Primary squamous cell carcinoma of the thyroid: a case report

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Abstract
Primary squamous cell carcinoma of the thyroid is a very rare thyroid malignancy (less than 1% of thyroid cancers) with unfavorable clinical evolution and median survival less than one year, due to highly local tumor invasiveness with airway obstruction, metastases and treatment complications. We present a 62-year-old female patient with a fixed, rapidly increasing 5 cm right thyroid nodule, generating compressive signs and significant weight loss, resembling anaplastic thyroid carcinoma. Thyroid hormones, antithyroid antibodies and calcitonin were normal. Computed tomography (CT) scan revealed mediastinal extension of the tumor and excluded the presence of lymph nodes or other tumors (T3N0M0). Total thyroidectomy was performed and histopathological evaluation revealed squamous cell carcinoma, which was confirmed by immunohistochemistry, showing diffuse positivity for CK7, CK19, CK34βE12, galectin-3, EGFR, focal positivity for p63 and negativity for TTF-1 and CD5. Subsequently, the patient underwent chemotherapy (Paclitaxel, Cisplatin, Epirubicin) and radiotherapy (40 Gy), but tumor recurrence was noticed one month after surgical resection and continued to grow despite treatment. Nodal and metastases status remained negative at regular follow-up. The patient died within one year after diagnosis. External radiotherapy and chemotherapy were not efficient in our case. New treatment options are needed to improve outcome in primary squamous cell carcinoma of the thyroid.

Keywords: primary squamous cell carcinoma, thyroid, CK7, CK19, EGFR, p63.

Introduction
Primary squamous cell carcinoma of the thyroid (PSCCT) is a highly aggressive malignancy with poor prognosis, comparable to that of anaplastic thyroid carcinoma, with a median survival time 9–12 months [1, 2] and a 20% three-year survival rate [1]. It represents less than 1% of all thyroid malignancies [1, 3–5], 0.36% according to the study presenting the largest patients series [2] and a Japanese cohort of 8365 patients with thyroid cancer [6]. A recent meta-analyses conducted on 89 patients (52.8% from East Asia, 22.5% from North America and 10.1% from Europe) indicated that mean age at diagnosis is 63 years, and women are almost twice affected then men. Most patients present with an enlarging neck mass (70% with extrathyroidal extension, 48.3% with regional lymph node involvement) with compressive signs – dysphonia, dysphasia, dyspnea. There is no consensus for PSCCT management because of the rarity of cases; complete removal of the tumor has an advantage for survival, given the relative resistance to radiotherapy and poor response to chemotherapy [1].

Since there is no squamous epithelium in the normal thyroid gland, origin of PSCCT is a matter of debate. There are several theories trying to explain it. The theory of embryonic remnants postulates evolution of PSCCT from squamous cells belonging to thyroglossal duct or branchial arch remnants. Another theory proposes that PSCCT develops by squamous metaplasia of benign (chronic thyroiditis, follicular adenoma) and malignant thyroid lesions (papillary thyroid cancer – PTC), or dedifferentiation of malignant thyroid cells, but there are only a few cases of PSCCT associated with these thyroid conditions [4, 7]. PSCCT may arise “de novo” from the follicular epithelium.

Aim
In this paper, we aim to present a patient with PSCCT, emphasizing the diagnostic and management challenges issued by this aggressive, extremely rare thyroid malignancy.

Case presentation
A 62-year-old female patient presented for a rapidly growing mass on the lower right side of the neck for two months duration, that generated pain irradiating in the right shoulder, dysphonia, dyspnea, hoarseness, stridor. The patient also complained of fatigue and severe weight loss (10 kg in the past two months). Family history was unremarkable and personal history was positive for mild hypertension and fatty liver disease; tonsillectomy was performed in adolescence. The patient was obese (body mass index – BMI 33 kg/m²) with a central distribution of the adipose tissue and had varicose veins. Physical examination revealed a large (5 cm), firm, tender thyroid nodule in the right lobe, fixed to the underlying tissue, with impalpable inferior pole (Figure 1).
On ultrasound examination, the nodule had 40/45/57 mm, was hypoechoic, inhomogeneous, with multiple microcalcifications, descending in the retrosternal area; satellite lymph nodes were not detected. The right vocal cord still retained mobility on laryngoscopy. Contrast enhanced CT scan showed a right thyroid mass with parietal calcifications, with tracheal impingement to the left, progressing in the superior mediastinum, in close proximity to the right brachiocephalic trunk (Figures 2 and 3). No other masses or lymph nodes were detected in the brain, neck, thorax, abdomen and pelvis (T3N0M0).

