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Case Report
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Papillary Thyroid Carcinoma Hobnail Variant: A Report of Two Cases and Literature Review

Arrangoiz R[1], Moran R[2], Corona L[3], Boy J[3], Cordera F[1], Caba D[1], Muñoz Juarez M[1], Moreno E[1] and Luque-de-Leon E[1]*

[1]Department of Surgical Oncology, Sociedad Quirurgica S.C., American British Cowdray Medical Center, Mexico

[2]Department of Surgery, American British Cowdray Medical Center, Mexico

[3]Department of Pathology, American British Cowdray Medical Center, Mexico

Abstract

An uncommon subtype of Papillary Thyroid Carcinoma (PTC) called Hobnail variant of Papillary Thyroid Carcinoma (HPTC) has recently been described and is distinguished by an aggressive behavior and somewhat poor prognosis. More than 100 cases have been published. HPTC is histological categorized by a predominantly micro papillary growth pattern and hobnail appearance of cells due to the apically placed bulging nuclei. To determine the diagnosis of a HPTC at least 30% of cells in the tumor are needed to display a hobnail-micro papillary pattern, though minor hobnail-micro papillary features are of consequence and should be noted in a pathology report. Fine needle aspiration cytology of these tumors will show micropapillary structures, loss of polarity, discohesiveness, and hobnail cells with teardrop appearance and soap bubble-like pseudo-nuclear inclusions. All these findings provide evidence for a preoperative diagnosis of HPTC, which may help to render a decision regarding the appropriate management (thyroid lobectomy *vs*. total thyroidectomy). Compared to patients with classic PTC, patients with HPTC frequently have extrathyroidal extensions, exhibit nodal or distant metastasis, and respond poorly to radioiodine treatment, factors which influence increased deaths among this subgroup of patients with PTC. We present two cases of PTC with prominent hobnail features and we will be reviewing the clinical, histological, and molecular characteristics of this aggressive variant of PTC.

Keywords: Thyroid cancer; Papillary thyroid cancer; Variants of papillary thyroid cancer; Hobnail variant of papillary thyroid cancer; Aggressive variants of papillary thyroid cancer

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Correspondence:

Rodrigo Arrangoiz, Department of Surgical Oncology, Sociedad Quirurgica S.C., American British Cowdray Medical Center, Av Carlos Graef Fernandez, #154-515, Colonia Tlaxala, Delegacion Cuajimalpa, Mexico, Tel: +52-5255-1664-7200;

E-mail: rodrigo.arrangoiz@gmail.com

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Introduction

Thyroid neoplasm's are divided based on the cell of origin, which could be, from the thyroid follicular cells and the neuroendocrine, parafollicular cells (C cells) [1]. Differentiated thyroid cancer includes Papillary Thyroid Carcinoma (PTC), Follicular Thyroid Carcinoma (FTC), Hurthle cell carcinoma (oxyntic cells), poorly differentiated carcinoma, and anaplastic carcinoma [2]. Differentiated thyroid cancers represent more than 90% of thyroid cancer cases [2-5]. Between the years 2010 to 2014, an average of 63,229 patients per year, were diagnosed with thyroid cancer [2,3,6]. Of these 63,229 patients, 89.4% had PTC, 4.6% had FTC, 2.0% had Hurthle cell carcinoma, 1.7% had Medullar Thyroid Carcinoma (MTC), and 0.8% had Anaplastic Carcinoma (ATC) [6].

The incidence of thyroid cancer has been increasing significantly since the mid 1990s, with an estimated incidence in the United States of America of 52,890 new cases of thyroid cancer (12,720 in men and 40,170 in women) for the year 2020 [6]. This cancer represents the most common endocrine neoplasia and represents approximately 3% of all malignant tumors in humans, with 75% of the cases occurring in women [7,8], and two thirds of the cases occurring in people under 55 years of age [7]. The less aggressive forms of these tumors are more common in women and younger people [2,8]. The mortality rate from thyroid cancer has been maintained stable in women but has increased approximately 1% per year since the year 1983 in men and will be responsible for approximately 2,180 deaths from thyroid cancer (1,040 men and 1,140 women)in the year 2020 [6]. The relatively low mortality rate compared to the incidence is due, in part, to the indolent nature of the vast majority of thyroid tumors.

Patients with of differentiated thyroid cancer usually have an excellent long-term prognosis, with 5-years survival rates close to 100% for localized disease [2,6,8]. In spite of low mortality rates, local

Table 1: Patient characteristics.

