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(CASE REPORT)

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Metastatic spindle epithelial tumor with thymus-like element (SETTLE) to the lung: Case report of a rare tumor and a brief review of the literature

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Abstract

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) is an extremely rare thymus-like thyroid tumor that mostly occurs in children, teenagers, and young adults. We report a case of a 26-year-old male with a slowly growing, painless neck mass that developed over 4 months duration. Thyroid function tests, serum calcitonin, and carcinoembryonic antigens values were all within normal values. MRI showed a well-demarcated, lobulated, 4 × 3 cm heterogeneous, mixed solid-cystic mass in the thyroid with marked internal vascularity. FNA cytology showed spindle cells, but there was no definitive diagnosis. Total thyroidectomy was performed, including the entire mass. There was no local invasion, and the parathyroid glands were preserved. The histomorphologic features and immunohistochemistry (IHC) profile were supportive of the diagnosis of SETTLE.

Two pulmonary nodules of metastatic SETTLE were discovered 3 years later and were completely surgically removed, and no adjuvant therapy was given. At 16 months following a metastasectomy, the patient was free of disease before being lost to follow-up. SETTLE is a rare tumor, which represents a diagnostic challenge because it is histomorphologically similar to other tumors of the thyroid and the thymus. Awareness of this tumor is important so it can be included in the differential diagnosis of a neck mass. Metastasis can occur years after initial treatment, and long-term follow-up is mandatory.

Keywords: Thyroid; Thymus; Spindle cells; Epithelial cells; Immunohistochemistry; Molecular

1. Introduction

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) is a rare malignant neoplasm of the thyroid that often presents as a slow-growing, painless neck mass. This presentation can be mistaken for other benign or malignant thyroid tumors. [1] Although SETTLE typically remains silent clinically, it has a significant potential for late metastatic spread, frequently to the lungs. Metastasis can occur many years or decades after the initial diagnosis and treatment. This brings the necessity to continue monitoring for many years after the diagnosis and treatment. [2]

Histologically, SETTLE displays a distinctive biphasic architecture consisting of spindle-shaped and epithelial components arranged in fascicles and gland-like structures within a stromal background. [3] Immunohistochemical staining for SETTLE depicts positivity for cytokeratin and vimentin, and occasionally CD99, but thyroid markers such as thyroglobulin and calcitonin are typically negative. [4] These IHC markers are essential to differentiate SETTLE from

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other common thyroid and thymus neoplasms. As a rare neoplasm, SETTLE may be overlooked in the differential diagnosis of a neck mass or misdiagnosed as another entity.

Complete surgical excision of the primary tumor remains the mainstay of therapy. The efficacy of chemotherapy and radiation has not been proven for this tumor. [5] Given that SETTLE has a chance for long-term distant metastases, long-term follow-up is essential. In this report, we present a case of SETTLE in a young adult who developed pulmonary metastasis three years after initial treatment with total thyroidectomy, highlighting the importance of clinical awareness, accurate diagnoses, and proper management with long-term monitoring.

