Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma: A Clinicopathologic and Immunophenotypic Analysis of 22 Cases

Lester D. R. Thompson, MD,[1] Jacqueline A. Wieneke, MD,[2] and Clara S. Heffess, MD[2]

Abstract

Background: The diffuse sclerosing variant of papillary thyroid carcinoma (DSV-PTC) is an uncommon tumor making up about 2% of all papillary thyroid carcinomas. Previous studies have not comprehensively evaluated these tumors in a large series of patients.

Design: Twenty-two cases of DSV-PTC diagnosed between 1970 and 2000 were identified in the files of the AFIP. Histologic and immunohistochemical features were evaluated and patient follow-up was obtained.

Results: The tumors affected 14 females and 8 males, aged 6 to 49 yr (mean, 18 yr), with males presenting at a mean older age than females (24 vs 14 yr). Symptoms included an enlarging mass in the thyroid, present for a mean of 9.5 mo. While a dominant tumor was identified in a single lobe, bilateral disease was common (n = 16). The dominant mass ranged in size from 1.7 to 5.8 cm in diameter (mean, 3.8 cm). Histologically, all cases demonstrated a papillary carcinoma (conventional, solid, or follicular pattern) diffusely involving the gland. Extrathyroidal extension, lymphocytic thyroiditis, squamous metaplasia, increased fibrosis/sclerosis, and psammoma bodies were present to a variable degree. Both the papillary carcinoma and squamous metaplasia cells were strongly immunoreactive with CK19, thyroglobulin, and TTF-1. An increased number of S-100 protein immunoreactive dendritic cells were recognized. p53 was increased (>15%) in the tumor cells in 12 patients, while Ki-67 was increased in the tumor cells in two patients. Perithyroidal and cervical lymph node metastasis occurred in 18 (82%) patients. All metastases demonstrated histologic features similar to the primary. Complete resection (thyroidectomy in 18 patients) with lymph node dissection, yielded a 95% 5-yr survival without evidence of disease. One patient died of disease after a malignant transformation of the squamous metaplasia into squamous cell carcinoma.

Conclusions: The recognition of DSV-PTC can be made with the following features: classic to solid foci of PTC, lymphocytic thyroiditis, squamous metaplasia, increased fibrosis, and innumerable psammoma bodies. DSV-PTC is more biologically aggressive than conventional PTC, but the patients' survival is not significantly different. This diagnosis should lead the clinician to aggressively manage these patients (thyroidectomy and lymph node dissection) in an effort to achieve an excellent long-term clinical outcome.

Key Words: Thyroid; papillary carcinoma; diffuse sclerosing variant; histology; prognosis; immunohistochemistry; children.

[1]Southern California Permanente Medical Group, Woodland Hills, CA and [2]Department of Endocrine and Otorhinolaryngic–Head & Neck Pathology, Armed Forces Institute of Pathology, Washington, DC.

Address correspondence to Dr. Lester D. R. Thompson, Southern California Permanente Medical Group, Woodland Hills Medical Center, Department of Pathology, 5601 De Soto Avenue, Woodland Hills, CA 91365. E-mail: Lester.D.Thompson@kp.org

Endocrine Pathology, vol. 16, no. 4, XXX–XXX, Winter 2005

1046–3976/05/16:XXX–XXX/$30.00

Introduction

Papillary carcinoma is the most common malignant neoplasm of the thyroid gland worldwide. Women are affected more frequently than men, and generally present clinically at a relatively young age (mean, 40 yr). Overall survival is generally excellent. Variant histology with the diagnosis

of papillary carcinoma is well accepted, usually separated into "biologically aggressive" and "biologically indolent" types [1,2]. The diffuse sclerosing variant of papillary thyroid carcinoma (DSV-PTC) is recognized by extensive (commonly bilateral) lymph–vascular invasion by papillary carcinoma, prominent squamous metaplasia, innumerable psammoma bodies, in a background of lymphocytic thyroiditis and stromal fibrosis. It is the intention of this study to present the clinical data, histologic findings, immunophenotypic results, and patient management consequences in a retrospective review of 22 cases of DSV-PTC, comparing the findings with a review of the pertinent literature.

Materials and Methods

The records of 28 patients with tumors diagnosed as diffuse sclerosing variant of papillary thyroid carcinoma were selected. The cases were retrieved from the files of the Endocrine Tumor Registry of the Armed Forces Institute of Pathology (AFIP), Washington, DC, between 1970 and 2000. However, six patients were excluded from further consideration because of at least one of the following reasons: (1) Paraffin blocks were unavailable for additional sections or immunophenotypic analysis; (2) the original submitted case did not have sufficient demographic information supplied from which to obtain adequate follow-up information; and (3) only a single slide had been submitted, which was deemed insufficient to yield a definitive diagnosis. Therefore, the remaining 22 patients compose the subject of this study, chosen from a review of 28,583 (0.077%) benign and malignant primary thyroid neoplasms seen in consultation between 1970 and 2000. Ten cases were obtained from civilian sources, including university medical centers and foreign contributors, 10 cases from military hospitals, and 2 cases from Veterans Administration medical centers.

Materials within the Institute's files were supplemented by a review of the patient demographics (gender, age); symptoms and physical findings and duration at presentation; and past medical and surgical history, specifically radiation exposure (environmental or therapeutic). In addition, we reviewed radiographic, surgical pathology, and operative reports and obtained follow-up information from oncology data services by written questionnaires or direct communication with the treating physician(s) or the patient or patient's family members. Follow-up data, available for all patients, included information regarding tumor location, presence of recurrent disease, treatment modalities used, and the current patient status. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

The macroscopic pathology observations noted within this study were gathered from the individual gross descriptions of the neoplasms given by the contributing pathologists. Hematoxylin and eosin–stained slides from all cases were reviewed, with specific histologic features annotated as follows: exact tumor location; lateralization; tumor size (greatest dimension in centimeters); tumor encapsulation (presence or absence); tumor extension (intrathyroidal metastases; extrathyroidal); vascular invasion; architectural pattern of growth (papillary, follicular, solid, cystic); psammoma bodies (present or absent; ipsilateral or bilateral); squamous metaplasia; lymphocytic thyroiditis; fibrosis (present or absent and sclerotic/desmoplastic or thin and wispy); presence of lymph

Table 1. Immunohistochemical Panel

Antibody	Clone	Dilution	Company	Cellular conditioning
Cytokeratin cocktail	AE1/AE3	1:50	Boehringer Mannheim Biochemicals,	Protease digestion
	LP34	1:200	Indianapolis, IN & DakoCytomation, Carpinteria, CA	
CK19	K_s20.8	1:50	DakoCytomation	Protease digestion
TTF-1	8G7G3/1	1:80	Biocare Medical, Walnut Creek, CA	Steam
Thyroglobulin	DAK-Tg6	1:1600	DakoCytomation	n/a
CD117	C-19	1:1600	Biotechnology, Santa Cruz, CA	Steam
S-100 protein	rp	1:400	DakoCytomation	Enzyme digestion
bcl-2	124	1:20	DakoCytomation	Steam
CD99	12E7	1:80	DakoCytomation	n/a
p53	DO-7	1:200	DakoCytomation	Steam
Ki-67	MIB1	1:40	Immunotech, Westbrook, ME	Steam

Rp, rabbit polyclonal; n/a, not applicable.

nodes (perithyroidal, cervical, or other); presence of metastatic disease microscopically within lymph nodes; and the presence of other microscopic pathologic findings in the remaining tissues.

