Introduction

Spindle cell lesions of the thyroid gland are quite rare. Besides rare miscellaneous benign and malignant primary mesenchymal tumors and tumor-like lesions [1], they encompass reactive spindle cell stromal proliferations (nodular fasciitis-like areas) in papillary thyroid carcinoma [2] and spindle cell variants of medullary [3], papillary [4] follicular [5,6] and anaplastic [7] carcinoma. Furthermore, spindle cell epithelial tumor with thymus-like elements (SETTLE) represents a rare but distinctive type of primary thyroid neoplasm with spindle cell morphology and significant metastatic potential [8]. In addition, a variety of rare mesenchymal tumors and tumor-like lesions may present in the thyroid [1]. However, the occurrence of areas of bland-looking spindle cell metaplasia within benign thyroid nodules is quite uncommon and may be mistaken for a malignant or metastatic neoplasm. Some earlier reports on “atypical” variants of follicular adenoma might have represented similar metaplastic lesions [9]. We encountered two unusual benign follicular thyroid nodules (adenomas) that showed a predominance of spindle cells besides a minor follicular component and other unusual histological features that we think merit brief description. A thorough review of the available English literature revealed 14 well documented examples of this rare phenomenon [10-16]. The clinicopathological features of reported cases and our two cases are summarized in Table 1 and discussed in more details in the discussion section.

Case histories

Case 1

In 2009, a 77-year-old woman presented to the...
Spindle thyroid adenoma

surgical department of Waldkrankenhaus (Erlangen, Germany) with fatigue and difficulty with swallowing. Her medical history revealed a diagnosis of monoclonal gammopathy of unknown significance (MGUS; IgA-Kappa) since 2001 that did not necessitate medical treatment. She also has suffered from a chronic renal insufficiency (stage II; creatinine was 1.15 mg/dl). A bone marrow biopsy performed previously confirmed the diagnosis of MGUS but there was no evidence of myeloma. Ultrasound examination of the abdominal organs revealed no pathological findings. A thorough clinical workup revealed no significant abnormal findings. Ultrasonographic evaluation of the thyroid gland showed a large non-homogenous nodule 6x4x3 cm in the caudal right lobe of the thyroid extending retrosternally and displacing the trachea to the left side. A radionucleotide scintigraphy confirmed a cold nodule in the caudal right lobe. Based on suspicion of malignancy, the patient underwent bilateral thyroidectomy. She remained alive and well without evidence of recurrent disease or new neoplasms at last follow-up (2 years after surgery).

Case 2

In 2011, a 70 years old male was admitted to the Accident and Emergency department of Scarborough Hospital/ UK after he collapsed at home. He died 5 hours later in the Intensive Care Unit. He had a history of hypertension, hypercholesterolemia, left ventricular dysfunction, left nephrectomy for renal cell carcinoma in 2000 and inoperable prostatic carcinoma treated with chemotherapy in 2008. He was also diagnosed with MGUS in 2008. There was no evidence of myeloma.

At Autopsy, the left thyroid lobe was largely occupied by a 4x3 cm encapsulated tumor with dark tan cut-surface and extensive hemorrhage. The overlying thyroid capsule was intact and not infiltrated by the tumor. The right thyroid lobe looked normal.

Material and methods

Tissue specimens have been fixed in buffered formalin, embedded routinely and stained with Hematoxylin and Eosin for histological examination. In addition, representative sections have been stained with Congo Red for amyloid, Prussian blue for hemosiderin pigment and Masson-Fontana to detect melanin pigment. Immunohistochemistry was performed on 5 µm sections using a polymer Kit purchased from Zytomed (Zytomed systems Ltd., Berlin, Germany) according to the manufacturer’s instructions and the following antibodies: vimentin, pankeratin (KL1), CK18, CK5, CD117, protein S100, epithelial membrane antigen (EMA), thyroglobulin, thyroid transcription factor-1 (TTF-1), polyclonal carcinoembryonic antigen (CEA), calcitonin, synaptophysin, chromogranin A, desmin, α-smooth muscle actin, CD34, CD31, CD99, GFAP, p53, Melan A, HMB45 and Ki67/Mib1. In Case 1, electron microscopy was performed on formalin-fixed paraffin-embedded tumor tissue as described previously [17].

