NONINVASIVE ENCAPSULATED ANAPLASTIC THYROID CARCINOMA PROMISING AN EXCELLENT CLINICAL COURSE: A CASE REPORT AND REVIEW OF THE LITERATURE

F. Dirilenoglu^{1,*}, A. Kahraman Akkalp², H. Bag³, T. Atasever Rezanko², Z. Kucukodaci²

¹Near East University, Faculty of Medicine, Dept. of Pathology, Nicosia, Cyprus, ²Izmir Katip Celebi University Ataturk Training and Research Hospital, Dept. of Pathology, Dept. of General Surgery, Izmir, Turkey

Abstract

Context. Noninvasive encapsulated anaplastic thyroid carcinomas (NE-ATCs) have been described in few case reports, and consistently associated with favorable outcome compared to the classical ATCs.

Objective. Our aim is to remark a rare histological finding in ATCs, encapsulation, which has been associated with a favorable outcome.

Design. We have documented a rare case of an NE-ATC with its clinical, pathological, and molecular features. We also provided a thorough discussion of all the encapsulated ATCs reported in the literature.

Subjects and Methods. A 50-year-old woman with an unremarkable medical history, who presented with a thyroid nodule, and diagnosed as “follicular lesion of undetermined significance” by fine needle aspiration biopsy. The patient was lost to follow-up for six years and revisited upon her neck disturbances and underwent total thyroidectomy.

Results. Sections of the right lobe revealed a grossly encapsulated nodular lesion, measuring 75x55x55 mm. Histologically, the tumor consisted of both carcinomatous and sarcomatous components supported by immunohistochemical stains. Necrosis and atypical mitotic figures were evident. Capsular and/or vascular invasion was not identified. There were no BRAF codon 600, KRAS, NRAS mutations and RET/PTC rearrangement. During three-month follow-up, the patient was free of disease without adjuvant therapy.

Conclusion. Encapsulated ATCs tend to follow a favorable clinical course and may deserve conservative treatment approaches.

Key words: anaplastic carcinoma, thyroid, noninvasive, capsule, carcinosarcoma, good prognosis.

INTRODUCTION

Anaplastic thyroid carcinomas (ATCs) account for 0.8% of all thyroid malignancies, typically

associated with extrathyroidal extension and distant organ metastasis at the time of diagnosis (1, 2). All ATCs are considered as stage IV according to the American Joint Committee on Cancer (3). Contrarily, to date, a small number of encapsulated ATCs which are associated with favorable outcome have been documented in case reports.

Here, we aimed to present our case of a noninvasive encapsulated ATC (NE-ATC) with its clinical, pathological and molecular features. We also provided a comprehensive discussion of all the encapsulated ATCs reported in the literature.

CASE PRESENTATION

A 50-year-old woman presented with a neck mass which was found to be a thyroid nodule on physical examination. The past medical history of the patient was unremarkable. She did not live in an endemic goitre area and had no family history of a thyroid lesion. Laboratory tests for thyroid functions (TSH, fT3, and fT4), and parathyroid gland (parathormone, Ca²⁺) were in normal range. Ultrasound showed an iso-hyperechoic nodule measuring 65x53 mm and occupying the entire right thyroid lobe. No pathological lymph nodes were observed in the cervical region. Fine needle aspiration biopsy (FNAB) of the right thyroid nodule showed a few groups of slightly enlarged and otherwise uniform and bland-looking thyrocytes including nuclei without papillary or anaplastic features, arranged in microfollicular pattern within hemorrhagic background. The patient was diagnosed as “follicular lesion of undetermined significance (FLUS)” according to Bethesda 2007 classification. Following FNAB, the patient was lost to follow-up over six years. After this long period of time, the patient revisited with complaints of discomfort and pressure on her neck. On ultrasound imaging, the size of the previous thyroid nodules barely

*Correspondence to: Fikret Dirilenoglu MD, Near East University, Faculty of Medicine, Department of Pathology, Nicosia, Cyprus, 99138, E-mail: fikretdirilenoglu@gmail.com

Figure 1. a- Grossly, thick capsule can be readily appreciated; b- Low power view displaying an encapsulated tumor with some entrapped follicles (H&E, 40x); c- An area demonstrating both of the carcinomatous and sarcomatous components (H&E, 100x); d- Numerous atypical mitoses (H&E, 200x).

increased. The patient underwent total thyroidectomy upon her neck disturbances.

Gross examination

The specimen weighed 213 gr, and consisted of right lobe, isthmus, and left lobe measuring 75x70x55 mm, 35x15x12 mm, and 70x25x25 mm, respectively. Sections of the right lobe revealed a grossly encapsulated nodular lesion, measuring 75x55x55 mm and filling the lobe almost completely. Cut surface of the nodule was variably solid and cystic, extensively degenerated and partly necrotic. A small rim of uninvolved thyroid parenchyma was abutting the nodule (Fig. 1a). The nodule together with its capsule was submitted in total. In the left lobe, there were four well-defined, colloid-rich nodules.