Immunophenotypic analysis was performed in all cases with suitable material by a standardized Envision™ method employing 4-μm-thick, formalin-fixed, paraffin-embedded sections. Table 1 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block for each primary tumor. Proteolytic antigen retrieval, for antibodies as detailed in Table 1, was performed by predigestion for 3 min with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 *M* phosphate buffer, pH of 7.8, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution pH 6.0 (Citra, DakoCytomation Corporation, Carpinteria, CA) and heated for 20 min in a steamer. Following this, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 min before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded as absent to weak (0–1+), moderate (2+–3+) and strong (4+) staining, and the fraction of positive cells was determined by separating them into four groups: <10%, 11–50%, 51–90%, and >90%, especially for the proliferation markers.

Table 2. Literature Summary [3–21]

	n = 89
Gender	
Females	75
Males	14
Age at presentation (in years)	
Range	9–68
Average	27.6
Females (average)	25.7
Males (average)	38.5
Duration of Symptoms (in months)	
Range	1–120
Mean	14
Tumor size (cm)	
Range	3–7
Average	5.8
Outcome	
Alive (most not specified further)	53
Dead (not specified further)	20

A review of publications in English (MEDLINE 1966 to 2005) was performed, with cases specifically reported as "diffuse sclerosing variant of papillary thyroid carcinoma" included in the review (Table 2), with an emphasis on reports that

Table 3. Clinical Demographic Features of Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

	Number
Gender	
Females	14
Males	8
Age at presentation (years)	
All (mean)	18.0
All (range)	6–49
All (median)	14.0
Females (mean)	14.0
Males (mean)	24.0
Type of presentation	
Mass	16
Mass with neck enlargement (lymph nodes)	2
Asymptomatic (discovered during routine PE)	4
Duration of symptoms (months)	
Mean	9.5
Range	2–84
Females (mean)	12.0
Males (mean)	4.0
Radiation exposure	2

PE, physical exam.

were more than a single case report and that included histologic and outcome data [3–21]. Individual cases reported as part of a large series were not included. Cases that were called "sclerotic" papillary carcinoma were excluded, as they refer to fibrosis only and not the specific variant [22,23].

Results

Clinical Demographics and Presentation

The patients included 14 females and 8 males (Table 3), with a female:male ratio of 1.75:1, a difference which was statistically significant ($p = 0.02$). Even though the disease is statistically more common in females than males, there was no difference in their chance of developing a recurrence or of dying with disease. Their ages ranged from 6 to 49 yr, with an overall mean age at presentation of 18.0 yr (median, 14 yr). The average age at presentation for females was younger than males, at 14 and 24 yr, respectively, a difference that was statistically significant ($p = 0.006$). Older age at initial presentation, irrespective of age cut-off used, did not increase the chance of developing recurrence or the chance of dying with disease. The majority of the patients presented with diffuse enlargement of both lobes of the thyroid gland ($n = 13$), although a unilateral dominant nodule was noted in a single lobe of the thyroid in the remaining cases ($n = 9$). There were often associated symptoms related to compression/infiltration of the neck organs, such as hoarseness, dyspnea, dysphagia, difficulty breathing, difficulty swallowing, and/or pain. Overall, the duration of symptoms ranged from 2 to 84 mo, with an average of 9.5 mo. Females had a much longer mean duration of symptoms when compared to the males (12 vs 4 mo, respectively), a finding without explanation. There was no clinical evidence of thyroid dysfunction in most patients, with three exceptions: auto-antibodies, hypothyroidism, and hyperthyroidism in each of three different patients, respectively. Curiously, four tumors were discovered incidentally during routine school physical examinations, and were considered to be asymptomatic.

Diagnostic Investigations and Radiation Exposure History

Radioactive ^{131}I uptake roentgenographic procedures were performed in the majority of patients, although a detailed radiographic narrative was available in only 13. The scans were reported to show "cold" nodules in six cases, diffuse low-uptake in six cases, and no significant abnormalities in the remaining case. Ultrasonography was used in four patients, demonstrating a solid mass in three cases and no abnormality in the fourth. Serum antibody results were

Table 4. Macroscopic Features of Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

Feature	Number
Location (of dominant mass)	
Right lobe	7
Left lobe	2
Bilateral	13
Size (in cm)	
Range	1.7–5.8
Mean	3.8
Median	3.8
Females (mean)	3.7
Males (mean)	3.9
Radiation exposure (mean)	4.3

Table 5. Microscopic Features of Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

Feature	Number
Encapsulation	0
Growth pattern (dominant)	
Papillary	13
Follicular	6
Solid	17
Psammoma bodies	
Present	22
Bilateral	16
Unilateral	6
Squamous metaplasia (morules)	21
Lymphocytic thyroiditis	22
Sclerotic fibrosis (dominant)	16
Intrathyroidal metastasis/spread	22
Extrathyroidal capsular extension	21
Vascular invasion	20
Remaining tissue	
Parathyroid invasion	1
Squamous cell carcinoma present	1
Perithyroidal lymph node metastases	14
Cervical lymph node metastases	18
Site of lymph node metastases	
Ipsilateral	10
Bilateral or contralateral	8

available in only two patients: a patient with clinical Hashimoto's thyroiditis with auto-antibodies, and a patient with "hyperthyroidism" in which the T4 was elevated as part of Graves' disease. Two patients had a history of radiation exposure: one man worked as a radiology technician and the other man had worked in the Marshall Islands about 10 yr prior to the onset of his symptoms. Both patients are alive without evidence of disease.

