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Malignant teratomas of the thyroid gland: clinico-radiologic and cytomorphologic features of a rare entity

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Introduction Primary thyroid gland malignant teratomas are extremely rare and can pose diagnostic challenges on fine needle aspiration (FNA) due to their cytomorphologic heterogeneity. Recent next generation sequencing studies have identified recurrent DICER1 hotspot mutations in these tumors, suggesting that malignant teratomas of the thyroid should be considered a distinct pathological entity. Herein, we review the clinico-radiologic and FNA findings in a series of *DICER1* mutated malignant teratomas.

Methods We performed a retrospective case review of 9 FNAs from 5 patients with a histologically confirmed malignant teratoma of the thyroid gland from 2 large tertiary care pathology practices.

Results The patients included 4 females and 1 male, with an average age of 43 years (22-65 years). The nodules were centered within the thyroid gland and ranged from 1.7 to 10 cm in diameter. FNAs of primary thyroid teratomas demonstrate marked cellularity, epithelial proliferations, an absence of colloid, and a predominance of immature spindled cells, representing the mesenchymal and neural ectodermal components of these tumors. The FNA interpretations ranged from atypia of undetermined significance to overtly malignant. Three patients died of their disease and 2 are alive with no evidence of disease.

Conclusions Malignant thyroid teratoma is a rare entity with cytomorphologic overlap with other high-grade neoplasms of the thyroid. Recent molecular studies have defined recurrent *DICER1* mutations in

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malignant thyroid teratomas and propose these as a distinct clinicopathological entity. The features described here may be helpful in providing a correct prospective interpretation.

Background

Teratomas are germ cell neoplasms composed of tissues representing all 3 primordial germ cell layers (ie, endoderm, mesoderm, and ectoderm). The vast majority of teratomas occur in the ovaries or testes, but other midline anatomic sites including the sacrum, retroperitoneum, mediastinum, pineal gland, and cervical neck can give rise to these tumors. Approximately 5% to 10% of primary teratomas occur in the head and neck; and a subset of these affect the thyroid gland.[1-3]

Thyroid gland teratomas are rare neoplasms that are extremely challenging to diagnose on fine-needle aspiration (FNA) because of their cytomorphologic heterogeneity. Multiple case reports of benign and malignant thyroid gland teratomas have been presented,[4-13] but no case series specifically reviewing the FNA findings has been described. Recent next generation sequencing studies identified recurrent *DICER1* mutations in thyroid gland teratomas and it has been proposed that malignant thyroid teratomas are a distinct clinicopathological entity.[12,14] Herein, we review the FNA findings from this series of *DICER1* mutated malignant teratomas.

Materials and methods

We performed a retrospective case review of 9 FNAs from 5 patients with a histologically confirmed malignant teratoma of the thyroid gland from the Johns Hopkins Hospital and Southern California Permanente Medical Group. The histologic and molecular findings in 4 of these cases have been previously reported.[14] FNAs were interpreted according to The Bethesda System for Reporting Thyroid Cytopathology. Patient demographics, clinical information, and radiologic findings were obtained from the electronic medical records.

Results

Clinical and radiologic findings

Nine FNA specimens from five patients were identified and reviewed. Eight of the FNAs were thyroid aspirates and 1 was a metastatic nodule in the iliac bone in a patient with a history of malignant thyroid teratoma. The patients included 4 women and 1 man, with an average age of 43 years (range: 22-65 years). The clinical and radiologic findings are presented in Table 1. The nodule size was highly variable, ranging from 1.7 cm to 10 cm (mean: 4.8 cm) in diameter. All tumors were present within the thyroid gland and most of the patients presented with compressive symptoms. The radiographic findings correspond with the gross findings, where most of these tumors show some degree of cyst formation. One patient was found to have an incidental nodule while undergoing workup for hyperparathyroidism; interestingly, this patient had a rapid disease course and ultimately died of disease within a year of diagnosis (FNA 1 and 2 are the same patient, Tables 1 and 2). All patients except 1 had locoregional nodal metastases; distant metastatic sites included bone and lung. All patients with metastatic disease were treated aggressively with combination surgery, chemotherapy, and radiotherapy. Nevertheless, 3 of 5 patients died of their disease, with survival intervals of 1.1, 1.0, and 4.4 years, respectively.

Cytomorphologic findings

The cytomorphologic findings varied from overtly malignant smears with extensive necrosis, high mitotic rate, significant epithelial atypia, and frequently identified immature neural tissue, to deceptively bland changes, which in the context of an adult thyroid FNA, were interpreted as changes that could be consistent with lymphocytic thyroiditis with an exuberant stromal reaction (Table 2). Only 1 case had readily identifiable rosettes and immature neural matrix material. All cases showed numerous clusters or sheets of spindled cells.

