

Total thyroidectomy associated to chemotherapy in primary squamous cell carcinoma of the thyroid

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Abstract

Primary squamous cell carcinoma of the thyroid (PSCCT) is a rare malignant disease with rapid fatal prognosis. The onset is generally characterized by sudden bilateral latero-cervical lymphadenopathy. The Authors report patient of 58-year-old who referred for evaluation of rapidly aggravating bilateral latero-cervical lymphadenopathy. The US highlighted the presence of a hypoechoic nodular lesion characterized by peri and intra-nodular vascularization. Multilayer CT showed diffused involvement of mediastinal and bilateral latero-cervical lymph nodes, with no evidence of primary pulmonary neoplasia or elsewhere. The patient underwent total thyroidectomy. The peri-isthmus tissue was removed due to the presence of a small roundish formation, that was due to lymph node metastasis at histological examination. Histological diagnosis: PSCCT. The immunohistochemical panel of the thyroid lesion was indispensable for the differential diagnosis between PSCCT, medullary carcinoma, anaplastic carcinoma, and thyroid metastasis of neoplasia with unknown primitiveness. The patient underwent chemotherapeutic treatment with Carboplatin and Paclitaxel with modest improvement of dysphagia symptoms and reduction of 10-15% of the target lesions. The clinical course was characterized by loco-regional progression of the disease with exitus in 10 months after diagnosis. Survival and quality of life after surgical therapy and chemotherapy were like that of patients undergoing only chemotherapy. Due to the extreme rarity of the neoplasia, 60 cases described in Literature, no exclusive guidelines are reported for PSCCT. More extensive case studies are needed to evaluate the effects of total thyroidectomy with intent R0/R1 on improving survival and quality of life of patients with PSCCT. *Clin Ter 2019; 170(4):e231-234. doi: 10.7417/CT.2019.2138*

Key words: Chemotherapy, Squamous Cell Carcinoma, Survival, Thyroidectomy, Thyroid Cancer

Introduction

Primary squamous cell carcinoma of the thyroid (PSCCT) is a highly malignant neoplasm with a poor prognosis, with a median survival of 9-12 months and a median survival rate of 20% (1,2). It's a rare tumor and represents 1% of malignant thyroid neoplasms and presents a clinical

course like anaplastic carcinoma (3,4). Only 60 cases have been reported in the literature (5). The average age of patients at the time of diagnosis is 63 years; women are affected almost twice as much as men. The clinical onset is characterized by the presence of a mass in the neck from extra-thyroid spread of the neoplasm; lymph node involvement is reported in 48.3% of patients. Doubts persist about the tissue of origin of PSCCT for not being present in the thyroid squamous epithelium. Several hypotheses have been proposed on the origin of the PSCCT: a) from the squamous cells of the thyroglossal duct and from the branchial arch residues; b) from squamous metaplasia during chronic thyroiditis, follicular adenoma, follicular epithelium, papillary carcinoma (4-6). Immunohistochemistry is necessary for the differential diagnosis between primary squamous cell and metastatic squamous cell carcinoma of the thyroid (7,8). Positivity for thyroglobulin and PAX8 suggests a thyroid origin (7,8). However, multilayer total body CT is essential for the differential diagnosis of primary and secondary thyroid neoplasia. Total thyroidectomy seems to be associated with improved survival rate of patients with PSCCT characterized by radiochemical resistance (1,9). The authors report the case of a 58-year-old man undergoing total thyroidectomy for multinodular goiter and bilateral latero-cervical lymphadenopathy.