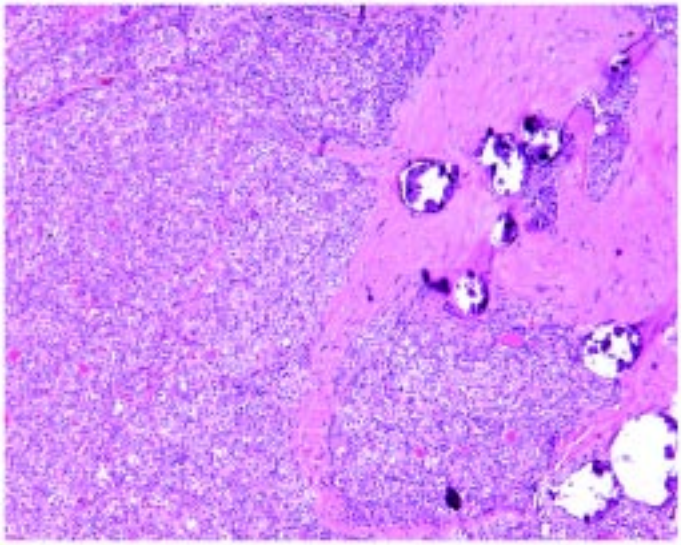
Pathologic Features

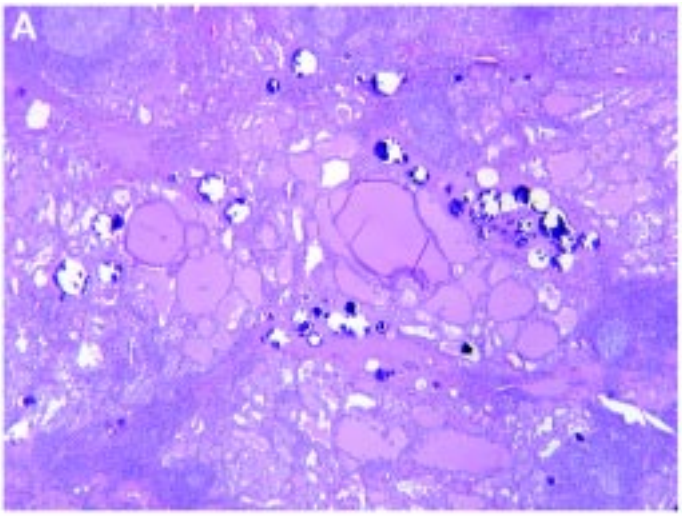
Macroscopic

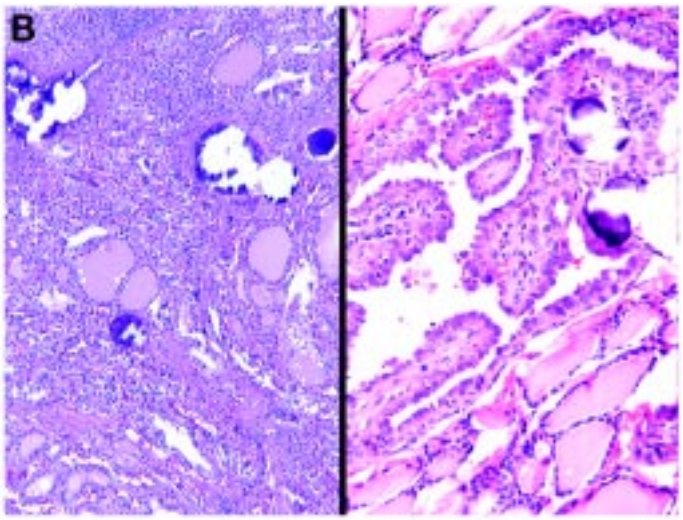
The masses in the thyroid gland specimens were diffusely infiltrative without any obvious circumscription or encapsulation. Bilateral involvement was seen most frequently (n = 13) (Table 4), although a dominant mass could be identified in the remaining nine tumors. The tumors varied from 1.7 to 5.8 cm in greatest diameter (mean, 3.8 cm), without a difference between the genders. On sectioning, the tumors were lobulated, multifocal, and nodular, with a firm to hard, pale to grayish–white appearance. The cut surface was "gritty," making it very difficult to section. Bright flecks or punctations of calcium were noted throughout. Vague patches of homogeneous to mottled, gray, "fish-flesh" material were separated from the nodules of tumor by bands of fibrosis. Occasional cystic masses were noted. Attachment to the surrounding adipose tissue or skeletal muscle was seen in many cases. When lymph nodes were examined, cystic degeneration and gross replacement was easily identified in most clinically palpable lymph nodes.

Microscopic

The thyroid gland was enlarged, with ill-defined nodular masses replacing much of the thyroid parenchyma. Infiltration into the perithyroidal adipose connective tissue and skeletal muscle was identified in 21 neoplasms. (Table 5 summarizes the microscopic characteristics.) Vascular invasion into small and medium sized vessels within the parenchyma and at the periphery of the gland was noted in 20 tumors. The predominant histologic pattern was character-







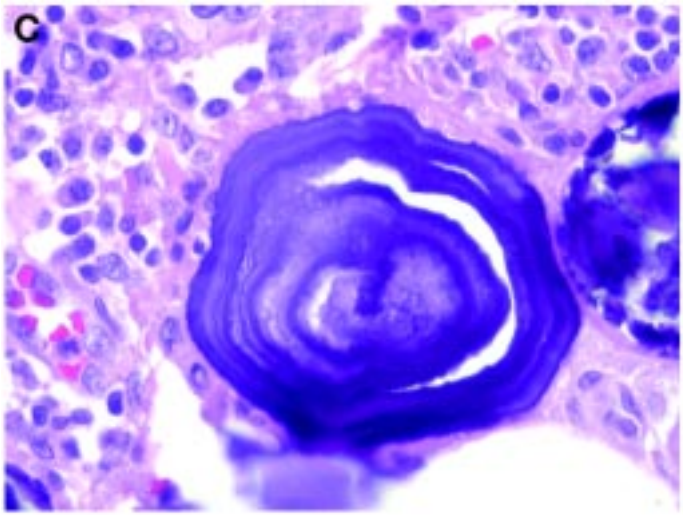


Fig. 1. *(top—center)* Solid pattern of papillary carcinoma with dense fibrosis (sclerosis) with a number of psammoma bodies identified.
Fig. 2. *(middle—left)* **(A)** A low power demonstrating innumerable psammoma bodies in clusters with lymphocytic thyroiditis. *(middle—right)* **(B)** Psammoma bodies were often highlighted in the fibrous septae of the thyroid, noted in the lymph–vascular channels (left). Viable papillary carcinoma was also noted in these same areas (right). *(bottom—center)* **(C)** The concentric lamellations of a true psammoma body. Degenerated material is noted in the center.

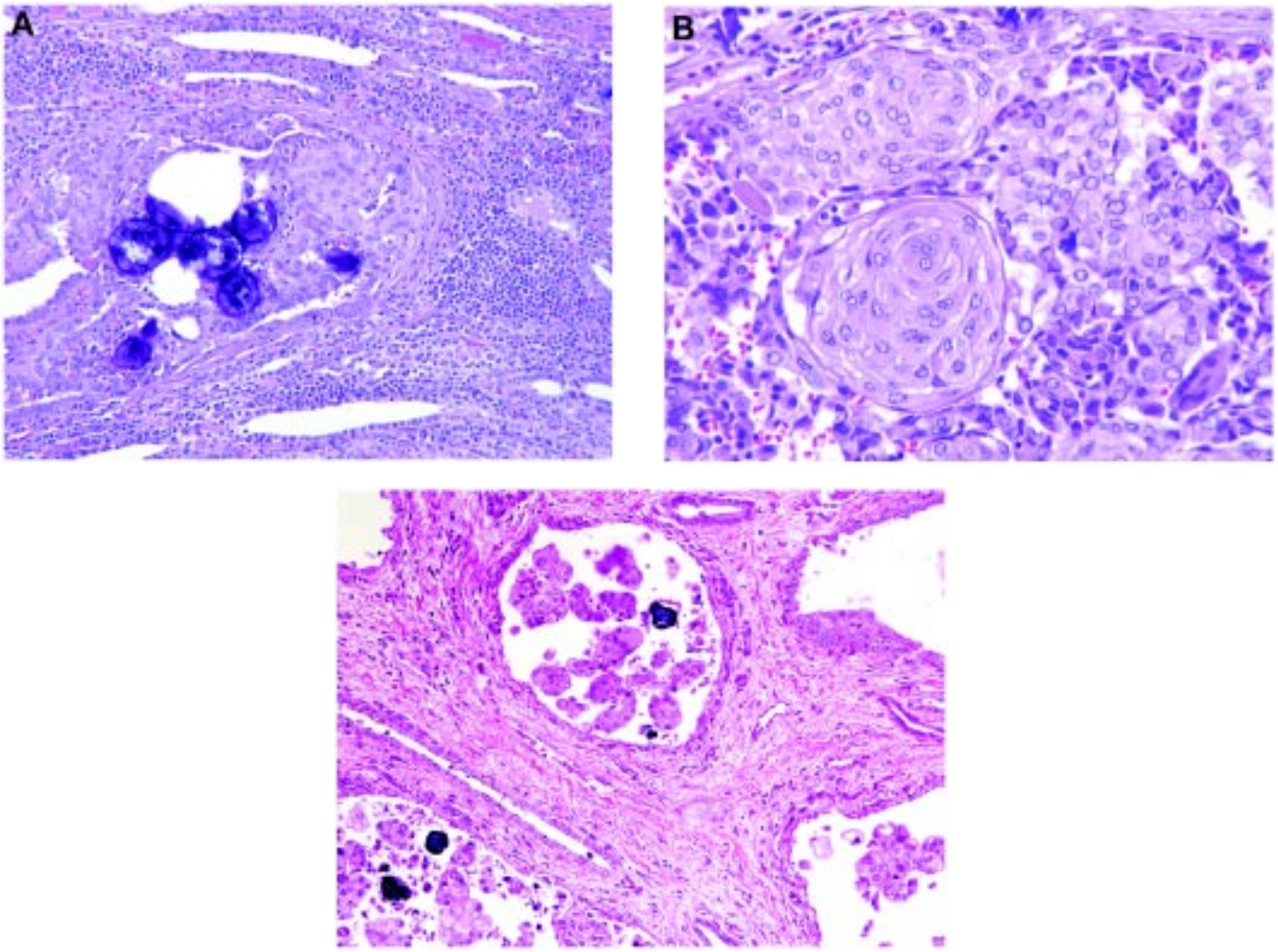


Fig. 3. *(top—left)* **(A)** Papillary carcinoma with focal squamous metaplasia within a lymphvascular channel. Psammoma bodies and lymphocytic thyroiditis are easily identified. *(top—right)* **(B)** Well developed squamous metaplasia of the follicular epithelium is noted (including intercellular bridges).
Fig. 4. *(bottom—center)* Dense fibrosis separates nodules of tumor. Lymph–vascular channel invasion is noted.

