Metastases to the Thyroid

Potential Cytologic Mimics of Primary Thyroid Neoplasms

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- Secondary tumors of the thyroid gland, although uncommon, can sometimes pose as diagnostic dilemmas on fine-needle aspiration cytology, frequently mimicking primary thyroid neoplasms. An accurate diagnosis of such lesions, however, is critical for patient management and prognosis. The present study reviews the cytologic aspects of secondary involvement of the thyroid, listing the most common primary malignancies that metastasize to this gland. Knowledge of such morphologic aspects, combined with prompt clinical correlation, is essential for the cytopathologist to achieve a proper, definite diagnosis.

(Metastases to the Thyroid—Pastorello & Saieg)

Metastatic tumors to the thyroid gland are unusual, with reported incidences as low as 0.1% in various clinical series.1–4 Secondary involvement of the thyroid (SIT) can be defined either by direct extension from surrounding structures or by metastatic spread from distant organs. A precise diagnostic evaluation of these cases is essential, as confirmed metastatic disease has crucial implications for clinical management and prognosis.5 Fine-needle aspiration cytology (FNAC) has proven in the past decades to be a safe, minimally invasive, accurate, and cost-effective diagnostic technique.6 In an appropriate clinicoradiologic setting, FNAC can play a key role in the diagnostic workup of metastatic neoplasms to the thyroid. Knowledge of cytologic features of these secondary lesions by the pathologist is critical to avoid false-negative diagnoses as well as to distinguish them from primary thyroid neoplasms. In the present study, we review the main cytologic aspects of SIT from the primary malignancies that most commonly metastasize to the thyroid gland.

CLINICAL OVERVIEW

Although the majority of thyroid nodules found in patients with known nontyroidal primary malignancies are benign, 17% can still be metastatic.7 In rare cases, SIT can also present as the first manifestation of a primary malignancy elsewhere.1 Adenocarcinomas from the kidney, breast, and lung, along with squamous cell carcinomas (mainly of head and neck, esophageal, and lung origin), represent the most common cancers associated with SIT. Malignant melanoma (MM) and carcinomas from the colon, stomach, prostate, and bladder have also been described in association with secondary involvement of the gland in a lesser percentage of cases.2,5,8 The presence of metastatic lesions to the thyroid usually indicates a poor prognosis, and it appears that most patients die shortly after the diagnosis.9,10 In such instances, treatment decisions should be individualized, as the impact of thyroidectomy in patients’ overall prognosis is limited.3,5

Women seem to be more affected by SIT, with a female to male ratio of 1.13:1 and a mean age within the sixth or seventh decade of life.3,4,11 The majority of these metastases are not synchronous, with rare cases being reported up to 24 years after the primary lesion diagnosis.12,13 Clinically evident SIT can present as a palpable mass (more than 70% of patients), vocal cord palsy, or thyroid dysfunction. On the other hand, a small subset of patients can be asymptomatic and show an incidentally detected thyroid lesion on imaging studies.5,14 As a matter of fact, incidental nodules are becoming more and more common, as positron emission tomography–computed tomography whole-body analysis is becoming standard of care and these thyroid nodules may often present with high standardized uptake values upon imaging.15

A new thyroid mass in a patient with a known history of a previous nontyroidal malignancy should raise the suspicion of SIT.2 Although imaging can be helpful in the diagnostic workup of these cases, radiology alone cannot be used conclusively to distinguish primary from secondary lesions, as findings are usually nonspecific. On ultrasound, SIT is usually represented by single or multiple nodules with ill-defined hypoechoic character, usually without evidence of microcalcifications.16,17 Fine-needle aspiration cytology can be of great value in these cases, providing a safe, rapid, and accurate diagnostic tool.3,5,10

FINE-NEEDLE ASPIRATION CYTOLOGY

According to major series published in the literature, aspiration cytology plays an important role in correctly assigning SITs as malignant and in great part also in accurately subtyping them according to their primary site.8,10,12,14 The cytologic pattern of SIT is affected mainly
by the type of the primary malignancy and the extent of thyroid involvement. Focal metastatic lesions may show an admixture of malignant cells and normal follicular cells, whereas diffuse SIT may yield a cytologic sample composed solely of malignant cells. Detection of atypical cells not conforming to criteria described for primary thyroid tumors should always raise the suspicion for SIT. It is also noteworthy that primary thyroid carcinomas are usually low-grade neoplasms, and the presence of frank atypia should always raise the suspicion of a metastatic mass. Although the importance of having the patient’s clinical history for an accurate diagnosis cannot be overemphasized, the pathologist must be familiar with the cytologic features of the most common primaries associated with SIT. 8,18 Furthermore, rapid on-site evaluation can also be of great value in such cases. Proven to significantly improve specimen adequacy, rapid on-site evaluation also allows the cytopathologist, in any suspicion of SIT, to collect material for a cell block preparation on which ancillary studies can be performed in order to confirm the secondary nature of these lesions, a technique not usually performed for routine thyroid nodule aspirations.19