A striking feature observed across most of the smears were epithelial proliferations with complex, often insular or morular/globular, fairly cohesive architectures (Figs. 1 and 2). Overt papillae or microfollicles were not present. Colloid was absent in the background but focally present within immature follicle-like structures (Fig. 3). The epithelial cells often appeared as monotonous thyroid follicular epithelium, but with varying degrees of atypia, showing an absence of intranuclear cytoplasmic inclusions and only rare nuclear grooves. Further, a large proportion of the epithelial constituents showed a monotonous immature cytology with increased nuclear-to-cytoplasmic ratio and an even to smooth distribution of chromatin (Fig. 3). Conspicuously absent were epithelial components associated with benign or immature teratomas, such as skin, gastrointestinal mucosa, pancreas, or liver tissues. Similarly, a prominent hematopoietic or lymphocytic population was not present, including an absence of lymphoglandular and tingible bodies.

Table 1 Clinical and radiologic characteristics.

FNA number	Age/sex	Location	Presenting symptoms	Size (cm)	Pertinent radiology	Metastasis	Time to metastasis	Site of metastasis	Treatment	Most recent status
1	60/Male	Thyroid, Right Lobe	Hyperparathyroidism led to ultrasound	1.7	US: TIRAD-5, solid hypoechoic nodule with lobulated margins, no echogenic foci, taller than wide	Yes	At initial presentation Land again at 6 months	Level VI LN	Surgery, chemotherapy and radiation	D
2	60/Male	Iliac Crest, Right	same patient as FNA 1	N/A	PET/CT: innumerable hypermetabolic osseous lesions throughout the appendicular axial skeleton	Yes	6 months following surgery	Wide spread osseous	XRT to spine	D
3	42/Female	Thyroid, Left lobe	Neck mass	8	CT: Large heterogeneous mass with cystic areas centered within thyroid; compression of multiple adjacent structures and concern for extracapsular spread	No	None	None	Surgery only; close follow up (quarterly imaging)	A
4	22/Female	Right thyroid lobe and isthmus	Neck mass	2.4	US: hypoechoic nodule(s) without calcification PET/CT: hypermetabolic right and left thyroid lobe and bilateral cervical nodes	Yes	At initial presentation	LN and then lung	Surgery, chemotherapy and radiation	D
5	29/Female	Right thyroid lobe	True vocal cord paralysis	10	US: Right thyroid is diffusely enlarged and inhomogenous w/multiple masses & a pedunculated mass (4.3 cm) inferiorly. Left lobe w/ heterogenous density CT: A large hypodense mass places the entire right thyroid with retrotracheal extension and displacement of trachea; cervical LAD	Yes	At initial presentation; 17 months; 51 months	LN; para aortic; clavicle	Surgery, chemotherapy and radiation	D
6-9	65/Female	Right thyroid lobe	Neck mass	1.9	CT: heterogeneous nodules in bilateral thyroid; cervical LAD with probable necrosis	Yes	At initial presentation	LN	Surgery and chemotherapy (BEPx4)	A

TIRAD, Thyroid Imaging Reporting and Data Systems; LAD, lymphadenopathy; CT, computed tomography; US, ultrasonography; bx, biopsy; LN: lymph node; BEP, bleomycin, etoposide, and cisplatin; D: dead of disease; A: alive without disease.

Table 2 FNA interpretation, diagnostic comments, and IHC in primary thyroid gland malignant teratomas.

FNA number	FNA interpretation	FNA comments	Thyroid tissue present	IHC
1	AUS (cytologic)	Background changes of lymphocytic thyroiditis and an exuberant stromal reaction.	Yes	Performed on surgical (see text)
2	Malignant epithelioid and spindle cell neoplasm, consistent with a metastasis of the patient's thyroid primary (same patient as FNA 1)	None	No	None
3	SFM	Unusual morphological features that are suspicious but not conclusive for a particular tumor type. The differential diagnosis includes PTC, medullary, insular carcinoma, poorly differentiated thyroid carcinoma, and a metastasis	Yes	Focal positive: CD56 and synaptophysin Negative for calcitonin, chromogranin, and TTF-1
4	Malignant (other): Primitive, undifferentiated neoplasm	Extensive necrosis; Small round blue cell with plasmacytoid appearance, dyscohesive, and high N:C ratio; no tingible bodies or lymphoglandular bodies; high mitotic rate. Differential includes malignant teratoma, Ewing/PNET, medullary, rhabdomyosarcoma or even thymic tumor	Yes	Proliferation Index: >95% Ki-67
5	Malignant (other): Poorly differentiated malignancy	Haphazard cellular smears with mature skeletal muscle (contaminant); atypical cell aggregates, although not cohesive, per se; rosettes and neural matrix material; small cells, with high nuclear to cytoplasmic ratio, with wisps of cytoplasm; mitoses increased	Yes	None
6 - 9	Malignant (other): Poorly differentiated malignancy with necroinflammatory debris	Necroinflammatory debris; loosely cohesive insular-like clusters of epithelial-type cells; skeletal muscle identified, but destroyed	Yes	Positive: vimentin, synaptophysin, NFP; Negative: keratin, TTF-1, thyroglobulin, CD99, desmin, MSA, AFP, myo-D1, GFAP, S-100 protein, chromogranin

AUS, Atypia of Undetermined Significance; SFM, Suspicious for Malignancy; N:C, nuclear-to-cytopasmic ratio; PTC, papillary thyroid carcinoma.

