Fine-Needle Aspiration Biopsy of Secondary Neoplasms of the Thyroid Gland: A Multi-Institutional Study of 62 Cases

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BACKGROUND: Secondary neoplasms of the thyroid gland (SNTGs) are uncommon, and it is important to recognize them in thyroid fine-needle aspiration biopsy (FNAB). **METHODS:** The authors report a cohort of 62 SNTGs from 7 institutions in the United States and Europe. Patients were identified retrospectively by searching through medical records of the respective institutions. All initial diagnoses were rendered by FNAB. **RESULTS:** SNTGs represented 0.16% of all thyroid FNABs and were more frequent among women (ratio of women to men, 1.2:1.0). The mean patient age was of 59 years (range, 7-84 years), the mean tumor size was 3 cm (range, 0.9-7 cm), and the mean interval from diagnosis of the primary tumor was 45 months (range, 0-156 months). Eighty-seven percent of SNTGs were diagnosed as malignant by FNAB, and there was a specific SNTG diagnosis in 93% of patients. Immunocytochemistry and flow cytometry, which were used in 30% of patients, were useful ancillary studies. Adenocarcinomas (n = 23; 37%) and squamous cell carcinomas (SCCs) (n = 22; 35.5%) represented the majority of SNTGs, followed by lymphoma (n = 5; 8%), melanoma (n = 5; 8%), adenoid cystic carcinoma (n = 3; 5%), and various sarcomas (n = 3; 5%). Adenocarcinomas originated from the kidney (n = 9; 39%), lung (n = 6; 26%), breast (n = 5; 22%), and colon (n = 3; 13%). SCCs originated mostly from the head and neck (n = 13; 59%), followed by lung (n = 3; 13%), esophagus (n = 3; 14%), and unknown primary sites (n = 3; 14%). **CONCLUSIONS:** Adenocarcinomas from the kidney, lung, breast, and colon along with SCCs represent the majority of SNTGs. The current results indicate that FNAB is a sensitive and accurate method for diagnosing SNTG; however, diagnostic difficulties can occur. Knowledge of clinical history and the judicious application of ancillary studies can increase the sensitivity and accuracy of FNAB for detecting SNTGs. ***Cancer (Cancer Cytopathol)*** **2015;123:19-29.** *© 2014 American Cancer Society.*

KEY WORDS: thyroid; secondary neoplasm; metastasis; renal cell carcinoma; squamous cell carcinoma; adenocarcinoma; lymphoma; adenoid cystic carcinoma; fine-needle aspiration; cytology.

INTRODUCTION

Secondary neoplasms of the thyroid gland (SNTGs), representing either metastases or direct extension of tumors from adjacent anatomic structures, are uncommon. Their reported incidence varies substantially, however, ranging from 0.1% to 3% in clinical series.[1-15] They have been reported as incidental findings in autopsy studies[16-18] with a frequency of 4.4% to 24% in patients with a known primary cancer or widespread

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malignancy in which clinically occult thyroid micrometastases may be detected.[4,19-22] In the United States and Europe, the most commonly reported primary tumor resulting in symptomatic SNTG is renal cell carcinoma (RCC), closely followed by carcinomas of the breast, lung, and colon.[5,23-25] Secondary lymphoma, melanoma, sarcoma, and head and neck squamous cell carcinoma (SCC) also account for a significant proportion of SNTGs.[22,24,25] Over the past 3 decades, fine-needle aspiration biopsy (FNAB) has emerged as the leading test for the initial evaluation of patients with thyroid nodules.[27-31] The detected incidence of SNTGs may actually be increasing, akin to papillary thyroid microcarcinomas, as a result of increased surveillance over the last few decades by imaging studies, including ultrasound and ultrasound-guided FNAB,[2,4,6] and the longer survival of patients with disseminated cancer. Although the use of FNAB in the workup of primary thyroid tumors has been well studied, only isolated case reports and a few small series have detailed the cytologic evaluation of SNTGs in thyroid FNABs.[2,4,5,7,8,14,16,26,32,33]

The FNAB diagnosis of an SNTG is important because it has critical implications for patients' clinical management and prognosis. Patients who have metastasis to the thyroid have a poor prognosis in general, and most die shortly after the confirmation of distant metastasis,[1-5,16,23,25] although prolonged survival has been reported in a rare subset of patients after surgery for an isolated thyroid metastasis.[1,3,6,25,34] On occasion, thyroid metastases can also represent the first clinical manifestation of an occult, nonthyroid primary tumor.[33-35]

In the current report, we present a large FNAB series of SNTGs, consisting of 62 cases from 7 tertiary care medical centers in the United States and Europe. We discuss the major cytologic features of SNTG in thyroid FNAB specimens and the diagnostic challenges that selected SNTGs can cause.

MATERIALS AND METHODS

Seventy-six cases of SNTG were collected from 7 major teaching hospitals, including 5 in the United States (Massachusetts General Hospital [MGH] and Brigham and Women's Hospital [BWH], Boston, Mass; Johns Hopkins Hospital [JHH], Baltimore, Md; Virginia Commonwealth University Health System [VCU], Richmond, Va; and State University of New York [SUNY] Upstate Medical University, Syracuse, NY) and 2 in Europe (Geneva University Hospital [HUG], Geneva and Cantonal Institute of Pathology [CIP], Locarno, Switzerland).

