CLINICAL CASE

LATE ANAPLASTIC SHIFT IN DIFFERENTIATED THYROID CARCINOMA: SURGERY AS PIECE OF MULTIDISCIPLINARY PUZZLE

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Abstract

Late anaplastic shift of differentiated thyroid carcinoma represent a very rare event, still controversial as genomic and epigenetic associated factors and also as adequate management. The neoplasia is resistant to traditional radioiodine therapy and TSH (Thyroid Stimulating Hormone) suppression treatment that works well for most of follicular and papillary thyroid cancers. We aim to introduce a case of mix anaplastic/undifferentiated and differentiated thyroid cancer of papillary type to which thyroid surgery was performed and close post-operative follow-up is also introduced. This is a 63-year old non-smoking male, with irrelevant personal and family medical and surgical history, admitted for recent dysphonia. Thyroid function was normal as well as serum calcitonin and parathormone. Specific thyroid autoimmune background was negative. Ultrasound showed a macronodule of 2.28 by 2.25 by 2.3 cm at the level of third median part of the left lobe with an irregular shape (the left lobe has 6.48 by 2.57 cm and the right lobe has 4.66 by 1.33 cm without any relevant nodule on this side). Paralysis of recurrent laryngeal nerve was also confirmed. Palliative subtotal thyroidectomy with left latero-cervical lymphadenectomy was done. Pathological report showed poorly differentiated/undifferentiated/anaplastic carcinoma (of 2.5 by 1.7 cm) with residual areas of papillary thyroid carcinoma associating tall and columnar cells of oxyphil type (oncocitar variant), and, also, out of 14 lymph nodes 7 had invasion of mostly papillary thyroid cancer with tall and columnar cells and restrain areas of undifferentiated carcinoma. Ki67 was 40% in undifferentiated areas versus 10% in papillary carcinoma. 5 months after, the patient had a large extensive mass at left thyroid area with local invasion. Radiotherapy was introduced. Despite recent advance in genetic features, therapeutical options are still limited for every day practice in cases with late anaplastic/undifferentiated shift from differentiated thyroid carcinoma and delayed diagnosis. Surgery is part of the management and probably is most useful in extremely early stages of disease, and every time when it is feasible the rational is to apply it since radioiodine therapy and chemotherapy as not useful in this particular situation.

Keywords*: thyroid, cancer, thyroidectomy*

Introduction

Late anaplastic shift of differentiated thyroid carcinoma represent a very rare event, still controversial as genomic and epigenetic associated factors and also as adequate management [1,2]. This form is part of undifferentiated carcinomas of follicular cell origin, and it is considered the most aggressive form, with a very poor prognosis [1,2]. Various genetic/epigenetic factors have been correlated with the condition like BRAF, TP53 or BCL 11A [1,2]. Different transcriptomes anomalies when compare to differentiated thyroid cancer are found in growth factors expression as Fibroblast Growth Factor or Vascular Endothelial Growth Factor [1,2]. Despite recent progress of genetic field, no clear conclusive points are highlighted yet [1,2].

Overall, anaplastic thyroid cancer represents <2% of malignancies which have thyroid as primary site, with the highest mortality and a median of survive of approximately 6 months [3,4].Unfortunately, the neoplasia is resistant to traditional radioiodine therapy and TSH (Thyroid Stimulating Hormone) suppression treatment that works well for most of follicular and papillary thyroid cancers [3,4].Surgery has a limited value especially in those cases where the tumoral mass involves only in a lesser extend the undifferentiated area and to a higher extent the differentiated part; also surgery is required as palliative intervention if tracheal compressive symptoms are developed [3,4].Future therapies with agents involving signal transduction pathways as Notch or nuclear factor kB [3,4].

