Title: Fine needle aspiration cytology of metastatic spindle cell follicular thyroid carcinoma: A case report

Short title: FNA of spindle cell follicular thyroid carcinoma

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ABSTRACT

Follicular thyroid carcinoma, spindle cell variant is extremely rare. The tumor is predominantly composed of spindle cells with a fusiform appearance that are arranged in intersecting fascicles. Fine needle aspiration biopsy of this entity has not been previously described. We report a case of a 58-year-old woman who presented with metastasis to a left neck lymph node 15 years after the original diagnosis. Fine needle aspiration cytology showed numerous bland, spindled to epithelioid cells with thin, elongated and plump nuclei with finely granular chromatin and inconspicuous nucleoli. The tumor cells had a moderate amount of cytoplasm with occasional elongated cytoplasmic tails. The cells were arranged in irregular aggregates with a fascicular pattern or singly dispersed. The tumor cells demonstrated positive staining for pan-keratin, PAX8, TTF-1 and thyroglobulin, which confirmed thyroid primary origin.

Keywords: spindle cell, thyroid follicular carcinoma, cytology, fine needle aspiration

INTRODUCTION

Spindle cell lesions of the thyroid gland are unusual and include reactive versus neoplastic processes. They may be derived from the follicular cells, C-cells, or mesenchymal components. The differential diagnosis includes post-fine needle aspiration (FNA) spindle cell nodule of the thyroid, Riedel thyroiditis, the fibrous variant of Hashimoto thyroiditis, solitary fibrous tumor, smooth muscle tumors, peripheral nerve sheath tumors, hyalinizing trabecular tumor, spindle epithelial tumor with thymus-like differentiation (SETTLE), carcinoma showing thymus-like differentiation (CASTLE), and the spindle cell variants of papillary, follicular, medullary, anaplastic, and squamous cell carcinoma.[1,2] Among these, the spindle cell variant of follicular thyroid carcinoma is extremely rare and only a few cases have been

reported, in which nearly all the tumor cells were spindle-shaped and arranged in an intersecting fascicular pattern. The cells are positive for keratin, thyroglobulin and thyroid transcription factor 1 (TTF-1).[2-4] FNA cytology of follicular thyroid carcinoma, spindle cell variant has not been reported previously.

CASE REPORT

The patient is a 58-year-old woman with a history of hypothyroidism and thyroid cancer who presented with enlarged left neck lymph nodes. She underwent thyroidectomy for a goiter 15 years prior at an outside hospital and a 3 cm thyroid cancer was found incidentally. The final pathology report was finalized as "low grade malignant neoplasm with features of follicular carcinoma, spindle cell variant" with capsular and lymphovascular invasion. She underwent a completion thyroidectomy and also had radioactive iodine ablation and has been on thyroid hormone therapy ever since. Recently, she was noted to have an elevated serum thyroglobulin level of greater than 3,000 ng/mL and a head and neck ultrasound showed a 3.3 cm mass in a left level IV neck lymph node, concerning for recurrent thyroid cancer. There were no other suspicious foci within the thyroid resection bed or other neck lymph nodes. Ultrasound-guided FNA biopsy was performed with rapid on-site evaluation. Five weeks later, the patient underwent radical left neck dissection with removal of level II, level III and level IV lymph nodes. One out of 29 lymph nodes was noted to have metastatic thyroid follicular carcinoma, spindle cell variant with a 3.5 cm tumor deposit. Bilateral pulmonary nodules up to 0.9 cm were also noted at that time. FNA biopsy of one of the lung nodules was performed 11 months later, however it was hypocellular and non-diagnostic. The patient has been followed for 14 months and no additional lesions have been noted.