Patients with SNTG were identified retrospectively by searching the electronic medical records of the respective institutions. The time frame of the searches varied for the different institutions (MGH, VCU, and HUG, 1992-2014; BWH, JHH, SUNY, and CIP, 1992-2006). The average number of thyroid FNABs performed annually during this time frame and the prevalence of malignant FNABs in each center was as follows: 1309 FNABs with 3.9% malignant for MGH, 525 FNABs with 4.8% malignant for BWH, 534 FNABs with 15% malignant for JHH, 400 FNABs with 9% malignant for VCU, 212 FNABs with 5.2% malignant for SUNY, 390 FNABs with 5.3% malignant for HUG, and 380 FNABs with 5.1% malignant for CPI.

Fourteen cases were excluded for the following reasons: 9 were primary or possible primary thyroid lymphomas; 2 were primary Langerhans cell histiocytosis of the thyroid; 2 were diagnosed as poorly differentiated carcinomas, but a primary thyroid carcinoma could not be entirely excluded; and 1 was diagnosed as leiomyosarcoma, but undifferentiated thyroid carcinoma (UTC) could not be entirely excluded. For the 62 remaining cases, including 21 from MGH, 13 from JHH, 12 from BWH, 6 from SUNY, 4 from VCU, 4 from CIP, and 2 from HUG, correlation was made with previous or concurrent histologic specimens when available. Forty-eight of 62 patients (77%) had a primary tumor site available for histologic comparison at the time of the review, and several had corresponding thyroid histology specimens or cell blocks. All cases included in the cohort had some form of tissue confirmation either through prior known primary tumor histology, concurrent biopsy of the SNTG, or post-FNAB follow-up biopsy of the SNTG. In addition, for all cases included in our FNAB cohort, the combined clinical, radiologic, and pathologic evidence was compelling enough to conclude that they were SNTGs, and these patients were managed clinically based on a diagnosis of SNTG. The following information was collected and analyzed for each patient: patient age and sex; the number, size, and location of the thyroid nodule(s) (based on ultrasound); concurrent and previous surgical pathologic diagnosis; interval between initial cancer diagnosis and SNTG FNAB diagnosis; cytologic features of SNTG; and ancillary studies used to support or

Table 1. Clinicopathologic Features of Patients With Secondary Neoplasms of the Thyroid Gland

Cancer Type/Origin	No. of Patients (%)	Sex: Women/Men	Age: Mean [Range]	No. of Tumor Foci[a]	Known Malignancy Before FNAB	Interval between FNAB and Initial Dx	No. with Prior Metastasis
ADC	23 (37)	16/7	59 [34-84]	Single, 13; multiple, 4; unknown, 6	Yes, 15; no, 3; unknown, 5	5 y; RCC, 7.3 y	Yes, 11; no, 6, unknown, 6
Kidney/RCC	9 (39)						
Lung	6 (26)						
Breast	5 (22)						
Colon	3 (13)						
SCC	22 (35.5)	8/14	63 [38-78]	Single, 11; multiple, 3; unknown, 8	Yes, 9; no, 5; unknown, 8	2 y	Yes, 5; no, 9; unknown, 8
H&N	13 (59)						
Lung	3 (14)						
Esophagus	3 (14)						
Uncertain	3 (14)						
Lymphoma	5 (8)						
Non-Hodgkin	4	4/0	63	Single, 1; multiple, 3	Yes	6 mo	Yes, 1; no, 3
Hodgkin	1	1/0	45	Multiple	Yes	13 y	Yes
Melanoma	5 (8)	2/3	59	Single, 3; unknown, 2	Yes, 3; unknown, 2	2.5 mo	Yes, 1; no, 2; unknown, 2
Skin	2						
Unknown	3						
AdCC	3 (5)	2/1	58	Single, 3	No	NA	NA
H&N	2						
Trachea	1						
Sarcoma	3 (5)						
Fibrosarcoma	1	1/0	47	Single	Yes	1 y, 9 mo	Yes
Liposarcoma	1	0/1	69	Single	Yes	3 y	Yes
Clear cell	1	0/1	7	Single	Yes	5 y, 4 mo	Yes
LCNEC	1 (1.5)						
GI	1	0/1	70	Single	Yes	0, Synchronous	No
Total	62	34/28; ratio, 1.2:1.0	Mean, 59	—	—	Mean, 3.7 y	—

Abbreviations: ADC, adenocarcinoma; AdCC, adenoid cystic carcinoma; Dx, diagnosis; FNAB, fine-needle aspiration biopsy; GI, gastrointestinal; H&N, head and neck; LCNEC, large cell neuroendocrine carcinoma; NA, not assessable; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.
[a] Tumor foci numbers were assessed by ultrasound.

confirm the diagnosis. All patient data, as well as representative FNAB cytologic slides, were reviewed further by 2 pathologists (H.W. and M.P.). All cytologic diagnoses of the study cohort were recorded using the equivalent diagnosis from *The Bethesda System for Reporting Thyroid Cytopathology*.[27,36] The cytologic slides were available for review in 71% of cases (n = 44 of 62). In cases without cytology material to review, the data were extracted from the patients' files. In all of these cases, however, there was also a history of a prior malignancy, and primary tumor tissue was available for pathologic correlation. In 12 cases, only liquid-based preparations were used in the cytologic evaluation, whereas all other cases included both alcohol-fixed smears and either liquid-based preparations (ThinPrep [Hologic, Marlborough, Mass] or SurePath [Becton, Dickinson and Company, Franklin Lakes, NJ]) or cytospins. This clinical investigation was conducted in accordance and compliance with all statues, directives, and guidelines of the Code of Federal Regulations, Title 45, part 46 and the Code of European Commonwealth Regulations and was conducted under institutional review board approval (2005-P-000936; MGH).