	Age	Nodule Size	ATA Risk Classification	Percentage of Hobnail cells	Lymphovascular Invasion
Patient 1	31 years	24.6 mm × 17.8 mm	Intermediate Risk	10%	Negative
Patient 2	33 years	27 mm × 14 mm	Intermediate Risk	40%	Positive

recurrence occurs in approximately 20% of the patients, and distant metastases occur in about 10% of patients at 10 years of the diagnosis [8]. Mortality from thyroid cancer has been increasing in recent years [2,5], which is why progress in the development of new systemic therapies for iodine refractory thyroid cancer is extremely important. We know that medical development in this field has been delayed compared to the progress observed in the treatment of other solid tumors, however, data from emerging clinical studies suggest that thyroid cancer can be treated with targeted agents, particularly tyrosine kinase inhibitors, show promising results that overshadow those previously seen with cytotoxic agents [9].

Histologic variants of PTC include follicular variant, tall cell variant, columnar cell variant, diffuse sclerosing variant, solid or trabecular variant, insular variant, and the recently recognized hobnail variant [10]. These histological variants of PTC show unique constellations of growth patterns, cell types, stromal changes, and molecular mutations. Approximately 10% to 15% of patients with the more aggressive variants of PTC (tall cell, columnar cell, solid, or hobnail variant) will have recurrent and metastatic disease [11]. Hobnail variant of Papillary Thyroid Carcinoma (HPTC) is an aggressive form of PTC, described in 2010 from the Mayo Clinic from a series of eight cases [12]. HPTC is strongly associated with aggressive clinicopathologic features, radioactive iodine refractoriness, disease progression, and a higher mortality rate compared to classic PTC [13-15]. The pathologist plays a key role in identifying these aggressive subtypes and in the multidisciplinary management of these patients [16].

We present two cases of PTC with prominent hobnail features and we will be reviewing the clinical, histological, and molecular characteristics of this aggressive variant of PTC.

Case Presentation

Case 1

A 31-years old male patient, with a Past Medical History (PMH) of a right testicular seminoma which was treated with a radical orchiectomy, and adjuvant chemotherapy with carboplatin. During follow-up a PET/CT scan was performed which showed a focal lesion in the thyroid gland that was metabolically active (SUV of 10.5). The patient has a 20 pack a year history of smoking for the past 12 years. Physical examination did not identify any pertinent findings. His initial laboratory results showed normal thyroid function. An ultrasound confirmed that the metabolically active lesion on the PET/CT was a thyroid nodule measuring 24.6 mm × 17.8 mm in size. An ultrasound guided FNA was performed and the results showed a PTC (Bethesda VI) (Figure 1). The preoperative ultrasound did not identify any abnormal lymph nodes in the central and lateral compartments.

The patient underwent a total thyroidectomy with no complications. The pathology reported showed a HPTC in 10% of the specimen. He was classified as intermediate risk based on the modified risk of structural recurrence of the American Thyroid Association (ATA). The case was presented in our tumor board and it was decided to offer him radioactive iodide treatment. He is two years out of the procedure and has an excellent response to treatment with no evidence of biochemical or structural recurrence (Table 1).

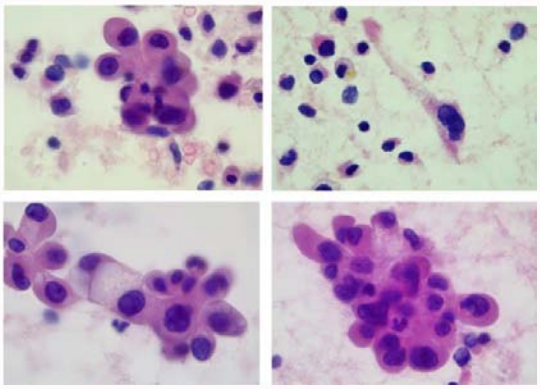

Figure 1: FNA biopsy showing classichobnail variant features.

Case 2

A 33-years old female patient with a long-standing history of goiter and a PMH of cancer in the family (grandfather GI cancer and an uncle with lymphoma). Her chief complaint was an intermittent cough. The patient had no obstructive symptoms, or any symptom or sign associated to either hyperthyroidism or hypothyroidism. During the evaluation, her physician noticed an enlarged thyroid nodule, and performed a thyroid ultrasound. FNA biopsy was performed which showed a PTC with a Bethesda VI score. On the physical examination, a prominent palpable left thyroid nodule was identified in the context of a multinodular goiter. The patient had no palpable lymphadenopathy. Her initial laboratory results reported normal thyroid function, with no abnormalities in the white or red blood cell count. The thyroid ultrasound found multiple nodules in the thyroid parenchyma, with a TI-RADS 3 score.