**Figure 1.** Metastatic renal cell carcinoma, clear cell type. A, On fine-needle aspiration cytology, malignant cells have abundant and vacuolated clear cytoplasm with hyperchromatic nuclei and occasional conspicuous nucleoli (smear). B, On thyroidectomy, the neoplasm is composed of clear cells with solid alveolar pattern and typical vessel formation. The neoplastic cells are positive for PAX8 (C) and negative for TTF-1 (D) on immunohistochemistry (Diff-Quik, original magnification ×1000 [A]; hematoxylin-eosin, original magnification ×200 [B]; original magnification ×200 [C and D]).

**Metastatic Renal Cell Carcinoma**

In multiple series, renal cell carcinoma (RCC) was the most common malignancy implicated in SIT.2,3,5,12 Interestingly, in comparison with other primaries, these tumors have been reported to be the most frequently associated with diagnostic pitfalls on FNAC, as their cytologic features commonly overlap with those of a Hurthle cell neoplasm or even macrophages.8

Samples from metastatic RCC usually show at least moderate cellularity, represented by large epithelial cells, mainly arranged in sheets or tridimensional clusters in a bloody background. Cytoplasm is often abundant and is slightly granular and acidophilic to clear, commonly resembling a Hurthle cell. Nuclei may exhibit mild to moderate hyperchromasia and pleomorphism, with distinct nucleoli (Figure 1, A).8,13,20,21

The distinction between SIT by RCC and Hurthle cell neoplasms can be aided with the use of ancillary techniques (Figure 1, B through D). An immunocytochemical (ICC) panel including thyroid transcription factor 1 (TTF-1) and thyroglobulin (thyroid markers) combined with CD10, RCC

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antigen, and carbonic anhydrase IX (CAIX) (RCC markers) has been suggested to help in such cases. In addition, in recent consensus guidelines, PAX2 and/or PAX8 were considered the most useful markers in the diagnosis of metastases of renal origin. Care should be taken, however, when interpreting such markers. CD10, for instance, can show variable expression in papillary thyroid carcinomas as well as tumors from adrenocortical origin. Likewise, PAX8 can be frequently positive in primary thyroid neoplasms. Therefore, ICC stains should always be interpreted as a panel and in light of clinical data (Table).

### Metastatic Breast Carcinomas

Breast carcinomas are among the most frequent tumors associated with SIT, representing up to 22% of cases, with invasive ductal carcinomas being the most frequent subtype. Smears from metastatic breast carcinomas are usually slightly to moderately cellular, often constituted by an admixture of malignant cells and rare benign follicular cells in a hemorrhagic background with scant colloid. The metastatic cells can be arranged singly or in small groups and show some nuclear enlargement, with clumped chromatin and occasional prominent nucleoli (Figure 2, A and B). On air-dried Romanowsky-stained smears, the presence of “magenta bodies” (purple cytoplasmic inclusions) can be of diagnostic utility. In moderately cellular samples with slight nuclear atypia, the cytologic features of metastatic breast carcinomas might overlap with those of a follicular neoplasm. Immunostaining for thyroid markers combined with GATA-3, mammaglobin, and estrogen/progesterone receptors has been suggested to aid in the differential diagnosis. Again, caution should be exercised when evaluating ICC markers alone. GATA-3, for example, can also be commonly expressed in a wide range of other entities, including squamous cell carcinoma, intra- thyroid parathyroid proliferations, and cervical parangliomas. Therefore, this stain should be interpreted among a panel of other confirmatory markers (Figure 2, C and D). As with parathyroid neoplasms and cervical parangliomas, for example, the addition of parathyroid hormone and chromogranin-A in the ICC panel can be of great utility. Routine use of GATA-3 with other markers of breast origin, that is, GCDFP15 and mammaglobin, is also advisable. Recently, lack of PAX8 expression and positivity for GATA-3 were also defined in solid cell nests, common ultimobranchial body remnants that can sometimes present with hyperplastic proliferations in the thyroid gland.