RESULTS

Clinicopathologic Features of Patients With SNTG

Table 1 summarizes the clinicopathologic features of patients with SNTGs. The mean prevalence of SNTGs from the various institutions that contributed to our cohort was 0.16% (range, 0.1%-0.2%) for all thyroid FNABs and 1.9% (range, 0.7%-3.1%) for all thyroid FNABs that were diagnosed as malignant. In contrast to primary thyroid cancers, SNTGs had a more equal sex distribution but still had a higher incidence among women (34 women vs 28 men; ratio of women to men, 1.2:1.0). The mean age of patients with SNTG at the time of clinically apparent thyroid involvement was 59

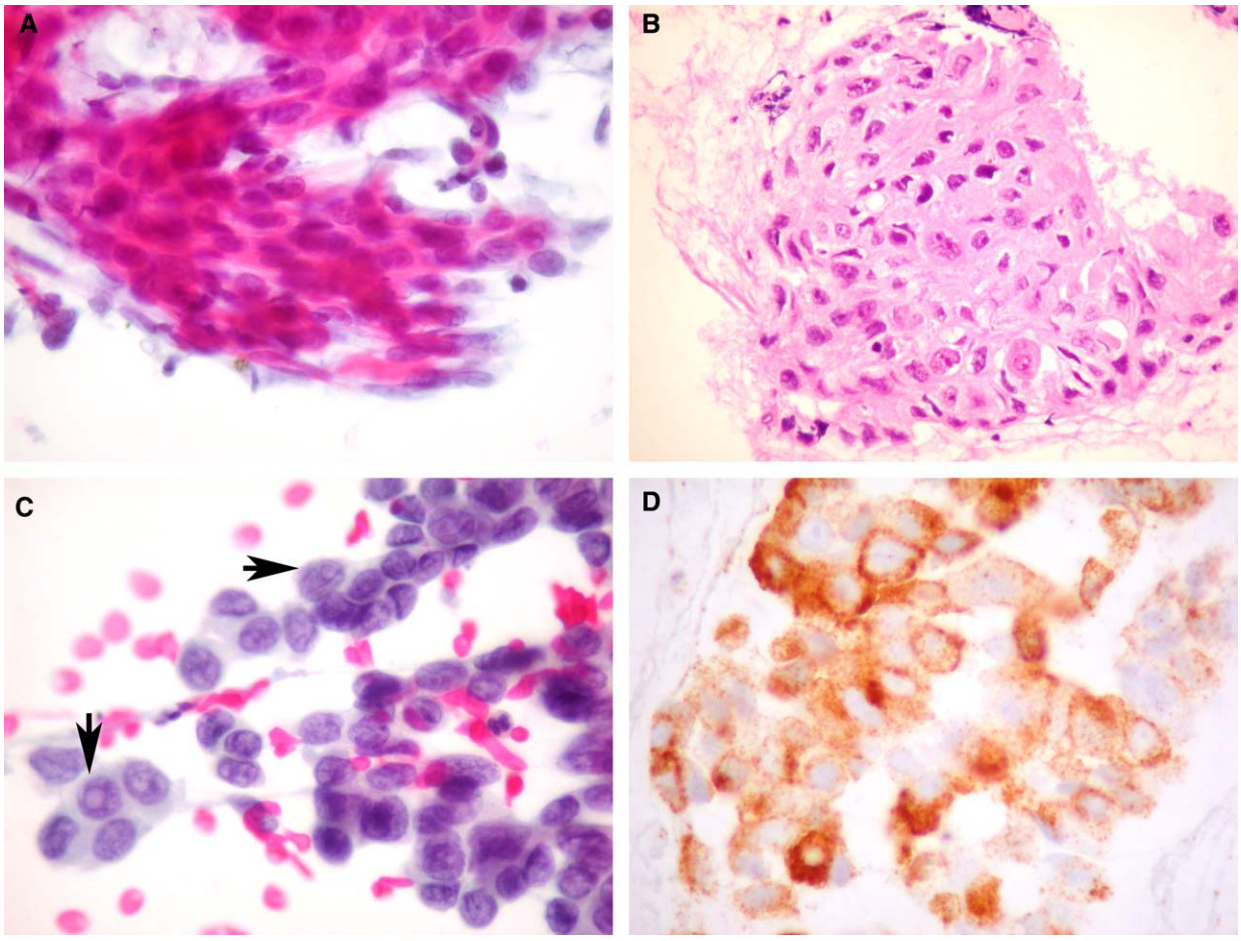

Figure 1. (A,B) Photomicrographs of metastatic squamous cell carcinoma reveal clusters of ovoid-to-elongated cells with dense, eosinophilic cytoplasm and moderate-to-marked nuclear atypia (Papanicolaou stain in A, hematoxylin and eosin [H&E]-stained cell block in B; original magnification ×200 in A and B). (C-E) Photomicrographs show metastatic, poorly differentiated neuroendocrine carcinoma composed of medium-sized cells with (C) scant cytoplasm and ovoid nuclei with "salt-and-pepper" chromatin, occasional nuclear pseudoinclusions (vertical arrow), and nuclear grooves (horizontal arrow), mimicking papillary and medullary thyroid carcinomas. The tumor cells were immunopositive for (D) chromogranin and (E) carcinoembryonic antigen and were immunonegative for calcitonin, thyroglobulin, and thyroid transcription factor 1, arguing against a primary thyroid neoplasm (Papanicolaou stain in C, H&E-stained cell block in D and E; original magnification ×400 in C-E). (F) Metastatic colon adenocarcinoma is composed of clusters of malignant cells with atypical, elongate nuclei in a necrotic background (Papanicolaou stain, original magnification ×200). (G) This is a metastatic renal cell carcinoma (Papanicolaou stain, original magnification ×400). (H) This Hodgkin lymphoma contains occasional Reed-Sternberg cells (red arrow) in a bloody and lymphoid background (Papanicolaou stain, original magnification ×200).