Clinical Case

58-year-old patient with no significant family, physiological and remote medical history for thyroid disease. For about 2 months, presence of worsening bilateral latero-cervical lymph node enlargement with deformation of the neck profile. On physical examination the lymph node formations which were not spontaneously painful and not painful to palpation, had a hard consistency and a diameter between 16 and 31 mm. The patient did not report any signs of compression or laryngeal, tracheal, and esophageal infiltration. Thyroid hormones (TSH, FT3, FT4), thyroglobulin (TG) and thyroid anti-peroxidase (anti-TPO) antibodies fall into the normal range. The diagnosis of medullary carcino-

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ma was excluded because calcitonin was within the normal range (<1.0 pg / ml, see N. 0.1-10). The echotomography (US) showed volumetric increase of the thyroid (right lobe diameter 42.8 mm, left lobe diameter 24mm, isthmus diameter 13.3 mm). The parenchymal echostructure appeared diffusely inhomogeneous with multiple pseudo-nodular images confluent in the right lobe. In the left lobe there was presence of hypoechoic nodular formation (with a diameter of 28x17 mm) with peri and intra-nodular vascularization. In the right laterocervical region, there was evidence of voluminous grossly roundish lymph node formations, which at the US showed loss of normal ecostructural features, disordered vascularization and a diameter between 16 -26 mm. In the left laterocervical region there was evidence of lymph node formation (with a diameter of 31x14 mm), with a roundish appearance and disordered vascularization. The patient underwent total thyroidectomy. The peri-isthmic tissue was removed due to the presence of a small roundish formation, that was due to lymph node metastasis at histological examination. The organ appeared increased in volume, with the right lobe tenaciously adherent to the band-like muscles and to the perithyroidal soft tissues due to extra-glandular neoplastic diffusion phenomena. The surface of the gland presented an irregular appearance with presence, when cut, of multiple areas of greyish color with poorly defined margins. On histological examination, the parenchyma appeared as the site of diffused proliferation of medium and large epithelial cells arranged in nests and solid cords (Fig. 1).

The nuclei appeared to be polymetric, often vesicular with evident and sometimes hyperchromatic nucleoli, large eosinophilic cytoplasm and occasional evidence of tight junctions between the cells. There was presence of desmosomes or spines, characteristic of the squamous cellular nature of the neoplasm (Fig. 2).

There were numerous atypical mitoses, some apoptotic bodies, foci of necrosis and multiple foci of endovascular invasion. The neoplasm extended to the perithyroidal soft tissues. In the peri-isthmic cells there was a metastatic lymph node with a parenchyma largely replaced by neoplastic proliferation. The immunohistochemical study showed positivity for CKAE1/AE3, CK5/6, CK19, p63, p53, TTF1

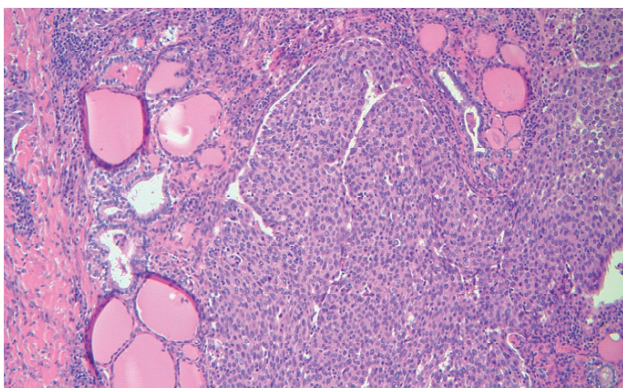


Fig. 1. H/E x 100 section from the thyroid gland showing infiltrative squamous cell carcinoma of thyroid.

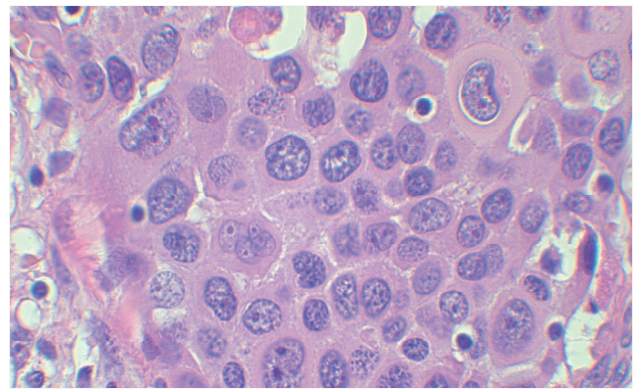


Fig. 2. Desmosomes are evident between neoplastic cells demonstrating a squamous differentiation (H/E x 600)

(weak and widespread), thyroglobulin (occasionally), and negativity for vimentin, galectin 3, CD56, chromogranin A, synaptophysin, NSE, HBME1, CD5 and calcitonin. The immunophenotypic profile of the proliferation is reported in the IHC panel (Fig. 3).