Results

Pathological findings: Case 1

The right lobe of the thyroid weighed 52 grams and measured 5.2 x 3.1 x 1.2 cm. An encapsulated nodule 5.5 cm in maximum diameter was seen attached to the caudal part of the right lobe. The cut-surface of this nodule was dark brown (Figure 1A). The periphery of the nodule was separated from the thyroid parenchyma by a thin capsule. Thorough histological examination (20 sections) showed a spindle cell proliferation with prominent and remarkably hyalinized blood vessels with evidence of thrombosis and recurrent bleeding (Figure 1B). There was a remarkable component of slender dendritic-like spindle cells that forms both organized fascicles and haphazardly arranged aggregates (Figure 1C), occasionally encasing blood vessels in an onion-skin pattern (Figure 1D). Several spindle cells contained granular dark pigment reminiscent of melanin (Figure 1D). This pigment was Prussian blue negative and Masson-Fontana positive suggesting melanin pigment. Amid these spindle cell areas were scattered and aggregated colloid-filled thyroid follicles (Figure 1C). Prussian blue stain displayed significant stromal hemosiderin in the interstitium and within macrophages. Congo Red stain demonstrated no amyloid deposits. Cellular atypia, coagulative necrosis, infiltrative growth and mitotic activity were absent. Immunohistochemistry revealed diffuse and strong expression of vimentin, pankeratin (KL1) (Figure 1E), cytokeratin 18, thyroglobulin (Figure 1F) and TTF-1 (Figure 1G) in both spindle cells and entrapped follicles. The spindle cells were negative for all other markers listed above in the
method section. The proliferation index (Ki67/Mib-1) was below 1% (almost zero). The left lobe showed benign nodular goiter without evidence of pigmentation or a spindle cell component. Electron microscopy on formalin-fixed paraffin embedded tumor tissue showed dense osmophilic material present within the lysosomes of the spindle cells consistent with the pigment seen on H&E stained sections. Melanosomes or premelanosomes were not detected (Figure 2).
Pathological findings: Case 2

The entire left thyroid lobe was processed for microscopic examination. It was almost completely replaced by a encapsulated lesion composed mostly of spindle cells in fascicles, whorls and singly in addition to occasional solid nodules of cuboidal cells and scattered aggregates of follicular cells occasionally forming colloid (Figure 3A). The spindle cells were plump and slender with, mostly, vesicular nuclei, inconspicuous nucleoli and eosinophilic cytoplasm. Bizarre, degenerative hyperchromatic spindle cells were seen in areas of extensive hyalinization (Figure 3B) but there were no mitoses or foci of necrosis. A few macro- and micro-follicles were present interspersed among the spindle cells. A remarkable feature was the presence of focal solid aggregates of spindle cells within a rich stromal vascularity closely mimicking a vascular lesion (Figure 3C, D) amid stromal hyalinization with focal calcifications. Examination of Congo Red-stained sections under polarized light demonstrated the presence of apple green birefringent deposits of amyloid in blood vessels' wall. The background thyroid parenchyma showed no amyloid. There were no nuclear features of papillary carcinoma. Immunohistochemistry showed almost identical findings as in case 1 with strong and diffuse staining for vimentin (Figure 3E), KL-1 and CK18 (Figure 3F) in the spindle cells and variable (less extensive than case 1) staining for thyroglobulin (20% tumor cells), TTF-1 (10%) and CK7 (10%). All other markers listed above were negative (Figure 3G). The proliferation index (Ki67/Mib-1) was well below 1%. The cause of death of the patient was cardiac amyloidosis which was part of systemic amyloidosis as illustrated by histopathological examination of other organs.