Histological examination showed a highly malignant epithelial proliferation (round-oval shaped squamoid cells with abundant eosinophilic cytoplasm and nuclei with anisochromia, anisokaryosis, atypical mitoses; some tumor cell areas presented concentric layers of keratinized cells – keratin pearls), with diffuse, infiltrative features, necrotic foci, calcifications, desmoplastic and fibrotic stroma with abundant lymphoplasmocytic infiltration and hyalinization areas (Figures 5–7), enclosed in a thick, fibrous capsule. Invasion of the capsule, adjacent thyroid tissue and muscles was noticed, and also perineural invasion. In order to confirm PSCCT and to exclude anaplastic, poorly differentiated thyroid carcinoma, thyroid carcinoma showing thymus-like differentiation, collision thyroid tumors, and extrathyroidal squamous cell carcinoma metastatic to the thyroid assessment of p63, CK7, CK19, CK34/βE12, galectin-3, TTF-1 and CD5 expression was accomplished by immunohistochemistry (IHC), LSAB–HRP (labeled Streptavidin Biotin–Horseradish peroxidase), using a panel of antibodies (Table 1).

Fine-needle aspiration cytology (FNAC) was performed, but non-diagnostic (absent follicular cells; many erythrocytes, lymphocytes and neutrophils). Laboratory data revealed normal thyroid function [thyroid-stimulating hormone — TSH 0.887 μIU/mL, free thyroxine — fT4 19.95 pmol/L], normal calcitonin (<2 pg/mL), normal antithyroid antibodies (antithyroid peroxidase antibodies — TPOAb 18 IU/mL, antithyroglobulin antibodies – TgAb 19.35 IU/mL) and low thyroglobulin level (1.39 ng/mL).

All the other laboratory findings were normal, except increased cholesterol level (231 mg/dL), and fasting blood glucose (144, 188, 144 mg/dL), which was consistent with newly diagnosed diabetes mellitus.

Thyroidecmy was performed and right vocal cord paralysis ensued. Macroscopic evaluation of the specimen revealed a 5.5/4.5 cm encapsulated, yellowish tumor with hemorrhagic areas, within the right thyroid lobe (Figure 4).

Table 1 – Antibodies used for IHC study of the tumor

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Manufacturer</th>
<th>Clone</th>
<th>Dilution</th>
<th>Antigen retrieval</th>
</tr>
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<tr>
<td>CD5</td>
<td>Thermo</td>
<td>SP19</td>
<td>1:50</td>
<td>Seven cycles citrate buffer</td>
</tr>
<tr>
<td>CK19</td>
<td>Leica</td>
<td>NCL-CK19</td>
<td>1:150</td>
<td>1.5 minutes pepsin without exposure</td>
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<td>TTF-1</td>
<td>Leica</td>
<td>NCL-TTF1</td>
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<tr>
<td>HBME-1</td>
<td>Dako</td>
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<tr>
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<td>Leica</td>
<td>NCL-GAL 3</td>
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</tr>
<tr>
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<td>34/βE12</td>
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</tr>
<tr>
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<tr>
<td>P63</td>
<td>Santa Cruz</td>
<td>SC-8431</td>
<td>1:200</td>
<td>Seven cycles citrate buffer</td>
</tr>
<tr>
<td>EGFR</td>
<td>Dako</td>
<td>E30</td>
<td>1:100</td>
<td>CSA II</td>
</tr>
</tbody>
</table>

CK: Cytokeratin; TTF-1: Thyroid transcription factor-1; HBME-1: Hector Battifora mesothelial antigen-1; EGFR: Epidermal growth factor receptor; TEDTA: Trypsin–Ethylenediaminetetraacetic acid; CSA II: Catalyzed signal amplification system.
Immunohistochemical study was performed on paraffin embedded tissue sections, which were incubated at 37°C for 24 hours, deparaffinized, hydrated, antigens were un-masked according to the manufacturer’s recommendations (Table 1), treated with hydroperoxide to block endogenous peroxidase, washed in distilled water and 1% phosphate-buffered saline (PBS), treated with 2% skimmed milk to block the non-specific sites, incubated with the primary antibodies, and subsequently, with a secondary biotinylated antibody, treated with Streptavidin–HRP, and then with DAB (3,3'-Diaminobenzidine) chromogen. Intense and diffuse expression of CK7 (Figure 8), CK34βE12 (Figure 9), diffuse expression of CK19 (Figure 10), galectin-3 (Figure 11), focal expression of p63 (Figure 12), along with CD5 (Figure 13), TTF-1 and HBME-1 negativity confirmed squamous cell carcinoma.

