Case Report
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Spindle Epithelial Tumor with Thymus-like Element (SETTLE): A Case Report

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Abstract

Objective – Spindle epithelial tumor with thymus-like element (SETTLE) is an extremely rare neoplasm of the thyroid gland. We present the first case of SETTLE in Croatia. **Case Report** – A 17-year-old girl with Hashimoto's thyroiditis was presented with an asymptomatic solitary thyroid nodule. Fine-needle aspiration cytology was suggestive of SETTLE. The patient underwent hemithyroidectomy and immunohistopathology confirmed the diagnosis. There is no evidence of local or distant disease recurrence at 8 years after surgery. **Conclusion** – SETTLE should be included in the differential diagnosis of thyroid gland tumors in children and adolescents. Surgical resection is the mainstay of treatment. Due to possible late metastases, a close and long-term follow-up is recommended.

Key Words: SETTLE ▪ Thyroid Gland ▪ Neoplasm ▪ Children.

Introduction

Spindle epithelial tumor with thymus-like element or differentiation (SETTLE) is a very rare thyroid tumor that is thought to originate either from the thyroglossal duct or from ectopic thymus cells (1). It occurs most frequently in adolescents, with an average age of 17.9 years (range 2 to 70 years) (2, 3). Men are more frequently affected than women, with a ratio of 1.8:1 (4). SETTLE is considered a low-grade malignancy due to its slow growth and indolent clinical course (1, 5). Metastases occur in 35% of patients within a 5-year follow-up and increase to 71% after 5 years (among the published cases), but are reported up to 20 years after the initial diagnosis, which underlines the need for long-term surveillance. The most common metastatic sites include lungs (60% of cases), kidneys, mediastinum, lymph nodes (often in the neck region), and liver (4, 5, 6).

We report an adolescent case of SETTLE who is disease-free at 8 years after surgery.

Case report

A 17-year-old girl was diagnosed with Hashimoto's thyroiditis at the age of 14. She had normal thyroid function (free thyroxine level in the reference range, slightly elevated thyroid-stimulating hormone), positive anti-thyroglobulin antibodies, and a hypoechoic and heterogeneous thyroid gland on the ultrasound examination. The patient required no replacement therapy and was followed-up regularly every six months. After three years of monitoring, a hypoechogenic nodule measuring 7×6×5 mm was discovered in the left lobe of the thyroid gland on a routine ultrasound examination. An ultrasound guided fine-needle aspiration was performed. Cytological analysis showed a

hypercellular appearance with coherent and single spindle-shaped epithelial cells associated with fibrovascular stroma, negative for thyroid transcription factor-1 (TTF-1), suggestive for SETTLE (Fig. 1). Based on this finding, surgical intervention was recommended. In the preoperative care she received a red blood cell transfusion due to severe iron deficiency anemia (hemoglobin 5.8 g/dL). Left thyroid lobectomy was performed. Histopathological evaluation revealed a neoplastic proliferation with a well-defined border predominantly composed of spindle cells with glandlike epithelial structures and ductular formations without significant atypia. Immunohistochemistry showed negative staining for CD5, carcinoembryonic antigen (CEA), S-100, vimentin, terminal deoxynucleotidyl transferase (TdT), thyroglobulin and calcitonin, scanty positivity for Bcl-2, and positivity for cytokeratin AE1/AE3 and CD99, which confirmed the diagnosis of SETTLE (Fig. 2). Molecular genetic testing was not performed.

The postoperative course was uneventful, and the girl was transferred to the Department of Pediatrics for further evaluation. Cytological analysis of the bone marrow aspirate revealed erythroid hyperplasia with myeloid : erythroid ratio 1:1 (normally 3-4:1), and dysplastic changes in erythroid precursors, resulting from chronic iron deficiency. Chest X-ray and abdominal ultrasound were normal. Multi-slice computed tomography (MSCT) of the chest revealed two solid nodules in the upper lobe <5 mm in diameter. A subsequent positron emission tomography (PET) scan was negative. The patient was presented to the Virtual Tumor Board of the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), and further