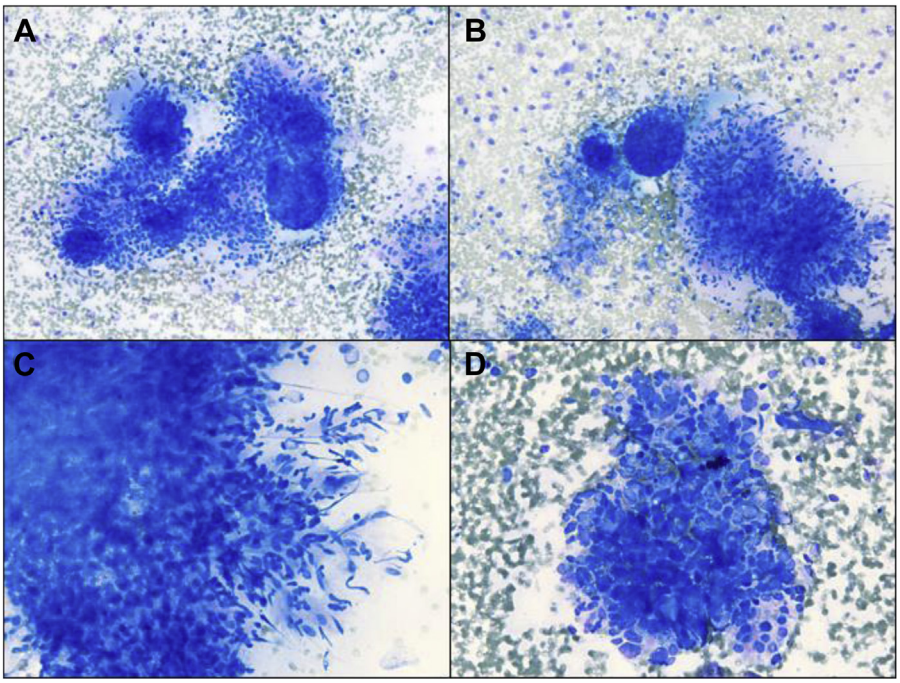

Figure 1 Malignant thyroid gland teratoma, FNA #1: A Biphasic admixture of epithelium is seen with a follicular-like, epithelial architecture intimately associated with oval to short spindly mesenchymal cells. The latter cells are embedded in loose myxoid stroma (A, B). High magnification illustrates the pleomorphic mesenchymal cells representing the rhabdomyosarcomatous component of malignant teratoma. Another field displays a tight group of primitive neoplastic cells representing a primitive neuroectodermal component (C, D). DiffQuik, low- to intermediate-magnification.

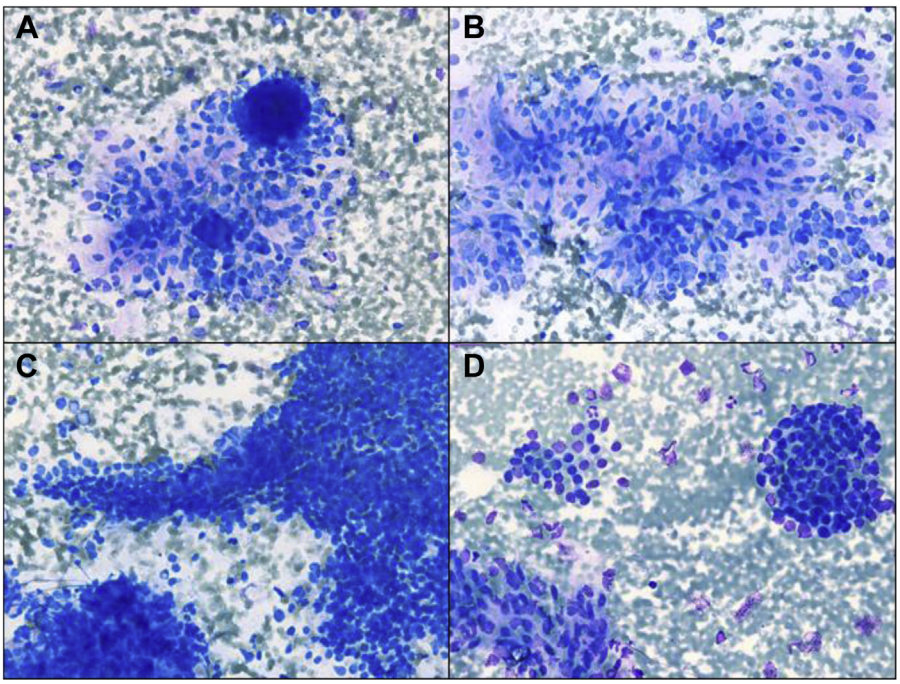

Figure 2 Malignant thyroid gland teratoma, FNA #1: The images highlight the sarcomatous component of the tumor with oval to short spindle cells intimately embedded in a loose myxoid stroma. These cells were immunoreactive (on resection) for desmin and myogenin (A, B). Other fields illustrate a large monolayered fragment of neoplastic epithelial cells, and several lymphocytes and neoplastic small round blue cells are seen in the background (C, D). Occasional cases showed neoplastic cells differentiating towards thyroid follicular epithelium in a follicular architecture (D). DiffQuik, low- to intermediate-magnification.

