Diffuse follicular variant of papillary thyroid carcinoma: a case report with a revision of literature

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Abstract

The diffuse follicular variant of papillary thyroid carcinoma (DFV-PTC) is a rare malignant thyroid condition. It represents an uncommon variant of papillary carcinoma characterized by a diffuse involvement of thyroid parenchyma, follicular architecture and nuclear features of PTC in absence of a surrounding capsule. Up to date few data have been collected about this entity and, at the best of our knowledge, only 24 cases have been reported in the literature. According to these reports DFV-PTC seems to occur preferentially in young women and shows more aggressive behavior than other papillary thyroid tumors. Herein we present an unusual case of DFV-PTC occurring in an 83 years old woman, involving the entire thyroid gland, without distinct or prevalent thyroid nodules. The tumor was clinically misdiagnosed as obstructive goiter.

Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy accounting for 85 to 90% of all thyroid cancers, the incidence of which is increasing worldwide. PTC and its well-differentiated follicular variant (FV-PTC) that represents about 20% of the PTCs, generally have a good prognosis.

In this variant malignant thyroid cells show the classical nuclear features of PTC but an exclusive or almost exclusive follicular pattern of growth arranged in a nodular structure. Capsule formation could be either incomplete or absent. Follicular architecture is largely prevalent, but a careful search for papillae usually demonstrates few scattered structures.[1-3] Diffuse follicular variant (DFV) of PTC is one of the rarest forms of PTC. Sobrinho-Simoes and colleagues described a diffuse form of FV-PTC characterized by diffuse involvement of the whole thyroid gland without formation of grossly distinct and encapsulated nodules.[4] To the best of our knowledge, 24 cases of this unusual PTC-subtype have been reported in the literature (Table 1).[4-8] The lesions were described to involve a single thyroid lobe or showed a bilateral extension with multi nodular neoplastic areas, with the largest nodule reaching a mean dimension of 3 cm. Moreover DFV-PTC invariably showed an aggressive behavior with occurrence of distant metastasis and poor survival.[5,6] Herein we report a new case of DFV-PTC occurring in 83 years old woman involving the whole thyroid gland, which was clinically misdiagnosed as colloid goiter.

Case Report

An 83-years-old woman was admitted to the emergency department of our institution for the appearance of symptoms such as dysphonia, dysphagia and severe orthopnea. The patient was a heavy smoker (more than 20/day).

The findings on physical examination were indicative for obstructive goiter with compression on the inferior mediastinal structures. The biochemical and serological analysis were in the normal range. Further evaluation with a computed tomography (CT) scan showed a solid heterogeneous lesion 7×8 cm extending to the retrosternal region, with right deviation of the laryngo-tracheal axis. In the context of the lesion a hypodense area with wall calcification was present. The CT scan was performed without contrast because the patient hypersensitivity. Considering the severe dysphagia and orthopnea the patient was immediately referred to surgery without a preoperative cytological evaluation of the thyroid condition. After surgery the patient was admitted to the Intensive Care Unit because of respiratory problems and tracheostomy was necessary. On gross examination of resected specimen, the thyroid gland was enlarged measuring 8×8×6 cm and was firm and fibrotic in consistency. Sectioned surface showed round, white-yellowish confluent areas that involved and replaced the entire parenchyma. No normal residual thyroid parenchyma was macroscopically identified. Thyroid capsule was largely infiltrated (Figure 1). Finally a careful sampling of the organ was performed for the final histological evaluation.

Histology showed a well-differentiated thyroid cancer with a diffuse follicular growth pattern, mainly constituted by micro-follicles containing a small amount of colloid, organized in confluent nodules of small to medium size with dense collagenous septa without a detectable tumor capsule. A careful observation of all histological sections showed many images of vascular invasion at the periphery of the tumor (Figure 2A) and revealed only few spot of necrosis and very rare mitotic figures. No psammoma bodies were found. Cytologically, the nuclei were sometimes enlarged, with typical PTC features consisting of grooves, overlapping and clearing. Occasionally, nuclear pseudoinclusions were also detected although conventional papillary structures could not be found (Figure 2B). To confirm the diagnosis of follicular variant of papillary thyroid carcinoma and to reveal the residual normal thyroid tissue, the expression analysis of two putative thyroid cancer associated antigens, namely galectin-3 and HBME-1, was performed by using a biotin-free immunohistochemical procedure.[9,10]