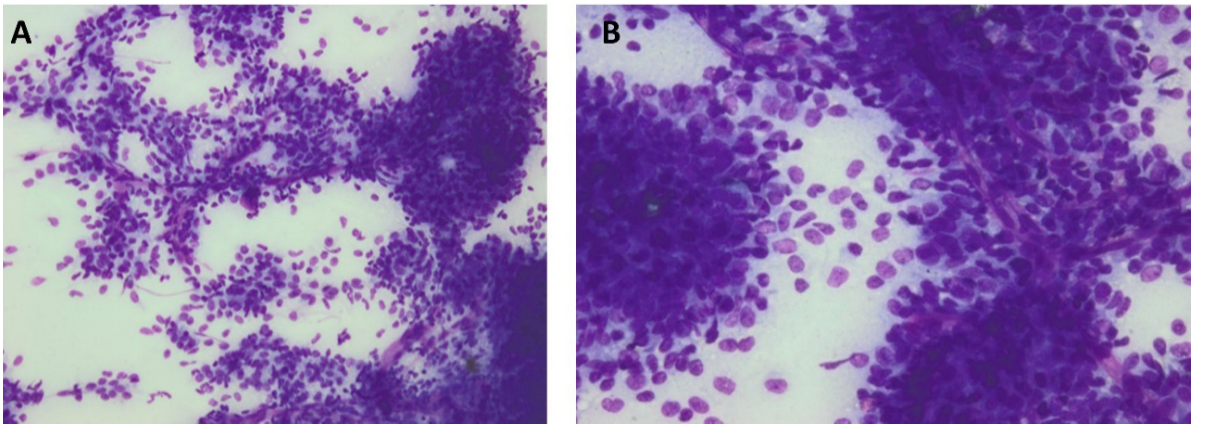

Fig. 1. *Fine needle aspiration cytology of the thyroid nodule showing coherent and single spindle-shaped epithelial cells with central fibrovascular stroma (May-Gruenwald-Giemsa; Fig.1A 40×; Fig. 1B 100×).*

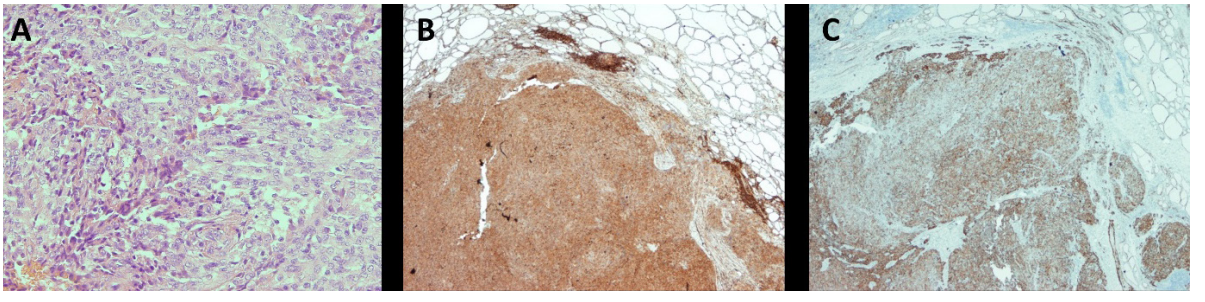

Fig. 2A. *Thyroid SETTLE showing high cellularity and biphasic pattern composed of spindle cells and epithelioid cells with glandular and ductular structures (HE, 200×). The tumor cells show positive immunostaining for CD99 (Fig. 2B, 20×) and AE1/AE3 (Fig. 2C, 20×).*

surveillance was recommended. She has been on regular follow-up and has been asymptomatic with no recurrence at 8 years after surgery.

Discussion

SETTLE is an extremely rare thyroid tumor that typically occurs in young adults, although the occurrence in young children and the elderly has been reported (2, 3). It was first described in 1991 by Chan and Rosai, who defined SETTLE as a distinct clinicopathological entity after studying eight neoplasms in the neck region of children and young adults, originally diagnosed as malignant teratoma of the thyroid, epithelial cell tumor of the thyroid with mucinous cyst, and thyroid thymoma (7). As of end of 2023, more than 100 cases of SETTLE have been documented in the literature (8).