Case presentation

Presentation

This is a 63-year old non-smoking male, with irrelevant personal and family medical and surgical history, admitted for recent dysphonia. He had a thyroid ultrasound done as outpatient which revealed a left thyroid lobe with a nodule of 2.4 by 1.7 cm (centimeters) – consistent for TIRADS5, and also local large lymph nodes highly suspected for a malignancy as: left supraclavicular of 2.6 cm, next to left common carotid artery of 2.2 cm, submandibular of 1.5 cm (Figure 1). Also, computed tomography showed multiple lymph nodes at paratracheal and paraaortic level.

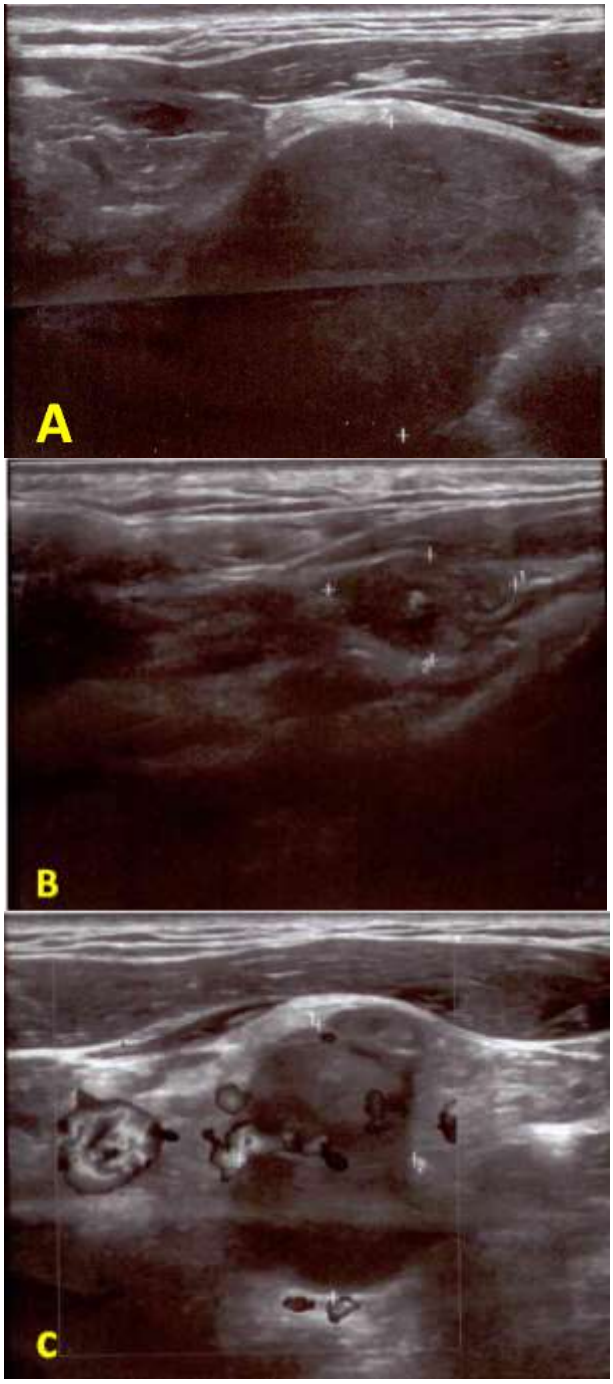

Figure 1 - Anterior cervical ultrasound with multiple local lymph nodes which are highly suspected for a malignancy on 63-year-old male who accuses dysphonia since last 2-3 weeks. A. supraclavicular of 2.6 cm maximum diameter; B. submandibular of 1.5 cm; C. laterocervical of 2.2 by 1.4 cm

On admission, thyroid function was normal as well as serum calcitonin and parathormone. Specific thyroid autoimmune background was negative. A second cervical

ultrasound confirmed the macronodule of 2.28 by 2.25 by 2.3 cm at the level of third median part of the left lobe with an irregular shape (the left lobe has 6.48 by 2.57 cm and the right lobe has 4.66 by 1.33 cm without any relevant nodule on this side). Paralysis of recurrent laryngeal nerve was also confirmed. A newly discovered type 2 diabetes mellitus is confirmed based on fasting blood glucose level of 324 mg/dL, and oral antidiabetic medication is offered to the patient (metformin 1000 mg per day).

