Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) in a Child, Diagnostic and Treatment Challenge: Case Report

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Tumor Epitelial Fusiforme com Diferenciação Semelhante ao Timo (SETTLE) em Criança, Desafio Diagnóstico e Tratamento: Relato de Caso

Tumor Epitelial Fusiforme con Diferenciación Similar al Timo (SETTLE) en un Niño, Desafío Diagnóstico y Terapéutico: Informe de Caso

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ABSTRACT

Introduction: Spindle cell epithelial tumor with thymus-like differentiation (SETTLE) is an extremely rare and difficult-to-diagnose thyroid tumor that derives from ectopic thymic cells or branchial pouches. This thyroid tumor variant is usually found in children, adolescents, and young adults, and is rarely observed in elderly patients, in addition to having great potential for metastatic spread. The classic presentation is a painless and usually asymptomatic cervical mass in the topography of the thyroid. Its serum markers are nonspecific. Given the scarcity of data on this neoplasm and the importance of alerting to this diagnostic possibility, a case report was carried out on a patient diagnosed with SETTLE, focusing on the differential diagnosis and treatment of this tumor variant, aiming to add more information about this condition to the literature. **Case report:** A 2-year-old male child who presented with a potentially malignant thyroid tumor mass with immunohistochemical analysis indicative of SETTLE. The patient underwent imaging tests and fine needle aspiration biopsy, which helped in the decision for an initial surgical approach. Thyroidectomy was performed, followed by long-term oncological follow-up. **Conclusion:** SETTLE is a rare thyroid tumor with slow metastatic potential that affects mostly children and adolescents and is difficult to diagnose, requiring attention to differential diagnosis. The main diagnostic test is immunohistochemical analysis and the main treatment is surgery, followed by prolonged follow-up.
Keywords: Thyroid Neoplasms/surgery; Thyroidectomy; Head and Neck Neoplasms/surgery; Case Reports; Child, Preschool.

RESUMO

Introdução: O tumor epitelial fusiforme com diferenciação semelhante ao timo (SETTLE) é um tumor da tireoide extremamente raro e de difícil diagnóstico que deriva de células tímicas ectópicas ou bolsas branquiais. Essa variação tumoral tireoidiana geralmente é encontrada em crianças, adolescentes e adultos jovens, e raramente é observada em pacientes de idade avançada, além de possuir grande potencial para disseminação metastática. A apresentação clássica é uma massa cervical indolor e normalmente assintomática na topografia da tireoide. Seus marcadores séricos são inespecíficos. Diante da escassez de dados sobre tal neoplasia e da importância em alertar para essa possibilidade diagnóstica, foi realizado um relato de caso sobre um paciente diagnosticado com SETTLE, com foco no diagnóstico diferencial e tratamento dessa variante tumoral, objetivando agregar à literatura mais informações a respeito dessa condição. **Relato do caso:** Criança de 2 anos, do sexo masculino, que apresentava uma massa tumoral na tireoide com potencial de malignidade e com análise imuno-histoquímica indicativa de SETTLE. O paciente foi submetido a exames de imagem e à punção aspirativa por agulha fina, que auxiliaram na decisão por uma abordagem inicial cirúrgica. A tireoidectomia foi realizada, seguida de acompanhamento oncológico em longo prazo. **Conclusão:** O SETTLE é um tumor raro da tireoide, com lento potencial metastático, que afeta mais crianças e adolescentes, e é de difícil diagnose, necessitando atenção para o diagnóstico diferencial. Tem como principal exame diagnóstico a análise imuno-histoquimica, e o principal tratamento é a cirurgia, seguida de acompanhamento prolongado.
Palavras-chave: Neoplasias da Glândula Tireoide/cirurgia; Tireoidectomia; Neoplasias de Cabeça e Pescoço/cirurgia; Relato de Caso; Pré-Escolar.

