Spindle epithelial tumour with thymus-like differentiation: report of two cases

S Karaisli¹, M Hacıyanlı¹, S Gücek Hacıyanlı¹, C Tavusbay¹, EO Gur¹, E Kamer¹, D Arikan Etit²

¹Department of General Surgery, Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey

²Department of Pathology, Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey

ABSTRACT

Spindle epithelial tumour with thymus-like differentiation (SETTLE) is a very rare neck malignancy arising from thymic tissue or branchial pouch, mostly seen in the early decades of life. SETTLE is thought to be a low-grade neoplasm but distant metastases have been reported. Fewer than 50 cases have been reported in the PubMed database.

We report on the four-year follow-up for a 13-year-old boy, with no signs of recurrence or distant metastasis. In addition, a 45-year-old woman was admitted to hospital with neck mass. Fine-needle aspiration biopsy was compatible with medullary thyroid carcinoma but serum levels of calcitonin were normal. Total thyroidectomy and central compartment lymph node dissection was planned with an initial diagnosis of medullary thyroid carcinoma. At surgery, frozen section analysis converted our diagnosis to SETTLE and the intraoperative strategy was changed.

SETTLE should be considered in a patient with normal serum calcitonin levels in the presence of suspicious medullary thyroid carcinoma at fine-needle aspiration biopsy. Frozen section analysis may help to manage the intraoperative strategy. This report describes the first case of SETTLE successfully diagnosed by frozen section analysis.

KEYWORDS

CASTLE – Frozen section analysis – Medullary thyroid carcinoma – SETTLE – Thyroidectomy

Accepted 9 June 2019

CORRESPONDENCE TO

Serkan Karaisli, E: skaraisli@hotmail.com

Background

Spindle epithelial tumour with thymus-like differentiation (SETTLE) is a rare malignant tumour of the thyroid gland. SETTLE is believed to arise from thymic tissue or branchial pouch remnants showing thymic or branchial pouch differentiation.¹ SETTLE is thought to be a low-grade neoplasm owing to its slow-growing behaviour.¹ To the best of our knowledge, fewer than 50 cases have been reported in the PubMed database. We report two cases of SETTLE, including the four-year follow-up results of a case reported recently² and a new case treated successfully.

Case history

Case 1

A 15-year-old boy was admitted to the general surgery polyclinic complaining of a rapidly growing neck mass. There was no evidence of distant metastases. A total thyroidectomy without lymph node dissection was performed. The patient was discharged uneventfully on postoperative day 1. Histopathological and immunohistochemical analysis revealed a diagnosis of SETTLE in the right lobe of the

thyroid. The patient remained well at the four-year follow-up, with no tumour recurrence or metastasis on imaging studies.

Case 2

A 45-year-old woman presented with an asymptomatic neck mass detected during a routine check-up. There was no significant medical history and no risk factors for thyroid cancer. Neck ultrasonography showed that the mass was in the peripheral zone of the right thyroid lobe. It measured 23 × 18 mm in diameter with predominantly solid and a few small cystic components. Fine-needle aspiration biopsy of the nodule was compatible with medullary thyroid carcinoma but levels of serum calcitonin and carcinoembryonic antigen (CEA) were normal. Screening of the parathyroid glands and adrenal glands showed no abnormalities.

Owing to the suspicion of medullary thyroid carcinoma, the patient underwent total thyroidectomy and central compartment lymph node dissection and a specimen was sent for frozen section analysis intraoperatively. The frozen section analysis was reported as being suspicious for carcinoma showing thymus-like elements or SETTLE in the

right lobe. This progress changed the operative strategy. The lateral neck dissection was not performed because of the absence of suspicious metastatic lymph nodes. The bilateral recurrent laryngeal nerves were preserved by using intraoperative neuromonitoring during surgery. No postoperative complications related to surgery were observed. The postoperative course was uneventful and the patient was discharged on the first postoperative day.

Pathological examination revealed a partially encapsulated brownish white tumour 3.5 cm in diameter involving a mature teratoma consisting of mature cartilage and glandular tissue. A neoplastic process of spindle cells with a low mitotic rate was observed. Necrosis was absent. Immunohistochemical staining was positive for vimentin, smooth muscle actin, cytokeratins and B-cell lymphoma-2 (Bcl-2) and negative for the typical markers of the thyroid gland malignancy such as thyroglobulin, thyroid transcription factor-1 (TTF-1), calcitonin, CEA and S-100 (Fig 1). A final diagnosis of SETTLE was established with these negative reports. The surgical margin was free from tumour cells. Although no other treatment had been applied, the patient had remained well during 24 months with no recurrence or metastasis. Written informed consents were obtained from the patients who participated in this study.

