was elaborately and definitively addressed by Ashfaq et al.[12] More recently, Albores-Saavedra et al.[31] reported 5 cases of macrofollicular thyroid papillary carcinoma that demonstrated a minor insular pattern and found that the biologic behavior in these 5 cases was no different than the clinical outcome of the 24 cases of macrofollicular thyroid papillary carcinoma without an insular growth pattern.

The differential diagnosis of thyroid papillary carcinoma of columnar cell type has been detailed by Gaertner et al.[4] We only wish to address the issue of differentiating the columnar cell type from the tall cell type of thyroid papillary carcinoma. The definition of ''tall'' cell has included a cell that is twice as tall as it is

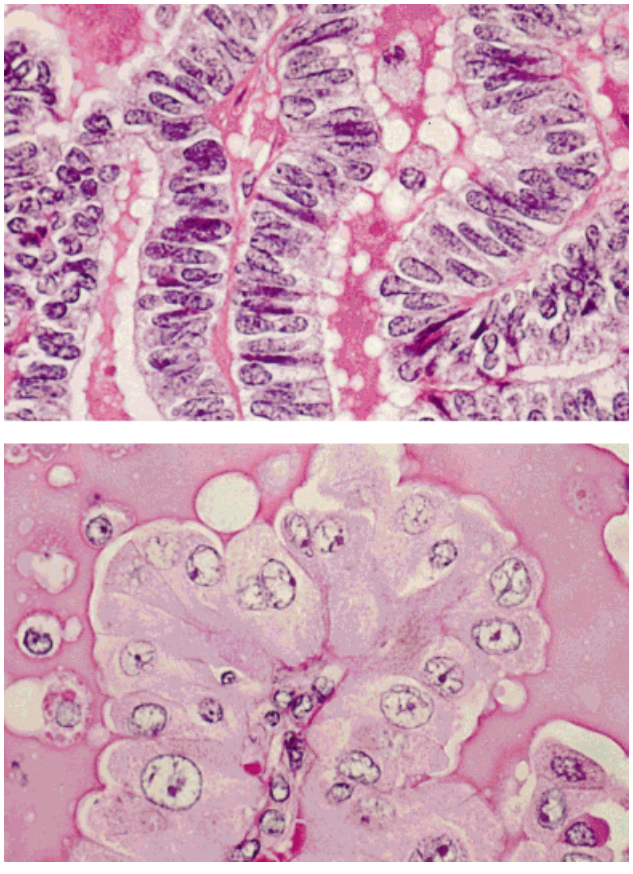

FIGURE 9. Thyroid papillary carcinoma of columnar cell type (top) and the thyroid papillary carcinoma of ''tall'' cell type (bottom) both include cells that are twice as tall as they are wide. However, the overall cytomorphologic features of these tumors are entirely different.

wide.[32] Using this definition, columnar cells are ''tall'' cells. This concept of a ''tall'' cell potentially may engender confusion between these two histologic entities. In our experience, the characteristics (other than being twice as tall as wide) of the ''tall'' cell type papillary carcinoma include the presence of cells with prominent eosinophilic and finely granular cytoplasm, enlarged nuclei with intranuclear inclusions, nuclei that are situated in the center or basilar portions of the cell, and sharp delineation of the cell membranes (Fig. 9). The columnar cells do not have these features but show nuclear stratification, a feature not present in the tall cell type. Reports of a mixed tall cell and thyroid papillary carcinoma of columnar cell type appear in the literature[1,9,15] but we did not find any mixed columnar and tall cell tumors in our cases.

Aggressive biologic behavior in thyroid papillary carcinomas has been reported to be associated with increased immunoreactivity with LeuM1[33] and EMA.[34] The tumors in the two patients who died of their tumors (Cases 5 and 16) expressed reactivity with both LeuM1 and EMA. However, both LeuM1 and EMA were found in the tumors of two other patients (Cases 13 and 14) who were alive and free of disease at last follow-up. The tumor in another patient (Case 1) also expressed LeuM1 and EMA reactivity but this patient died shortly after surgery due to surgical complications. Based on these findings, unequivocal correlation between the presence of LeuM1 or EMA reactivity with the biologic behavior of thyroid papillary carcinoma of columnar cell type cannot be determined. S-100 protein reactivity can be observed in thyroid papillary carcinomas.[35] We have no explanation as to why our cases were nonreactive with S-100 protein.

A potential diagnostic problem may occur in the face of cervical lymph node metastases with nuclear stratification, absent colloid, and absent thyroglobulin reactivity. In Case 10 in the current study cervical lymph node metastasis occurred 4 years after the removal of the primary thyroid tumor. The metastatic focus was identical histologically to the primary tumor. However, colloid was not present and the tumor was thyroglobulin negative. Pathologists should be aware of these findings and should not exclude a thyroid origin for such a tumor. In this setting, elevated serum thyroglobulin levels may be of assistance but are not always reliable in confirming the diagnosis. In the absence of a primary tumor localized to another site, such as the upper aerodigestive tract, clinical evaluation to exclude a possible primary thyroid tumor should be initiated.

Thyroid papillary carcinoma of columnar cell type is a unique histologic subtype but not a unique clinical type of tumor. The demographics, clinical presentation, therapy, and biologic behavior of this tumor type are the same as those of the usual type of thyroid papillary carcinoma and are not determined on the basis of cell type or growth pattern. Unlike the diffuse sclerosing type of thyroid papillary carcinoma, which has a tendency to metastasize via lymphatic and hematogenous pathways, thyroid papillary carcinoma of columnar cell type showed no such specific tendencies. Based on our findings, as well as those documented in the literature, the presence or absence of extrathyroidal invasion represents the single most important parameter in predicting the behavior of these tumors. Tumors confined to the thyroid gland are associated with an excellent prognosis and can be managed conservatively (less than total thyroidectomy with or without radioactive iodine therapy) whereas tumors that invade beyond the thyroid capsule with extension into perithyroidal soft tissues behave more aggressively, necessitating more aggressive management (total thyroidectomy with supplemental radioac-

tive iodine therapy) and evaluation for disseminated (visceral) disease.

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