Discussion

Because of their rarity, spindle cell thyroid lesions may be challenging. Careful exclusion of unusual and paucicellular spindle cell variants of common thyroid cancer is of utmost importance for appropriate therapy and prognosis. Medullary carcinoma not uncommonly displays spindle cell morphology, infiltrates between thyroid follicles and rarely shows melanin pigment [18]. However, unlike our cases, medullary carcinoma usually shows higher cellularity, clear-cut malignant features and immunoreactivity with calcitonin and/or CEA [3]. Amyloid deposits in our case 2 were vascular (part of systemic amyloidosis) in contrast to the isolated stromal amyloid seen in medullary carcinoma.
Spindle thyroid adenoma

Anaplastic carcinoma is an important consideration in elderly patients with spindle cell thyroid mass. While diagnosis of classical anaplastic carcinoma poses no difficulty, a rare paucicellular spindle cell variant of anaplastic carcinoma has been described [7]. Although bland looking, this unusual variant displays similar permeation and plugging of arteries by tumor cells as seen in conventional anaplastic carcinoma and the clinical course seems to be similarly aggressive.

Spindle cell thyroid lesions may represent direct extension of neoplasms within adjacent cervical soft tissue, the proximal esophagus or the larynx [19]. These include in particular spindle cell carcinoma, desmoid fibromatosis and

Figure 3. Pathological features of case 2. A: irregular fascicles of bland-looking spindle cells with scattered solid aggregates of follicular cells with clear cytoplasm and a few follicles. B: prominent vascular hyalinization associated with bizarre degenerative spindle cells lacking mitotic activity and true atypia. C: circumscribed hypervascularized nodules of spindle cells closely mimicked a vascular lesion. D: higher magnification of C. E: strong diffuse vimentin expression in the spindle cells. F: CK18 was more strongly expressed in the follicles than in the spindle cells. G: CD34 highlighted prominent vessels but the tumor cells were negative for this marker.
rare miscellaneous sarcomas. Desmoid fibromatosis may rarely arise within the thyroid gland and should be excluded by appropriate histological features and staining for alpha-smooth muscle actin and nuclear staining with beta-catenin. Rare papillary carcinomas may be associated with an exuberant spindle cell mesenchymal fibroblastic/myofibroblastic proliferation forming short fascicles separated by edematous stroma, collagen and foci of hemorrhage [1, 2]. These spindle cells do not stain for keratins and thyroglobulin but instead show myofibroblastic or fibroblastic phenotypes [1, 2]. Metaplastic spindle cell foci have been rarely observed in papillary carcinoma and microinvasive follicular carcinoma [10,16]. These metaplastic foci occasionally show similar nuclear features as the basic neoplasm and they express marker of follicular cells and lack myofibroblastic differentiation. Thus, in such cases, the background follicular component should be carefully examined for nuclear and architectural features of papillary carcinoma and excessive sectioning of the tumor capsule is necessary to exclude invasion as evidence of follicular carcinoma. A rare pure spindle cell follicular carcinoma has also been described but, by definition, this rare variant shows clear-cut capsular and vascular invasion [5].

Fine needle aspiration (FNA)-associated nodule of the thyroid is another consideration [20]. Diagnosis of this lesion is based on a recent history of FNA and the characteristic florid fibro/myofibroblastic reaction associated with erythrocyte extravasation and hemorrhages. SETTLE tumors are usually composed of lobules of spindle cells intermixed with tubulopapillary epithelial component. These rare neoplasms are definitionally keratin positive but they lack follicular line of differentiation (thyroglobulin and TTF-1 negative) [8]. Riedel’s thyroiditis is characterized by paucicellular highly collagenized tissue with variable but generally prominent plasma-cell rich inflammatory infiltrate and associated obliterator phlebitis without atypia. Rare sarcoma metastasis to multinodular goiter may result into similar histology as our cases and should be carefully excluded by history of sarcoma, malignant cytology and lack of follicular differentiation [21].