Discussion

SETTLE is a rare neoplasm and is thought to arise from embryonic remnants of branchial pouches or ectopic thymus.¹ It arises predominantly in childhood and adolescence. A growing painless single thyroid nodule is the only presentation. SETTLE may be a possible diagnosis in the early decades of life, as thyroid nodules are unusual in childhood. SETTLE occurs more commonly in males than in females, and largely affects the right thyroid lobe. In contrast to most thyroid neoplasms, no predisposing factors such as iodine deficiency, ionising radiation, genetic or environmental factors has been found to be related to SETTLE.⁵

Diagnosis is difficult. There is no specific serum marker for diagnosis. Thyroid function tests and levels of CEA and calcitonin are within normal limits. A SETTLE tumour is usually described as a heterogeneous lesion at ultrasound and a lesion including solid and cystic components at computed tomography. Fine-needle aspiration biopsy is rarely diagnostic.⁵ The differential diagnosis of SETTLE includes a group of tumours which have spindle and epithelial components, namely, synovial sarcoma, sarcomatoid anaplastic carcinoma, malignant melanoma, carcinoma showing thymus-like elements and spindle-cell variant of medullary thyroid carcinoma. SETTLE has a highly cellular biphasic pattern and includes sheets of spindle cells and glandular epithelium.⁴ Nuclear pleomorphism, atypical mitosis and tumour necrosis are unusual entities. Low awareness of the presence of SETTLE due to its rarity makes diagnosis challenging.⁵ Immunohistochemical study is the gold standard method for establishing a definitive diagnosis of SETTLE.⁵

In a comprehensive review of the literature,⁵ immunoreactivity for pan-cytokeratin, smooth muscle actin, c-kit and vimentin and no immunoreactivity for thyroglobulin, calcitonin, S-100 protein, chromogranin, synaptophysin, CD34 and TTF-1 were reported. Bcl-2 immunoreactivity is controversial. Folpe *et al* reported immunoreactivity of Bcl-2 in 88% of their patients,⁵ while some authors declared no immunoreactivity for Bcl-2.⁵ Positive staining for p63 was found in only in two cases in the literature.^{2,6} Immunohistochemistry features were consistent with those in the literature in our second patient and Bcl-2 immunoreactivity was also observed. The final diagnosis of SETTLE was determined by immunohistochemistry studies in both patients.

In the literature review,⁵ all patients with SETTLE undergo surgery, including thyroid lobectomy and total thyroidectomy with or without neck lymph node dissection. Although it was reported that most of patients underwent thyroid lobectomy, two patients developed a second SETTLE tumour on other lobe of thyroid and total

Figure 1 (a) Tumour composed of well-confined spindle cells, separated by a capsule from the thyroid tissue (haematoxylin and eosin staining; original magnification, $\times 10$). (b) Tumour containing biphasic cell proliferation consisting of spindle and epithelial cells. Mucous deposits are seen between cells (haematoxylin and eosin staining; original magnification, $\times 10$). (c) Immunopositivity of the tumour with cytokeratin AE1/AE3 (original magnification, $\times 20$).

thyroidectomy was performed.⁵ Our second patient had total thyroidectomy and central compartment lymph node dissection, owing to an initial diagnosis of medullary thyroid carcinoma. It was thought that frozen section analysis might be helpful to confirm or eliminate medullary thyroid carcinoma, because of the discordance between the fine-needle aspiration biopsy and preoperative levels of serum markers such as calcitonin and CEA. As we predicted, frozen section analysis eliminated a possible diagnosis of medullary thyroid carcinoma.

Although SETTLE is believed to be a low-grade neoplasm, distant metastases have been reported. Development time for distant metastasis is long, up to 25 years, and lung, lymph nodes, bone and kidney are the usual sites.⁵ Radiotherapy is recommended for locally advanced tumours and bone metastasis while chemotherapy may be performed in presence of distant metastasis. Long-term follow-up is recommended to detect possible delayed metastasis.⁵

Conclusion

SETTLE is a rare thyroid neoplasm. Final diagnosis is difficult before histopathological examination of a surgical specimen. Medullary thyroid carcinoma is included in the differential diagnosis. SETTLE should be considered in a patient with normal serum calcitonin and CEA levels in the presence of suspicious medullary thyroid carcinoma at fine-needle aspiration biopsy. We believe that frozen section analysis may be used to confirm or eliminate

diagnosis rapidly. Thus, operative strategy may be planned during surgery.

Acknowledgements

Written informed consent was obtained from the patients who participated in this study and also to publish their photographs. The authors thank all the general surgery staff for their cooperation. This manuscript was presented as a poster at the 8th National Endocrine Surgery Congress, 27–30 April 2017, Antalya, Turkey.

References

1. Recondo G Jr, Busaidy N, Erasmus J *et al.* Spindle epithelial tumour with thymus-like differentiation: a case report and comprehensive review of the literature and treatment options. *Head Neck* 2014; **37**: 746–754.
2. Tavusbay C, Etit DA, Kadioglu E *et al.* Spindle epithelial tumor with thymus-like element (SETTLE): a case report. *Indian J Surg Oncol* 2017; **8**: 231–233.
3. 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): 402–412.
4. Misra RK, Mitra S, Yadav R, Bundela A. Spindle epithelial tumor with thymus-like differentiation: a case report and review of literature. *Acta Cytol* 2013; **57**: 303–308.
5. Folpe AL, Lloyd RV, Bacchi CE, Rosai J. Spindle epithelial tumor with thymus-like differentiation: a morphologic, immunohistochemical, and molecular genetic study of 11 cases. *Am J Surg Pathol* 2009; **33**(8): 1,179–1,186.
6. Lee FY, Wen MC, Jan YJ, Wang J. The predominant monophasic variant of spindle epithelial tumour with thymus-like differentiation (SETTLE) of neck soft tissue with late pulmonary metastasis. *Pathology* 2010; **42**(2): 188–190.