ized by the presence of a pentad of findings: (1) A solid, papillary and/or follicular arrangement of remarkably atypical thyroid epithelial cells with the cytomorphonuclear features of papillary carcinoma (Fig. 1); (2) innumerable psammoma bodies identified throughout the parenchyma, particularly within lymph–vascular channels (Figs. 2A–C), creating marked scoring artifacts or "chatter" in the cut section; (3) foci of metaplastic squamous epithelium (Figs. 3A,B); (4) extensive lymphocytic thyroiditis comprised of mature lymphocytes, plasma cells, and immunoblasts arranged around germinal centers although usually without oxyphilic (oncocytic, Hürthle, "Askanazy-cell") metaplasia of the follicular epithelial cells (Figs. 2A and 3); and (5) dense, desmoplastic, sclerotic-type fibrosis separating the thyroid parenchyma into multiple nodules (Fig. 4). The cytomorphologic features of thyroid papillary carcinoma included nuclear enlargement, irregularities in nuclear size

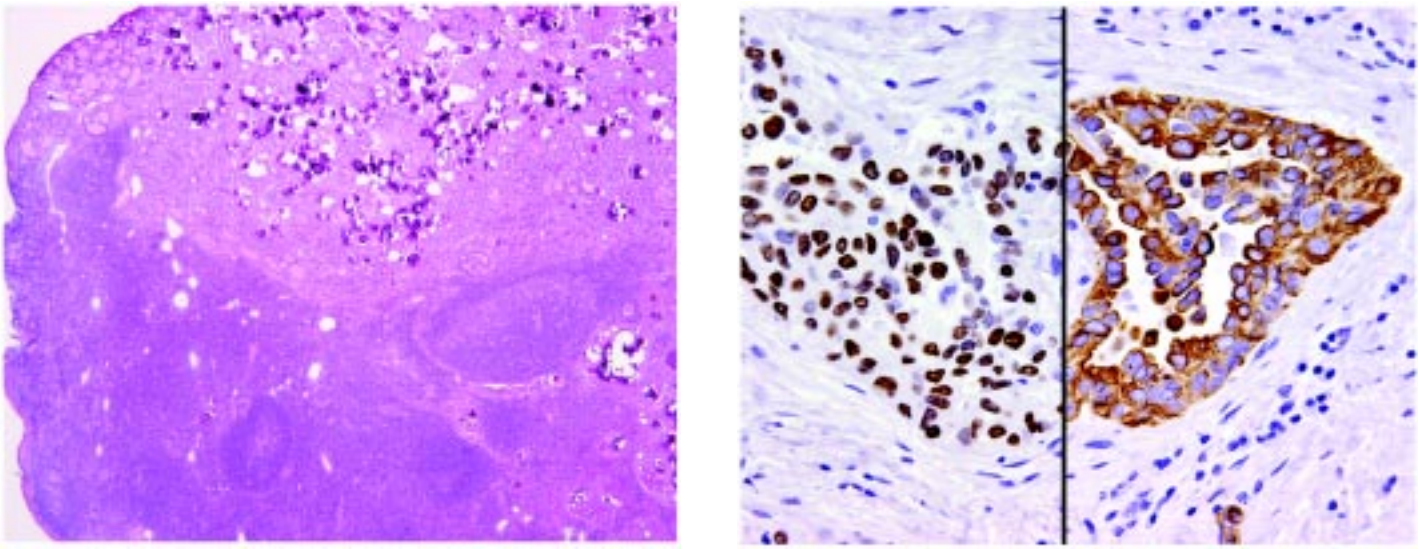


Fig. 5. *(left)* A lymph node of the cervical region filled with both metastatic papillary carcinoma, squamous metaplasia and psammoma bodies.
Fig. 6. *(right)* TTF-1 (left) and CK19 (right) highlight the cells of a papillary carcinoma and areas of squamous metaplasia identified in a vascular channel (immunohistochemistry).

and shape, dispersed to optically clear-appearing nuclear chromatin, crowding or overlapping nuclei, nuclear grooves, and intranuclear cytoplasmic inclusions. Occasional giant cells could be seen in the colloid-filled spaces. Tumor necrosis was absent. Adenomatoid nodules were seen in three cases. One patient demonstrated a malignant transformation of the squamous metaplastic foci into a well-differentiated squamous cell carcinoma.

Nineteen patients had lymph node sampling performed at the time of the initial surgery. Eighteen patients had histologic evidence of cervical lymph node metastasis, with one patient demonstrating only perithyroidal lymph node metastasis. Unilateral (ipsilateral) lymph node metastases were noted in 10 patients, with bilateral (ipsi- and contralateral) lymph node metastases documented in 8 additional patients. While we did not prosect the original specimens, when lymph nodes were counted in separately embedded blocks, it was common to have many lymph nodes in the cervical chain affected (e.g., 36 of 58; 23 of 35; and 25 of 44). All of the samples examined demonstrated both solid and papillary arrangements to the papillary carcinoma in addition to innumerable psammoma bodies (Fig. 5). Five of the lymph nodes also contained areas of squamous metaplasia intimately associated with the areas of papillary carcinoma.

Immunohistochemical Results

All of the foci of papillary carcinoma and the areas of squamous metaplasia were immunoreactive with keratin (Table 6). Furthermore, these same areas were all immunoreactive with both CK19 and TTF-1 (Fig. 6), support to the notion that the squamous metaplasia is arising from thyroid follicular epithelial cells. Thyroglobulin is a capricious stain with difficulties in interpretation related to its presence in the serum and therefore, the tendency for a high background. In spite of this difficulty, thyroglobulin was immunoreactive in nearly all of the foci of papillary carcinoma and 73% of the foci of squamous metaplasia. In addition, in the lymph node samples tested, similar reactivity was identified. S-100 protein is known to be reac-

Table 6. Immunohistochemical Panel Results

Antigen/antibody	Number (percentage) of positive results	
	Papillary carcinoma	Squamous component
Cytokeratin cocktail	15/15 (100%)	15/15 (100%)
CK19	14/14 (100%)	13/13 (100%)
TTF-1	13/13 (100%)	13/13 (100%)
Thyroglobulin	15/16 (94%)	11/15 (73%)
CD117	1/15 (7%)	n/a
S-100 protein	12/15 (80%)	11/14 (79%)
bcl-2	10/14 (71%)	n/a
CD99	1/15 (7%)	n/a
p53 (>15% of cells reactive)	12/15 (80%)	11/13 (85%)
Ki-67 (1% or more cells positive)	8/15 (53%)	n/a

n/a: not analyzed.