2. Case presentation

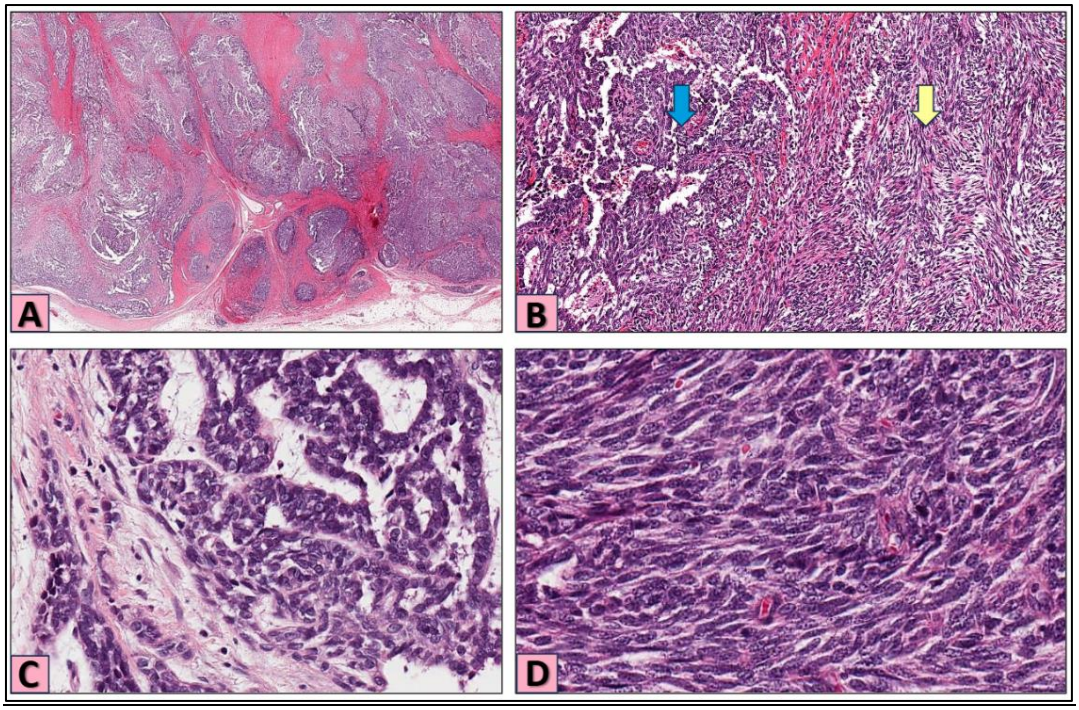
A 26-year-old male was referred by his primary physician to the endocrine clinic with a painless swelling of the neck, gradually increasing in size for 4 months, and involving the anterior part of the neck over the thyroid gland. In the last few weeks, grew significantly larger. There was no history of associated symptoms such as dysphagia, dyspnea, hoarseness, and systemic complaints, including weight loss or fatigue. Also, there was no significant past medical or family history. The functional activity of the thyroid gland was evaluated based on thyroid-stimulating hormone (TSH), free T4, and free T3, which were within the normal range normal range, suggesting that the lesion could not have originated from the thyroid follicular epithelium. The serum calcitonin and CEA levels of medullary thyroid cancer were also within normal ranges. Blood counting, metabolic, and serum calcium were normal. These findings indicated the lack of systemic disease or parathyroid involvement.

A neck MRI was done and it demonstrated a well-demarcated, lobulated mass of about 4 × 3 cm in the right lobe and the isthmus of the thyroid gland. The lesion had both solid and cystic components with marked internal heterogeneity. On T1-weighted images, the lesion showed isointensity to the surrounding muscle, and some hypointense spots were demonstrated, possibly representing cystic or necrotic foci. T2-weighted sequences showed hyperintensity compatible with myxoid degeneration or fluid. Post-contrast enhancement emphasized the vascular solid components, where viable tumoral regions and their internal architecture were defined. Fine needle aspiration (FNA) biopsy was performed, showing only spindle cells, but a definitive diagnosis could not be obtained. Because of the features observed on imaging and indeterminate cytology, and due to concern for the known risk of sampling the vascular thyroid tissue, the multidisciplinary tumor board recommended total thyroidectomy including the mass. The operation proceeded uneventfully, and the mass was completely removed without encroachment on the neighboring organs. The parathyroids were left in situ.