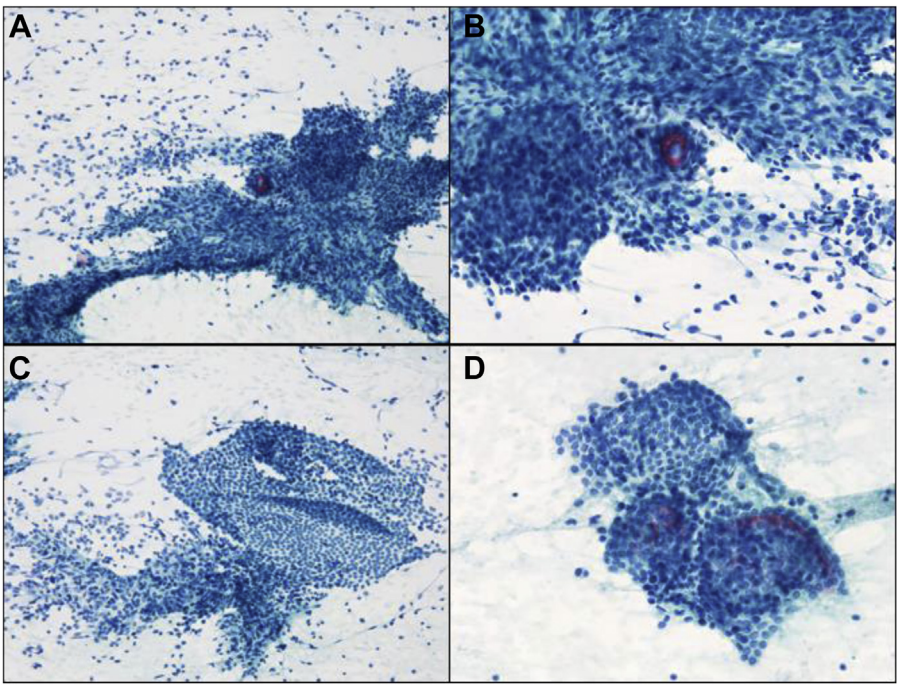

Figure 3 Malignant thyroid gland teratoma, FNA #1: Some cases displayed large fragments of epithelium showing crowded oval nuclei with focal presence of colloid (A, B). Occasional fields showed the neoplastic epithelium in flat monolayered architecture, and in one case, the FNA interpretation of AUS was rendered with a note raising the possibility of PTC (C, D). Papanicolaou stain, low- to intermediate-magnification.

Admixed with some the proliferative epithelial clusters was a chrondomyxoid component (Fig. 2). Large fragments of mature cartilage were rare or absent. When present the chrondomyxoid component frequently appeared less mature and as a supporting matrix to the predominant epithelial proliferation. Mature skeletal muscle was identified in 2 cases, but interpreted as a contaminant from the procedure.

The overtly spindled clusters appeared sarcomatoid, with variable amounts of cytoplasm around hyperchromatic nuclei. Additionally, some of the smears showed a background of dyscohesive and singly dispersed plasmacytoid cells. Some of these areas gave the impression of medullary carcinoma, which prompted ancillary studies for neuroendocrine markers and calcitonin in 1 case (Table 2).

In the case where the epithelial component predominated, Atypia of Undetermined Significance was invoked. In contrast, the 6 cases with overt necrosis, mitotic figures, and small round blue cells were interpreted as Malignant: Other (Bethesda category VI), designated further as primitive, undifferentiated, or poorly differentiated neoplasms or malignancies. One case was interpreted as suspicious for malignancy with an explanatory note providing a broad differential that included insular carcinoma, medullary carcinoma, poorly differentiated carcinoma, metastasis, or papillary thyroid carcinoma.

Overt features of malignancy were surprisingly varied. Small round blue cells with high nuclear-to-cytoplasmic ratios or other primitive neural elements such as rosettes were only seen in 2 cases. Two cases suggestive an insular-like process (Fig. 4). Features common in primary thyroid gland malignancies, such as papillary thyroid carcinoma (PTC)-nuclear features or architectural disorder, were not present, although suggested in a comment as possible features of an unusual variant of medullary carcinoma, PTC, insular, or poorly differentiated carcinoma.

Histologic findings

At resection, the histologic sections varied in the proportion of primitive spindled and epithelial elements; with immature neural tissue ranging from very a minor constituent to readily identifiable. A representative histologic section of primitive spindled and epithelial elements is illustrated in Fig. 5. After resection, this patient went on to develop widespread osseous metastases within the axial skeleton (Fig. 6). An iliac crest metastasis underwent FNA (Fig. 7).