SETTLE usually presents as a painless mass in the neck region. Some cases present with thyroiditis with normal thyroid function. Radiologic methods are not sensitive for the diagnosis (1, 5). Fine needle aspiration with cytology is seldom diagnostic for SETTLE as it is rarely considered, and easily confused with other entities (e.g. spindle cell variants of medullary, papillary, and anaplastic thyroid carcinoma and thymoma) (9, 10). An accurate diagnosis requires detailed histology, and immunohistochemistry is the mainstay of diagnosis (2, 5). Macroscopically, SETTLE is generally a well-defined mass ranging in size from 1.8 to 12 cm (11). The outer surface of the tumor is firm and has a white gray to brown color. A cystic or lobular structure with remnants of thyroid tissue at the periphery of the tumor may be found in cross-section (2). Microscopically, the tumor may present as a confined or infiltrating form with fibrous bands that incompletely divide it into lobes. The tumor consists primarily of spindle cells and, to a lesser extent, glandular structures. It exhibits high cellularity, elongated or oval nuclei with irregular borders and a low degree of cell pleomorphism. Mitoses are rare, and necrosis, hemorrhage or ischemia are almost never present. Under the electron microscope, the spindle cells show cytoplasmic tonofilaments, desmosomes and a basal lamina consisting of epithelial cells (1, 2, 7). Distant metastases have the same morphological structure as the primary tumor. Immunohistochemistry shows positivity for cytokeratin (CK) 7 and AE1/AE3, while vimentin and epithelial membrane antigen (EMA) show different expressions (12, 13). Rarely spindle cells show myoepithelial differentiation, resulting in reactivity to CD99 and Bcl-2. Positive staining for CD117, integrase interactor 1 (INI-1) and transducer-like enhancer of split 1 (TLE1) is described. The staining for CD5, CEA, S-100, TdT, calcitonin, neuron-specific enolase (NSE), thyroglobulin, synaptophysin and chromogranin is negative, that helps distinguish SETTLE from other thyroid tumors (5, 13). In our patient, immunoreactivity for CD99 and AE1/AE3 was confirmed, while staining for CD5, CEA, S-100, TdT, vimentin, thyroglobulin and calcitonin was negative. Recent molecular studies have shown specific *KRAS* gene pathogenic variants at codons 13 and 15 (14). The distinction between SETTLE and ectopic thymoma, anaplastic spindle cell carcinoma of the thyroid gland, medullary thyroid carcinoma and synovial sarcoma is challenging. Ectopic thymoma is a benign tumor that usually occurs in women with an average age of 42.7 years, is dominated by lymphocytes in the histology and stains positive for CD20 and TdT. Anaplastic spindle cell carcinoma of the thyroid gland rarely occurs in children. It is characterized by numerous mitoses and necrotic areas, and stains positivity for CEA. Medullary thyroid carcinoma arises from parafollicular "C" cells and has round or polygonal, sometimes spindle-shaped cells with nuclei that may be oval, elongated or irregular. It shows positive staining for CEA, amyloid, chromogranin, synaptophysin and calcitonin. Synovial sarcoma occurs mainly in children and shows similar immunohistochemistry with positivity for keratin, vimentin, EMA, CD9 and Bcl-2. Unlike SETTLE, synovial sarcoma shows monomorphic and hyperchromatic cells, mitotic activity, and specific molecular changes - translocations t(X;18) (p11.2;q11.2) involving the *SS18* gene on chromosome 18 and *SSX1, SSX2, SSX4* genes on chromosome X (2, 5, 13).

Surgery (usually hemithyroidectomy) is the treatment of choice for SETTLE, even in the presence of metastases at the time of diagnosis (8, 11). Metastatic disease can be treated with adjuvant chemotherapy and radiotherapy, but clinical trials do not exist, and evidence-based treatment guidelines have not been established. Five-year survival rates reach 90%, but even after total resection, late metastases, especially to the lungs, can occur, necessitating long-term patient monitoring (2).

Our case suggests considering SETTLE in a differential diagnosis of thyroid malignancies in the young population presenting with a thyroid nodule on clinical examination or found incidentally on ultrasound. Close cooperation among pediatric oncologists, radiologists, cytologists, pathologists, and surgeons, is very important in the management of SETTLE. Due to the rarity of the tumor and in the absence of published diagnostic and therapeutic guidelines, future international collaborative efforts are needed.

Conclusion

SETTLE is an extremely rare thyroid tumor with metastatic potential. Although rare, SETTLE should be included in the differential diagnosis of thyroid gland tumors in children and adolescents. Standardized diagnostic and therapeutic guidelines are not available. Due to a propensity for late metastases, long-term patient monitoring is recommended.

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Conflict of interest: The authors declare that they have no conflict of interest.

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