RESUMEN

Introducción: El tumor epitelial de células fusiformes con diferenciación similar al timo (SETTLE) es un tumor tiroideo extremadamente raro y difícil de diagnosticar que se deriva de células tímicas ectópicas o bolsas branquiales. Esta variante del tumor tiroideo se encuentra generalmente en niños, adolescentes y adultos jóvenes, y rara vez se observa en pacientes de edad avanzada, además de tener gran potencial de diseminación metastásica. La presentación clásica es una masa cervical indolora y habitualmente asintomática en la topografía de la tiroides. Sus marcadores séricos no son específicos. Dada la escasez de datos sobre esta neoplasia y la importancia de dar a conocer esta posibilidad diagnóstica, se realizó un reporte de caso en un paciente diagnosticado con SETTLE, centrándose en el diagnóstico diferencial y tratamiento de esta variante tumoral, con el objetivo de agregar más información sobre esta condición a la literatura. **Informe del caso:** Un niño de sexo masculino de 2 años, quien presentó una masa tumoral en tiroides con potencial maligno y con análisis inmunohistoquímico indicativo de SETTLE. Al paciente se le realizaron pruebas de imagen y biopsia por aspiración con aguja fina, lo que ayudó en la decisión de un abordaje quirúrgico inicial. Se realizó tiroidectomía, seguida de seguimiento oncológico a largo plazo. **Conclusión:** SETTLE es un tumor tiroideo raro, con potencial metastásico lento, que afecta más a niños y adolescentes y es de difícil diagnóstico, requiriendo atención al diagnóstico diferencial. La principal prueba diagnóstica es el análisis inmunohistoquímico y el tratamiento principal es la cirugía, continuada de un seguimiento prolongado.
Palabras clave: Neoplasias de la Tiroides/cirugía; Tiroidectomía; Neoplasias de Cabeza y Cuello/cirugía; Informe de Caso Raro; Preescolar.

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INTRODUCTION

Spindle cell epithelial tumor with thymus-like differentiation (SETTLE) is a rare neoplasm in the thyroid gland with a low malignancy rate due to its slow metastatic power to the lymph nodes, which can be found in children and young adults. The literature described only 47 cases until 2024[1-3], with the first reported case in Brazil in 2010[4]. In most cases, its clinical presentation consists of a previous painless, or little painful, cervical mass. More symptomatic presentations are rare. Thyroid function serum markers and known tumor markers are nonspecific[5]. Diagnosing this tumoral variant is difficult, as it can often be confused with other thyroid carcinomas due to the scarce knowledge about it, the nonexistence of specific markers, and little specific cytological characteristics[1].

The ultrasound exam shows heterogeneous lesions, while computer tomography on the thyroid topography reveals nodules with solid and cystic components, in addition to being able to evaluate regional lymph nodes or distant metastases. Fine needle aspiration puncture (FNAP) shows variable characteristics, making it difficult to determine the type of tumor.

Treatment is surgical, via total or partial thyroidectomy[5]. Radiotherapy and chemotherapy are reserved for more advanced tumors or tumors that show metastasis. Prolonged oncological follow-up is essential to assess the recurrence or metastasis, which can happen decades after surgical treatment[5,6]. With proper surgical treatment and screening in the long term, the prognosis is usually favorable to patients.

From a histological analysis of the surgical piece, the SETTLE presents a biphasic pattern, including spindle cells and glandular epithelium[6]. The immunohistochemical analysis is the gold standard for diagnosis as it provides enough evidence to determine this tumoral variant, such as positivity for cytokeratin (CK), vimentin, CD99, smooth muscle actin (SMA), INI-1 and BCL-2 negativity for thyroid markers like thyroglobulin and thyroid transcription factor 1 (TTF1) and for cluster of differentiation 5 (CD5) and CD20[1,4,7,8].

This report aims to document and analyze the case of a patient afflicted by a SETTLE epithelial tumor on the thyroid gland and the surgical approach to the patient. The study has been approved by the *Hospital das Clínicas da Universidade Federal de Minas Gerais* (UFMG) Research Ethics Committee, approval report number 168140 (CAAE (submission for ethical review): 02839212.4.0000.5149), according to Resolution no. 466/12[9] of the National Health Council (CNS).

CASE REPORT

A two-year-old male patient was referred from pediatric endocrinology for surgical evaluation. He presented a palpable mass in the anterior cervical region, with stony consistency, mobile and painful.

The thyroid ultrasound showed a solid, hypoechoic, voluminous nodule (1.9 cm^3), measuring 22x14x12 mm (longitudinal x transversal x anteroposterior measurement – LxTxAP), lobulated contours, in contact with the thyroid capsule, occupying a reasonable portion of the left lobe and predominantly peripheric flow to Doppler TI-RADS 5 (Thyroid Imaging Reporting and Data System – classification of thyroid nodules by the American College of Radiology as moderately suspicious for malignancy).

The microscopic findings of the thyroid FNAP showed an amorphous and hemorrhagic background, with numerous spindle cells of hyperchromatic nuclei with finely granular chromatin, at times isolated and other times grouped three-dimensionally, sometimes showing papillae with stromal axis, rare nuclei with outlines of pseudoinclusions and no detectable nuclear clefts. Cytology conclusion: neoplasm of uncertain malignant potential.

