Thyroid carcinomas are infrequent compared to malignancies arising in other body sites or organs, comprising less than 1% of all cancers diagnosed in the United States. Most primary thyroid carcinomas are low-grade, well differentiated, and follow a protracted clinical course with excellent prognosis. Although cervical lymph node metastases are common with papillary carcinomas, distant metastases of differentiated thyroid cancer are infrequent and reported to be in the range of 7% to 23%. The great majority of metastatic thyroid cancers offers little diagnostic difficulties, but on occasions may cause diagnostic dilemma.

The pattern of spread differs with the type of thyroid cancer. They also have different predilections for metastatic sites. For example, anaplastic carcinomas are known for extensive local as well as widespread involvement of the multiple organs and sites. Metastasis to distant organs such as lungs, bones, liver, and brain are more frequent with follicular, poorly differentiated, or insular, medullary, and Hürthle cell carcinomas and less frequent with papillary carcinomas. On the other hand, cervical lymph node metastases are extremely common with papillary carcinomas but can also occur with Hürthle cell, medullary, and anaplastic carcinomas. Involvement of the serous membranes with effusions is associated with papillary and anaplastic carcinomas and not documented with other types of thyroid cancers.

The metastatic involvement of different body sites by primary thyroid carcinomas can be observed in one of the several settings described here:

1. A known history of thyroid cancer with a clinical diagnosis of local or distant metastasis at a later date. A new disease process or a neoplasm in the organ suspected of involvement by the metastatic thyroid cancer is often a possibility, which must be ruled out (Fig. 15.1).
2. Patients present with a palpable thyroid mass associated with cervical lymphadenopathy. This pattern is more frequent with papillary and medullary thyroid carcinomas. Sometimes both sites are biopsied simultaneously, with the thyroid biopsy offering nondiagnostic results. In such instances, the thyroid origin must be determined (Fig. 15.2).
3. Recurrent thyroid cancer at the thyroidectomy site, a frequent occurrence with Hürthle cell carcinomas (Fig. 15.3).
4. The patient presents with metastatic thyroid malignancy at a distant site with subsequent discovery of a palpable thyroid nodule. These thyroid cancers are generally silent. The patient presents with signs and symptoms related to the site of metastasis, such as bone pain, weakness, hemoptysis, and cough (Figs. 15.4 to 15.7).

**FIGURE 15.1.** A, B. Recurrence/metastasis versus a different neoplastic process metastatic papillary carcinoma. Smears of bronchial brushings from a patient with a history of papillary thyroid carcinoma, who presented with hemoptysis 4 years later. The morphology of these malignant cells is consistent with metastatic papillary carcinoma. Since both carcinomas will be reactive to TTF-1, immunostaining with thyroglobulin is recommended to rule out primary adenocarcinoma of the lung. C, D. Bronchial brushings from a woman in her thirties with a history of papillary thyroid carcinoma resected several years earlier, who now presented with obstructive pulmonary symptoms. Bronchoscopy was done to rule out metastatic carcinoma. A lesion was found in the bronchus. The neoplastic cells are forming syncytial tissue fragments. Their cytoplasm is scanty, and the nuclear chromatin is very granular. A cytologic diagnosis of carcinoid tumor was made and confirmed by lobectomy. E. FNA of a mediastinal mass suspected of metastatic carcinoma, in a 58-year-old woman with thyroidectomy, 6 years earlier for papillary carcinoma. The aspirate shows a large population of immature plasma cells, suggesting a diagnosis of multiple myeloma, which was later confirmed.
FIGURE 15.2. Simultaneous aspiration biopsies of thyroid nodule and cervical lymph node. This patient had a palpable thyroid nodule and cervical lymphadenopathy. Fine-needle aspiration biopsy of the thyroid was unsatisfactory. A, B. Aspiration biopsy of the cervical lymph node showing cells with cytomorphology consistent with medullary carcinoma. C. Histologic section of the thyroidectomy showing medullary carcinoma. Metastases were present in the lymph nodes.

FIGURE 15.1. (Continued)
usually associated with cervical lymphadenopathy with extensive cystic change (Fig. 15.8). The cystic metastasis may be misinterpreted clinically as branchial cleft cysts. Occult thyroid carcinomas with distant metastases are rare.

6. Previous needle biopsy or surgery for a thyroid lesion misinterpreted as benign and metastasis occurring at a later date (Fig. 15.9).
FIGURE 15.6. Silent thyroid malignancy presenting with distant metastases. Poorly differentiated “insular” carcinoma presenting as a pulsatile mass involving the sternum in a 69-year-old woman. The patient was later found to have a large thyroid mass. A. FNA of the thyroid showing a syncytial-type tissue fragment of small follicular cells with enlarged, crowded nuclei consistent with the diagnosis of insular carcinoma. B. Imprint of the resected sternal mass with cells similar to those seen in thyroid carcinoma.