The proliferation index, evaluated by Ki 67, was equal to 80%. The histopathological picture gave us evidence on the diagnosis of carcinoma that was poorly differentiated with multiple foci spread throughout the thyroid, aspects of squamous differentiation and extensive intravascular diffusion and perithyroidal soft tissues. The neoplasm was present at the margins of surgical resection. Postoperative staging included: clinical examination, US, multi-layer total-body CT and segmental bone scintigraphy (after total-body and ^{99m}Tc -MDP radiopharmaceuticals administration), with 740 MBq administered activity. The scintigraphic images did not document the presence of areas of altered setting of the osteotropic tracer of secondary skeletal significance. At the multilayer CT the pulmonary parenchyma appeared symmetrical and normo-ventilated bilaterally with absence of focal alterations. No lesions were seen in the trachea and the large arterial and venous vessels. Presence of gross lymph node packs in pre-tracheal, retrosternal, hilar, bronchial bifurcation and at the aorto-pulmonary window. The lymph nodes were increased in volume and presented central areas of necrotic-colliquative degeneration. The pleural sinuses were free of effusion. Absence of focal hepatic changes. Pancreas, spleen, adrenal glands and kidneys without significant alterations. Not increased abdominal lymph nodes. No changes in brain density were demonstrated. The ventricular system appeared in axis and of normal amplitude. At the oncological examination, performed 8 weeks after the surgical treatment, bilateral lymph node packs of 5 cm diameter were appreciated in the bilateral latero-cervical region and in the supra-clavicular fossa. The patient, performance status 2, reported pain of this objectivity (VAS score=5), which resulted in painkiller therapy with major opioids (oxycodone 20 mg twice daily). The radiotherapeutic option was excluded due to the massive extension of the recovery of the illness, and the poor performance status. The immunotherapeutic option was not available as