Microscopic examination

Low power magnification displayed a well-demarcated nodule that was surrounded by a thick collagenous capsule (Fig. 1b). Approximately eighty percent of the tumor consisted of necrotic and hemorrhagic areas. The tumor included carcinomatous and sarcomatous components. Carcinomatous component comprised solid islands and irregular nests, and sarcomatous component was composed of spindled cells dispersed among carcinomatous areas. The neoplastic cells in both components showed features of anaplasia, including bizarre and pleomorphic nuclei with some of them containing prominent nucleoli (Fig. 1c). There were many accompanying multinucleated giant cells. The tumor had marked mitotic activity

Figure 2. a- Cytokeratin AE1/AE3 was positive only in carcinomatous component (100x); b- Vimentin highlighted sarcomatous cells (40x); c- P53 positivity (200x); d- Thyroglobulin negativity (40x).

and demonstrated numerous atypical mitotic figures (Fig. 1d). Capsular and/or vascular invasion was not identified. There was no evidence of a preexisting well-differentiated thyroid carcinoma. At the periphery of the tumor, there were only small foci of entrapped thyroid follicles. Sections from the isthmus and left lobe exhibited benign hyperplastic nodules as well as a peri-isthmus reactive lymph node.

Immunohistochemical and molecular studies

Tumor cells were stained in the fashion of a carcinosarcoma. Predominating spindled cells were diffusely positive for vimentin, but they lacked of any identifiable line of differentiation (Fig. 2a). Epithelial cells were highlighted by cytokeratin AE1/AE3 and EMA antibodies (Fig. 2b). Eighty percent of the cells showed strong p53 positivity (Fig. 2c). Ki-67 (MIB1) labeling index was found 8% at the “hot spot” (calculated by using ImmunoRatio, a web-based automated image analysis application). E-cadherin was

diffusely positive in carcinomatous component, while there was no positivity at all in sarcomatous tumor cells. Staining for TTF-1, thyroglobulin, calcitonin, p63, synaptophysin, S100, caldesmon, smooth muscle actin, desmin, CD31, and beta-catenin were all negative (Fig. 2d).

There was no BRAF codon 600, KRAS, NRAS mutations and RET/PTC rearrangement in both carcinomatous and sarcomatous components of the tumor.

To sum up, histological and immunohistochemical findings were consistent with an NE-ATC.

Treatment and follow-up

Imaging studies confirmed that there was no evidence of regional or distant metastasis. During a six years follow-up, the patient was doing well and free of disease without adjuvant chemotherapy or radiotherapy.

DISCUSSION

ATC is one of the most notorious malignancies due to its highly aggressive clinical course with a 5-year survival rate of less than 10% (4). Most of the patients present with a rapidly growing neck mass which invades surrounding vital structures along with distant metastases (2). Considering this relentless behavior, it has been very surprising to encounter an ATC with such an unusual pathological and clinical presentation in our case. Although exhibiting typical morphology of an anaplastic carcinoma, the tumor was enclosed entirely in a capsule without unfavorable prognostic

factors, i.e. local or distant metastasis, lymph-vascular invasion.

Coming across an unusual case always brings along the questions of other differential diagnoses. We excluded other diagnostic possibilities, such as the other primary thyroid malignancies and metastatic tumors, by clinical findings, typical morphological features, and using our broad-spectrum immunohistochemical workup. Particularly, a metastatic carcinosarcoma was excluded by comprehensive imaging studies before and after surgery, as well as relying on the fact that the patient had the same thyroid lesion without any issues for six years.

Table 1. Review of the literature including the patients with encapsulated anaplastic thyroid carcinoma (5–9)

Study	Diagnostic terminology	Clinical history	Size/ Location	Preexisting lesion	Histological features			Molecular features	Outcome
					Morphology	VI	Capsule		
Voutilainen <i>et al.</i> 1999 (5)*	ATC	NA	NA	Follicular carcinoma	NA	NA#	NA#	NA	Alive after 156 months.
Guimarães <i>et al.</i> 2000 (6)	Encapsulated ATC	Asymptomatic nodule for 5 years	50 mm/ isthmus	No	NA	NA	Yes	NA	Free of disease at 35 months
Ito <i>et al.</i> 2003 (7)	Encapsulated ATC without invasive phenotype	Sudden enlargement of the nodule after 15 years of follow-up Hypothyroidism	75 mm/ right	Follicular tumor	Spindle cell type	NA	No	NA	Free of disease at 57 months
Rapkiewicz <i>et al.</i> 2009 (8)	Encapsulated ATC	Follicular carcinoma metastatic to rib Exposed to radiation	41 mm/ left	Follicular carcinoma	Focal squamous differentiation	Yes	Yes	NA	New bone metastasis probably from follicular carcinoma No information regarding outcome
Dibelius <i>et al.</i> 2014 (9)	Noninvasive ATC	Incidentally identified 5 years after the diagnosis of a metastatic squamous cell carcinoma Prior chemoradiation	31 mm/ right	Follicular lesion which was believed to represent a follicular adenoma, or less likely an adenomatoid nodule	Lymphoepithelial-like, and angiomatoid areas	No	No	NA	Free of disease at 14 months postoperatively No adjuvant therapy
Current case Dirilenoglu <i>et al.</i> 2017	Noninvasive encapsulated ATC	Diagnosed six years after a FLUS diagnosis by FNAB	75 mm/ right	Follicular lesion	Carcinosarcoma	No	No	No BRAF codon 600, KRAS, NRAS mutations or RET/PTC rearrangement	Free of disease at nine months postoperatively No adjuvant therapy

