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CASE REPORT

MALIGNANT COLLISION TUMORS OF THYROID: TWO CASE REPORTS

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Abstract

Collision neoplasm is when two different types of tumors affect the same organ. Collision tumors of the thyroid are extremely rare. This paper describes two cases of patients who had these mixed tumors. The first case is a 59-year-old male patient who presented complaining of mass that was growing for over a year. After a thorough investigation the patient was initially diagnosed with Papillary Thyroid Carcinoma (PTC) and thyroidectomy was performed, however further histologic evaluation of the gland revealed PTC and Medullary Thyroid Carcinoma (MTC). The second case was of a 21-year-old female who presented with a neck swelling for only a month. Radiograph showed two nodules of variable sizes on right and left lobes. After an FNA a diagnosis of PTC was made. The patient later on had a complete thyroidectomy. Histology of the gland revealed PTC in right lobe and Oncocytic carcinoma in left lobe. Since CT tumors are rare, the diagnosis could be challenging. Although, it is of great importance as in some cases the management depends on it. The reported cases here shed the light on the importance of careful and meticulous histological diagnosis, as the accompanied tumors with PTC were both incidentally found.

Keywords: *Collision Tumors, Papillary Carcinoma, Medullary Carcinoma, Oncocytic Carcinoma.*

INTRODUCTION

Thyroid is the most common endocrine gland affected by cancer. Of all types of malignancies, Papillary Thyroid Carcinoma (PTC) is the most frequent. It accounts for (90%) of thyroid tumors.[1] PTC is considered a well-differentiated thyroid tumor arising from follicular cells. The long-term survival rate for PTC is (90%) with good prognosis in most patients.[2] It has been linked to a number of chromosomal mutations including; RET rearrangements, RAS and BRAF point alterations.[3] Diagnosing is dependent on several nuclear features which are sometimes difficult to detect. In these cases, certain thyroid markers as HBME-1, CK19 and RET

are used. However, the most specific to PTC is RET.[4]

Medullary Thyroid Carcinoma (MTC) is a relatively less common tumor of the thyroid gland. It represents only (2%) of all thyroid malignancies[1]. unlike PTC, it is a neuroendocrine tumor which originates from the para-follicular cells also known as "C cells" of the thyroid.[5] These specialized cells are responsible for secreting Calcitonin. As a direct consequence, high Calcitonin level is a considered a hallmark for diagnosing MTC.[6] The genetic alterations associated with MTC are similar to those of PTC, with RET proto-oncogen being the major mutation.[7] In contrast to PTC, it is known to have a more aggressive nature and is more likely to metastasize. Thus, having a much lower survival rate (50%) over the period of 10 years.[8]

Oncocytic cell carcinoma is another less common tumor (2%).[1] The responsible cells are called "Hurthle Cells" and was previously termed "Hurthle cell carcinoma" (HCC). They are believed to arise from the thyroid follicle and was once classified as Follicular Carcinoma subtype.[9] This tumor has also been linked to RET mutations.[10]

Co-occurrence of two thyroid tumors is an extremely rare event. These cancers are named "collision tumor", which is when two different tumors affect the same organ. They represent only 1% of all tumors of thyroid. MTC and PTC reported to be the most common duo.[11] Histologically, it can be presented as two separate tumors surrounded by normal thyroidal tissue or as one tumor with interlapping characters.[12] This paper covers two of these unusual events, of two patients with collision cancerous neoplasms, whereas the first patient had suffered from mixed papillary-medullary carcinoma. The second, had papillary and oncocytic carcinoma.

CASES PRESENTATIONS

Case One

A 59-year-old male patient presented to the department of endocrinology in King Abdullah Medical City in Makkah, Saudi Arabia in October, 2023 complaining of a neck swelling that had been growing gradually for over a year. His medical history was only relevant for diabetes. Upon clinical examination, a right thyroid mass was observed.

Blood tests revealed a low Thyroglobulin Tumor marker level in serum (<1.4 ng/mL) normally (3.68-64.15ng/mL) as opposing to the Thyroid Stimulating Hormone (TSH) which was remarkably elevated (12.74 mIU/L) as normal lies within (0.55-4.78 mIU/L). Both thyroid hormones were within normal limit, T4 Free Thyroxine (0.40 ng/dL) normal range is (0.7-1.48 ng/dL) and T3 Free Triiodothyronine was (2.98 pg/mL) normal levels (1.88-3.18 pg/mL) (Table 1).