FIGURE 15.7. Silent thyroid malignancy presenting with distant metastases. A 65-year-old man with a low-grade prostate adenocarcinoma was found to have multiple lung nodules and a large pleural effusion on CT scan during the follow-up examination. The scan also revealed a superior mediastinal mass extending superiorly and involving the left lower pole of the thyroid. The serum PSA (prostate-specific antigen) levels were within normal limits. A. These smears from the aspirated pleural fluid show malignant cells in syncytial tissue fragments with an acinar pattern. B. These malignant cells demonstrate large cytoplasmic vacuoles. Note the intranuclear inclusion (arrows). C. Positive reactivity to TTF-1 supports both the lung adenocarcinoma and thyroid papillary carcinoma. D. Positive reactivity to thyroglobulin confirms the thyroid origin. E. Histologic section of a 1-cm papillary carcinoma which infiltrated the extrathyroidal soft tissues.
7. The metastasis from a differentiated thyroid cancer may dedifferentiate into insular or anaplastic types (Fig. 15.9) and may require extensive workup to determine the primary source.

The following paragraphs describe the cytologic features of metastatic thyroid cancers of different histologic types in different organs or sites and their differential diagnosis.

**LYMPH NODES**

Papillary thyroid carcinomas show a great propensity for cervical lymph node involvement, estimated to be in the range of 46% to 47%. This involvement may be ipsilateral, contralateral, or bilateral. The metastatic process may also involve the mediastinal lymph nodes. A lateral neck mass or a cervical lymphadenopathy is the initial presenting sign in about 21% of papillary thyroid carcinomas. A few are associated with occult lesions few millimeters in size, neither palpable nor detectable on imaging or ultrasound (Fig. 15.8). A fine-needle biopsy of the enlarged lymph nodes involved by papillary carcinoma offers an accurate diagnosis, especially when the lesion is solid, but tends to be a diagnostic problem with cystic degeneration. Clinically, cystic lesions in the lateral neck are often diagnosed as branchial

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**FIGURE 15.7.** (Continued)
Immunostainings with thyroglobulin are often confirmatory. False-negative diagnoses are frequent with extensive cystic degeneration (refer Chapter 17).

It must be realized, however, that not all papillary carcinomas in cervical lymph nodes are thyroidal in origin. The differential diagnoses for metastatic papillary carcinomas include primary sites such as lungs, kidneys, or ovaries. Metastatic renal cell carcinomas in cervical lymph nodes have been interpreted as papillary thyroid carcinoma from the cytologic samples obtained by fine-needle biopsy, with negative findings in subsequent thyroidectomies. Immunostaining for thyroglobulin in these cases were nondiagnostic. This author’s experience with metastatic papillary cystadenocarcinoma of the ovary interpreted as metastatic papillary thyroid cancer, is illustrated in Figure 15.10. Thyroidectomy had failed to confirm the papillary carcinoma. The tumor subsequently recurred in the neck and was aspirated, which showed a cytologic pattern inconsistent with the primary thyroid. A history of ovarian cystadenocarcinoma was later made available. Pulmonary adenocarcinomas metastatic to the cervical lymph nodes also present a cytologic pattern identical to that of papillary thyroid carcinomas, including psammoma bodies. Both papillary thyroid carcinomas and pulmonary adenocarcinomas react
positively to TTF-1; however, papillary thyroid carcinomas will react to thyroglobulin.

Medullary thyroid carcinomas frequently metastasize to the cervical lymph nodes (Fig. 15.2). Occasionally, cervical lymphadenopathy may be the presenting sign. A characteristic pleomorphic cell pattern in cytologic samples obtained by fine-needle biopsy offers a correct diagnosis (see medullary carcinoma, Chapter 12). However, a monomorphic pattern with small cells may mimic a small cell carcinoma. Cervical paraganglioma must also be considered with large polyhedral cells. Positive immunostaining for calcitonin and increased serum calcitonin levels will support the diagnosis of medullary carcinoma. The involvement of cervical lymph nodes by follicular carcinoma is an exceptional event.

Hürthle cell carcinomas may involve the cervical lymph nodes but rarely present as an initial sign. Local recurrences are very frequent with Hürthle cell carcinomas (Fig. 15.3). Poorly differentiated or insular carcinoma and anaplastic thyroid carcinoma do metastasize to the cervical lymph nodes and are no diagnostic problems.

**RESPIRATORY SYSTEM**

With generalized, widespread involvement, lungs are frequent sites for metastatic anaplastic carcinomas and, less frequently, from insular carcinomas, Hürthle cell, follicular and medullary carcinomas.