The immunostaining showed intense and diffuse positivity of the cytoplasm (galectin-3) and plasma membrane (HBME-1) of neoplastic cells, highlighting the presence of few scattered islands of residual normal parenchyma, which was invariably unreactive (Figure 2C,D). Expression analysis of p53 was also performed and showed a complete negativity of neoplastic cells as expected to occur in well-differentiated thyroid carcinomas. Additionally, BRAF (V600E) mutational analysis was evaluated by sequencing analysis and no mutation was detected (data not shown).

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Discussion

Diffuse follicular variant of papillary thyroid carcinoma was firstly described by Sobrinho-Simoes and colleagues.[4] As reported by Ivanova and colleagues,[5] that have collected the richest clinical records of DFV-PTC, this kind of tumor seems to be more frequent in young women (26.8±3.3), even though few cases have been encountered in males.[6-8] Clinically, the patients had a poor prognosis due to the aggressiveness of the carcinoma frequently diagnosed in an advanced stage.[5-7] From a pathological point of view, the tumor grossly involves either one thyroid lobe or the whole gland. Sectioned surface of the specimen showed neither the presence of a capsule nor a clear-cut delineation between the tumor and the adjacent parenchyma. Microscopically, the cytological features are similar to those of classic FV-PTC. Images of vascular invasions are usually promptly detected. Regarding the phenotype, the expression of the putative thyroid cancer associated markers galectin-3 and HBME-1 is expected.[6,9,10] Furthermore this immunostaining allows to recognize the few scattered areas of normal thyroid parenchyma intermingled with the exuberant neoplastic tissue.

Herein, we present an unusual case of diffuse follicular variant of papillary thyroid carcinoma, occurring in an elderly woman, clinically misdiagnosed as thyroid goiter.

Histologically, the neoplasia involved the whole thyroid gland with only scattered residual islands of normal thyroid parenchyma. In contrast to all the other reported DV-FTC that reached the maximum diameter of 3 cm, the case we observed reached 8 cm in size. Cytologically the classical nuclear features of PTC, namely nuclear grooves, clearing, overlapping, and nuclear pseudoinclusions were promptly detected, although no papillary structures were histologically observed. Architecturally, the tumor showed a follicular pattern of growth with a micro-follicular predominant appearance. According to the other reported cases, only rare mitosis were observed, but some spots of necrosis were found.

The extracapsular extension of the tumor and images of vascular invasion were predictive of an aggressive behavior. This was confirmed by the co-existence of multiple pulmonary metastatic nodules at time of diagnosis, discovered at total body CT-scan and characterized at FNA-cytology.

Considering the reported occurrence of BRAF (V600E) mutation[6,8] likely responsible of aggressive behavior a genetic evaluation was performed. The case reported herein carried a wild-type BRAF. The occurrence of BRAF V600E mutation does not seem indeed to be strictly related to this specific histotype. Furthermore Albores-Saavedra and colleagues described lesions reaching a maximum dimension of about 11 cm with a macrofollicular growth pattern but organized in encapsulated nodules.[11] These cases, considering the presence of multiple capsulated lesions could be better classified as multifocal FV-PTC. Moreover in these specific cases, the prognosis was surprisingly good

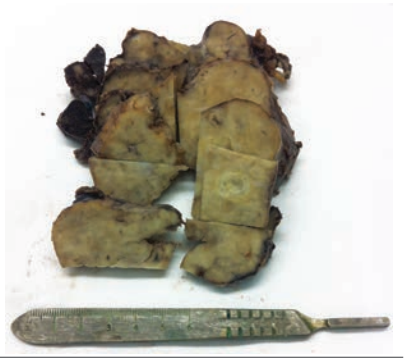

Figure 1. Grossly, the thyroid gland was enlarged, firm and fibrotic in consistency. The infiltration of the capsule is seen. Sectioned surface showed round, white-yellowish confluent areas involving the entire thyroid gland; no normal residual thyroid parenchyma is macroscopically visible.