years (range, 7-84 years). In 58% of patients (n = 36), a prior malignancy was known at the time of FNAB, but 18% of patients (n = 11) had no known history of a prior malignancy. The mean size of the SNTG nodules was 3 cm (range, 0.9-9.1 cm), and the mean time interval between the primary tumor identification and the FNAB diagnosis of an SNTG was 3.7 years (range, from birth [synchronous] to 13 years; median, 2.5 years). Of the 2 patients who had the longest intervals between primary diagnosis and thyroid metastasis detected by FNAB, 1 had RCC and developed thyroid metastasis 12 years after the initial diagnosis, and the other had classic Hodgkin lymphoma of the cervical and mediastinal lymph nodes and was diagnosed with thyroid involvement 13 years later.

FNAB Diagnoses and Cytologic Features

In our cohort, adenocarcinoma (n = 23; 37%) and SCC (n = 22; 35.5%) were the most common SNTGs (Table 1, Fig. 1). Among the adenocarcinomas, 39% (n = 9) originated from the kidney, 26% (n = 6) originated from the lung, 22% (n = 5) originated from the

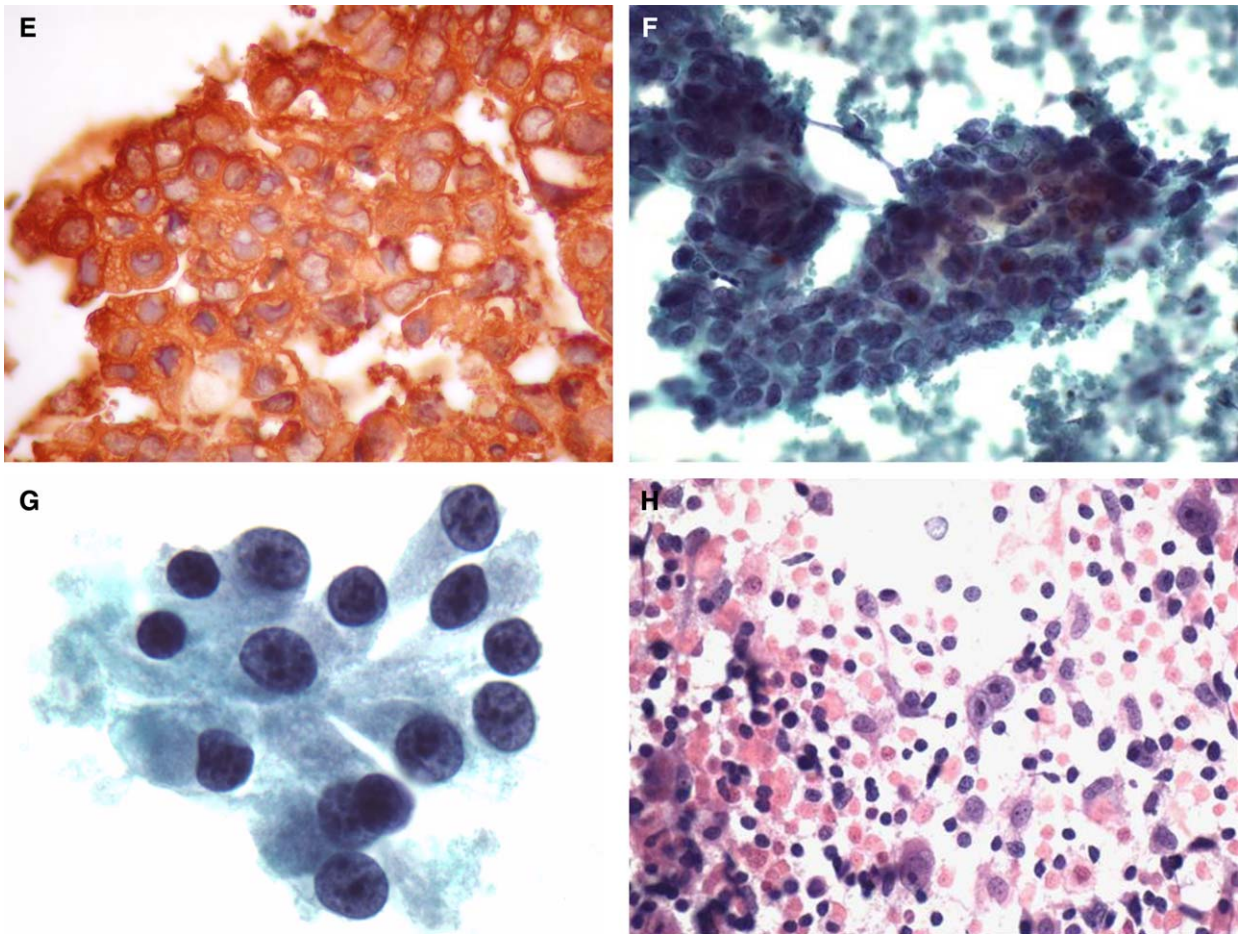

Figure 1. Continued

breast, and 13% (n = 3) originated from the colon (Table 1). Among the SCCs, 59% (n = 13) originated from the head and neck, including 3 with direct extension to the thyroid gland from the larynx. The remaining SCCs were evenly split between origins in the lung (n = 3), esophagus (n = 3), and unknown primary sites (n = 3).