Values for calcitonin, anti-thyroglobulin (anti-Tg), thyroglobulin (Tg), calcium, thyroid-stimulating hormone (TSH), thyroxine (T4), anti-TSH receptor antibody (TRAB), and anti-thyroid peroxidase antibody (anti-TPO) were within the reference values for that age.

The patient was submitted to total thyroidectomy associated with cervical and mediastinal lymphadenectomy ipsilateral to the nodule (levels VI and VII), and the surgical piece was sent for anatomopathological study.

The patient evolved well in the immediate postoperative period and was discharged on the day after the surgery with no signs or symptoms of hypoparathyroidism.

The macroscopic analysis of the anatomopathological study showed a deformed thyroid measuring 5.0x2.5x1.5 cm, covered by a smooth and opaque capsule. Two nodular formations were found, the bigger one measuring 3.5x2.0x1.2 cm and the smaller one measuring 2.0x1.5x0.7 cm. The thyroid microscopy showed a biphasic neoplasm constituted by a spindle cell and organoid component, with outlines of glandular and papillary structures. No relevant necrosis areas or mitotic activities were observed. The nodules described in the macroscopy correspond to thymic cells with neoplasm-free vascular congestion. Moreover, five reactive lymph nodes were assessed, all neoplasm-free. The study of the surgical piece suggested a SETTLE-compatible histology.

The complementary immunohistochemical analysis was positive for betacatenin in cytoplasm, CD5 negative,

cytokeratin-19 (CK19) negative, thyroglobulin positive in thyroid follicles but negative in neoplasm, vimentin positive, and 10% Kiel 67 (Ki67) positive.

The patient has been undergoing clinical and imaging monitoring with head and neck surgery and pediatric oncology for two and a half years, with no signs of recurrence to date.

DISCUSSION

The World Health Organization (WHO) recognizes three types of thymic tumors of the thyroid region, with benign and malignant tumors sharing a thymic epithelial differentiation referred to as "thymoma family" and "thymic carcinoma family". They are said to have been developed from ectopic thymus or branchial pouch remnants[10]. Described for the first time by Chan[3] in 1991, SETTLE is one of those rare neoplasms.

SETTLE predominates in children, adolescents, and young adults. It seems to prevail in male patients. In contrast with the most common thyroid neoplasms, no predisposing factors, such as iodine deficiency, ionizing radiation, genetic or environmental factors, have been associated with SETTLE[5].

SETTLE is clinically painless at first, with an indolent or slightly painful cervical mass on the thyroid topography being the most frequent clinical manifestation. The presence of thyromegaly may or may not be associated with the disease. An extensive literature review showed the difficulty in diagnosing the disease since, in addition to being rare, there is no specific serum marker for this affliction. Moreover, the CEA, thyroid function, and calcitonin levels are within the normal limits[11].

Suspicion of the diagnosis is greater in the first years of life, given the epidemiology of the tumor and the fact that thyroid nodules are uncommon at this age. The FNAP biopsy is rarely diagnosed, although in patients with normal serum calcitonin levels and with FNAP showing medullary thyroid carcinoma, SETTLE is a diagnosis to consider[5].

Due to this difficulty in determining SETTLE, it is essential to pay attention to the differential diagnosis, excluding other similar forms of neoplasms, including a group of tumors that present spindle-shaped and epithelial components, namely, synovial sarcoma, anaplastic sarcomatoid carcinoma, malignant melanoma, carcinoma showing thymus-like elements (CASTLE) and spindle-shaped variant of medullary thyroid carcinoma[3,5,11].

Immunohistochemical study is the gold standard for diagnosis. Immunohistochemical analysis presents key information to define a SETTLE diagnosis, like positivity for CK, vimentin, and CD99, and negativity for thyroglobulin and CD20, marking this as the primary test to detect this tumoral variant and conclude the differential diagnosis[1]. In the presented case, immunohistochemistry was positive for beta-catenin in cytoplasm, CD5 negative, CK19 negative, thyroglobulin negative, vimentin positive, and 10% Ki67 positive. Such findings corroborate the SETTLE diagnosis. A negative CK19 result is not uncommon, but it does not hinder the tumoral variant diagnosis, given that the literature does not highlight CK19 as a specific marker for this tumor. The SETTLE differential diagnostic evaluation involves a combination of morphological characteristics and an array of immuno-markers that might include CK, but not necessarily CK19, since other immunohistochemical findings conclude the diagnosis[7].