Ancillary studies

Immunohistochemical stains were performed on 3 of the cells blocks from the FNAs. Synaptophysin showed immunoreactivity in 2 cases and 1 was positive for CD56 and another for NFP. FNA 3 was initially considered medullary carcinoma, but calcitonin, chromogranin, and TTF-1 were negative. Interestingly, cases 6-9 showed a number of immunonegative results, including keratin, TTF-1, thyroglobulin, CD99, desmin, actin, myo-D1, GFAP, S-100, and chromogranin.

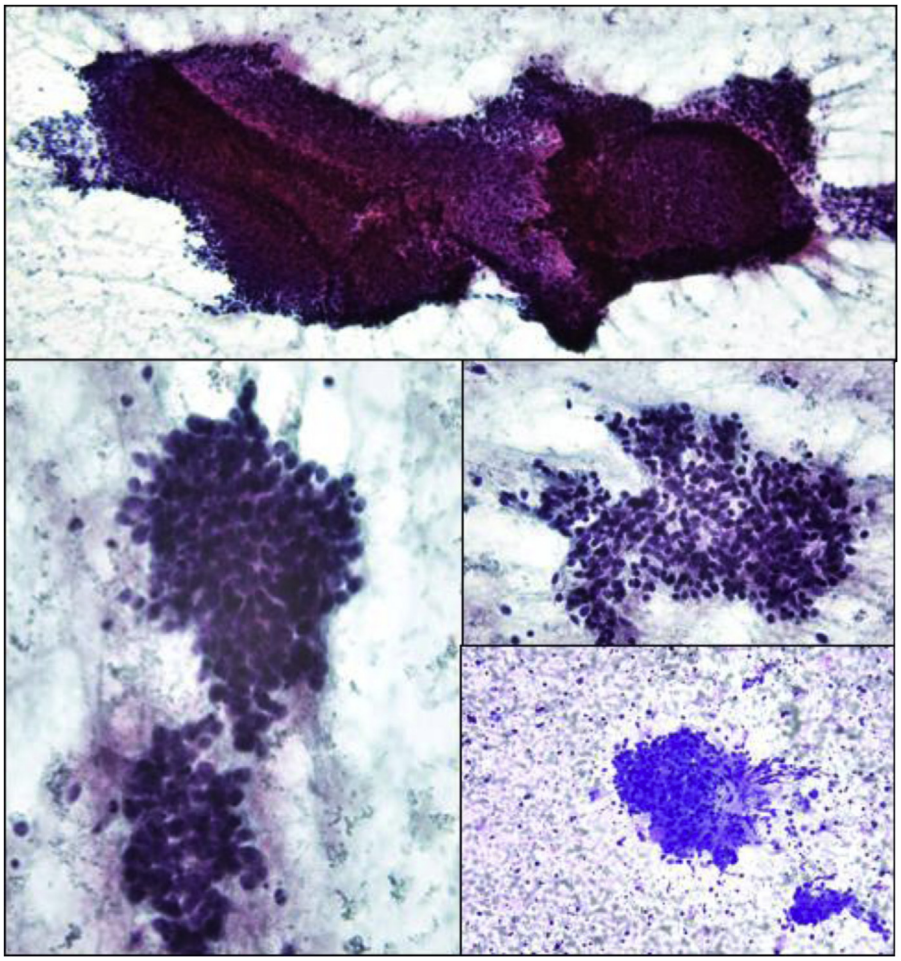

Figure 4 Fig. 7 Metastatic thyroid teratoma, iliac crest FNA #2: Hypercellular smears show predominantly a population of small round blue cells, seen in a dyscohesive single cell pattern. Higher magnification shows fine nuclear chromatin. On immunostaining, the primitive neural components were positive for synaptophysin and INSM-1. Papanicolaou and DiffQuik, low- to intermediate-magnification.

Immunohistochemistry studies were performed on the surgical resection matched to FNA 1. The immunohistochemistry (IHC) showed epithelial cells positive for keratins, PAX-8, and TTF-1; spindled cells focally positive for desmin and myogenin, and cartilage positive for S100 protein; while CD99, synaptophysin and INSM-1 were negative in all components. Importantly, Ki-67 was widely variable between the components and ranged from very low to 90%.

Discussion

Teratomas are germ cell neoplasms that have classically been thought to arise from misplaced embryonic rests.[1] Cervical and primary thyroid teratomas are extragonadal germ-cell tumors showing elements from all three embryonic layers (ectoderm, mesoderm, and endoderm). Those tumors developing from within the thyroid gland are well described in the literature, but there are fewer than 60 cases.[15] These thyroid teratomas have a broad age range of affected patients and divergent clinical outcomes. On one end of this spectrum are benign and immature thyroid teratomas that occur almost exclusively in infants and children less than 2 years of age.[2] On the other are malignant thyroid teratomas that appear to affect adults and rarely older children. As in other anatomical sites, teratomas are graded on a histologic spectrum based on the proportion of immature neuroectodermal component present.[1] The malignant tumors are aggressive and associated with significant morbidity and mortality. Although benign and immature teratomas can cause morbidity and rarely death due to mass effect, they are thought to have an excellent prognosis after complete excision.[2]