Other less common SNTGs were 5 secondary lymphomas (including large B-cell lymphoma [n = 2], small lymphocytic lymphoma [n = 2], and Hodgkin lymphoma [n = 1]); 5 malignant melanomas; 3 adenoid cystic carcinomas (AdCCs), including 1 with direct thyroid extension from the trachea; 3 metastatic sarcomas, including 1 retroperitoneal dedifferentiated liposarcoma, 1 gastroesophageal fibrosarcoma, and 1 clear cell sarcoma from the kidney in a child; and 1 large cell neuroendocrine carcinoma of the gastrointestinal tract (Table 1, Fig. 1).

Cytologically, the cellularity in the FNAB was highly variable, but cell clusters of different sizes were identified in 77% of samples (n = 34 of 44). A background of benign thyroid follicles was present in a minority of samples (20.5%; n = 9 of 44). A useful diagnostic feature in approximately 33% of FNABs was the presence of focal tumor necrosis. The necrosis, as expected, was correlated to SNTGs with higher grade features, but not to any particular type of tumor. Overtly malignant nuclear features, including pleomorphism, crowding, coarse hyperchromatic chromatin, and prominent nucleoli, were present in 67.5% of SNTGs. Low-grade nuclear features, however, were present in approximately 33% of SNTGs, including 7 RCCs, 4 secondary lymphomas, 2 malignant melanomas, 1 SCC, and 1 clear cell sarcoma.

Accuracy of FNAB and Differential Diagnosis

In our cohort, 87% of SNTGs (n = 54) were diagnosed as "malignant" by FNAB, 8% (n = 5) were deemed nondiagnostic because of absent or scant diagnostic material, and 5% (n = 3) were diagnosed as "suspicious for a

Table 2. Clinicopathologic Features of Patients With Cytohistologic Discrepancy

Sex	Age, y	Size, cm	Lobe	No.	Cytologic Dx	Histologic Dx	Prior Dx	Time From Dx	Prior Metastasis
Man	62	1.0	Left	Multifocal	Suspicious for follicular neoplasm	RCC	Yes	NA	No
Woman	73	2.0	Right	1	Suspicious for follicular neoplasm	RCC	No	NA	No
Woman	59	3.5	Right	1	Suspicious for follicular neoplasm	RCC	Yes	6 y	No
Woman	68	NA	Left	1	Malignant: Papillary thyroid carcinoma	AdCC	No	NA	No
Woman	47	3.5	Right	1	Malignant: Poorly differentiated thyroid carcinoma	AdCC	No	NA	No
Man	70	7.0	Left	1	Malignant: Malignant thyroid tumor, NOS	Melanoma	Yes	3 mo	No
Woman	60	3.8	Left	1	Malignant: High-grade carcinoma (papillary vs anaplastic?)	SCC	No	NA	Cervical LN

Abbreviations: AdCC, adenoid cystic carcinoma; Dx, diagnosis; LN, lymph nodes; NA, not available; NOS, not otherwise specified; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

follicular neoplasm." No SNTGs were diagnosed as "benign," "atypia of undetermined significance/follicular lesion of undetermined significance," or "suspicious for malignancy." Among the SNTGs that were diagnosed as "malignant," a specific SNTG diagnosis or a diagnosis consistent with SNTG was given in 93% of cases (n = 50); whereas, in 7% of cases (n = 4), a primary thyroid malignancy, including papillary thyroid carcinoma (PTC) (n = 1), poorly differentiated thyroid carcinoma (PDTC) (n = 1), and high-grade thyroid carcinoma not otherwise specified (n = 2), was given (Table 2). Eighty-one percent of SNTGs (n = 50 of 62) were accurately classified by FNAB.

FNAB Cases of SNTG With Diagnostic Difficulty

The SNTGs with adequate cellularity that caused diagnostic problems by FNAB included RCC (n = 3), AdCC (n = 2), malignant melanoma (n = 1), and poorly differentiated SCC (n = 1) (Table 2). Three of the 9 RCCs in our series were misclassified as a primary thyroid follicular neoplasms (Table 2, Fig. 2), including 2 with a previous history of RCC, and 1 was nondiagnostic because of scant material. The RCCs with adequate cellularity had similar cytologic features: large epithelial cells were arranged in 3-dimensional clusters and small sheets. The cells had abundant, delicate, and mildly granular, eosinophilic cytoplasm; dark central nuclei with mild-to-moderate pleomorphism; and distinct nucleoli (Fig. 2). The cytologic features resembled those of Hurthle cells.

Three AdCCs (including 1 solid variant) were represented among the SNTGs, and 2 were misinterpreted as PTC and PDTC, respectively (Table 2). The AdCCs consisted of basaloid cells with scant cytoplasm and small, oval, uniform, and hyperchromatic nuclei (Fig. 2). Two AdCCs contained pale-staining globules of matrix material.

Use of Ancillary Techniques

In 30% (n = 19) of the SNTG FNAB cases, ancillary studies were used in the evaluation. Ancillary techniques consisted mostly of immunocytochemistry (n = 18 of 62) with various antibodies used either singly (eg, cluster of differentiation 20 [CD20; B-lymphocyte antigen] to confirm B-cell lymphoma) or as a panel, including keratin, thyroglobulin, thyroid transcription factor 1 (TTF-1), paired box gene 8 (PAX-8), calcitonin, carcinoembryonic antigen, CD45 (lymphocyte common antigen), S-100, human melanoma black 45 (HMB-45), Melan-A, CD68, galectin-3, HBME-1 (Hector Battifora mesothelial-1), cytokeratin 7, cytokeratin 20, chromogranin-A, synaptophysin, CD56, carbonic anhydrase IX (CAIX), GCDFP-15 (gross cystic disease fluid protein 15), ER (estrogen receptor), and PR (progesterone receptor). However, ancillary studies were used in only 14% of the cases (1 of 7) with diagnostic difficulty described above. Flow cytometry was performed in only 1 case.