Table 1. *Blood investigation*

Blood investigation for Case # 1		
Test	**Case 1 Value**	**Normal Range**
Thyroglobulin Tumor Marker	<1.4 ng/mL	3.68 - 64.15 ng/mL
Thyroid Stimulating Hormone (TSH)	12.74 mIU/L	0.55 - 4.78 mIU/L
T4 Free Thyroxine	0.40 ng/dL	0.7 - 1.48 ng/dL
T3 Free Triiodothyronine	2.98 pg/mL	1.88 - 3.18 pg/mL

An ultrasound of the gland revealed multiple thyroid nodules; two nodules related the left lobe and were scored 3 according to TIRADS. Both were solid, smoothly round and were notably smaller; N1 was found mid-lobe while N2 was observed inferiorly. An additional nodule related to the isthmus was observed. It was irregular and located to the right side. The nodule suggested high malignancy and marked score 5.56.

A CT scan of neck with IV contrast displayed an anterior mass in the neck at the midline extending to the right side. It appeared attached to the thyroid isthmus and inferior right lobe. A Focus of hyperdense central calcification was noted. Infiltration to the platysma muscle and the inferior part of the sternomastoid was suspected. Moreover, there were a

few bilateral prominent cervical lymph nodes at the level III measuring 7 mm.

The patient underwent total thyroidectomy and neck dissection. The right lobe measured 7.5 x 5.5 x 4.0 cm and the left lobe was 4.5 x 2.5 x 2.0 cm. Central neck lymph node with radical neck dissection was performed. No post-operative complications were reported.

When the specimen was grossed, the serial sectioning of gland's left side was insignificant. however, the right lobe unraveled a partially solid and partially cystic lesion occupying the entire tissue with focal areas of calcification. H&E interpretation reported a malignant neoplasm in the right thyroid lobe arranged in a papillary pattern (Figure 1). The neoplastic papillae were lined with classical nuclear features of Papillary Carcinoma, these characteristics are: nuclear enlargement, grooving, overlapping and frosted glass appearance (Figure 2). The cancer cells infiltrated adjacent skeletal muscles but no evidence of invasion whatsoever was found. Furthermore, in segments from the left lobe a 0.3 cm tumor was discovered incidentally, it was composed of loosely cohesive groups of polygonal cells and few cells had marked nuclear enlargement embedded in the hyalinized fibrous stroma. Interestingly, only one part out of eleven of the central group of lymph nodes was found positive for Metastatic Medullary carcinoma, yet, no distant metastasis was observed.

Calcitonin, TTF1, Thyroglobulin, PAX8 and CD45 stains were ordered. However, neoplastic cells in left lobe and metastatic lymph node were highlighted and therefore, positive for both Calcitonin and TTF1 solely. (Figure1) - A diagnosis of Papillary carcinoma in the right lobe together with Medullary carcinoma in the left lobe was finalized (Table 2).

Table 2. *Details of the case*

Case number	**Patient one**		**Patient Two**	
Tumor Site	Thyroid Right lobe	Left Lobe	Thyroid Right lobe	Left Lobe
Size	6x5x3 cm	0.3x0.3 cm	1.2x1x1 cm	3.5x2.5x1.5 cm
Histological diagnosis	Papillary Carcinoma	Medullary Carcinoma	Papillary Carcinoma	Minimally invasive Oncocytic Carcinoma
Tumor Necrosis	Not Identified	Not Identified	Not Identified	Not Identified
Angioinvasion	Not Identified	Not Identified	Not Identified	Not Identified
Lymphatic Invasion	Not Identified	Not Identified	Not Identified	Not Identified
Perineural Invasion	Not Identified	Not Identified	Not Identified	Not Identified
Extra Thyroidal Extension	Present, invading one muscle strap	Not Identified	Not Identified	Not Identified
Lymph Node Metastasis	0/11 Negative	1/11 Positive	Not Identified	Not Identified
Nodal Level Involved	None	Level VI	Not Identified	Not Identified
Distant Metastasis	Not Identified	Not Identified	Not Identified	Not Identified
Pathologic Stage Classification	pT3b	pT1a	pT1b	pT2
	pN0	pN1a	pN0	pN0
Other findings	Lymphocytic Thyroiditis		Lymphocytic Thyroiditis	