EGFR expression was positive in 60% of tumor cells (Figure 14).

Figure 5 – Malignant epithelial cells showing aniso-karyosis and anisochromia; central keratin pearl (HE staining, ×200).

Figure 6 – Tumor area with abundant stromal lymphoplasmocytic infiltration (HE staining, ×100).

Figure 7 – Thyroid follicles interspersed with tumor cells nests (HE staining, ×100).

Figure 8 – Diffuse and intense CK7 positivity in tumor cells (IHC staining, ×100).

Figure 9 – Diffuse and intense CK34βE12 positivity in tumor cells (IHC staining, ×100).

Figure 10 – Diffuse and intense CK19 positivity in tumor cells (IHC staining, ×100).
Postoperatively, the patient underwent L-Thyroxine treatment, five monthly chemotherapy sequences of Paclitaxel 300 mg, and local external beam radiation therapy – EBRT (40 Gy). Local infracentimetric recurrence was detected by ultrasonography a month after surgery, progressively increasing to 4 cm at six months despite all therapeutic efforts (Figure 15). Exhaustive enhanced CT reevaluation at six months confirmed local recurrence extending into the mediastinum and to the overlying skin, and absence of any other detectable masses or lymph nodes. Palliative chemotherapy with Cisplatin 100 mg/m² + Epirubicin 100 mg/m² was initiated, with subsequent anemia, and the patient died 12 months after diagnosis, of unknown causes (airway was not totally compromised).

Discussion

Clinical presentation suggested an aggressive thyroid malignancy. FNAC in the presented case was non-diagnostic. A possible explanation for the absence of squamous cell carcinoma (SCC) cells in FNA aspirate might be the fact that they are firmly held within the tumor by fibrosis and desmoplastic stromal reaction [8, 9]. In a recent meta-analysis, the predictability of diagnosis in FNAC is less than one third of the patients; more than half of the cases are diagnosed as papillary thyroid carcinoma and 15% are non-diagnostic [1].
Histological diagnosis of squamous cell carcinoma of the thyroid (SCCT) is based on identification of squamous differentiation in all tumor cells (however, half of PSCCT are poorly differentiated, and secondary SCCT are frequently poorly differentiated) and of intercellular bridges [4].

Collision tumors (coexisting, histologically distinct carcinomas) must be managed according to the most aggressive component [10]. Up to 43% of papillary thyroid carcinomas contain regions of squamous cell metaplasia. TFF3 (trefoil factor 3) is a novel biomarker to distinguish between adenocarcinomas (93.7% positive) and squamous cell carcinomas (96.3% negative) of the lung, colon, rectum, stomach, cervix, esophagus and larynx, and might also be useful to diagnose thyroid SCC [11]. Also, many anaplastic carcinomas have squamoid regions [4]. In anaplastic thyroid carcinoma with squamoid differentiation, squamoid cells do not display atypical mitoses features [12], and are mixed with spindle, giant cells and syncytial elements [7]. Immunohistochemistry is mandatory to differentiate SCCT from anaplastic carcinoma and carcinoma showing thymus-like elements (CASTLE). Also, PSCCT must be distinguished from secondary SCCT (metastasis or adjacent tissue). Also, PSCCT must be distinguished from anaplastic carcinoma and carcinoma showing thymus-like differentiation (CASTLE) [19], which has a less aggressive biological evolution compared to PSCCT.

Calcitonin immunostaining was not performed since hormonologic assessment revealed a normal calcitonin value, excluding thyroid medullary carcinoma.

Though diagnosing PSCCT is difficult, the major challenge is represented by its management.

Complete resection of the tumor may improve survival, and postoperative radiotherapy and chemotherapy would help to achieve a better outcome in certain cases [11].

Given the fact that PSCCT highly express EGFR [20, 21] (as in the presented case), targeting EGFR would have been of benefit.

Recently, a promising therapeutic agent – pseudolaric acid B – was shown to have cytostatic effects by cell cycle arrest in SW579 thyroid squamous cell carcinoma cell line [22].

Conclusions

Primary squamous cell carcinoma of the thyroid is a very rare and aggressive thyroid malignancy, with challenging diagnosis and poor prognosis. Detailed description of every case is necessary for better knowledge, which would improve management of the affected patients. FNAC may not be useful in such cases. In the presented case, radiotherapy and chemotherapy were not able to control local recurrence growth. Given the high invasiveness of this tumor, it is almost impossible to achieve complete resection. Novel treatment options are needed.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Corina Lichiardopol and Valeriu Șurlin had equal contribution to the paper.

References


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Received: January 13, 2016

Accepted: August 24, 2016