DISCUSSION

In this report, we present data from 62 patients who had SNTGs initially diagnosed by FNAB from 7 tertiary care

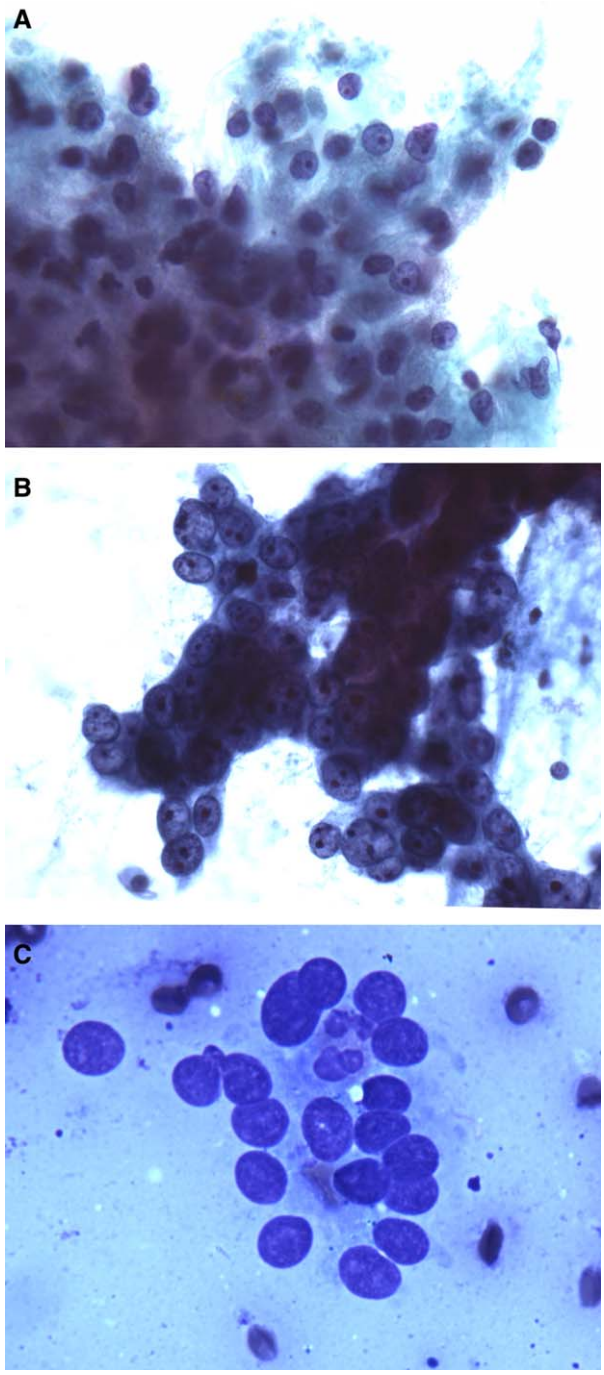

Figure 2. (A) A metastatic renal cell carcinoma composed of clusters of tumor cells with oncocytic features and bland nuclei was misinterpreted as a Hurthle cell neoplasm (Papanicolaou stain). (B,C) Adenoid cystic carcinoma with basaloid and microfollicular features can be misinterpreted as a primary thyroid carcinoma (Papanicolaou stain, original magnification ×200 in A-C).

medical centers in the United States and Europe. To the best of our knowledge, this is the largest FNAB series of SNTGs in the English language literature reported to date.

Epidemiology and Clinicopathologic Features of SNTGs

The incidence and relative rates of SNTG, as recently reviewed by Chung et al[24] and Montero et al,[25] have demonstrated variability; however, as supported by the results from our cohort, SNTGs are rare, with a mean prevalence of 0.16% of all aspirated nodules.[1-23,37] Reports of SNTGs are influenced by the case type (eg, autopsy vs clinical), study period (eg, before or after the implementation of FNAB for thyroid nodules), and geographic region of the study and also by the thoroughness of the investigations to identify SNTGs. Involvement of the thyroid gland by an SNTG can also take several forms, including a solitary nodule; numerous, small, discrete nodules (<2 mm); or diffuse involvement, which may be variably symptomatic and/or detectable.[38] An autopsy study from 1962 revealed an SNTG incidence of 9.5% with the following types and proportions of tumors: melanoma, 39%; breast carcinoma, 21%; RCC, 12%; lung carcinoma, 11%; lymphoma, 10%; head and neck SCC, 10%; colorectal carcinoma, 4%; and gastric carcinoma, 2%.[22] In contrast, a study of 9118 FNABs from the Mayo Clinic between 1985 and 1994 identified 43 cases of metastatic carcinoma to the thyroid gland (incidence, 0.5%) with the following sites of origin: kidney, 33%; lung, 16%; breast, 16%; esophagus, 9%; uterus, 7%; and skin, 5%.[2] In our multicenter FNAB series, we did not exclude secondary lymphomas of the thyroid gland or SCC arising through direct extension into the thyroid gland, which, together, accounted for 6% of the SNTGs in our series. SCC was almost as common as adenocarcinoma, with most cases (59%) originating from the head and neck, including 3 with direct extension to the thyroid gland. It is possible that the high percentage of head and neck SCCs in our cohort may have been influenced by the patterns of patient referral to the academic institutions that contributed to our study and also by having a large volume of head and neck pathology. Most adenocarcinomas originated from the kidney (39%), followed by lung (26%), breast (22%), and colon (13%).