FNA CYTOLOGY

The Diff-Quik and Papanicolaou-stained direct smears prepared from the left neck lymph node FNA biopsy were cellular and showed numerous bland, spindled to epithelioid cells with thin, elongated and plump nuclei with finely granular chromatin and indistinct nucleoli (Fig. 1). The cells were arranged in cohesive groups with a fascicular pattern (Fig. 1A and 1B). The tumor cells contained a moderate amount of cytoplasm with occasional elongated cytoplasmic processes (Fig. 1D). Dispersed single cells with stripped nuclei were also noted. The smear background contained blood. Definitive lymphoid material was not present. The H&E-stained section cut from the cell block showed numerous cohesive groups of bland spindle cells with plump nuclei and a moderate amount of ill-defined eosinophilic cytoplasm arranged in a fascicular pattern (Fig. 2A). Mitotic activity, marked nuclear atypia and necrosis were not present on the direct smears or the cell block slide. Immunocytochemical stains demonstrated positive staining for pan-keratin, PAX8 (Fig. 2B), thyroglobulin (Fig. 2C) and TTF-1 (Fig. 2D). Stains for calcitonin and monoclonal CEA were negative in the cells of interest. These cytomorphologic and immunocytochemical features were compatible with metastasis from the patient's primary thyroid follicular carcinoma, spindle cell variant.

HISTOLOGY

Histologic examination of the left neck level IV mass showed spindle cells with plump or elongated nuclei arranged in nested, trabecular and fascicular growth patterns that were separated by delicate fibrovascular septa (Fig. 3A). The tumor cells contained oval to elongated nuclei with finely granular chromatin (Fig. 3B). There was no nuclear clearing, intranuclear pseudoinclusions or diffuse grooves identified. Mitoses were rare, and measured up to 2 per 10 high power fields. No tumor necrosis was seen. Immunohistochemical stains showed that the tumor cells were diffusely and strongly positive for TTF-1, showed patchy positivity for thyroglobulin, and were negative for calcitonin, chromogranin, p63

and S-100. These findings were also consistent with metastatic follicular thyroid carcinoma, spindle cell variant.

MOLECULAR STUDIES

A limited panel of molecular studies was performed on a formalin-fixed paraffin-embedded block from the resection specimen. The tumor cells were negative for *BRAF* and *KRAS* mutations, but were positive for the *NRAS* G12D mutation.

DISCUSSION

The differential diagnosis of spindle cell lesions in lymph nodes includes reactive granulomatous lymphadenitis, inflammatory myoblastic tumors, follicular dendritic cell tumors and metastatic tumors (including sarcoma, carcinoma and melanoma). The metastatic tumors could be low grade, consisting of spindle cells arranged in a fascicular pattern with uniform, bland nuclei and finely granular chromatin without evident mitotic activity and necrosis, or high grade, with pleomorphic, hyperchromatic nuclei with frequent mitoses and necrosis. Clinical history is crucial for further classification of these tumors. In our case, the cytology specimen showed numerous bland, spindled to epithelioid cells with thin, elongated or plump nuclei with finely granular chromatin and indistinct nucleoli. The tumor cells were arranged in cohesive groups with a fascicular pattern and contained a moderate amount of cytoplasm with occasional elongated cytoplasmic processes. No necrosis and only rare mitoses were noted. The cellular features suggested a low-grade malignant neoplasm. The patient had a history of thyroid cancer 15 years prior and was treated with total thyroidectomy and radioactive iodine. Although unusual for spindle cell morphology in thyroid cancer, we did consider the possibility of a spindle cell neuroendocrine tumor (medullary thyroid carcinoma or carcinoid tumor of the lung), sarcoma,

melanoma, and spindle cell carcinoma. A panel of immunohistochemical stains was performed. The tumor cells were positive for pan-keratin, PAX8, TTF-1 and thyroglobulin and were negative for calcitonin, S100, p63, chromogranin and monoclonal CEA. The positive staining for pan-keratin and the negative staining for S100 excluded melanoma and sarcoma. Negative staining for calcitonin, chromogranin and CEA also exclude medullary thyroid carcinoma and other neuroendocrine tumors. The positive staining for PAX8, TTF-1 and thyroglobulin suggested a thyroid origin tumor with the differential including the spindle cell variant of follicular carcinoma, papillary carcinoma and anaplastic carcinoma. Anaplastic carcinoma is the most aggressive tumor of the thyroid characterized by the presence of polygonal, giant and spindle cells in variable proportions with frequent mitoses and necrosis and typically does not stain with thyroglobulin and TTF-1.[5] Our tumor is distinguished from anaplastic thyroid carcinoma because of the absence of pleomorphism, mitotic activity and necrosis. The spindle cell variant of papillary thyroid carcinoma is composed of spindle cells arranged in fascicles with a mesenchymal-like appearance, but the cells retain the classic nuclear features of papillary thyroid carcinoma (pseudoinclusions, irregular nuclear membranes, grooves).[6-7] The cytologic features of papillary thyroid carcinoma were absent in this case. Follicular dendritic cell sarcoma typically arises from lymph nodes and also consists of a spindle cell proliferation with a storiform or fascicular growth pattern. The tumor cells are positive for dendritic cell markers CD21, CD23, and/or CD35 and are negative for keratin.[8] The positive keratin staining in our tumor excludes the possibility of a follicular dendritic cell sarcoma.