The tumor was well circumscribed, and histological examination was biphasic (both epithelial and spindle elements). The epithelial component was organized into glandular, tubular, and solid structures, whereas the spindle cells component was organized in a fascicle pattern, such as soft tissue sarcomas. The stroma of the tumor was heavily sclerosed. Foci of thymic differentiation were supported by a sparse infiltrate of lymphocytes and structures resembling Hassall's corpuscles, and there were also focal mucinous areas. (Figure 1 A, B, C, D)

Differential diagnoses of the tumor were at the tumor level (Table 1). They included synovial sarcoma, medullary thyroid carcinoma, anaplastic carcinoma, ectopic thymoma, malignant teratoma, intrathyroidal thymoma, spindle cell variant of papillary thyroid carcinoma, primary thyroid sarcoma, and metastatic lesions. The results of IHC ruled out these options. Thyroglobulin, PAX8, TTF-1, chromogranin A, and synaptophysin showed negative reactivity for the tumor as well. Tumor cells expressed 34βE12 (diffusely in both epithelial and spindle elements), CK7, CD99, BCL2, and CD117. The immunoprofile, as well as the morphologic findings and thymic derivation findings, were consistent with the diagnosis of SETTLE.

There was mild hoarseness and throat discomfort after surgery, which disappeared within two weeks . A substitution treatment with levothyroxine was started. Three years after surgery, surveillance imaging detected two right lung nodules (2.0 and 1.5 cm) that were resected surgically. On histopathology, metastatic SETTLE was confirmed. No adjuvant treatment was given, and 16 months following the pulmonary resection, the patient was free of tumor with no evidence of recurrence or metastasis before he was lost to follow-up.



1A Low power view showing tumor organized into glandular, tubular, and solid structures (H&E stain X20); 1B: Intermediate power view showing biphasic tumor, glandular component (Blue arrow), and spindle cell component (Yellow arrow) (H&E stain X40); 1C: High power view showing epithelial glandular cells with mild to moderate atypia and rare mitosis (H&E stain X60); 1D: High power view showing cellular spindle cells arranged in fascicle pattern with mild to moderate atypia and rare mitosis (H&E stain X60)

Figure 1 Histomorphology of Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE)

3. Discussion

3.1. History, epidemiology, and WHO classification

Spindle epithelial tumor with thymus-like differentiation (SETTLE) and carcinoma showing thymus-like differentiation (CASTLE) are malignant tumors of the thyroid gland. Both are classified as being part of the intraepithelial thymoma type of thyroid cancer due to their resemblance to thymic tissue and presumed origin from related remnants. [6] These two tumors should be included in the differential diagnosis of a neck mass and distinguished from other thyroid and thymus neoplasms. In comparison, intrathyroid thymic carcinomas (ITC) are slow-progressing tumors with thymic epithelial differentiation that demonstrate expression of cytokeratins, CD5, p63, CD117, CEA, p53, and BCL2, with the absence of thyroid follicular markers and EBV-related markers. [7] [8] ITC must be considered when determining possible populations at risk, since ITC affects adults with a high occurrence in Asians. [7] [8]

SETTLE is a rare malignant tumor of the thyroid, with only a few cases reported in the literature. [2] SETTLE is thought to arise from embryonic remnants of the pharyngeal pouches, particularly the third and fourth, which then become incorporated into the thyroid during embryonic development. [4] One of the defining features of SETTLE, and central to its classification, is its distinctive histology. These tumors exhibit a "biphasic growth pattern," characterized by uniform spindle cells arranged in fascicular or reticular patterns, alongside epithelial structures that may appear tubulocystic or papillary. [2] This pattern helps pathologists distinguish SETTLE from other thyroid and soft tissue tumors that can have similar histomorphology. [4] [9]

Although its histologic appearance is distinctive, SETTLE is classified by the World Health Organization (WHO) as a tumor of uncertain histogenesis, a category defined by its lack of clear follicular or parafollicular origin. [7] Instead of expressing typical thyroid markers such as calcitonin, thyroglobulin, and TTF-1, SETTLE is consistently negative for these, but shows expression of epithelial and thymic-associated markers, including CK7, CD117, CD99, and BCL2. [5] Because of these distinct features, SETTLE is classified based on its histologic similarity to thymic tissue, not by markers typically expressed in thyroid tumors.