### Metastatic Malignant Melanoma

Malignant melanomas are known for the ability to metastasize to almost any organ and for a wide range of histologic presentations. These tumors represent around 4% of all primaries associated with SIT. Cytologic samples of metastatic MMs to the thyroid often resemble the morphologic aspect of the primary tumor, and cytology can be therefore highly variable. Smears are usually cellular, characterized by single or loosely clustered malignant cells, sometimes admixed with few background residual follicular cells. Metastatic cells can assume different appearances, including plasmacytoid, spindle shaped, and/or epithelioid. Nuclei are usually enlarged, often exhibiting large nucleoli and cytoplasm can be abundant and granular (Figure 3, A through C). The presence of intracytoplasmic melanin granules can help in the evaluation of such cases, but that is, unfortunately, not a common finding. Distinction of MMs from primary thyroid neoplasms can be sometimes challenging. Some MMs have been reported to present with a somewhat papillary architecture and irregularly indented clear nuclei with grooves, as well as intranuclear cytoplasmic inclusions, findings suggestive of papillary thyroid carcinoma. Immunocytochemical staining with thyroglobulin and TTF-1 combined with melanocytic markers is of great utility.

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markers, for example MART1 (melanoma antigen recognized by T cells 1), HMB-45 (human melanoma black 45) (Figure 3, D), S-100 protein, and microphthalmia transcription factor (MITF), can be useful in these cases.35,36 Undifferentiated (anaplastic) thyroid carcinoma (UTC) can be difficult to distinguish from MM. These 2 lesions affect the same age group and can present as cellular smears with pleomorphic discohesive cells. It is also noteworthy that both neoplasms can be negative for thyroglobulin on ICC. The use of PAX8 staining can be of great help in such cases, as this marker was reported to be positive in up to 76% of undifferentiated (anaplastic) thyroid carcinomas and consistently negative in melanomas.25,37 Melanocytic markers can also aid in such distinction.4,5,8,17,33

Lastly, medullary thyroid carcinomas (MTCs) should also be included in the differential diagnosis when evaluating cases suspicious for SIT by MM. Although rare, the pigmented variant of MTC can present with findings overlapping those of MM, including focal positivity for HMB45. In contrast to MMs, however, MTCs are usually immunoreactive for TTF-1 and calcitonin.38 Calcitonin-negative MTCs have, however, been reported in the literature.39 Taking these rare cases into account, staining for CGRP (calcitonin gene–related peptide) and monoclonal CEA (carcinoembryonic antigen) can be of diagnostic utility, as these markers are expressed in most MTCs.40,41

Metastatic Sarcomas

A significant rise in the number of reported sarcomas metastatic to the thyroid has been shown in a recently published series, in contrast to earlier studies. According to the authors, shifts in the latest editions of the World Health Organization classification of tumors as well as improvement in diagnostic techniques might have contributed to this. Metastatic sarcomas to the thyroid can show a wide spectrum of cytologic presentations, as these tumors represent a large and heterogeneous group of neoplasms. Knowledge of the patient’s clinical history is essential, as cytopathologic features often mirror those from the primary tumor. It is noteworthy, though, that not all spindle cell proliferations on thyroid FNAC should be regarded as metastatic sarcomas. Undifferentiated and anaplastic thyroid carcinomas and MTCs, as well as metastatic metaplastic carcinomas (Figure 4, A and B) and melanomas, can often
Figure 3. Metastatic malignant melanoma. A, Cellular sample constituted by discohesive malignant cells in a bloody background (smear). B, Higher magnification shows atypical cells with occasional nuclear inclusions, a potential mimic of papillary thyroid carcinoma (smear). C and D, Previously resected nasal mucosa neoplasm constituted of sparsely pigmented epithelioid cells, positive for HMB45 (D), reported as mucosal melanoma (hematoxylin-eosin, original magnifications ×200 [A and C] and ×1000 [B]; original magnification ×200 [D]).

Figure 4. Metastatic metaplastic carcinoma of the breast, spindle cell type. A, Loosely arranged large atypical cells with spindle cell morphology in a bloody background. B, Previously resected breast neoplasm exhibits atypical spindle cells arranged in a storiform pattern (hematoxylin-eosin, original magnification ×200).
show spindle-cell cytology. An ICC panel including smooth muscle actin (SMA), desmin, S100, CD34, calcitonin, and cytokeratin pool AE1/AE3 combined with thyroid and melanocytic markers may aid the differential diagnosis in such instances.34,42,43

CONCLUSIONS

Metastases to the thyroid gland, although rare, may sometimes pose as diagnostic dilemmas and eventually lead to unnecessary surgery or, even worse, undertreatment of a metastatic disease. Thyroid FNAC, along with certain ancillary techniques, can be a safe, rapid, and accurate diagnostic tool in the evaluation of secondary tumors of this gland. However, metastatic malignancies may sometimes mimic primary thyroid neoplasms on cytology and cause potential diagnostic dilemmas. In this scenario, prompt correlation to clinical history, along with rapid on-site examination ensuring material is properly triaged, is essential to achieve a definite diagnosis on cytologic material. As primary and secondary lesions have different implications in handling and prognosis, it is crucial for the pathologist to be aware of the main cytologic features associated with both entities, in order to achieve the best possible clinical management of the patient’s current disease.

References