SNTGs, in contrast to primary thyroid tumors, occur in a nearly equal sex distribution, as supported by our findings and those of others.[2,5,24,34] One exception in our series was SCC, which was more frequent in men than in women. In addition, patients with SNTGs in our FNAB series were significantly older (mean age, 59 years) than the average population that presents with a thyroid

nodule and undergoes FNAB (mean age, 50 years).[39] Patients with SNTGs typically present in their sixth or seventh decade of life,[1,3-5,24,34] akin to patients with UTC. Therefore, the increased likelihood of a possible SNTG should be considered when interpreting FNAB of thyroid lesions in patients aged >50 years.

The interval between primary tumor identification and thyroid metastasis confirmed by FNAB ranged from birth (synchronous) to 13 years in our cohort. The interval was significantly longer in patients with SNTGs from RCC than in those with SNTGs from other sites (mean, 7.3 years vs 2.9 years; $P = .016$). These data are similar to those reported in several previous clinicopathologic reports.[2,4-6,23,24,34] The interval between a primary diagnosis of RCC and the identification of thyroid metastasis can be very long,[2,6,22,24,40-42] and previous reports have indicated that SNTGs from RCC may occur as much as 27 years after resection of the primary cancer.[2,42] Therefore, any thyroid nodule arising in a patient who has a previous history of malignancy, especially RCC, should be considered a potential metastasis until proven otherwise, even when the history of a nonthyroid cancer is remote.

It is noteworthy that 2 of our FNAB cases (3%)—a lung adenocarcinoma and a melanoma—presented as a single metastatic focus within a larger follicular adenoma, and both malignancies were accurately diagnosed by FNAB. This uncommon phenomenon of tumor-to-tumor metastasis involving a thyroid follicular adenoma has been observed in several case reports,[14,35,43-49] mostly with carcinomas from the lung, kidney, breast, and colon, and sometimes as the initial presentation of the carcinoma.[35] It has been suggested that some thyroid diseases, including follicular neoplasms and nodular goiter, may increase the risk of developing a thyroid metastasis in patients with nonthyroid cancer.[24,46,49] Although poorly understood, this phenomenon may be related in part to increased and/or altered blood flow in the thyroid gland.

Accuracy of FNAB and Differential Diagnosis of SNTG

On the basis of histologic data, cytologic case reports, and small FNAB series, there is an SNTG subset that exhibits morphologic features overlapping with those of primary thyroid carcinomas, including PTC, follicular thyroid carcinoma, medullary thyroid carcinoma, PDTC, and UTC, and, thus, constitutes a potential pitfall in cytologic evaluation.[24,26,32,50-56] Clearly, a major challenge in the diagnosis of SNTG is related to the wide variety of histologic types and primary tumor origins that can be encountered. In addition, the diagnosis of SNTG by FNAB can be made more difficult by a lack of clinical history indicating an extrathyroid cancer or by a long lag time between primary diagnosis and the development of an SNTG.[6,23,25,34,40,49] FNAB, as demonstrated in our series and by others,[2,6,24,26,32,33] is a sensitive and effective tool for the detection and diagnosis of SNTGs. In the most recent review by Chung et al,[24] the accuracy of FNAB in different combined studies was 74%, and 87% of SNTGs in our series were accurately diagnosed as secondary thyroid malignancies. The nondiagnostic rate for our SNTGs was 8%, which is less than the average overall nondiagnostic rate for thyroid FNAB.[57,58] When inaccurate, FNABs of SNTGs most often were interpreted as primary thyroid malignancies, as benign, or as nondiagnostic.[24]

The accuracy of FNAB for the diagnosis of SNTG is not surprising given the features of most SNTG aspirates, which include high cellularity with overt, malignant cytologic features, together with the finding that >50% of patients have a known extrathyroid malignancy. Combined cytoplasmic, nuclear, and background features in the FNAB smears of SNTGs are usually sufficient to render a diagnosis of malignancy in most cases. In our cohort, approximately 33% of SNTGs exhibited at least focal tumor necrosis, and high-grade nuclear features were identified in a majority of our cases. The high-grade nuclear atypia observed in most SNTGs is sufficient to differentiate them from the most common primary thyroid malignancies, including PTC, follicular thyroid carcinoma, PDTC, and medullary thyroid carcinoma. Nevertheless, there is significant overlap with UTC, which arises in an age group similar to that of patients with SNTGs and also exhibits hypercellularity, malignant nuclear features, and background necrosis.[59] Immunocytochemistry with thyroglobulin and TTF-1 often is not useful to support a diagnosis of UTC, because both are frequently lost in UTC. In contrast, the expression of PAX-8, a transcription factor involved in thyroid function and differentiation, is retained in most UTCs (76%)[60,61] and, thus, is most useful for identifying UTC. The caveat is that PAX-8 is also expressed in some cancers of extrathyroid origin, including RCC.[62] The presence of a concurrent, well differentiated thyroid carcinoma component (eg, PTC), a dimorphic population of cells, and/or a neutrophilic infiltrate may be helpful cytologic clues for UTC.[59,63]

Benign-appearing follicular cells were identified in 20.51% of SNTGs in our cohort. Although follicular cells may be more likely to be admixed in SNTGs that present as multiple, discrete nodules rather than as a large, solitary nodule, we were not able to identify a correlation between the presence of follicular cells in FNABs of SNTGs and the size or number of SNTG nodules in our cohort. The frequent occurrence of follicular cells in FNABs of SNTGs may be explained by the predominant interstitial pattern of infiltration of the thyroid parenchyma (ie, in between normal follicles) by SNTGs, as described by Rosai et al,[5,38] or by the excursion of the fine needle into surrounding "normal" thyroid parenchyma.