Several reports indicate that SETTLE predominantly affects children and young adults, with a slight male predominance and an average age of approximately 19. [1] Patients typically present with a non-tender, slowly enlarging cervical

swelling and are usually without concomitant symptoms unless the mass is large. It is generally a slow-growing tumor, with an identifiable risk of distant metastasis. Metastasis to the lungs is most common and can be seen many years following the initial treatment. Metastases as late as 22-25 years after the first resection of the tumor have been reported in SETTLE. [10] Hence, there is a need for close monitoring for early diagnosis and management.

There are no known environmental or genetic risk factors for SETTLE. Research Investigators also reported that it does not appear to be associated with prior thyroid conditions or radiation exposure. [5] This lack of clear predisposing factors, combined with the small number of reported cases, makes early diagnosis challenging. Additionally, the nonspecific clinical presentation and lack of common thyroid markers increase the risk of misclassification of the tumor.

3.2. Clinical presentation and imaging

SETTLE tends to present as a painless, gradually enlarging mass in the lower anterior neck, typically originating from one lobe of the thyroid. (11) The mass is usually noticed incidentally or reported by the patient due to cosmetic changes. Systemic symptoms or any changes in the lab values are generally rare. Even local compressive symptoms, including voice changes, dysphagia, or shortness of breath, are quite rare and, when present, are more typically related to the size of the lesion. [12] [13] The mass is usually firm, well-circumscribed, mobile, and not tender. Lymph node involvement is unusual. In our case, the patient was a 26-year-old male who presented with a progressively enlarging neck mass over four months, without any compressive or systemic complaints, stereotypically consistent with patterns reported in the literature. [8] [11]

The radiological findings in SETTLE have not been well established because of the rarity of the tumor. On CT, reported findings described SETTLE as a generally well-defined, lobulated, and heterogeneous solid cystic mass. Post-contrast, the tumor enhances heterogeneously, and some parts of the mass take up contrast more than other parts, with varying degrees of vascularity and varied internal composition. [14]

Ultrasound, which is typically the first imaging study ordered when a thyroid mass is suspected, frequently reveals a heterogeneous lesion that is in keeping with the solid and cystic appearance of the tumor on CT. The tumor is frequently characterized as a solid nodule with findings that can be benign in appearance. However, such characteristics are not unique to SETTLE and can also be found in other thyroid nodules. [1] [15] MRI findings for SETTLE generally show a tumor with isointensity on T1-weighted images, slightly hyperintensity on T2-weighted images, sometimes with a more varied signal, and heterogeneous enhancement after contrast administration. Although PET-CT is not normally done for the initial diagnosis of SETTLE, which typically shows the tumor as a "cold" nodule, increased uptake of the radioactive substance may be visualized, aiding in differentiating from other, less aggressive, tumors. [5] [14]

The anticipated imaging appearance of SETTLE is that of a well-circumscribed, heterogeneous mass with solid and cystic components, most often arising within the thyroid gland. Although not pathognomonic for SETTLE, all these findings should be suspicious for this rare tumor when seen in a young patient. Ultimately, it does require a biopsy and some lab testing. [5]

Fine needle aspiration was performed in our case, but it showed only spindle cells, which is unfortunately insufficient to make the diagnosis of SETTLE. FNA cytology can be successfully diagnostic preoperatively if both tumor components are sampled, with sufficient material obtained for IHC and molecular studies. [13] However, the tumor's biphasic structure limits the utility of cytology alone if only one cellular component is sampled. [13] A definitive diagnosis often depends on complete surgical excision and subsequent histologic and immunohistochemical evaluation [8].