Recent work has sought to understand the molecular underpinnings that accounts for the histologic and clinical gamut associated with these curious tumors by performing next generation sequencing on a group of benign, immature, and malignant teratomas.[14] Four of 5 patients reported in this series were included in the molecular analyses from that paper, which identified recurrent hotspot mutations in the *DICER1* gene. The *DICER1* gene is located on chromosome

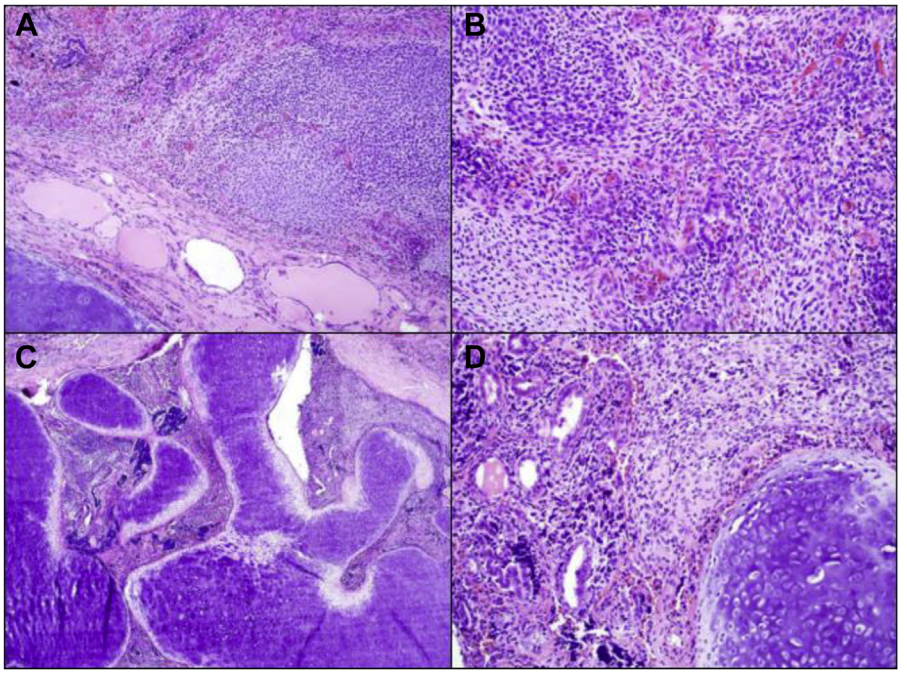

Figure 5 Malignant thyroid gland teratoma, FNA #3: Hypercellular smears displaying primitive small round blue cells in a more cohesive architecture. Absence of colloid or amyloid in the background was an important feature across all examined slides. However, due to the immunostaining with synaptophysin and CD56, and negativity for calcitonin and chromogranin, a diagnosis of neuroendocrine tumor was suggested with a differential including insular and medullary carcinoma. On resection, these cells likely comprise the primitive neural component. Papanicolaou and DiffQuik, low- to intermediate-magnification.