Table 7. Patient Outcome

Treatment	No. of patients (yr)	Alive, no evidence of disease (yr)	Dead, with disease (yr)
All patients	22 (16.3)	21 (17.0)	1 (1.5)
Range of follow-up (yr)	1.5–31	3.5–31	1.5
Recurrences	2 (22.2)	2 (22.2)	n/v
Females	14 (17.7)	14 (17.7)	n/v
Males	8 (13.9)	7 (15.7)	1 (1.5)
Radiation exposure	2 (9.5)	2 (9.5)	n/v

yr: mean years of follow-up or survival; n/v: no value.

tive in papillary carcinoma [6,18], but is also reactive in normal thyroid follicular epithelium, as well as in the areas of squamous metaplasia: both nuclear and cytoplasmic reactivity was identified. Furthermore, an increased number of S-100 protein immunoreactive follicular dendritic reticulum cells were recognized, usually in the areas of lymphocytic thyroiditis. bcl-2 was faintly immunoreactive in the papillary carcinoma foci in 71% of cases tested. CD117 and CD99 were focally immunoreactive in a single case. p53 and Ki-67 were strongly positive in a few nuclei in both the papillary carcinoma and areas of squamous metaplasia in the cases evaluated. p53 was expressed in >15% of the tumor nuclei in 12 cases (in the papillary carcinoma areas) and in 11 of 13 cases in the squamous areas (85%). Ki-67 was expressed in >15% of the tumor nuclei in the papillary carcinoma areas in only two patients, although 1–14% of nuclei were positively stained in 8 of 15 cases tested. None of the areas of squamous differentiation were highlighted with the Ki-67. Although axiomatic, immunohistochemistry was not requisite for the diagnosis of diffuse sclerosing variant of papillary thyroid carcinoma.

Clinical Treatment and Patient Outcome

Follow-up was available in all patients (Table 7). All patients were treated with surgical excision, including thyroid lobectomy or partial thyroidectomy with (n = 1) or without (n = 3) lymph node dissection and total thyroidectomy with lymph node dissection (n = 18). The three patients managed by lobectomy without lymph node dissection also did not have postoperative ^{131}I radiotherapy: all were alive at last follow-up without evidence of recurrence or lymph node metastasis (mean follow-up, 17.8 yr). The patient with a lobectomy and lymph node dissection received ^{131}I radiotherapy immediately postoperatively. She developed a recurrence in the bed of the previous surgery 3 yr later, which was managed by ^{131}I radiotherapy: she is alive without evidence of disease 27.7 yr after the initial presentation. Of the 18 patients managed by total thyroidectomy and lymph node dissection, 15 had postoperative ^{131}I radiotherapy: all are alive without evidence of disease a mean of 14.1 yr after initial presentation. Three patients did not have postoperative ^{131}I radiotherapy: two are alive without evidence of disease a mean of 24.7 yr after initial presentation. One patient died 1.5 yr after presentation and is described in more detail below.

Recurrences developed in three patients. A 6-yr-old girl, as described above, had a lobectomy and lymph node dissection only, followed by postoperative ^{131}I radioablative therapy. A recurrence in the bed of the previous surgery (right neck) 3 yr later was managed by additional ^{131}I radiotherapy: she is alive without evidence of disease 27.7 yr after the initial presentation. The second patient, a 14-yr-old girl initially presented with right supraclavicular lymphadenopathy. A lymph node biopsy confirmed the diagnosis of metastatic papillary thyroid carcinoma. A thyroidectomy and right modified radical neck dissection was performed shortly thereafter with follow-on ^{131}I radioablative therapy. Within 2 yr, a recurrence developed within the right bed of the thyroid gland. Surgery and a second round of ^{131}I radiotherapy was instituted. She is alive without any recurrence or metastatic disease 23.8 yr after the initial therapy.

The third patient to develop a recurrence was the only patient to die of disease. This 49-yr-old man (the *oldest* patient at initial presentation) suffered a malignant transformation of the metaplastic squamous epithelium into a squamous cell carcinoma. Both the papillary carcinoma and the squamous cell carcinoma were present in the lymph nodes and lungs (wedge biopsy proven) within a couple months of his initial presentation. Intercurrent chemotherapy did not halt the progression of the disease, and he died with widespread metastases (papillary and squamous cell carcinoma) only 1.5 yr after his initial presentation. Metastases were documented in his brain, lungs, liver, adrenal glands, bone marrow, and multiple lymph nodes.

Overall survival for all patients was excellent, with a mean follow-up period of 16.3 yr (Table 7). Only one patient died of disease (as described above), with the all of the remaining 21 patients (95.5%) alive at the time of last contact without evidence of disease, a mean of 17.0 yr after initial presentation.

When controlling for gender, there is no difference ($p = 0.366$) in patient outcome between females (mean, 17.7 yr) and males (mean, 13.9 yr). A tumor size of ≥5.0 cm produced a statistically significant difference ($p = 0.0448$) in length of patient follow-up: <5 cm: 18 patients, mean, 18.2 yr; ≥5.0 cm: 4 patients, mean, 8.2 yr. The two patients with prior radiation did not have a statistically significant shorter survival ($p = 0.282$).

Stage

Perithyroidal soft tissue, adipose connective tissue, and/or skeletal muscle invasion by the papillary thyroid carcinoma was identified in 21 patients, which, by definition, places these tumors in the p-stage III or IV category. However, using AJCC criteria [24], all of these patients younger than 45 yr ($n = 20$) are by definition p Stage I! The single patient who did not have extrathyroidal capsular extension was alive at 27.8 yr. The only patient older than 45 yr at initial presentation was a man with neoplastic extrathyroidal extension and squamous cell carcinoma.

Discussion

Papillary thyroid carcinoma has a number of well-recognized histologic variants, including follicular, macrofollicular, oncocytic, clear cell, tall cell, columnar cell, solid, cribriform, and diffuse sclerosing variant, to name the majority of variants recognized by the World Health Organization [1]. The DSV-PTC comprises 0.1% up to 4% of papillary carcinomas [2,3,6,8–10,13,16–18,20,21,25,26], a figure similar to the results of this study.

Age and Gender

The patients were all relatively young, even when compared to the mean age for papillary thyroid carcinoma in general. This study had a mean age of 18 yr, slightly younger than the mean age of patients reported in the literature of 27.6. [3,4,6,8–10,13,17,18,20,21]. Similar to the literature, male patients tended to be older on average (mean, 24 yr) than the female patients (mean, 14 yr), a finding with statistical significance ($p = 0.006$) [4,17,21, 27,28]. The vast majority of patients are female, with a gender ratio of 5.4:1 female to male ($p = 0.02$) [4,6,8–10,13,14,18,20, 21,28], although conventional papillary carcinoma is also more common in female patients.

Presentation and Other Thyroidal Diseases

Nearly all patients present with a mass lesion in the neck, often accompanied by palpable lymphadenopathy of the cervical lymph nodes. Compression-related symptoms are not uncommon. Patients often have symptoms for a long duration (about 1 yr) [3,4,6,8–10,20,28], perhaps because about 30% of patients have antithyroid antibodies of various types (antithyroglobulin, antimicrosomal antibodies) as part of Hashimoto's thyroiditis [3,4,6,8,10, 18,20,21,25]. Much of the emphasis was on the differential *between* lymphocytic thyroiditis and papillary carcinoma rather than their coexistence. DSV-PTC rarely interferes with the functional capacity of the thyroid gland, with patients managed initially for an autoimmune disease with associated diffuse enlargement of the gland, rather than for a discrete mass in the thyroid. Radiographic studies are of limited value as they show a "diffuse" process.

The diagnosis of DSV-PTC can be made with fine needle aspiration (FNA), especially if there is cervical lymph node enlargement by metastatic disease [5,8,12, 21,29,30]. In this clinical series, 82% of patients had cervical lymph node metastasis at the time of initial presentation, making FNA an effective method of diagnosing papillary thyroid carcinoma, even though the exact variant may not be suggested.

Radiation exposure, either therapeutic or environmental, is a known etiologic agent of PTC. However, in this series and in those reported in the literature [4,27,31], few patients experienced prior radiation. Specifically, in two separate groups of patients, DSV-PTC was present in 8% of patients with previous radiation and 9% of patients without radiation exposure [31]. Therefore, while a specific epidemiologic link between radiation exposure and the development of DSV-PTC has not been absolutely established, the approx 9% of patients with radiation exposure suggests it may be one of many etiologic factors. Interestingly, prior radiation does not adversely impact the patient outcome ($p = 0.282$).