3.3. Pathology, Immunohistochemistry

Several reports described SETTLE as a well-circumscribed, firm, and encapsulated mass, with a lobulated cut surface showing fibrous bands. It is also reported to show areas of hemorrhage, necrosis, and cystic changes. [12] The biphasic pattern, characterized by two distinct cell types, epithelial and spindle cells, is the key feature of SETTLE. The spindle cells are bland and mitotically quiescent, and they are intermingled with glandular structures to form fascicles. [10] The tumor of our patient displayed most of these reported features. The differential diagnosis is broad, and the use of IHC studies is essential to differentiate SETTLE from its mimics. SETTLE cells are consistently diffusely immunoreactive for high molecular weight cytokeratin (e.g., 34βE12) and positive for some epithelial markers (e.g., cytokeratin). They are, however, negative for thyroid-specific markers like TTF1 and thyroglobulin, helping in the distinction between SETTLE and other thyroid cancers. [2] [10] [15]

For final diagnosis, molecular analysis becomes increasingly important, particularly for differentiating SETTLE from synovial sarcoma (SS). The SS18-SSX fusion gene is pathognomonic for SS and is generated by the recurrent chromosomal translocation t(X;18) (p11;q11). [10] When a tumor lacks this fusion gene form, it is not supportive of the diagnosis of SS. There are no definitive molecular markers for SETTLE, underlining the importance of accurate diagnosis by extensive histology and immunohistochemistry. The IHC markers that were employed to distinguish the two cell components of SETTLE from its mimics are summarized in Table 1.

Table 1 IHC markers used to distinguish the two cell components of SETTLE from its mimics

Stain	Spindle Cells	Epithelial Cells	Key Differentiator From
Cytokeratins (AE1/AE3)	Negative or Focal	Strongly Positive	Differentiates from tumors lacking an epithelial component.
p63 / p40	Positive	Positive	Strong, diffuse staining is characteristic. Helps differentiate from some thyroid cancers.
CD99	Positive	Variable	Staining can be similar to synovial sarcoma, so it is not a standalone differentiator.
Bcl-2	Positive	Variable	Also, often positive in synovial sarcoma.
CD5	Positive	Positive	A marker of thymic differentiation, its presence strongly supports SETTLE.
Calcitonin	Negative	Negative	Rules out Medullary Thyroid Carcinoma.
Thyroglobulin / TTF-1	Negative	Negative	Rules out most primary Thyroid Carcinomas.
STAT6	Negative	Negative	Rules out Solitary Fibrous Tumor.

3.4. Pathophysiology, pathogenesis, molecular

The exact histogenesis of SETTLE continues to be a matter of continued study and controversy. The most widely accepted theory is that SETTLE arises from branchial pouch remnants or ectopic thymic tissue in the thyroidal area [16]. This hypothesis finds support in the 'thymus-like differentiation' of the tumor, that is, its histologic similarity to embryonic thymus. A direct thymic lineage has not been formally proven yet. Most investigations aimed at characterizing thymic markers, including CD20, CD5, and TdT-immature T lymphocytes, have been negative in SETTLE cases. [1] [5]

Recent developments in molecular sequencing have started to allow insights into the genetic landscape of SETTLE, providing further lines of evidence to understand its pathogenesis. Although SETTLE lacks the distinctive translocations of its morphologic mimic, synovial sarcoma, next-generation sequencing has revealed recurrent genetic changes. While no single, recurrent genetic alteration or hallmark mutation has been identified in SETTLE, KRAS and NRAS mutations have been reported in some individual cases. One study analyzed five well-defined cases of SETTLE and found: [17]. More extensive sequence analysis in a limited number of SETTLE cases has identified pathogenic KMT2C and KMT2D mutations [4]. KMT2D (also known as MLL2) is a histone methyltransferase that plays a major role in chromatin remodeling. Mutations in this gene have been observed in a variety of developmental disorders and cancer. KMT2C (MLL3) is another histone methyltransferase, and its mutations are observed in several human cancers. [4]. While CTNNB1 mutations might not be a common driver mutation in SETTLE, they can occur in some cases, and the landscape of mutations in SETTLE is more complex than a simple absence of CTNNB1 mutations to distinguish it from other tumors. [18]

The discovery of these genetic changes provides evidence that the deregulation of chromatin remodeling and RAS pathways may be implicated in the tumorigenesis and progression of SETTLE. However, due to the scarcity of SETTLE, additional large molecular investigations are required to completely delineate its genetic landscape and find recurrent oncogenic drivers, with potential therapeutic implications.