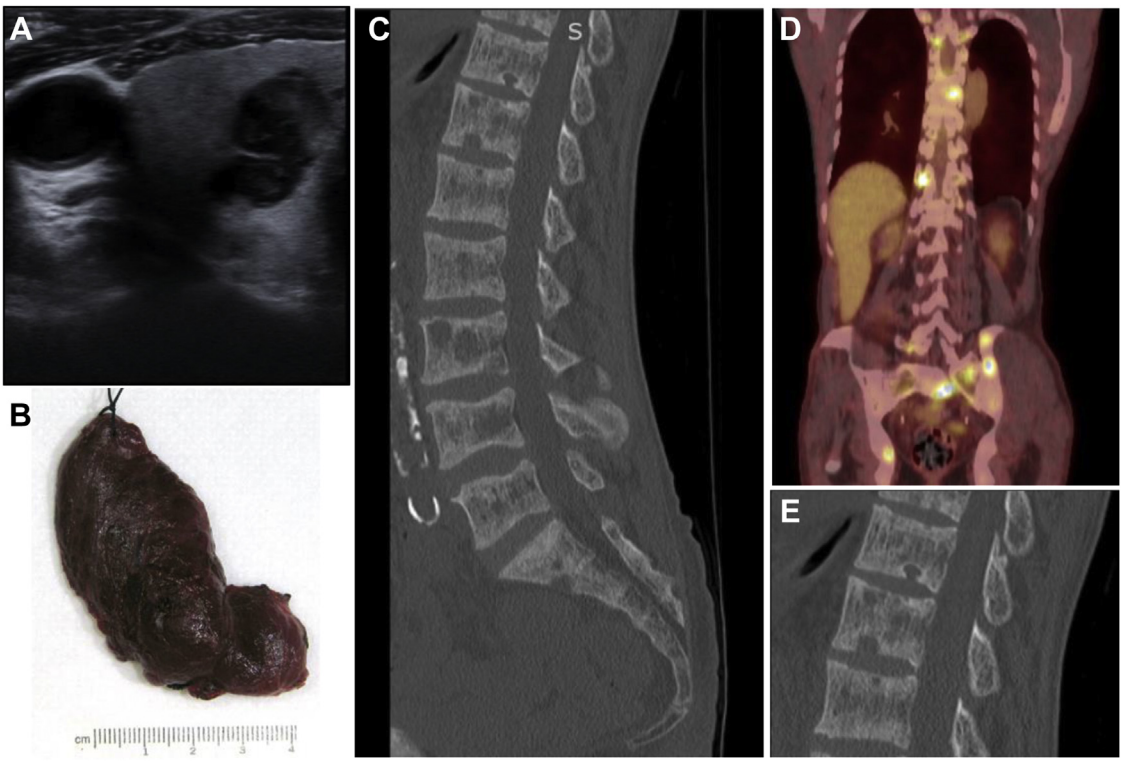

Figure 6 Malignant thyroid gland teratoma, Thyroidectomies (A&B-Patient #1; C&D-Patient #2): Some malignant thyroid teratomas show a paucity of immature neural tissue and are instead composed of pleomorphic spindled and primitive epithelial cells (A, B). Vascular invasion (not shown) can be readily identifiable in these aggressive primitive tumors. Primitive epithelial proliferations (C) in complex architectures and immature cytology are often found closely associated with primitive spindled cells and immature cartilage. Rosettes were focally present in this specimen, which would be INSM-1 immunoreactive (D) (H&E, low and intermediate magnification).

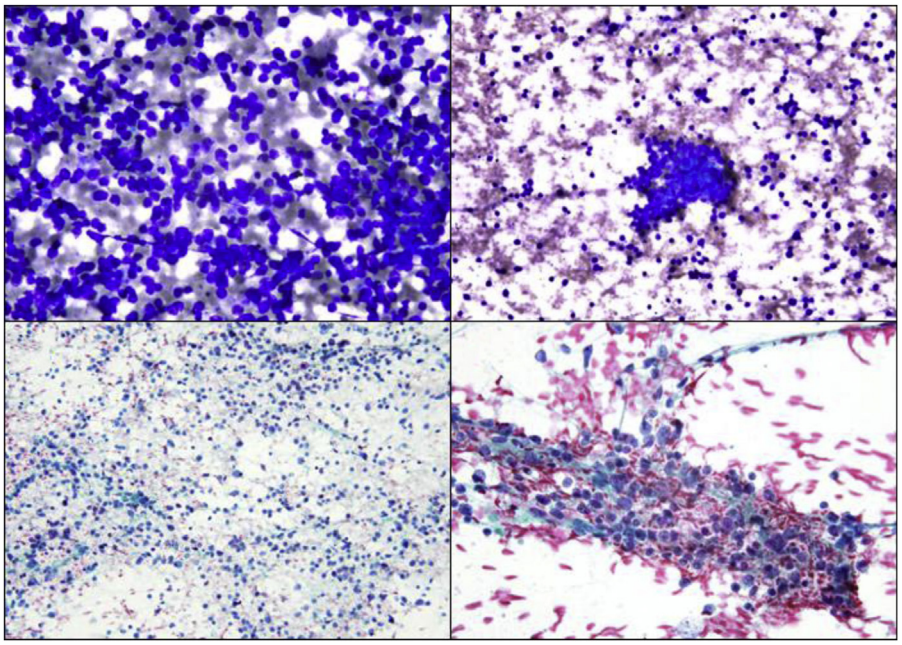

Figure 7 Representative radiographic and gross images, metastatic thyroid teratoma (Patient described in FNA #1 and FNA #2): In one of the cases, the patient presented with a TIRAD-5, solid, hypoechoic nodule with lobulated margins, no echogenic foci, taller than wide, 1.7 cm thyroid nodule on ultrasonography (A). The diagnosis of AUS led to a hemithyroidectomy where a 1.7 cm tan-pink solid mass was identified in the inferior pole (B). Six months after surgery, this patient was found to have wide-spread axial skeleton metastases (C, E) which were strongly FDG-avid on PET scan (D). Ultrasound, computed tomography, positron emission tomography.

14q32 that encodes for an enzyme critical in microRNA processing. This tumor suppressor gene was initially described in 2009, and was subsequently found to play a critical role in the development of pleuropulmonary blastoma and cystic nephroma, and subsequently identified as pathogenic in ovarian Sertoli-Leydig tumor, embryonal rhabdomyosarcoma, Wilms tumor, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma, pineoblastoma, pituitary blastoma, anaplastic sarcoma of the kidney, intracranial sarcoma, Mullerian adeocasarcoma, some well-differentiated thyroid carcinomas, and some thyroid multinodular hyperplasias.[14,16-18]

Although rare, primary malignant thyroid teratoma is a diagnostic consideration in any younger patient presenting with a high-grade thyroid tumor and rapid or symptomatic thyroid enlargement. The cytologic features of malignant thyroid teratoma make a definitive diagnosis difficult, especially because the features used for teratoma grading are histologic.