Histologic Findings

In general, the tumor is characterized by diffuse involvement of one or both of the thyroid lobes, and while a "dominant" mass may be palpated, it is often difficult to accurately define the extent of the tumor. The involvement of the entire gland is due to the striking proclivity for lymph–vascular invasion, a finding further substantiated by the nearly ubiquitous prevalence of lymph node metastases at presentation. In addition, the inordinate number of psammoma bodies, well recognized to represent the calcified remnants of necrotic tumor cells in lymphatic channels, give even further support to the peculiar ability of this tumor to permeate the lymphatics [2,6,17,20,27].

The gland is hard with the cut surface of the neoplastic tissue appearing pale,

grayish–white with whitish streaks of fine, reticulated gritty, calcium material (psammoma bodies). The borders are irregular with extensive infiltration of the thyroid parenchyma. The majority of cases do not have discrete nodules, even after they have been formalin fixed [4,6,20,27]. A "fish-flesh" appearance reflects the areas of lymphocytic thyroiditis. Extension of the tumor into the perithyroidal adipose connective tissue and skeletal muscle is common, seen in substantially more than 70% of cases reported in the literature [4,20, 27,28], and in almost all of the cases in this series (95%).

The tumors are large, although the exact extent of disease is difficult to measure due to the extensive infiltrative nature of the disease. Size does not appear to be an independent prognostic factor, because most patients are <45 yr of age, the most significant factor in prognosis.

The diagnosis of DSV should be made when there is a *combination* of the following histologic findings, as nearly all DSV tumors are fundamentally identical:

1. A solid, papillary, and/or follicular arrangement of papillary carcinoma cells.
2. Innumerable psammoma bodies within the tumor and throughout the remaining parenchyma.
3. Metaplastic squamous epithelium.
4. Extensive lymphocytic thyroiditis.
5. Dense, desmoplastic, sclerotic-type fibrosis (broad bands of collagenous tissue).

The characteristic architectures of papillary carcinoma (solid, follicular, and/or papillae) can be seen in DSV-PTC. The solid pattern seems to be more common, and typical papillae may be difficult to find. However, complex, branching papillary structures are identified. In follicular areas the follicles are elongated with scant colloid present. The uninvolved thyroid parenchyma is often atrophic.

Psammoma bodies are found in association with tumor cells and within lymphatic spaces or within the tumor stroma. Numerous, variably sized tumor nests permeated the lumina of dilated lymphatics, showing an admixture of papillary and solid growth and squamous metaplasia along with psammoma bodies. The massive number and diffuse distribution of psammoma bodies is unique to this variant of PTC.

Squamous metaplasia by itself can be seen in papillary carcinoma, but usually not to the extent identified in the DSV. Nearly every case will have squamoid or squamous metaplasia to a variable degree, often extensive [2,4,6,20,25,27]. Interestingly, epidermal keratins are present in the papillary carcinoma and in the squamous metaplasia. In this clinical series, the areas of papillary carcinoma and squamous metaplasia were both immunoreactive with keratin, CK19, thyroglobulin, TTF-1, and S-100 protein, a different immunohistochemical finding from that of other authors [6,9,32,33]. S-100 staining was difficult to interpret due to heavy background staining. More specifically, though, the presence of TTF-1 immunoreactive squamous metaplasia supports the contention that the papillary carcinoma cells undergo transformation or maturation to squamous metaplastic cells, but still maintain an identical immunophenotypic expression to papillary carcinoma cells. In fact, metastatic foci in lymph nodes often contain areas of squamous metaplasia juxtaposed to areas of classic papillary carcinoma, further supporting the notion that it is a single tumor with a "biphasic" histologic appearance [16]. We did not perform studies for *ret/PTC* rearrangements or *BRAF* mutations in this study, but perhaps a future microcapture laser dissection evaluation of the papillary carcinoma and

the areas of squamous metaplasia may serve to resolve this question.

The diffuse nature of the neoplastic proliferation may also account for the diffuse host response of a lymphocytic and histiocytic infiltrate throughout the gland. It is important to point out that while autoantibodies are found in the serum of many of these patients, the substantiating histologic triad of increased lymphocytes, germinal center formation, and oxyphilic metaplasia is not well developed. In fact, oxyphilic (oncocytic or Hürthle) metaplasia is sparse to nonexistent in nearly all cases [2,6,16,25,27]. Although the lymphocytes are known to be an immunological host reaction, the increased number of S-100 protein immunoreactive Langerhans interdigitating reticulum cells scattered throughout the lymphoid aggregates and between the tumor cells suggests that these antigen-presenting cells are attracting the lymphocytes, or in some way mediating the process [6,9,10,13,18,20]. It has been posited that dense or heavy Langerhans cell infiltrate into the tumor confers an indolent clinical course [13,18], but since so many of the patients have an excellent prognosis irrespective of the presence of S-100 protein, this theory is not proved in this clinical study.

Furthermore, there is a known aberration of major histocompatibility complex class II antigen and HLA-DR antigen expression in DSV-PTC, suggesting that the immunologic epiphenomenon may be associated with the autoimmune thyroiditis and that the reaction is initiated by the neoplastic process rather than as a preexisting disease [9,15,18]. In fact, it has been shown in a few cases with less extensive disease or no disease in the contralateral lobe that lymphocytic thyroiditis is absent [4,6]. Comparison has been made between inflammatory carcinoma of the breast and DSV-PTC, where both lack a discrete tumor mass, both have widespread lymphatic invasion, and both have a heavy inflammatory reaction, resulting in a clinical impression of mastitis or thyroiditis [4]. However, rapid progression of this "thyroiditis" should raise one's index of suspicion for this variant of papillary carcinoma.

The high number of psammoma bodies in DSV-PTC may cause the increased fibrosis through a mechanical blockade of the lymphatics. The marked sclerosis in DSV-PTC seems to be assembled immediately adjacent to lymphatic vessels. The haphazard arrangement of thin bundles of smooth muscle in the sclerotic stroma immediately adjacent to vessels suggests splaying of the vessel wall smooth muscle by the sclerosis and/or neoplastic cells [6]. However, papillary carcinoma in general is known to be associated with sclerosis, but just not to the same degree seen in the DSV. Perhaps the truly excess number of psammoma bodies in this variant does contribute to the remarkable fibrosis, an aspect requiring further elucidation [6,10,16,20,26,27].

When this pentad of findings is present, the clinical (i.e., metastatic potential) and prognostic implications of the diagnosis will become meaningful in the management of DSV-PTC. It is imperative to note that none of these morphologic features is uniquely specific for the diagnosis of DSV-PTC. Furthermore, not every one of the features will always be present in every case. But, having once seen this unique constellation of findings, it is not forgotten. It would seem that DSV-PTC is a marked overexpression of features seen in classic papillary carcinoma. Therefore, adequate sampling of the thyroid gland is requisite to achieve diagnostic accuracy.

Lymph node metastases (perithyroidal or cervical lymph nodes) are seen in >80% of patients (unilateral or bilateral disease). Metastatic deposits consist of papillary thy-

roid carcinoma, squamous metaplastic foci, and psammoma bodies [3,4,6,8,27,28]. It is important to note that squamous islands in lymph nodes in young patients should raise the possibility of a thyroid gland primary, and specifically a PTC [4,21]. The high frequency of lymph node metastases with the DSV-PTC dictates an aggressive clinical evaluation of the cervical lymph nodes, with sampling of clinically suspicious lymph nodes.

While a number of immunohistochemical markers have been proposed to confirm the diagnosis of papillary carcinoma, including S-100 protein, HLA-DR, estrogen receptor, high-molecular-weight cytokeratins (CK), CK19, RET/PTC (rearrangement), HBME-1 and galectin-3, none is specific for these tumors. Nevertheless, a combination can be helpful in reaching a diagnostic decision in difficult cases [32,34]. In general, however, DSV-PTC is a morphologic diagnosis and does not require immunophenotypic analysis.