The patient underwent total thyroidectomy with no complications. The final pathology report showed a multifocal PTC consisting of 30% classic pattern, 30% oxyntic pattern and 40% hobnail pattern (Figure 2). She was classified as intermediate risk based on the modified risk of structural recurrence of the American Thyroid Association (ATA). The case was presented in our tumor board and it was decided to offer her radioactive iodide treatment. She is 18 months out of the

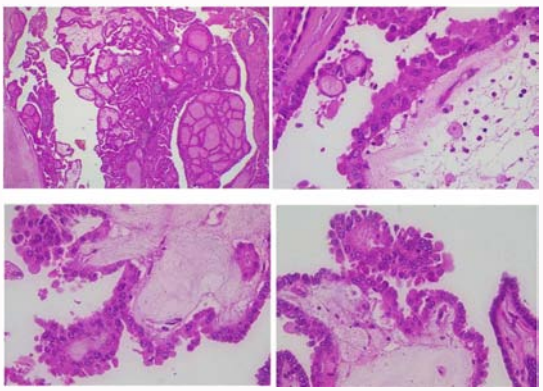

Figure 2: Final pathology report showing hobnail features.

Table 2: Cases reported in the literature with the type of mutation identified.

Studies	# Cases	% BRAF Mutation	% Lymphovascular Invasion	Other Mutations
Asioli et al. [12]	8	0.5	0.875	
Lino-Silva et al. [22]	7	N/A	0.715	
Asioli et al. [17]	24	N/A	0.708	
Lubitz et al. [11]	12	0.8	0.42	RET/PTC1, RET/PTC3
Asioli et al. [23]	5	0.6	0.8	
Amacher et al. [24]	6	0.33	0.75	
Lee et al. [21]	10	0.8	0.8	
Ieni Aet al. [25]	8	0.5	0.5	
Morandi et al. [26]	18	0.833	0.833	TP53, TERT, PIK3CA
Teng et al. [13]	18	0.94	0.111	PIK3A, hTERT, CTNNb1, EGFR, AKT1, RET/PTC1/RET/PTC3
Total Number of Cases	**116**			

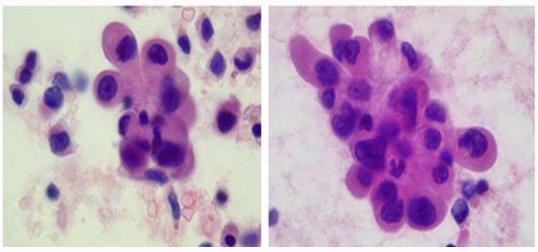

Figure 3: The histologic features of HPTC includes papillary and micropapillary structures, lined with cells containing eosinophilic cytoplasm and apical localated nuclei with prominent nucleoli, that produce a surface bulg.

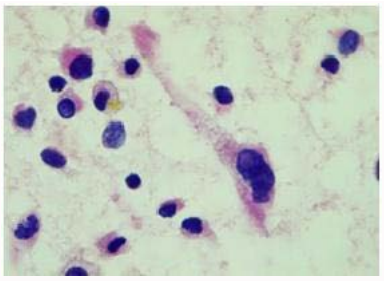

Figure 4: Comet like cell with an elongated eosinophilic cytoplasm, with nuclear pseudo inclusions.

procedure and has an excellent response to treatment with no evidence of biochemical or structural recurrence (Table 1).

Discussion

HPTC is an aggressive form of PTC that shows unique constellations of growth patterns, cell types, stromal changes, and molecular mutations [12]. These patients will have increased incidence rates of recurrent and metastatic disease [17]. HPTC is also strongly associated with aggressive clinicopathologic features, radioactive iodine refractoriness, disease progression, and a higher mortality rate compared to classic PTC [18]. The pathologist plays a key role in identifying these aggressive subtypes and in the multidisciplinary management of these patients [16].

In the literature there are roughly 100 cases reported of HPTC with a female predominance of 2:1, the average age of diagnosis is 53 years [11,12,15-18]. As most thyroid nodules today it is usually an incidental finding on an ultrasound performed for other reasons [3]. The most common sign when present is a palpable thyroid nodule, and in more advance cases it may be associated with dyspnea due to compression of trachea, cervical lymphadenopathy, and hoarseness [19]. Extra-thyroidal invasion was observed in roughly 43% of cases reported [12]. One of the main histological features found on the HPTC is the loss of polarity, which is one of the fundamental factors that give this variant its aggressive behavior along with poor cellular differentiation [13,14].

Fine needle aspirations are usually highly cellular, with a bloody background, and scant colloid [18]. Cells are arranged in papillary like clusters and/or in micro papillary groups and a few cases show a predominant follicular pattern (Figure 3) [17]. The cells vary in size from small to medium with tear-drop cytoplasm, so called comet-like cells (Figure 4) [17]. Nuclei are apically placed, occasionally grooved, and produce a surface bulge leading to a hobnail appearance with high Nuclear/Cytoplasm (N/C) ratio (Figure 3) [14]. The presence on FNA of comet-like cells may lead to a preoperative suspicion of HPTC.