All of the malignant cases described here are thought to have arisen from within the thyroid gland. This is an important distinction from reported benign and immature teratomas that involve the central neck soft tissues without identifiable thyroid tissue.[14] Additionally, the absence of benign-appearing tissue elements, which helps defines benign or immature teratomas, was a universal feature in all 9 FNAs. Indeed, the cytologic overlap for malignant teratomas is not generally with benign/immature teratomas but rather with other high-grade neoplasm. At a histologic level, the tumors resected from these 5 patients showed predominantly primitive and undifferentiated spindled cells with varying proportions of immature neural tissue and admixed epithelial structures. Of the 9 FNAs, overtly malignant cells were seen in a minority, resulting in a Malignant-Not Otherwise Specified interpretation. This interpretation appears to be the most frequent interpretation identified in 6 case reports.[4,6,9,11-13] Four case reports also describe the FNA interpretation as suspicious for medullary carcinoma, which is a common diagnostic pitfall,[5,7,8,10] although no cases showed calcitonin immunoreactivity. Some cases, such as FNA 1, can appear deceptively bland, with interpretations yielding diagnoses of atypia of undetermined significance or suspicious for a follicular neoplasm.[3,19]

The literature also documents a similar staining pattern seen in 2 of our cases, with focal synaptophysin or CD56 reactivity and negative reactions with desmin, CD99, TTF-1, PAX8, and low molecular weight keratins. Interestingly, this is in contrast to the IHC pattern seen on surgically resected specimens where there is synaptophysin and INSM-1 reactivity in the neural elements; immature mesenchymal elements that express desmin and myogenin; and bland cuboidal or columnar cells that express keratins, TTF-1, and PAX8.[14] This geographically/regionally restricted pattern of staining makes it difficult to use IHC to confirm a malignant teratoma on limited biopsies or FNAs because the different elements can have different staining patterns.

A practical differential diagnosis list for thyroid teratoma is presented in Table 3. Although many of the entities

Table 3 Differential diagnosis.

Diagnostic entity	Salient features
Benign/self limited	
Sub-acute granulomatous (de Quervain) ghyroiditis	• Follicular cells admixed with multinucleated giant cells, lymphocytes, histiocytes, plasma cells • Late phase fibrosis • Clinical history
Hashimoto thyroiditis	• Bland, acellular fibrosis and lymphocytic infiltration • Frequent Hürthle cell change
Thyroid tumors	
Medullary thyroid carcinoma	• Presence of amyloid; plasmacytoid cells and/or spindle cells • calcitonin positive
Poorly differentiated thyroid carcinoma (insular)	• Variable histologic patterns • Absence of distinctive features of well differentiated thyroid carcinoma • Hypercellular smears with overlap; bland nuclei; single cells and clusters; absence of colloid
Anaplastic thyroid carcinoma	• Markedly pleomorphic; mitotic activity • PAX8(+); p63(+); p53 mutations
Papillary thyroid carcinoma w/fibromatosis/fasciitis-like stroma	• Classic nuclear features of papillary thyroid carcinoma • Associated spindle cell proliferation and loose stroma
Papillary thyroid carcinoma, cribiform- morular variant	• Presence of squamous metaplasia and morulae's helpful, but inconsistent • Columnar cells with subtle papillary thyroid carcinoma features • β-catenin nuclear positivity (in morules)
Hyalinizing trabecular tumor	• Nuclear features with tapered shapes and abundant intranuclear pseudoinclusions and groves • Hyaline material often globoid • Prominent population of polygonal cells
Small round blue cell tumors	
Ewing sarcoma	• Monomorphic; CD99(+), NKX2.2(+), EWSR1 rearranged
Rhabdomyosarcoma	• Myogenin or myo-D1(+)
Spindle cell tumors	
Solitary fibrous tumor	• Bland, monomorphic spindle cells; prominent vessels; intermixed benign thyroid • STAT6 positive; *NAB2-STAT6* gene fusion
Synovial sarcoma	• Biphasic variant with spindle and epithelial cells • Monophasic variant, usually shows monotonous bland spindle cells • TLE(+), BCL2(+), CD99(+), keratin(+); *SS18-SSX gene fusion*

presented are malignant diagnoses, the myriad and bizarre cytomorphologies of thyroid teratoma should give pause to firmly committing to a specific overtly malignant (or benign) diagnosis. Benign entities with a nonspecific robust stromal reaction could explain many of the findings present on FNA. Because thyroid gland teratomas lack the nuclear features of PTC but do appear neoplastic (hypercellularity, architectural atypia, and the absence of colloid), Atypia of Undetermined Significance, suspicious for follicular neoplasm (SFN), or Suspicious for Malignancy may be used with qualifications listed in a comment, while overtly malignant cases could be further evaluated with ancillary studies.

In summary, malignant thyroid teratoma is a rare entity with cytomorphologic overlap with other high grade neoplasms of the thyroid. Recent molecular studies have defined recurrent *DICER1* mutations in malignant thyroid teratomas an propose these as a distinct clinicopathological entity.

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