Other differential diagnoses of thyroid lesions with spindle cell morphology that could be metastatic include solitary fibrous tumor, spindle epithelial tumor with thymus-like differentiation (SETTLE), and carcinoma showing thymus-like differentiation (CASTLE).[9-10] These tumors are composed of a spindle cell proliferation with fascicular or storiform architecture, but they were excluded given the positivity for

TTF-1 and thyroglobulin. CASTLE can be distinguished from other thyroid neoplasms by positive staining for CD5, high molecular weight keratin and p63.[11] Our tumor was negative for p63 and therefore was not consistent with CASTLE.

The original pathology report was finalized as “low grade malignant neoplasm with features of follicular carcinoma, spindle cell variant.” The slides of the original tumor resection were not available for review. Based on the cytomorphologic features the immunoprofile and the patient’s prior clinical history we concluded that this was a metastatic follicular thyroid carcinoma, spindle cell variant that recurred 15 years after the patient’s initial diagnosis.

The spindle cell variant of follicular thyroid carcinomas is rare and the clinical behavior is unknown. Classic follicular thyroid carcinoma typically demonstrates hematogenous metastases to bone, lung, brain and liver. Our case showed metastasis to single left neck lymph node after 15 years of remission which is unusual for classic follicular thyroid carcinoma and is much more common in cases of papillary thyroid carcinoma. However, the nuclear features of papillary carcinoma are lacking in our case. Molecular studies revealed that our tumor was positive for *NRAS* and negative for *BRAF* and *KRAS*; these findings are more consistent with follicular carcinoma. Our patient also showed multiple small pulmonary nodules, which although not confirmed by FNA were clinically concerning for metastatic disease. The clinical behavior of our case appeared to be most consistent with a low-grade follicular thyroid neoplasm.

Spindle cell proliferations in the thyroid are rare. They can be seen in cases of multinodular goiter, follicular adenoma, follicular carcinoma and papillary carcinoma.[2,6] The spindle cells consistently demonstrate strong staining for TTF-1 and thyroglobulin, which supports the follicular origin of the these cells.[2]

In summary, we report the FNA cytology findings of a case of follicular thyroid carcinoma, spindle cell variant with metastasis to a right neck lymph node. Although unusual with pure spindle cell morphology this is a relatively low-grade follicular thyroid carcinoma with expression of thyroglobulin, TTF-1, PAX8 and mutation in *NRAS* G12D.

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Figure Legends

Fig. 1 The spindled tumor cells arranged in a cohesive fascicular pattern (A, Diff-Quik stain, x200). The spindled cells contain thin, elongated, and plump nuclei with finely granular chromatin (B, Diff-Quik stain x400 and C, Papanicolaou stain, x400). There was a moderate amount of cytoplasm with occasional elongated cytoplasmic processes (D, Papanicolaou stain x400).

Fig. 2 The cell block showed cohesive fragments of tumor cells with elongated nuclei and moderate to abundant, ill-defined eosinophilic cytoplasm (A, H&E stain x400). The tumor cells were positive for PAX8 (B, x400), thyroglobulin (C, x400) and TTF-1(D, x400)

Fig. 3 Resection of the lymph node showed tumor cells arranging in a nested and trabecular growth patterns that were separated by delicate fibrovascular septa (A, H&E stain x200). Focal intersecting fascicles were noted (B, H&E stain x400)