Papillary thyroid carcinoma with anaplastic dedifferentiation in the lymph node metastasis – a rare form of presentation even for a tall cell variant

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Abstract
Papillary thyroid carcinoma (PTC) is well known as a differentiated thyroid carcinoma with an established treatment protocol and high survival rates. Nevertheless, its tall cell variant (TCV) is more frequent diagnosed with larger tumor size, advanced age and metastasis comparing to other PTC cases, resembling an increased level of aggressiveness attributable to the histological subtype according to recent studies. We present the case of a 60-year-old woman who came for a recently increase of the thyroid and a left laterocervical mass associated with pain and alteration of general status. Thyroidectomy revealed a TCV of PTC with infiltration of the extrathyroid tissue. The laterocervical mass posed difficulties to surgical excision but in a second attempt proved to be an undifferentiated carcinoma. The findings were associated to a rapid deterioration of the patient’s general condition finalized with death within less than three months from the initial presentation.

Keywords: thyroid, papillary carcinoma, anaplastic degeneration.

Introduction
Thyroid carcinoma has an overall excellent prognosis: among the United States of America (USA) reported of 13 thyroid cancer cases/100 000 adjusted for age and gender, the mortality is 0.5% with a 97.9% five years survival [1]. Among these cases, papillary thyroid carcinoma (PTC) accounted for 87.3%, compared to 0.9% for the very poor prognosis anaplastic carcinoma [1]. In spite of these data, studies on large cohort of patients revealed that tall cell variant (TCV) of PTC represents around 8% and it is a more aggressive form of PTC than classic forms [2] because it was associated with larger size tumors, bilaterality, multifocality and extrathyroidal invasion [3]. It was believed that TCV’s worse prognosis is related to older age at presentation, larger tumor size, and high frequency of extrathyroid tumor extension [3–8] but recent findings sustain an aggressiveness associated to the histological type itself [9–12].

The undifferentiated thyroid cancer is rare and recent reports showed a marked decreasing trend in some regions from Romania [13]; nevertheless, these cases remains challenging due to low frequency but also to some benign appearance in the diagnostic moment. Our patient was diagnosed with a tall cell variant of PTC but the complete diagnosis was revealed under the ‘pressure’ of clinical worsening. This case, through its particular aspect of concomitant rare dedifferentiation of the lymph node metastasis from the moment of diagnosis with rapid lethal outcome in less than three months of evolution since the presentation, is meant to highlight the importance of the classically “intermediate”, aggressive variants of PTC, which might need a precocious diagnostic and vigorous treatment as early as is possible.

Case report
We present the case of a 60-year-old woman admitted to the Department of Endocrinology, “Elias” Hospital, Bucharest, Romania for a recently increase in thyroid volume with a painful left laterocervical tumor. According to the patient’s statement, all the claims were less than one month old being associated to an intense fatigability, pain in the left arm and difficult deglutition.

From the medical history, the patient has surgical menopause due to subtotal hysterectomy and bilateral...
annexectomy at age of 39 years due to an ovarian mucinous cystadenocarcinoma followed by chemotherapy with no evidence of relapse in the last 20 years. One month before admittance in our department, a CT (computerized tomography) scan of the abdomen and cervical region was done; no evidence of supraclavicular tumor was seen on the image.

At clinical examination, medium volume polynodular goiter with increased consistency and a left supraclavicular inhomogeneous and spontaneously painful tumor around 3 cm in diameter. No clinical signs of thyroid dysfunction were obvious at clinical exam. Cervical region ultrasound examination revealed a micronodular right lobe of the thyroid, an enlarged left lobe comprising a 3.4 cm diameter solid nodule with suspicious features; on the left cervical and supraclavicular area, a 3 cm hypoechoic conglomerate was seen, resembling a lymph nodes aggregation.

Laboratory findings: increased erythrocyte sedimentation rate (ESR – 56 mm/h), normal blood count and routine biochemical blood tests within normal range except an increased cholesterol and triglyceride levels. Euthyroid state was confirmed by the laboratory results: thyroid-stimulating hormone (TSH) 1.34 μIU/mL, free thyroxin (fT4) 1.13 ng/dL and serum calcitonin level was normal (5 pg/mL).