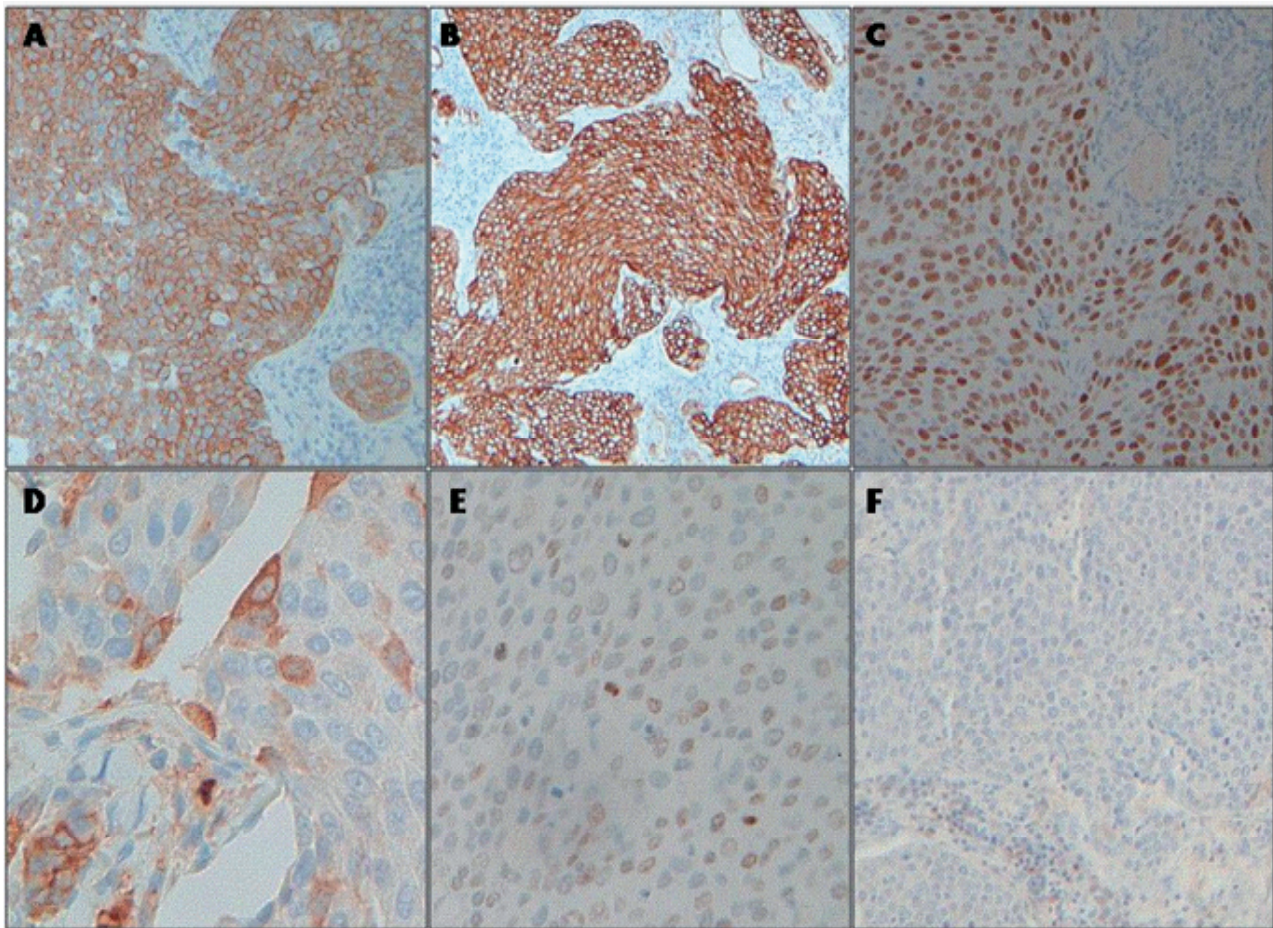


Fig. 3. Immunohistochemistry results: Tumor shows diffuse positivity for CKAE1/AE3 (A), CK5/6 (B) e p63 (C), scattered thyroglobulin- positive cells (D) and TTF-1-positive cells (E) and negativity for calcitonin (F).

standard treatment in Italy, repayable by AIFA. The patient underwent first-line chemotherapy treatment according to the scheme which consisted of Carboplatin AUC 4 and Paclitaxel 175 mg / m² every 21 days. The 4 treatment cycles, except for alopecia, were well tolerated without any G3-G4 grade toxicity according to CTCAE V.4.2. At the end of the chemotherapy treatment, the patient reported improvement of the painful symptomatology, which allowed the reduction of the daily dosage of opioids (oxycodone 5 mg twice daily). At the multilayer CT re-evaluation, instrumental stability of the disease according to the Recist criteria was highlighted, with a tendency to reduce all target lesions by 10-15%. Based on the good clinical and instrumental response and the excellent tolerability to chemotherapy treatment, it was decided to subject the patient to a further 3 cycles with Carboplatin and Paclitaxel. The subsequent clinical course was characterized by rapid loco-regional progression of the disease with infiltration of the internal carotid artery by bilateral lateral-cervical lymph node metastases, and exitus in 10 months after diagnosis.