Differential Diagnosis

We report an unusual malignant transformation of the squamous metaplasia into a squamous cell carcinoma, which resulted in the man's death within 1.5 yr of the initial presentation. Although uncommon, this finding has been previous reported [11,35]. In our case, there were areas of transformation between squamous metaplasia and frankly invasive squamous cell carcinoma. By the time of the patient's death, the squamous cell carcinoma was the dominant feature, rather than the DSV-PTC. Furthermore, squamous cell carcinoma was also identified in the lymph node metastatic deposits. The differential diagnostic considerations encompass a squamous cell carcinoma of thyroid origin (extremely unusual) and direct extension into the thyroid gland or invasion from a squamous cell carcinoma arising within the neck organs. Extensive work-up may be required to exclude such an eventuality. Primary squamous cell carcinoma or squamous cell carcinoma that has metastasized to or invaded into the gland will not have psammoma bodies, extensive lymphocytic thyroiditis, nor the presence of characteristic papillary thyroid carcinoma [11,35]. Therefore, we believe it is reasonable to suggest malignant transformation of squamous metaplasia to squamous cell carcinoma, albeit very rare.

The very pronounced vascular dissemination of neoplastic cells raises the differential diagnosis of metastatic carcinoma to the thyroid gland. A pulmonary adenocarcinoma can metastasize to the thyroid gland with a papillary architecture and psammoma bodies, while also immunoreacting with TTF-1. However, the heavy inflammatory response, dense fibrosis, and areas of squamous metaplasia are not seen. Thyroglobulin, while difficult to interpret at times, will not be positive in a pulmonary primary.

Mucoepidermoid carcinoma (MEC) of the thyroid is an exceedingly uncommon variant characterized by anastomosing compact clusters of epidermoid cells and mucocytes encircled by fibrous stroma. The goblet-like mucus cells line ducts or glandular spaces and are associated with extravasated mucin. The squamous differentiation may be overt or subtle, associated with areas of hyaline bodies. The nuclear features of papillary carcinoma (delicate, pale chromatin, nuclear grooves, and intranuclear cytoplasmic inclusions) are common, while frank papillary carcinoma is seen in up to 50% of cases. Furthermore, lymphocytic thyroiditis is a common finding. This aggregate of findings can mimic a DSV-PTC, although extensive intravascular invasion, psammoma bodies, and the almost universal

lymph node metastasis are lacking in MEC [36–39]. Interestingly, TTF-1 is immunoreactive in MEC along with P-cadherin neoexpression and alterations of the E-cadherin/catenin complex, findings similar to DSV-PTC [39–41], suggesting that P-cadherin is a marker of epidermoid differentiation in both MEC and DSV-PTC rather than a marker of biologic aggressivity [41].

Treatment and Patient Outcome

The peculiar clinical presentation of a diffuse enlargement of the gland with high prevalence of Hashimoto's thyroiditis-like signs and symptoms may lead to misdiagnosis and undertreatment. Therefore, fine needle aspiration in young patients with this clinical presentation, especially when accompanied by cervical lymph node enlargement, is imperative to accurately identify the underlying papillary carcinoma, albeit masquerading as lymphocytic (Hashimoto's) thyroiditis [3,8,9,17,27].

It has been suggested that papillary carcinoma with squamous metaplasia has a worse patient outcome [16]. However, of three patients described in this paper, two had a good patient outcome, while the third patient was 49 yr old with invasion into the larynx and trachea (pT4 lesion). No allowance was made for the influence of age or extrathyroidal extension. All of the cases in our clinical series had squamous metaplasia as one of the diagnostic features. Therefore, it would seem that the presence of squamous metaplasia is not an independent prognostic factor for DSV-PTC.

Total thyroidectomy with bilateral lymph node dissection (sampling) is advocated with/without postoperative ^{131}I radiotherapy to yield the best overall patient outcome: mean follow-up, 17 yr (5 yr survival, >90%) in this series, supported by similar findings reported in the literature [3,4,8,10,13,17,18,27,28]. Therefore, although the tumor is "biologically" aggressive with extensive lymph node metastases [2,6,26], the patient outcome is excellent, suggesting that correct early management can greatly impact the patient prognosis [18,26]. In fact, available data from a composite of the literature (see Table 1) suggest that the DSV-PTC may actually have a better long-term prognosis that classic PTC, although the overall numbers are too small to be statistically meaningful.

Surgical complications of recurrent laryngeal nerve palsy and permanent hypoparathyroidism are complications that usually develop in patients who were managed by limited surgery or who had repeat surgeries for metastatic lymph node disease or recurrence in the bed of the thyroid gland. When tumor has invaded the recurrent laryngeal nerve, sacrifice of the nerve is unavoidable. Therefore, initial aggressive therapy will perhaps serve to decrease these complications [8]. Local recurrences in the bed of the previous tumor can develop (14%), but are managed by surgery or postoperative ^{131}I radiotherapy [3,4,10].

Patient outcome appears *unaffected* by the stage of DSV-PTC [3,8,13,27,28], as the vast majority of patients (up to 100%) have regional lymph node metastases at initial presentation [3,4,6,14,20,27,28]. Whereas nearly all of the patients develop cervical lymph node metastases first, pulmonary metastasis is not rare, and is the most common site of distant metastasis in these patients.

Therefore, the widespread intrathyroidal growth, the nearly universal presence of lymph node metastases, and an increased incidence of distant metastasis justifies early total thyroidectomy with bilateral lymph node dissection (modified radical neck dissection) as the preferred surgical management, followed by ^{131}I radiation therapy

and hormone replacement therapy. It cannot be overstressed that early correct diagnosis and complete surgical eradication of the cancer will assure an excellent long term clinical outcome and patient prognosis [3,4,8,13,14].

Conclusion

DSV-PTC is a distinct thyroid neoplasm presenting in young female patients with signs and symptoms most suggestive of a thyroiditis, although the lymph node metastases are a clue to the underlying disease. The tumor involves both lobes in nearly all cases, containing areas of extrathyroidal extension and very extensive intravascular permeation by neoplastic cells. The histologic combination of a solid to papillary growth of papillary carcinoma cells, squamous metaplasia, extensive psammoma body formations, heavy sclerotic fibrosis, and lymphocytic thyroiditis will confirm the diagnosis, especially when these features are exaggerated in extent and degree. DSV-PTC is more biologically aggressive than conventional PTC, although the patients' survival is not significantly different. Nearly all patients have lymph node metastases at presentation, therefore, requiring aggressive surgical management by total thyroidectomy with lymph node dissection to achieve the best long-term patient outcome. In spite of the "biologically" aggressive presentation, nearly all of these patients, when managed as above, will experience an excellent long term clinical outcome.

Acknowledgments

Presented at the 92nd Annual Meeting of the United States and Canadian Academy of Pathology, Washington, DC, March 22–28, 2003. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense.