The differential diagnosis of HPTC in FNA includes conventional PTC and tall-cell variant of PTC which is characterized by eccentric nuclei, columnar cells, abundant cytoplasm, and distinct cell borders [4,10,12]. Both variants are characterized by the absence of cytologic hobnail appearance and comet-like cells.

HPTC was originally described using the following criteria for the histological diagnosis [12]:

- Non-solid variant of PTC.
- ≤ 10% of the tumor showed tall/columnar cell or diffuse sclerosing features.
- Loss of polarity/cohesiveness with hobnail features in ≥ 30% of tumor cells.
- PTC features are present showing papillary and micro papillary structures in the histopathologic smears.
- High magnification shows nuclear pleomorphism, occasionally pseudo-inclusions with multiple soap bubble-like inclusions, and possibly mitotic figures.
- Along with the PTC cellular findings HPTC can show papillary and micro papillary structures closely linked by cells containing eosinophilic cytoplasm and apically located nuclei with

prominent nucleoli.

- The cells that line these complex papillary structures have increased nuclear to cytoplasmic ratios and apically placed nuclei that produce a surface bulge (hobnail).

Molecular profile HPTC

The most common genetic abnormalities identified in PTC include RET/PTC rearrangements and BRAF V600E mutations [2,4,11,20] (Table 2). Epigenetic pathways, such as aberrant methylation of thyroid-specific genes involved in iodine metabolism or tumor suppression, may lead to loss of radioactive iodine avidity and increased tumor growth, invasion, and metastases [2,4,11,20].

The most commonly occurring mutation reported in patients with HPTC is a BRAF V600E mutation which is associated with extra thyroidal extension, lymph node metastasis, distant metastasis, recurrences, and mortality [11,21]. BRAF is a proto-oncogene located at chromosome 7q24 that encodes a serine/threonine kinase from the family of RAF-kinase, which plays a central role in the transduction of signals along the RAS/RAF/MEK/ERK pathway regulating cell growth, differentiation, and apoptosis [11,12]. Another mutation commonly identified is the RET/PTC1 rearrangements which was observed in roughly 30% of the cases [2,4]. Other less commonly reported mutations are the *TP53*, *PIK3A*, *hTERT*, *CTNNb1*, *EGFR*, *AKT1*, and NOTCH, without mutations of *CDKN2A*, *PTEN*, and *ALK* [2,4,11].

PTC is the most common differentiated thyroid cancer, with a dramatic increase in incidence in recent years [2,6,7]. Classically, PTC has an excellent overall survival [2,4,6], however some patients have tumors with an aggressive biology characterized by local recurrence, regional and distant metastasis [2,6,7]. It is necessary to identify which tumors will have a more aggressive biology so appropriate management can be provided. One of the Histologic factors that can help us differentiated the PTC that will have a more aggressive clinical course is the Histologic variant of PTC [10]. One of these variants is HPTC, which has been observed to have a more aggressive course compared to the classic PTC variant [13,22,23].

In a big, institutional series of primary PTC [17]; the prevalence of HPTC was only 0.6% (22/3551 cases) hence, there continues to be much to be learned about this new variant of PTC. Amacher et al. [24], in a recent article analyzed pure HPTC and other cases in connotation with poorly differentiated and ATC. They theorized that the hobnail features may be an indicator of a higher-grade transformation, because hobnail features are more common in poorly differentiated thyroid carcinomas [24]. They revealed that hobnail features are most frequently related with poorly differentiated thyroid carcinoma (4/18 cases), compared with conventional PTC patients (6/478); only one of ATC examined had hobnail features [25,26]. Nevertheless, in agreement with Turin criteria, the diagnosis of poorly differentiated carcinoma is mainly made on by morphology and includes solid/trabecular/insular tumors with absence of conventional nuclear features of PTC, and existence of at least one of the following: convoluted nuclei, mitotic activity (≥ 3/10 HPF), or tumor necrosis [27]. If HPTC does not fit the former criteria it cannot be considered as poorly differentiated; thus, the designation as a moderately differentiated thyroid carcinoma.

Conclusion

HPTC strict definition is the presence of ≥ 30% of hobnail type cells, but due to the lack of evidence in the literature regarding recurrence rates and mortality the finding of greater than 10% hobnail type cells must be taken into consideration as an indicator of a possible aggressive behavior. We need more evidence to comprehend the molecular mechanism of tumor genesis, tumor progression, and to create new targeted therapies that are tailored for this aggressive variant of PTC.

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