Management

The patient was referred for surgery: intra-operatory a firm mass at the level of left lobe was found associating muscular, esophageal, and recurrent nerve invasion with multiple local lymph nodes, thus palliative subtotal thyroidectomy with left latero-cervical lymphadenectomy was done. Pathological report showed poorly differentiated/undifferentiated/anaplastic carcinoma (of 2.5 by 1.7 cm) with residual areas of papillary thyroid carcinoma associating tall and columnar cells of oxyphil type (oncocitar variant), with other areas of squamous type, and also necrosis of 5 %, and large invasion into peri-thyroid fibro-conjunctive and muscle tissues (pT4B, G3 grading of differentiation, stage T4B). Out of 14 lymph nodes 7 had invasion of mostly papillary thyroid cancer with tall and columnar cells and restrain areas of undifferentiated carcinoma. Immunohistochemistry was done as introduced in Table 1. The patient was offered daily levothyroxine of 100 μg with periodic TSH control. After thyroid surgery, no hypoparathyroidism was detected. Due to pathologic profile, radioiodine therapy was not considered optional.

Profile	**Reaction**	**Observations**
thyroglobulin	negative	in undifferentiated carcinoma
	positive	in papillary carcinoma
TTF1	negative	in undifferentiated carcinoma
	positive	in papillary carcinoma
CK7	positive	in tumoral cells
PAX8	negative	in undifferentiated carcinoma
	positive	in papillary carcinoma
Ki67	40%	for undifferentiated carcinoma
	10%	for papillary carcinoma

Table 1 - Immunohistochemistry report on a 63-year old male with poorly differentiated/undifferentiated/anaplastic carcinoma and residual areas of papillary thyroid carcinoma associating tall and columnar cells of oxyphil type (oncocitar variant)

Current admission

The patient felt well and return to further therapy only 5 months after thyroidectomy was done. Despite apparently well state of health of the patient (who continued to have dysphonia), the thyroid ultrasound showed empty right thyroid area (post-operatory aspect), and a large hypo-echoic mass consistent with left lobe area of 4.8 by 2.8 by 2.7 cm, with irregular shape, without vascularization, as shown in Figure 2. Also, right cervical lymph nodes of 1.6 by 0.9 cm with microcalcifications and increased peripheral vascularization, of 1.08 by 0.66 cm, respective of 0.82 by 0.4 cm, and left cervical of 2.8 by 1.2 by 1.3 cm with hypo-echoic, solid, globule-like aspect, having a well-defined shaped (Figure 2).