References

1. LiVolsi VA, Albores-Saavedra J, Asa SL, et al. Papillary carcinoma. In: De Lellis RA, Lloyd RV, Heitz PU, Eng C, eds. Pathology and genetics of tumours of the endocrine organs and paraganglia. World Health Organization classification of tumours. Kliehues P, Sobin LH, series eds. Lyon, France: IARC Press, 2004;57–66.
2. Vickery AL, Carcangiu ML, Johannessen JV, et al. Papillary carcinoma. Semin Diagn Pathol 1985;2:90–100.
3. Albareda M, Puig-Domingo M, Wengrowicz S, et al. Clinical forms of presentation and evolution of diffuse sclerosing variant of papillary carcinoma and insular variant of follicular carcinoma of the thyroid. Thyroid 1998;8:385–391.
4. Carcangiu ML, Bianchi S. Diffuse sclerosing variant of papillary thyroid carcinoma. Clinicopathologic study of 15 cases. Am J Surg Pathol 1989;13:1041–1049.
5. Caruso G, Tabarri B, Lucchi I, et al. Fine needle aspiration cytology in a case of diffuse sclerosing carcinoma of the thyroid. Acta Cytol 1990;34:352–354.
6. Chan JK, Tsui MS, Tse CH. Diffuse sclerosing variant of papillary carcinoma of the thyroid: a histological and immunohistochemical study of three cases. Histopathology 1987;11:191–201.
7. Chow SM, Chan JK, Law SC, et al. Diffuse sclerosing variant of papillary thyroid carcinoma—clinical features and outcome. Eur J Surg Oncol 2003;29:446–449.
8. Fujimoto Y, Obara T, Ito Y, et al. Diffuse sclerosing variant of papillary carcinoma of the thyroid. Clinical importance, surgical treatment, and follow-up study. Cancer 1990;66: 2306–2312.
9. Gómez-Morales M, Alvaro T, Muñoz M, et al. Diffuse sclerosing papillary carcinoma of the thyroid gland: immunohistochemical analysis of the local host immune response. Histopathology 1991;18:427–433.

10. Hayashi Y, Sasao T, Takeichi N, et al. Diffuse sclerosing variant of papillary carcinoma of the thyroid. A histopathological study of four cases. Acta Pathol Jpn 1990;40:193–198.
11. Kebapci N, Efe B, Kabukcuoglu S, et al. Diffuse sclerosing variant of papillary thyroid carcinoma with primary squamous cell carcinoma. J Endocrinol Invest 2002;25:730–734.
12. Kumarasinghe MP. Cytomorphologic features of diffuse sclerosing variant of papillary carcinoma of the thyroid. A report of two cases in children. Acta Cytol 1998;42:983–986.
13. Macák J, Michal M. Diffuse sclerosing variant of papillary thyroid carcinoma. Cesk Patol 1993;29:6–8.
14. Martín-Pérez E, Larrañaga E, Serrano P. Diffuse sclerosing variant of papillary carcinoma of the thyroid. Eur J Surg 1998;164:713–715.
15. Matias-Guiu X, Esquius J. Aberrant expression of HLA-DR antigen in diffuse sclerosing variant of papillary carcinoma of thyroid. J Clin Pathol 1989;42:1309.
16. Mizukami Y, Nonomura A, Michigishi T, et al. Diffuse sclerosing variant of papillary carcinoma of the thyroid. Report of three cases. Acta Pathol Jpn 1990;40:676–682.
17. Moreno Egea A, Rodriguez Gonzalez JM, Sola Perez J, et al. Clinicopathological study of the diffuse sclerosing variety of papillary cancer of the thyroid. Presentation of 4 new cases and review of the literature. Eur J Surg Oncol 1994;20:7–11.
18. Schröder S, Bay V, Dumke K, et al. Diffuse sclerosing variant of papillary thyroid carcinoma. S-100 protein immunocytochemistry and prognosis. Virchows Arch A Pathol Anat Histopathol 1990;416:367–371.
19. Scott GC, Meier DA, Dickinson CZ. Cervical lymph node metastasis of thyroid papillary carcinoma imaged with fluorine-18-FDG, technetium-99m-pertechnetate and iodine-131-sodium iodide. J Nucl Med 1995;36: 1843–1845.
20. Soares J, Limbert E, Sobrinho-Simões M. Diffuse sclerosing variant of papillary thyroid carcinoma. A clinicopathologic study of 10 cases. Pathol Res Pract 1989;185:200–206.
21. Wu PS-C, Leslie PJ, McLaren KM, et al. Diffuse sclerosing papillary carcinoma of thyroid: a wolf in sheep's clothing. Clin Endocrinol (Oxf) 1989;31:535–540.
22. Ryska A, Nozicka Z, Hovorková E, et al. Sclerosing papillary carcinoma of the thyroid with tubular features. Pathol Res Pract 2000;196: 339–343.
23. Schröder S, Pfannschmidt N, Böcker W, et al. Histopathologic types and clinical behaviour of occult papillary carcinoma of the thyroid. Pathol Res Pract 1984;179:81–87.
24. Thyroid. In: Greene FL, Page DL, Fleming ID, et al., eds. AJCC cancer staging manual. New York: Springer-Verlag, 2002:77–87.
25. Chan JK. Papillary carcinoma of thyroid: classical and variants. Histol Histopathol 1990;5: 241–257.
26. Siegal A, Mimouni M, Kovalivker M, et al. Latent childhood thyroid carcinoma in diffuse lymphocytic thyroiditis. J Surg Oncol 1983;23:155–157.
27. Nikiforov Y, Gnepp DR. Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991–1992) from the Republic of Belarus. Cancer 1994;74:748–766.
28. Khan AR, Abu-Eshy SA. Variants of papillary carcinoma of the thyroid: experience at Asir Central Hospital. J R Coll Surg Edinb 1998; 43:20–25.
29. Ohori NP, Schoedel KE. Cytopathology of high-grade papillary thyroid carcinomas: tall-cell variant, diffuse sclerosing variant, and poorly differentiated papillary carcinoma. Diagn Cytopathol 1999;20:19–23.
30. Damiani S, Dina R, Eusebi V. Cytologic grading of aggressive and nonaggressive variants of papillary thyroid carcinoma. Am J Clin Pathol 1994;101:651–655.
31. Nikiforov YE, Rowland JM, Bove KE, et al. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Res 1997;57: 1690–1694.
32. Cheung CC, Ezzat S, Freeman JL, et al. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001;14:338–342.
33. Ivanova R, Soares P, Castro P, et al. Diffuse (or multinodular) follicular variant of papillary thyroid carcinoma: a clinicopathologic and immunohistochemical analysis of ten cases of an aggressive form of differentiated thyroid carcinoma. Virchows Arch 2002;440: 418–424.
34. Sahoo S, Hoda SA, Rosai J, et al. Cytokeratin 19 immunoreactivity in the diagnosis of pap-

illary thyroid carcinoma: a note of caution. Am J Clin Pathol 2001;116:696–702.
35. Harada T, Shimaoka K, Katagiri M, et al. Rarity of squamous cell carcinoma of the thyroid: autopsy review. World J Surg 1994;18:542–546.
36. Chan JK, Albores-Saavedra J, Battifora H, et al. Sclerosing mucoepidermoid thyroid carcinoma with eosinophilia. A distinctive low-grade malignancy arising from the metaplastic follicles of Hashimoto's thyroiditis. Am J Surg Pathol 1991;15:438–448.
37. Wenig BM, Adair CF, Heffess CS. Primary mucoepidermoid carcinoma of the thyroid gland: a report of six cases and a review of the literature of a follicular epithelial-derived tumor. Hum Pathol 1995;26:1099–1108.
38. Baloch ZW, Solomon AC, LiVolsi VA. Primary mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia of the thyroid gland: a report of nine cases. Mod Pathol 2000;13:802–807.
39. Albores-Saavedra J, Gu X, Luna MA. Clear cells and thyroid transcription factor I reactivity in sclerosing mucoepidermoid carcinoma of the thyroid gland. Ann Diagn Pathol 2003;7:348–353.
40. Rocha AS, Soares P, Machado JC, et al. Mucoepidermoid carcinoma of the thyroid: a tumour histotype characterised by P-cadherin neoexpression and marked abnormalities of E-cadherin/catenins complex. Virchows Arch 2002;440:498–504.
41. Rocha AS, Soares P, Seruca R, et al. Abnormalities of the E-cadherin/catenin adhesion complex in classical papillary thyroid carcinoma and in its diffuse sclerosing variant. J Pathol 2001;194:358–366.