Primary small cell carcinoma of the thyroid with peripheral neuroectodermal tumour (PNET) features.

Clinical history

24-year-old male with a 5cm nodule in the left lobe of the thyroid. The patient was euthyroid and was submitted to left lobectomy. A couple of months later, following a diagnosis of “poorly differentiated thyroid carcinoma”, the patient was submitted to right lobectomy plus isthmectomy and left cervical lymphadenectomy, followed by radioactive iodine treatment. The case was sent to us for consultation after this second surgery. The patient is alive and well 12 years after the first surgery.

Macroscopic description

Whitish nodule measuring 5.3cm in its largest dimension. The isthmus and the right lobe (2nd surgery) were apparently normal. The same holds true – no signs of neoplastic disease, i.e., no metastases – in the left cervical lymph nodes.

Histologic description, histochemistry and immunohistochemistry

The tumour has pushing borders except in some foci displaying an infiltrative growth pattern. The whole tumour is composed by fairly regular nests of neoplastic cells that present entrapped follicular structures. The neoplastic cells are monotonous, have an epithelioid phenotype, high nucleo-cytoplasmic ratio and large, uniform nuclei exhibiting prominent nucleoli. The mitotic index is very high and comedo-type necrosis is observed in several neoplastic cell nests.

PAS staining was negative in the cytoplasm of the neoplastic cells.

The neoplastic cells diffusely expressed AE1.AE3, CAM 5.2, CK19, p63, p53 and CD99. There was focal expression of 34βE12, CEA and bcl2. The neoplastic cells did not express thyroglobulin, calcitonin, TTF-1, CK5, CK7, CK20, chromogranin, synaptophysin, vimentin, S100 protein, desmin, CD5, CD56, WT1 and c-KIT. The Ki67/Mib1 labeling index was about 50%.

Molecular study

The cytogenetic study using fluorescent in situ hybridization disclosed the presence of the structural rearrangement EWSR1/FLI1.

Discussion

The diagnosis of poorly differentiated thyroid carcinoma (PDTC) made when the tumour was first seen was not confirmed by the negativity for TTF1 and thyroglobulin in the neoplastic cells (Immunoreactivity for such markers was indeed restricted to entrapped “normal” follicular cells) (6,11).
After having ruled out the possibility of PDTC we were left with the diagnosis of small cell malignant tumour, primary or metastatic (7,10). The histologic appearance was compatible with the second hypothesis, i.e., it might be an intrathyroidal metastasis from a clinically occult small cell (neuroendocrine?) carcinoma (primary in the lung? other location?). The age of the patient (24y) and the absence of any neuroendocrine immunohistochemical marker did not support, however, such possibility. Total body computed tomography and magnetic resonance imaging excluded the existence of any other primary tumour, contributing to rule definitively out the possibility of a metastatic carcinoma. (The benign course of the disease we are now aware of settles any doubt one might have had about its metastatic nature). Most authors question the existence of bona fide primary small cell neuroendocrine carcinomas of the thyroid, whereas others think they may exist, constituting a sort of almost undifferentiated counterpart of medullary carcinoma (2,6,7,10). The unequivocal absence in the case herein described of any immunohistochemical marker of neuroendocrine differentiation (Chromogranin, synoptophysin and CD56 negativity) turned the aforementioned discussion useless in spite of its academic interest. Furthermore, the immunoreactivity for AE1.AE3, CAM5.2, CK19 and 34βE12, showed the carcinomatous (non-neuroendocrine) nature of this primary small cell tumour of the thyroid.

While progressing in the characterization of the neoplastic cells regarding their cytokeratin profile we decided, taking into consideration the young age of the patient and the diffuse CD99 immunoreactivity (and despite the absence of PAS positivity in the neoplastic cells and of any rosette-like pattern in the tumour), to search for the EWSR1 gene translocation. The structural rearrangement EWSR1/FLI1 was detected throughout the tumour and the diagnosis of primary peripheral neuroectodermal tumour (PNET) of the thyroid was advanced.

There are at least three cases of PNET/Extraosseous Ewing sarcoma (EWS) of the thyroid on record (1,4,9) that resemble the case here reported except regarding the prominence of epithelial differentiation. Cruz et al (5) reported recently a primary small cell tumour with basaloid features in the thyroid that also shares similar morphological and immunohistochemical features with the present case (e.g. diffuse positivity for cytokeratins and p63 and negativity of neuroendocrine markers). The expression of cytokeratins has been variably reported in PNET/EWS and thought to be related with different EWS variants (8). Taking all this into consideration we propose to classify our case as “Primary small cell carcinoma of the thyroid with PNET features”. The study of a much larger number of cases is necessary to clarify the histogenesis of this (these?) type(s) of thyroid tumours (3,5,9), and to have an idea on its (their?) natural history, namely whether the benign course of the present case, despite its highly malignant histological and immunohistochemical features, is an exception or not.

References