The patient was referred to the surgery for total thyroidectomy and left cervical tumor ablation. Total thyroidectomy was performed without laterocervical tumor ablation due to difficulties raised by surrounding tissues infiltration. On gross examination, the left lobe showed a 3.5/2/1.5 cm nodule, unencapsulated, with irregular infiltrative margins and grey color on cut section.

Histopathological evaluation

Serial 3-μm sections had been cut from paraffin blocks and stained with Hematoxylin and Eosin (HE). The immunohistochemistry (IHC) was performed on 3 μm sections from 10% formalin-fixed paraffin-embedded tissues according to the IHC method an indirect bistadial technique performed with a polymer based detection system [EnVision™ Dual Link System- HRP (horseradish peroxidase), DAKO, Carpinteria, CA, USA]. Tissue sections were spread on poly-L-Lysine-coated slides immersed in three changes of xylene and rehydrated using a graded series of alcohol. Antigen retrieval was performed in microwave oven. In each section, endogenous peroxidase was blocked by 20 minutes incubation in 3% hydrogen peroxide. The sections were incubated with primary antibody: cytokeratin (CK) 7 (DAKO, 1:50, OVTL12/30), vimentin (Leica, 1:50, V9), CK19 (Leica, 1:100, b170), hematopoietic progenitor cell antigen (CD34) (DAKO, 1:50, QBend10), CD31 (DAKO, 1:50, JK70A), epithelial membrane antigen (EMA) (DAKO, 1:50, E29), antibodies against high molecular weight cytokeratin-34βE12 (DAKO, 1:50, 34betaE12), carcino-embryonic antigen (CEA) (DAKO, 1:50, IL-7), thyroid transcription factor (TTF1) (Leica, 1:100, SP724), thyroglobulin (DAKO, 1:500, polyclonal), chromogranin A (Leica, 1:200, 5H7), epidermal growth factor receptor (EGFR) (SIGMA, 1:100, 29.1.1), desmin (DAKO, 1:50, D33) and human Ki67 protein (DAKO, 1:100, Mib-1) at room temperature for one hour. The DAKO EnVision™ Detection System-HRP was then applied for 30 minutes. Finally, the sections were incubated in 3,3’-diaminobenzidine hydrochloride for 5 minutes, counterstained with Meyer’s Hematoxylin and mounted. The slides were examined and photographed on Leica DM750 microscope. Negative controls were obtained by replacing the primary antibody with non-immune serum. As a positive control, a thyroid tissue section was used.

HE stained section showed tumor proliferation with features of PTC with TCV and Hürthle cells invading the fibroadipose and muscular perithyroid tissue, with a chronic thyroiditis background (Figure 1, a and b).

Histopathological diagnosis: laterocervical tumor, confirmed by two certified pathologists was fibroadipose tissue with massive infiltration of undifferentiated carcinoma areas and necrosis (Figure 2).

Immunohistochemical evaluation for the laterocervical tumor: the tumor cells presented a diffuse expression for vimentin (Figure 3a); diffuse positive staining for CK7 and CK19 (Figure 3b). EMA was found focal positive in tumoral cells; CD31 was positive in blood vessels and few tumoral cells; the expressions of TTF1, polyclonal CEA, thyroglobulin, chromogranin A, CK 34βE12 and EGFR were found negative. Desmin was negative in
tumoral cells and positive in the vessels; CD34 was expressed only in blood vessels and Ki67 was positive in about 50–55% on the tumor cells (Figure 3c).

Evolution of the patient was to a lethal outcome in less than three months since the presentation moment.

Discussion

Our case had TCV of PTC with areas of Hüthle cells in the thyroid and undifferentiated carcinoma into the lymph nodes. A very pertinent question would be: it was the same disease?