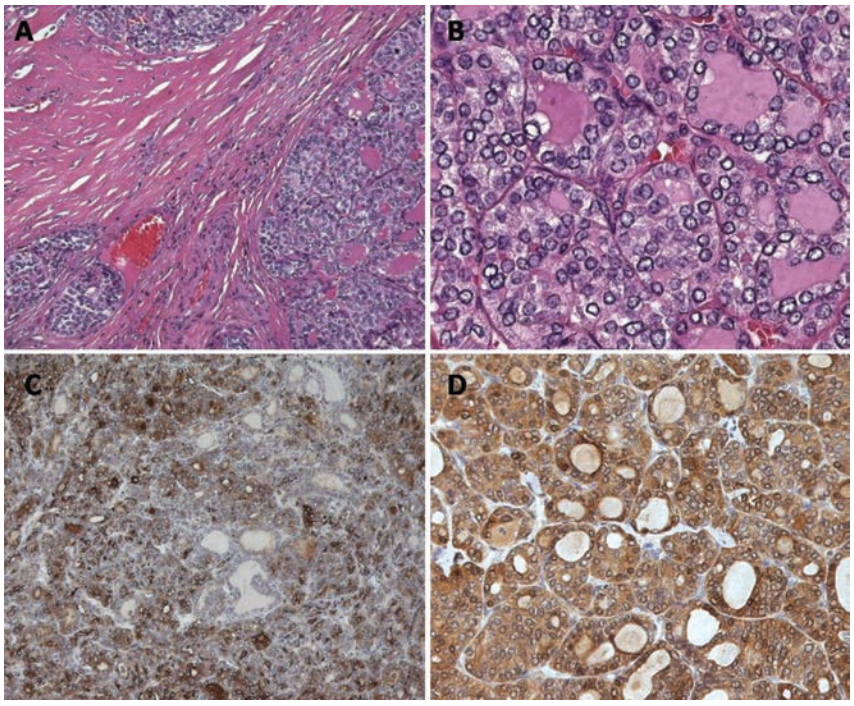

Figure 2. A) Neoplastic cells are arranged in a follicular pattern of growth. Lympho-vascular invasion is visible at the periphery of the tumor [hematoxylin and eosin (H&E) staining, magnification 25×]. B) Typical cytological features of well-differentiated papillary thyroid carcinoma are visible: nuclear pseudoinclusions, grooving and clearing are present (H&E staining, magnification 200×). C) HBME-1 is expressed on the plasma-membrane of tumor cells (Indirect immunoperoxidase, magnification 25×). D) Galectin-3 staining is intensively positive in the cytoplasm of tumor cells (direct immunoperoxidase, magnification 100×).

Table 1. Reported cases of diffuse follicular variant of papillary thyroid carcinoma.

Study	Number of cases	Age (average)	Gender	Tumor dimension, cm	Phenotype	BRAF status
Sobrinho-Simoes *et al.*[4]	8	NS	NS	NS	NT	NT
Ivanova *et al.*[5]	10	26.8±3.3	NS	2.5±0.3	NT	NT
Cha *et al.*[6]	1	69	M	NS	Galectin-3+	V600E
Mizukami *et al.*[7]	1	13	M	NS	NT	NT
Gupta *et al.*[8]	4	32	3F, 1M	2.4	NT	V600E (2) wtBRAF(2)

NS, not specified; NT, not tested.

compared to the poor prognosis usually reported in DFV-PTC. These facts clearly demonstrate that the aggressive behaviors of DFV-PTC may be likely due to the extracapsular extension and/or vascular invasion. Delayed diagnosis indeed plays an important role in the natural evolution of this malignancy.

Conclusions

In conclusion, we confirm the biologically aggressive behavior of DFV-PTC although the tumor is generally well-differentiated as demonstrated by the histology and immunophenotype, in particular the lack of p53 and BRAF mutation. Nonetheless, the real role of BRAF mutation and its incidence in DFV-PTC can form the baseline for further biological studies. The present report demonstrates that this tumor can occur in a wide range of age and not only in young women. Most important, this condition can be clinically misdiagnosed as diffuse colloid goiter. For this reason in the presence of a diffuse thyroid enlargement, in particular without sharp nodules at thyroid eco-scan, a simple FNA-cytological evaluation is imperative.

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