NA: not available, VI: vascular invasion, SCC: squamous cell carcinoma, ATC: anaplastic thyroid carcinoma, FLUS: follicular lesion of undetermined significance, FNAB: fine needle aspiration biopsy.

* One case in a series of 33 ATCs (a microscopic anaplastic carcinoma focus within an encapsulated follicular thyroid carcinoma).

Possibly no capsular/vascular invasion.

To date, encapsulation has been reported only by a small number of ATC cases in association with a favorable prognosis (Table 1) (5–9). Remarkably, all of these patients but one was either followed up for years for an asymptomatic lesion, or they have found to have an ATC coincidentally after pathological examination. Only in the case of Rapkiewicz *et al.*, the patient presented with metastasis, presumably resulting from the pre-existing follicular carcinoma (8). What is more, none of these cases showed gross capsular invasion, although the differences have been shown in the presence or extent of capsular invasion. Of four cases with encapsulated ATC, two cases had no invasion beyond the capsule and the others had only microscopic extracapsular extension. We agree with Dibelius *et al.* in considering the absence of gross capsular invasion as a key factor underlying the clinical behaviour of these tumors (9). Hence, our case with an NE-ATC would be expected to follow a favorable outcome.

Comparison of the histological findings other than encapsulation among the reported encapsulated ATCs did not yield a certain feature which might be of prognostic relevance. They showed a variety of morphology including pleomorphic, anaplastic, poorly cohesive epithelial cells, or spindled cells. In one case, angiomatoid and lymphoepithelial-like features were denoted (9). Squamous differentiation was also documented (8). In our case, pleomorphic, squamoid epithelial cells as well as pleomorphic spindled cells, and numerous giant cells were identified.

Nevertheless, some other pathologic factors reflecting the overall tumor biology should be carefully sought for a precise prognostication. Rapkiewicz *et al.* reported an encapsulated ATC arising from a follicular carcinoma demonstrating microscopic extracapsular invasion, lymph-vascular invasion as well as a component of poorly differentiated carcinoma in which the patient developed a metastatic bone lesion at presentation (8). The term “Incidental ATC” has been suggested for those cases featuring only microscopic foci of anaplastic carcinoma arising in association with a better differentiated thyroid carcinoma (10). This finding may portend a favorable prognosis as seen in the case of a patient with encapsulated ATC, who had the longest survival by 156 months at the time of publication, in a series of 33 ATC patients (5). Another series investigating prognostic factors and therapy in ATC patients excluded three cases showing microscopic foci of ATC due to the distinct difference in their outcome compared to the other patients with

evident ATC component (11).

Most of the ATCs develop associated with preexisting well-differentiated thyroid lesions (12). Accordingly, all but one of the documented encapsulated ATCs was found to be associated with a preexisting follicular lesion. Not surprisingly, we have also identified a small but well-preserved area of entrapped follicles. Review of the FNAB smears dating back to six years prior to surgery was consistent with FLUS without evidence of a carcinoma. In this case, either sampling of the anaplastic foci was not achieved or there was not a development of an anaplastic transformation at the time of FNAB (13). In the case of a late-stage transformation from a long-standing benign lesion or a well-differentiated thyroid malignancy to an anaplastic carcinoma, the patients may benefit from an earlier resection before a widespread disease occurs. The other possible way ensuring a prolonged history might be the difference in biology of these tumors which renders them slowly growing. This explanation could be more reasonable if an encapsulated ATC developed in the earlier stage or truly *de novo*.

In conclusion, we presented an extremely rare case of an NE-ATC which has been stable for over six years. The diagnosis was made coincidentally after thyroidectomy had been performed supposedly for a benign goitre. This unusual presentation is remarkable in an anaplastic carcinoma which is usually expected to demonstrate a rapid and aggressive clinical course. This case has provided another proof that encapsulated ATCs may account for a distinct entity, and particularly NE-ATCs may deserve a lower staging and more conservative treatment approaches.

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from the patient included in this manuscript.

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