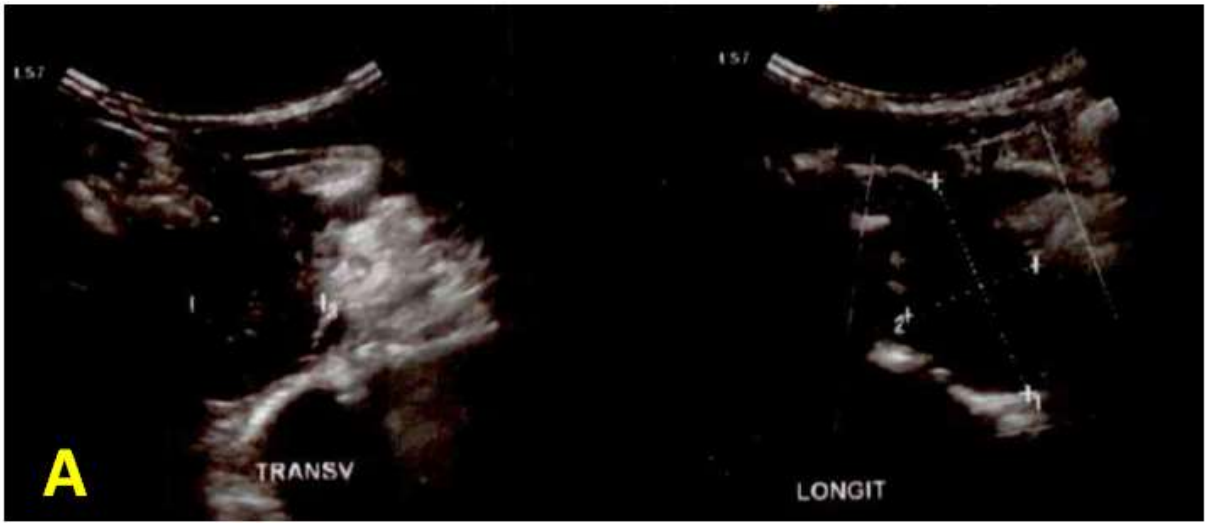

Figure 2 - 63-year old male with late anaplastic shift from papillary thyroid cancer; 5 months after subtotal thyroidectomy the tumour aggressively extended. Thyroid ultrasound shows a large hypo-echoic mass consistent with left lobe area of 4.8 by 2.8 by 2.7 cm, with irregular shape, without vascularisation (A). Also, right cervical lymph nodes of 1.6 by 0.9 cm with microcalcifications and increased peripheral vascularisation, of 1.08 by 0.66 cm, respective of 0.82 by 0.4 cm (B), and left cervical of 2.8 by 1.2 by 1.3 cm with hypo-echoic, solid, globule-like aspect, having a well-defined shaped. (C)

Computed tomography confirmed the large left mass at the level of thyroid area of 3.8 by 3.3 by 4.8 cm with mass effect on trachea and esophagus with posterior extension up to vertebral bodies (Figure 3). The tumor has dense, spontaneous heterogeneous and iodophile structure; longitudinal extension is 4.5 by 6.05 cm. The minimum tracheal diameter is of 1.62 by 1.56 cm. Lymph nodes at the level of left cervical area of 1.3 by 1.6 cm, and others at superior mediastinum of 1.8 by 2.1 cm, and bilateral cervical area (Figure 3). Since the tumor early locally relapsed and aggressively continued its post-operatory evolution, currently presenting as a large mass of radioiodine resistant type, this was not considered an option and further radiotherapy was recommended to the patient. A very poor prognosis is expected.

Discussions

This is the case of an adult male without a prior history of thyroid condition who was diagnosed with aggressive undifferentiated carcinoma, a late anaplastic shift from papillary thyroid cancer which was still recognizable at

the level of thyroid nodule and local lymph nodes metastases based on pathological report and immunohistochemistry reaction.