Pulmonary involvement in differentiated thyroid cancers (follicular and papillary) is reported to be 10% for follicular carcinomas and 2% to 14% for papillary carcinomas. Metastases to the lungs denote advanced disease. Rarely do thyroid carcinomas initially manifest with signs and symptoms of pulmonary involvement. These range from cough, hemoptysis, fever, and pleural effusion to opacities in lung fields on chest x-rays. Both miliary infiltrates and macronodular densities have been described. Direct extension into the trachea may occur. Metastatic thyroid cancer can be identified from cytologic samples such as sputum, bronchial brushings and washings, transbronchial or transthoracic percutaneous fine-needle biopsy (Figs. 15.11 to 15.13), and pleural fluid (Fig. 15.7). Primary lung cancer must be ruled out when papillary carcinoma is identified from the respiratory specimens, since primary lung cancers are more common than metastatic...
thyroid cancers. Follicular carcinomas also spread to the lungs (Fig. 15.14), and with poorly differentiated types, ancillary studies are needed to confirm the diagnosis. Hürthle cell carcinomas are known to involve the lungs. When occurring as an endobronchial lesion (Fig. 15.15A), Hürthle cell carcinomas (Fig. 15.15A, B) may be difficult to differentiate from granular cell tumor since both show cells with abundant granular cytoplasm (Fig. 15.15C).

Medullary carcinomas may metastasize to the lungs (Fig. 15.16A). With a spindle cell pattern, medullary carcinoma must be differentiated from a spindle cell carcinoïd tumor of the lung (Fig. 15.16B).

**BODY CAVITY FLUIDS**

Metastatic thyroid cancers are rarely encountered in body cavity fluids. Among the thyroid cancers, anaplastic and papillary carcinomas tend to metastasize to the pleural cavities (Figs. 15.7, 15.17 to 15.19). Their cytologic presentation may cause some diagnostic difficulties, as the fluid medium may initiate regressive changes such as marked cytoplasmic vacuolization, resulting in considerable deviation from the usual cytologic patterns. Also, papillary carcinoma in pleural cavities must be differentiated from either primary lung adenocarcinomas or papillary carcinomas from other body sites.

**SKELETAL SYSTEM**

The skeletal system is a frequent site for metastatic thyroid cancer, especially follicular, Hürthle cell, insular, and anaplastic types. The incidence is reported to be 9%. The osseous lesions are often osteolytic, involving long bones as well as flat bones such as the pelvis and sternum. Pulsatile lesions are described as a characteristic
feature of metastatic follicular carcinomas to the bones. The presenting signs and symptoms include bone pain and weakness, and pathologic fractures may occur. The metastatic tumor may extend into the adjacent soft tissues. Fine-needle biopsy is a helpful diagnostic technique (Figs. 15.4 to 15.6, 15.20) but may present interpretative difficulties if the tumor is less differentiated.

**FIGURE 15.16.** A. FNA of a metastatic medullary thyroid carcinoma to the lung. Note the intranuclear cytoplasmic inclusions (arrow). B. FNA of a spindle cell carcinoid tumor of the lung demonstrating morphologic similarity to the medullary carcinoma cells.

**FIGURE 15.17.** Anaplastic carcinoma metastatic to the pleura. A–D. Bizarre isolated malignant cells in pleural fluid. E. Cell block preparation of the pleural fluid showing similar malignant cells.

**FIGURE 15.18.** A, B. Papillary carcinoma metastatic to the pleura. The carcinoma cells in pleural fluid have bizarre nuclei and marked cytoplasmic vacuolization resembling mucin-producing adenocarcinoma. The Alcian blue stain on the cell block preparation did not reveal the presence of mucin, indicating that the cytoplasmic vacuoles represent degenerative changes in the fluid medium.
rare and uncommon sites such as uvea, skin, spleen, parotid gland, and urinary bladder have been reported. A case of metastatic medullary carcinoma metastasizing to the thigh seen in consultation is illustrated in Figure 15.21.

**SUMMARY**

Majority of the thyroid cancers are of differentiated type and metastasize to distant organs only infrequently. Cervical lymph node involvement is common with papillary carcinomas. A history of thyroid cancer is necessary for correct identification of a metastatic tumor and can be confirmed by immunostains such as thyroglobulin, TTF-1, or calcitonin, especially in the presence of overlapping patterns.

**REPORTING CYTOLOGIC FINDINGS**

*Author Recommendations/BSRTC:*

- **Malignant, Specified Site:** Consistent with metastatic thyroid carcinoma.

- **Malignant, Specified Site:** Consistent with metastatic medullary carcinoma. Immunoreactive to calcitonin.

**FIGURE 15.19.** A. Metastatic papillary carcinoma in pleural fluid showing a syncytial tissue fragment with a psammoma body. B. Different example of metastatic papillary carcinoma in pleural fluid from a patient with a history of thyroid carcinoma. Note the marked cytoplasmic vacuolization and intranuclear cytoplasmic inclusion.

**FIGURE 15.20.** FNA of metastatic follicular carcinoma to the bone. A. Low power showing a cellular aspirate composed of syncytial tissue fragments of malignant cells with a follicular pattern. B. Higher magnification highlighting the neoplastic follicles with enlarged nuclei (Romanowsky stain).

**FIGURE 15.21.** Metastatic medullary thyroid carcinoma to the thigh. (Courtesy of Ami J. Walloch, MD, and Rashead Hammadeh, MD, Christ Hospital, Oaklawn, IL.)

**MISCELLANEOUS SITES**

Other organs or sites involved less frequently by thyroid cancer include the breast, the liver, and the central nervous system. Single case reports of various types of thyroid cancers involving
REFERENCE


SUGGESTED READINGS