Including our cases, 16 well documented benign thyroid nodules with spindle cell metaplasia/component have been reported (Table 1). They affected 10 women and 6 men at a mean age of 55 yrs (range, 27-77). Histology of the epithelial component corresponded to follicular adenoma (n=10) and multinodular goiter (n=6). The size of the spindle cell foci ranged from 2 mm to several centimeters. They constituted from 1% to >95% of the background nodule. In a few cases, the lesion was so dominated by spindle cells that the follicular nature was difficult to establish [10,13,16]. Histologically, the spindle cell areas showed either a nodular or diffuse pattern or a combination thereof. They uniformly expressed vimentin, pankeratin, thyroglobulin and TTF-1 but did not stain for high molecular weight keratins, CD34, calcitonin, smooth muscle and myofibroblastic markers. The spindle cells in our case 1 and in the case reported by Magro et al [13] showed peculiar meningioma-like concentric whorls surrounding numerous thick-walled hyalinized blood vessels. Interestingly, all reports including our cases showed a Ki67 index of <1% indicating that these benign nodules containing metaplastic spindle cells are non-proliferative lesions. This finding is of great value in excluding malignant spindle cell lesions including primary and metastatic carcinomas and sarcomas. Our cases and previous reports are consistent with previous observation that cells of papillary carcinoma and follicular adenoma may assume a fibroblast-like morphology in tissue cultures but maintain reactivity with cytokeratin, thyroglobulin, and vimentin suggesting epithelial-mesenchymal transition [22].

Two further findings in our cases merit short comments. The black discoloration of one case showed ultrastructural features consistent with black thyroid induced by long-term use of minocycline [23]. However, the pigmentation in our case was restricted to the tumor and absent in the background thyroid, thus representing the opposite situation as would be expected in minocycline-induced pigmentation [23]. However, rare cases of black adenoma associated with minocycline therapy have been reported [24]. The pigment in black thyroid is positive with the Fontana-Masson stain, negative with iron stain and can be bleached with potassium permanganate suggesting a melanin-like pigment [24]. Electron microscopic examination failed to demonstrate melanosomes or premelanosomes [24], similar to our case. Our patient had no recent history of minocycline intake but information regarding the remote drug history was inconclusive. A remarkable but unexplained observation in our 2 cases is the concurrence of
Table 1. Clinicopathological features of reported benign thyroid follicular nodules with spindle cell metaplasia (n=16)