SCC was among the most common SNTG in our series and was accurately diagnosed in 96% of cases. SCC involving the thyroid gland may represent direct extension of a laryngeal or tracheal SCC, a metastasis from a distant site, a primary SCC of the thyroid gland, or a component of UTC.[64,65] All of these forms of SCC involving the thyroid gland are associated with a very poor prognosis, but primary thyroid SCC either alone or as part of UTC is the least common and is associated with the worst prognosis (median survival, <6 months).[65] Because cytomorphology alone cannot establish the primary site of origin of SCC, detailed clinicoradiologic correlation is required. In addition, when formalin-fixed, paraffin-embedded cell block material is available, PAX-8 immunostaining can be applied, because subsets of primary thyroid SCCs and UTCs are positive for this marker.[65] A cytologic diagnosis of SCC secondarily involving the thyroid gland is usually straightforward,[3] because most patients have a history of extrathyroid SCC.[64] In our FNAB series, only 1 SCC case, which was diagnosed as a high-grade carcinoma, raised a differential diagnosis with a primary thyroid tumor.

FNAB Cases of SNTG With Diagnostic Difficulty

In accord with observations by others, metastatic RCC was the most common pitfall in our series, in that it was misdiagnosed as a follicular neoplasm in 3 of 9 cases. This is particularly problematic when metastatic RCC presents as a solitary thyroid nodule many years after nephrectomy or for cases in which the cytopathologist is unaware of the history of RCC.[32] In our cohort, 1 metastatic RCC to the thyroid gland occurred 12 years after the patient underwent primary nephrectomy for cancer. Both cytologically and histologically, metastatic RCC, with its uniform pattern of cells, low-grade to intermediate-grade nuclear features, and oncocytic cytoplasm, can be difficult to distinguish from a primary Hurthle cell tumor, with which RCC shares many cytomorphologic features.[66] If a differential diagnosis of metastatic RCC is considered, then ancillary markers can be used effectively, because RCCs typically are immunocytologically positive for RCC antigen, CAIX,[67] and CD10 and negative for thyroglobulin and TTF-1. In contrast to the differential diagnosis of primary versus metastatic SCC, PAX-8 is not useful for the distinction between an RCC and a Hurthle cell neoplasm, because it is expressed in both.[62]

Secondary AdCC, whether a metastasis to the thyroid or a direct extension from the upper respiratory tract, is very rare.[33,50,68] Two of 3 AdCCs in our series were misinterpreted as PTC and PDTC, respectively. The diagnosis of secondary AdCC in the thyroid gland is further complicated by the recently described adenoid cystic pattern of some primary thyroid tumors, including PTC[51,53,54,69] and PDTC.[55] In contrast to AdCC, PTC with an adenoid cystic pattern exhibits the classic nuclear features of PTC rather than hyperchromatic nuclei. Furthermore, ancillary markers for AdCC, including thyroglobulin, PAX-8, and TTF-1 for PTC, and CD117, and MYB, can be useful.[51,52,70]

Molecular Studies for the Diagnosis of SNTG in FNAB

To our knowledge, the value of gene expression classifier tests like Afirma (Veracyte, South San Francisco, Calif) as an ancillary test for diagnosing SNTG in thyroid FNAB has not been evaluated to date. It is noteworrhy that, in 1 of our cases of RCC that was diagnosed as malignant, an Afirma test was performed and was reported as "suspicious" with a comment that the genetic signature identified was similar to that observed in RCC. Because of the rarity of SNTG, however, it will be difficult to assess the value of the Afirma test for this purpose in prospective or retrospective studies. In addition, these molecular tests are significantly more costly than a panel of immunostains, which usually can solve problematic cases and may be performed retrospectively on archival material.

Limitations

Our study has several limitations. Most patients who were included in our cohort had FNAB material and the primary tumor available for histologic comparison at the time of the review. When patients were not in a palliative

clinical setting, some of them also had corresponding thyroid histology available. In a small subset of patients, however, there was no cytohistologic material available for review, and the data were extracted from the patient's files. All cases that were included in our FNAB cohort did eventually have some form of tissue confirmation of an SNTG or confirmation of a nonthyroid cancer reported to support the interpretation of an SNTG. In addition, the cytologic workup, including the use of cell blocks, ancillary studies, and corresponding tissue biopsies, was quite variable among patients in our FNAB series, in part because of the diverse sources of cases from 7 different institutions. Information regarding patient follow-up and clinical outcome was not readily available in many of the cases and extended beyond the scope of our study.

Conclusions

Overall, FNAB is a sensitive and accurate method for the detection and diagnosis of SNTGs. Adenocarcinomas originating from the kidney, lung, breast, and colon along with SCCs are the most common secondary thyroid tumors. Diagnostic difficulties occur when samples are limited (paucicellular) or when secondary tumors, such as metastatic RCC, closely mimic a primary thyroid neoplasm. Having access to an accurate and complete clinical history and the judicious use of ancillary studies in difficult cases can increase the effectiveness of FNAB for detecting SNTGs.

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