The choice between a total thyroidectomy or a lobectomy is controversial due to a lack of studies that assess the disease's recurrence with long-term follow-up. If, on one hand, data suggests a low recurrence of the tumor, on the other hand, the few metastasis cases were only described in patients with prolonged post-surgery follow-up. No data recommends or not recommends performing a prophylactic lymphadenectomy[5]. In the case presented, the medical team opted for total thyroidectomy and lymphadenectomy of the recurrent chain ipsilateral to the tumor and upper mediastinum due to the high suspicion of malignant neoplasm, in addition to the tumor's size and the patient's age.

Chemotherapy and radiotherapy are reserved for patients in advanced stages of SETTLE to control tumoral growth, with infiltrative local disease, vascular invasion, or metastatic disease[5,6].

Although the initial behavior is quite painless, with a five-year survival rate of over 80%, it is not unusual to find late locoregional and distant metastases in patients followed up in the long term[10], with cases ranging from two to 25 years of follow-up after surgical treatment[5]. Thus, the extreme importance of a prolonged patient follow-up.

CONCLUSION

This study reported the case of a 2-year-old male child with SETTLE, a rare tumoral variant of low malignancy and difficult diagnosis, with no specific markers, which requires attention to its differential diagnosis since it can often be misdiagnosed as other thyroid tumors. The primary diagnosis medium is immunohistochemical analysis, with CK, vimentin, and CD99 positivity and thyroglobulin and CD20 negativity being the main findings reported as indicative of SETTLE. Other tests like ultrasound and FNAP tend to be inconclusive. Surgery is the main treatment, with chemotherapy and radiotherapy used only in patients in advanced stages. Long-term post-surgical follow-up is essential since this type of carcinoma may evolve with late metastases.

CONTRIBUTIONS

All the authors have substantially contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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REFERENCES

1. Kathamuthu K, Janardan C, Ramkumar S, et al. Spindle epithelial tumor with thymus-like differentiation (SETTLE) misdiagnosed as papillary thyroid carcinoma: a case report. Cureus. 2022;14(11):e31574. doi: https://www.doi.org/10.7759/cureus.31574
2. Chadha P, Kamboj M, Pasricha S, et al. Spindle epithelial tumor with thymus-like elements (SETTLE): a diagnostic challenge with distinct therapeutic implication; case report. Diagnostic Pathol. 2024;19(108):1-8. doi: https://doi.org/10.21203/rs.3.rs-4209973/v1
3. Chan JK, Rosai J. Tumors of the neck showing thymic or related branchial pouch differentiation: a unifying concept. Hum Pathol. 1991;22:349-67.
4. Magnata Filho LA, Bordallo MA, Pessoa CH, et al. Thyroid spindle epithelial tumor with thymus-like differentiation (SETTLE): case report and review. Arq Bras Endocrinol Metabol. 2010;54(7):657-62. doi: https://doi.org/10.1590/s0004-27302010000700011
5. Ippolito S, Bellevicine C, Arpaia D, et al. Spindle epithelial tumor with thymus-like differentiation (SETTLE): clinical-pathological features, differential pathological diagnosis and therapy. Endocrine. 2016;51(3):402-12. doi: https://doi.org/10.1007/s12020-015-0716-5
6. Recondo G Jr, Busaidy N, Erasmus J, et al. Spindle epithelial tumor with thymus-like differentiation: a case report and comprehensive review of the literature and treatment options. Head Neck. 2015;37(5):746-54. doi: https://doi.org/10.1002/hed.23634
7. Folpe AL, Lloyd RV, Bacchi CE, et al. Spindle epithelial tumor with thymus-like differentiation: a morphologic, immunohistochemical, and molecular genetic study of 11 cases. Am J Surg Pathol. 2009;33(8):1179-86. doi: https://www.doi.org/10.1097/PAS.0b013e31819e61c8
8. Su L, Beals T, Bernacki EG, et al. Spindle epithelial tumor with thymus-like differentiation: a case report with cytologic, histologic, immunohistologic, and ultrastructural findings. Mod Pathol. 1997;10(5):510-4.
9. Conselho Nacional de Saúde (BR). Resolução nº 466, de 12 de dezembro de 2012. Aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Diário Oficial da União, Brasília, DF. 2013 jun 13; Seção I:59.
10. Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022;33(1):27-63.
11. Stevens TM, Morlote D, Swensen J, et al. Spindle epithelial tumor with thymus-like differentiation (SETTLE): a next-generation sequencing study. Head Neck Pathol. 2019;13(2):162-8.

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