Discussion

Primary squamous cell carcinoma of the thyroid (PSCCT) is a rare neoplasm, difficult to diagnose and with

an unfavorable prognosis (1,2). It is often poorly differentiated, that is why the immunophenotypic study is essential for a correct diagnosis. As reported in the literature, and also in this case, the immunohistochemical investigation and multilayer CT has proved to be an indispensable method for the differential diagnosis between PSCCT and extra-thyroid squamous cell carcinoma with secondary glandular localization (SCCT), which has a more frequent response and a better prognosis due to the increased sensitivity to radio-chemotherapeutic treatment (4). The morphological appearance of the proliferation of medium and large epithelial cells organized in solid nests and cords, the absence of papillary or follicular structures, the negativity of the immunophenotypic markers of galectin 3 and HBME1 allowed to exclude the diagnosis of papillary and follicular carcinomas. The normal value of serum calcitonin and the negativity of anti-calcitonin antibody in neoplastic tissue have excluded the diagnosis of medullary carcinoma. The negativity to the CD56, chromogranin A, synaptophysin and NSE markers excluded the neuroendocrine nature of the neoplasm. The morphological aspect of the lesion, which was poorly differentiated but never frankly anaplastic, and the immunohistochemical profile characterized by the p63 and cytokeratins 5/6 positivity, allowed the correct differential diagnosis between the PSCCT and the anaplastic thyroid carcinoma of which it shares the clinical aggressiveness,

treatment and inauspicious outcome. Squamous cell carcinomas of the thyroid are often associated with the most common papillary carcinoma, which sometimes presents aspects of squamous differentiation.

In our case, despite the extensive sampling of the organ, there were no signs of chronic thyroiditis and no presence of other types of thyroid neoplasia. The finding excluded the possible origin of this tumor from inflammatory or neoplastic lesions already present in the thyroid. The multilayer CT allowed to exclude the presence of primary epithelial neoplasms of the lung, larynx and of the nasopharynx, which can give metastases to the thyroid. Therefore, the total body multi-layer CT should be performed in all patients because it is an indispensable method to confirm the thyroid, pulmonary or extra-pulmonary origin of the squamous cell neoplastic lesions. In addition, our case also presented an occasional positivity for anti-thyroglobulin antibody in neoplastic cells, this fact supports the hypothesis of a primitive thyroid neoplasia.

As reported in the literature, in this clinical case a widespread and early lymph node involvement was demonstrated at the onset of the disease. The US of bilateral latero-cervical regions, and supra-clavicular areas, revealed enlarged roundish lymph node formations organized in packets and with altered echostructure. CT showed widespread involvement of mediastinal lymph nodes. The pre-tracheal, retrosternal, carenal, intrabronchial, hilar, and aortopulmonary lymph nodes were markedly increased in size and showed central areas of necrotic-colliquative degeneration. The lymph nodes of the upper and lower abdominal stations showed no appreciable volumetric changes and structural changes. Indication was given to total thyroidectomy which, in the most favorable cases, seems to be associated with improved survival (1). The intraoperative finding of extensive infiltrative phenomena of the perithyroidal tissues with involvement of surgical resection margins, the high cell proliferation index and intravascular diffusion, influenced for a rapidly unfavorable prognosis lesion, with a clinical course superimposable to anaplastic carcinoma. Due to the high local invasiveness, the complete surgical resection of the neoplasm was not possible. The clinical controls, US and CT performed in 8 weeks distance from the total thyroidectomy with emptying of the central compartment, showed a significant increase in the volume of the lymph nodes (diameter > 5 cm) in the bilateral latero-cervical area, which were of increased consistency, organized in big chains, due to cervico-thoracic compression dysphagia.

The first-line chemotherapeutic treatment with Carboplatin and Paclitaxel, well tolerated by the patient, resulted in an improvement of the painful symptomatology and instrumental stability of the disease.

The patient's exitus occurred 10 months after diagnosis, confirming the high malignancy of the PSCCT. Surgical therapy and chemotherapeutic treatment have not been proven to ensure acceptable local control of the disease. Survival and quality of life were comparable to that of patients treated only with chemotherapy (1,2,9,10).

Due to the extreme rarity of the neoplasia, 60 cases described in Literature, no exclusive guidelines are reported for the PSCCT. There is no unanimous agreement on risks, morbidity and quality of life after surgical treatment for the PSCCT. More extensive case studies are needed to evaluate the impact on survival from surgical therapy with intent R0 / R1.

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