The pathophysiology of SETTLE exhibits an indolent growth pattern, but a malignant process and, frequently, delayed metastasis occurring years after surgical intervention, most commonly to the lungs, as was the case with our patient.

The molecular understanding continues to unfold, but the clinical behavior calls for aggressive, long-term follow-up to guarantee the best patient outcomes. [19]

4. Management and outcome

SETTLE is usually managed surgically. This is typically a lobectomy or thyroidectomy, depending on the nodules' size and local aggressiveness. [17] Since SETTLE is a low-grade, slow-growing cancer, the prognosis with only surgery is generally favorable. However, late recurrence and metastasis are the most troublesome aspects, as the tumors recur in the lung or lymph nodes or other distant organs several years or decades after resection of the primary disease. [10] This is an irrational bias requiring long-term vigilance. Radiotherapy and chemotherapy are not commonly used as first-line treatment, but may have a place in the locally advanced and metastatic setting. [19]

The typically indolent natural history is underscored by the long-term follow-up of most of the SETTLE patients, some of whom have had metastases, and by times to progression. [10] This is in stark contrast to the clinical course of most other thyroid malignancies. The occurrence of late distant metastases in the SETTLE, on the other hand, that even if compared to other tumors in this age group, has a more favorable survival, makes it necessary to have a continuous follow-up and treatment of the patients over the years. [2] The difficulty here is to identify such a rare entity, and long-term follow-up is necessary to diagnose a metastatic disease in time.

4.1. What lies ahead for the diagnosis and treatment of SETTLE?

SETTLE a very rare tumor that is difficult to diagnose and manage over the natural history of the tumor. Improved insight into the molecular pathogenesis of SETTLE and developments in molecular profiling and genomic sequencing in the future may result in a more precise definition of SETTLE and its more consistent separation from its histologic mimickers. [20] Lack of explicit IHC markers and the biphasic nature of the tumor continue to necessitate reliance on the expertise of the histopathologist and a multidisciplinary approach.

Molecular biomarkers and recurrent genetic alterations may help in early diagnosis, prognostication of metastatic potential, and individualized therapies, especially in the setting of metastasis or relapse. Regarding the treatment, radical surgical resection is the cornerstone of treatment. [17] Nevertheless, more defined criteria for adjuvant treatment and further follow-up period will be required by larger case series and long-term follow-up results. International cooperation and registries may contribute to defining shared management pathways.

4.2. What did we learn from this case?

Uncommon thyroid neoplasms, like SETTLE may be missed if they are not included in the list of differential diagnoses of a thyroid mass; this may result in a missed or misdiagnosed thyroid mass and suboptimal patient treatment. However, when a correct diagnosis is established, with careful histologic and immunohistochemical assessment, then a single disease can open possibilities for expert treatment and success. This case raises the possibility of late metastases from an indolent primary tumor and demonstrates the importance of long-term follow-up in young healthy patients with SETTLE. With judicious interdisciplinary management and extensive follow-up, such patients are generally associated with a good prognosis.

Abbreviations

- Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE),
- Carcinoma showing thymus-like differentiation (CASTLE),
- intrathyroid thymic carcinomas (ITC),
- Immunohistochemistry (IHC),
- Fine needle aspiration (FNA),

5. Conclusion

This case of SETTLE in a young male emphasizes the need for a step-wise, comprehensive approach in the evaluation of a thyroid mass. There is a need for optimal imaging, adequate tissue sampling, and thorough histomorphological assessment in combination with an extensive immunohistochemical panel to provide the most accurate diagnosis. Knowledge of this neoplasm is important, such that it becomes a consideration in the differential diagnosis of a patient with a thyroid mass. The present case highlights the developing thyroid pathology where new entities are being

described and characterized. Hopefully, as we move towards a molecular understanding of these rare neoplasms along with larger series of cases, we will see improvements in diagnostic criteria and novel treatment regimens.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Author contributions

All authors contributed equally to producing this manuscript

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