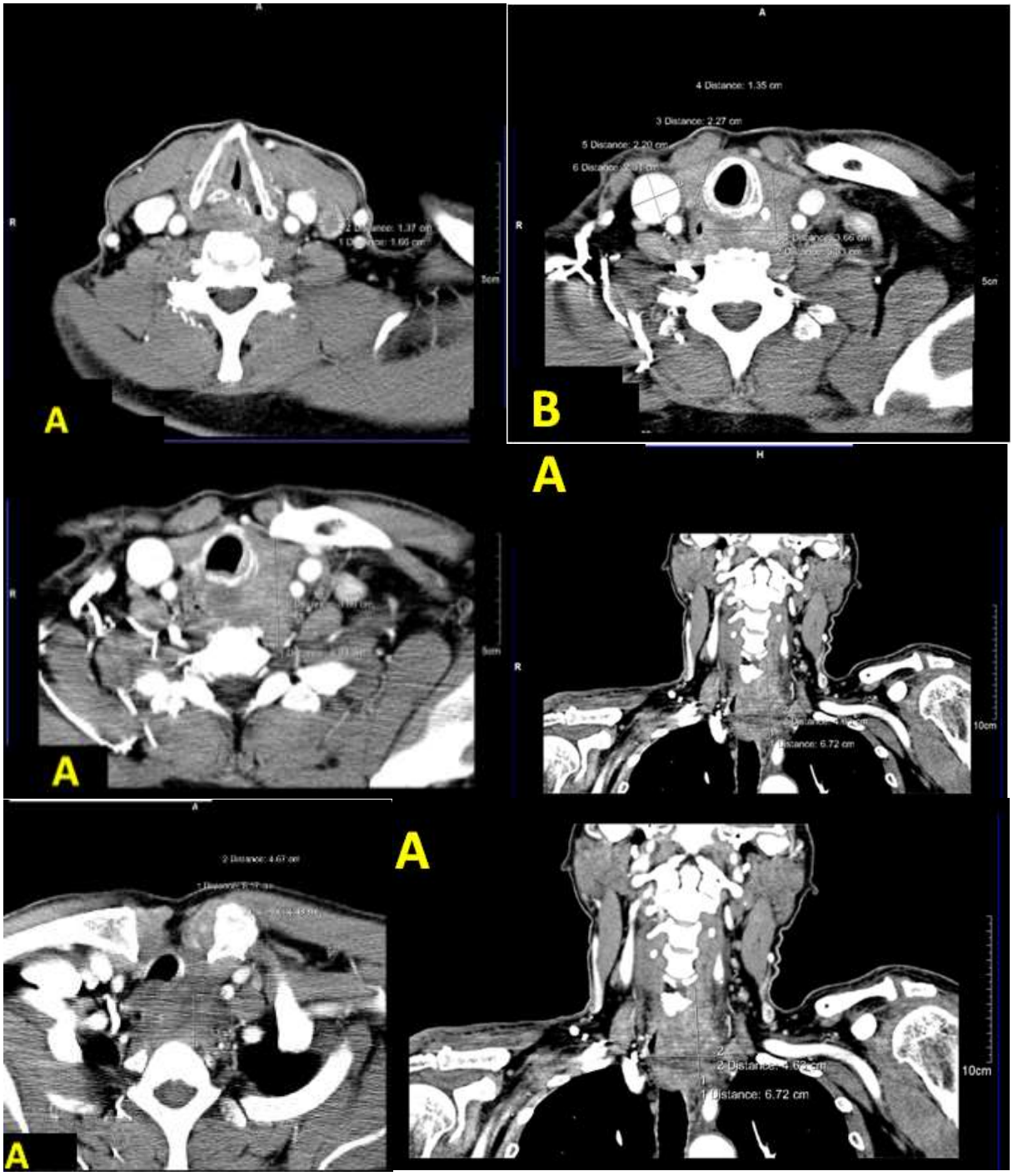

Figure 3 - The tumour has dense, spontaneous heterogeneous and iodophile structure; longitudinal extension is 4.5 by 6.05 cm (A). Lymph nodes at the level of left cervical area of 1.3 by 1.6 cm, and others at superior mediastinum of 1.8 by 2.1 cm, and bilateral cervical area (B). Different sections of the tumour are displayed below.

The detection of type 2 diabetes mellitus by the same time with thyroid cancer is most probably accidental, yet very suggestive for patient's compliance to period general medical control.

The most studied biomarkers for late anaplastic shift are: increased expression of P53 and Ki67, loss of expression for cyclin D2, bcl2, S100, and probably Her-2 [5]. Also, BRAF, RET, Notch pathways may be involved [3]. In this case, Ki67 was very high in non-differentiated areas, 4 times higher than the value from differentiated carcinoma. The use of surgery for undifferentiated carcinoma is limited

for curative purposes but in selected cases with early diagnosis and particular anatomy this may prove extremely useful [6].

Conclusions

Despite recent advance in genetic features, therapeutical options are still limited for every day practice in cases with late anaplastic/undifferentiated shift from differentiated thyroid carcinoma. Surgery is part of the management and probably is most useful in extremely early stages of disease, and every time when it is feasible the rational is to apply it since radioiodine therapy and chemotherapy as not useful in this particular situation.

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