The TCV of PTC is recognized as a more aggressive subtype, even if some doubts still exists regarding the link between the histotype and its evolution. The aggressive behavior of the TCV PTC is suggested by features like large tumor size at presentation, extrathyroid expansion or lymph node metastasis even from a microcarcinoma in the thyroid [14–17]. Hüthle cell papillary thyroid carcinoma is also a variant of PTC, with a more aggressive behavior comparing to PTC. The coexistence between TCV and Hüthle cell PTC was reported in 3% of the thyroid carcinoma cases in some series [18] with a greater likelihood of extrathyroid invasion and higher vascular invasion, distant metastasis and patient death. The so called “collision tumor” was reported as a mixed tumor in the thyroid and metastasized as a tall cell tumor to the lymph nodes and as a Hüthle cell carcinoma to lungs [19–21]. Based on these data, the presence of a lymph node metastasis was not a surprise in our patient.

In our case, the immunohistochemical phenotype of the lymph node tumor, with diffuse positive vimentin along with negative thyroglobulin and more than 50% Ki67 sustained the undifferentiated character of the metastasis. Finding the undifferentiated carcinoma in the lymph nodes is not a frequent situation, even when facing a more aggressive subtype of PTC, so dedifferentiation of the PTC metastasis raised as the most appropriate hypothesis.

The relevance of this interpretation is sustained, in the authors’ opinion by the particularities of the case: areas of Hüthle cell between TCV were identified, suggesting supplementary aggressiveness of the primary tumor. Dedifferentiation of the PTC metastasis is a rare event, but new insights from the BRAF(V600E) mutation studies could explain such an event. The proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutation was reported in 92.6% of the TCV of PTC and was associated to lymphovascular invasion, central compartment and lateral cervical lymph node metastasis, or multifocal tumors [12]. BRAF mutations are restricted to papillary carcinomas and poorly differentiated or anaplastic carcinomas arising from papillary carcinomas. They are associated with distinct properties of papillary carcinomas and may be responsible in progression to poorly differentiated and anaplastic carcinomas [22–25].

In spite of being recognized as a more aggressive variant, the classic TCV of the PTC had a lethal outcome after a longer period of time than our reported case [2]. The rapid aggravation and the lethal outcome within three months since the presentation moment was surprising when facing to a TCV of the PTC and sustains the de-differentiation of the lymph node metastasis.

Figure 2 – HE stained section from the laterocervical tumor, ×200.

Figure 3 – IHC for the laterocervical tumor: (a) Vimentin, ×200; (b) Cytokeratin 19, ×200; (c) Ki67, ×100.
An important issue should be mentioned regarding clinical evolution: after the first surgical intervention with complete thyroid, but failure of lymph nodes removal, the histological diagnosis of the thyroid tumor entitled the clinician to reassure the patient about certain therapeutic options and outcome. The obvious clinical worsening of the patient during the short period of time until first results were available made the second surgery an emergency. This aspect emphasizes both the relevance of clinical evolution in pointing the correct diagnostic and the need to use more sensitive IHC markers to predict malignancy outcome in thyroid tumors [26].

Taking into account the medical history of our patient, one might raise the question whether actual lymph node undifferentiated carcinoma was linked to the previous ovarian cancer but after 21 years this link is not probable.

In the same manner, the last hypothesis would be a concomitant occurrence of a TCV of PTC in the left thyroid lobe and an unknown origin undifferentiated lymph node metastasis. Even we cannot say is impossible, based on the imaging studies made before and in the moment of the diagnostic, the left cervical lymph nodes were the only tumor proved to be undifferentiated carcinoma from our patient body. Moreover, the ipsilateral position of the lymph nodes reported to the thyroid tumor made this hypothesis less likely.

Conclusions

Based on the patient’s medical history, the histopathological diagnosis and the results of the IHC staining panel, a diagnosis of anaplastic dedifferentiation in a cervical lymph nodes metastasis from a tall cell variant of papillary thyroid carcinoma is the most probable diagnosis in the presented case. The particular aspect of this case, besides the rare dedifferentiation of the lymph node metastasis, was its presence from the moment of diagnosis with rapid lethal outcome in less than three month of evolution since the presentation.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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