<table>
<thead>
<tr>
<th>No</th>
<th>Author/ref.</th>
<th>Age/Sex</th>
<th>Histological type</th>
<th>Size whole nodule cm</th>
<th>Size spindle cell areas cm</th>
<th>Spindle cell pattern</th>
<th>TTF1</th>
<th>TG</th>
<th>CK</th>
<th>Vimentin</th>
<th>CD34/SMA</th>
<th>Other findings/ diseases Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vergilio et al [10]</td>
<td>71 M</td>
<td>Follicular adenoma</td>
<td>NA</td>
<td>1 cm</td>
<td>Diffuse (&gt;95%)</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>No follow-up</td>
</tr>
<tr>
<td>2</td>
<td>Vergilio et al [10]</td>
<td>45 F</td>
<td>Follicular adenoma</td>
<td>NA</td>
<td>&gt;3 cm (~96%)</td>
<td>diffuse</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>No follow-up</td>
</tr>
<tr>
<td>3</td>
<td>Vergilio et al [10]</td>
<td>33 F</td>
<td>Follicular adenoma</td>
<td>NA</td>
<td>NA (~95%)</td>
<td>diffuse</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>No follow-up</td>
</tr>
<tr>
<td>4</td>
<td>Aker et al [11]</td>
<td>27 F</td>
<td>Follicular adenoma</td>
<td>4 cm</td>
<td>~90%</td>
<td>Diffuse</td>
<td>ND</td>
<td>Focal +</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Alive &amp; well 15 months</td>
</tr>
<tr>
<td>5</td>
<td>Magro et al [12]</td>
<td>54 M</td>
<td>Multinodular goiter</td>
<td>n.s.</td>
<td>1.5 cm</td>
<td>Nodular</td>
<td>n.s.</td>
<td>+</td>
<td>Focal +</td>
<td>+</td>
<td>-</td>
<td>Bizarre hyperchromatic cells, No follow-up</td>
</tr>
<tr>
<td>6</td>
<td>Magro et al [13]</td>
<td>69 F</td>
<td>Follicular adenoma</td>
<td>5 cm</td>
<td>~90%</td>
<td>Nodular</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Transitional meningioma-like pattern, 1 yr alive and well</td>
</tr>
<tr>
<td>7</td>
<td>Shikama et al [14]</td>
<td>60 F</td>
<td>Follicular adenoma</td>
<td>3.2 cm</td>
<td>~50%</td>
<td>Nodular</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>8</td>
<td>Hirokawa et al [15]</td>
<td>56 F</td>
<td>Multinodular goiter</td>
<td>n.s.</td>
<td>2 cm</td>
<td>Nodular</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>CD34-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>9</td>
<td>Hirokawa et al [15]</td>
<td>65 F</td>
<td>Multinodular goiter</td>
<td>0.3 cm</td>
<td>50%</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>CD34-</td>
<td>Concurrent multifocal papillary carcinoma, no follow-up</td>
</tr>
<tr>
<td>10</td>
<td>Hirokawa et al [15]</td>
<td>50 M</td>
<td>Multinodular goiter</td>
<td>5.7 cm</td>
<td>n.s.</td>
<td>Diffuse &amp; nodular</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>CD34-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>11</td>
<td>Matoso et al [16]</td>
<td>43 F</td>
<td>Multinodular goiter</td>
<td>n.s.</td>
<td>0.2-1.5 cm</td>
<td>Nodular</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>SMA-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>12</td>
<td>Matoso et al [16]</td>
<td>49 M</td>
<td>Multinodular goiter</td>
<td>n.s.</td>
<td>0.2-1.5 cm</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>SMA-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>13</td>
<td>Matoso et al [16]</td>
<td>62 M</td>
<td>Follicular adenoma</td>
<td>n.s.</td>
<td>0.2-1.5 cm</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>SMA-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>14</td>
<td>Matoso et al [16]</td>
<td>57 F</td>
<td>Follicular adenoma</td>
<td>n.s.</td>
<td>0.2-1.5 cm</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>SMA-</td>
<td>No follow-up</td>
</tr>
<tr>
<td>15</td>
<td>Current case 1</td>
<td>77 F</td>
<td>Follicular adenoma</td>
<td>5.5 cm</td>
<td>~80%</td>
<td>Diffuse</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Monoclonal gammopathy since 8 yrs Alive and well at 2 yrs</td>
</tr>
<tr>
<td>16</td>
<td>Current case 2</td>
<td>70 M</td>
<td>Follicular adenoma</td>
<td>Whole right lobe</td>
<td>&gt;50%</td>
<td>Diffuse &amp; nodular</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Bizarre hyperchromatic cells, Monoclonal gammopathy since 3 yrs, Autopsy case</td>
</tr>
</tbody>
</table>

NA, not available; ND, not done; n.s., not specified; CK, cytokeratin, SMA, smooth muscle actin.
the lesions with MGUS in both. Although this might be a mere coincidence, it is unusual and worth mentioning given the relative rarity of MGUS and the strictly rare occurrence of spindle cell follicular adenoma. Yativ et al found that anti-thyroglobulin antibodies were more frequent among patients with IgG gammopathy, although these patients had no clinical or biochemical evidence of thyroid disease [25]. Another report described a patient with MGUS who subsequently developed thyrotoxicosis, pretibial myxedema and thyroid-associated ophthalmopathy [26]. The authors postulated that the MGUS could be the cause of the subsequently observed thyroid pathology [26].

In summary we described further two cases of spindle cell follicular adenoma of the thyroid expanding their morphological spectrum and depicting potential diagnostic pitfalls related to this rare findings.

Address correspondence to: Abbas Agaimy, MD, Pathologisches Institut, Universitätsklinikum Erlangen, Krankenhausstraße 8-10, 91054 Erlangen, Germany. Tel: +49-9131-85-22288, Fax: +49-9131-85-24745, E-mail: abbas.agaimy@uk-erlangen.de

References


Spindle thyroid adenoma