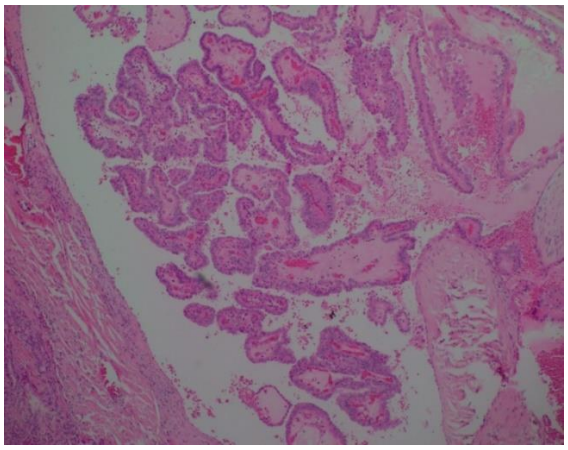

Figure 1. *Papillary carcinoma: complex branching papillary with fibrovascular cores (H&E magnification 10x)*

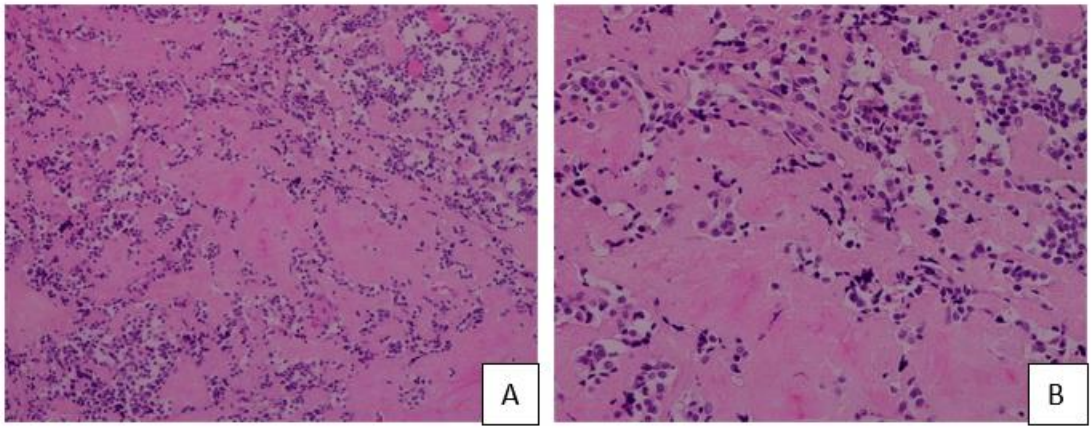

Figure 2*. Medullary carcinoma:* ***A)*** *nests & cords of cells present amidst acellular eosinophilic material (amyloid).* ***B)*** *Round to plasmacytoid cells. Cells have round nuclei with finely stippled to coarsely clumped chromatin*

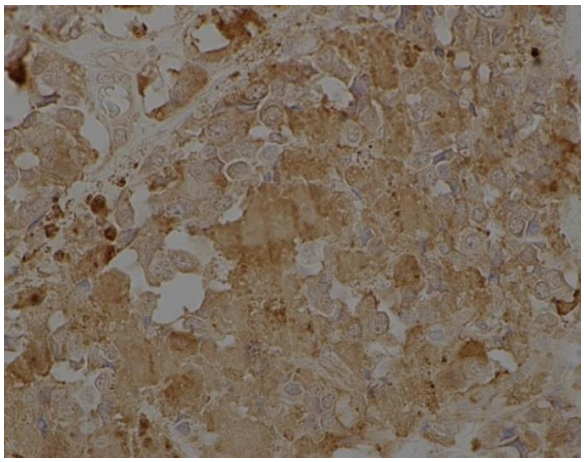

Figure 3. *(IHC): Calcitonin positive in medullary carcinoma*

Case Two

A 21-year-old woman presented in an outpatient clinic complaining of a persistent neck mass for a month. The patient's past medical history was not contributory. On examination it was apparent.

Blood work revealed T3 was 3.25 pg/mL normal within (1.88-3.18 pg/mL) but T4 (0.87 ng/dL) reference range is (0.7-1.48 ng/dL) and TSH levels were (4.702 mIU/L) normal range between (0.55-4.78 mIU/L). All other tests ordered including CBC and blood indices were not contributory (Table 3).

Table 3. *Blood investigation*

Blood investigation for Case # 2		
Test	**Value**	**Normal Range**
Thyroglobulin Tumor Marker	Not tested	3.68 - 64.15 ng/mL
Thyroid Stimulating Hormone (TSH)	4.702 mIU/L	0.55 - 4.78 mIU/L
T4 Free Thyroxine	0.87 ng/dL	0.7 - 1.48 ng/dL
T3 Free Triiodothyronine	3.25 pg/mL	1.88 - 3.18 pg/mL

The patient was ordered an ultrasound for her neck. In the right lobe a solid nodule observed. it had ill-defined margin and was given a high TIRADS score 5. As for the left counterpart, another nodule was located inferiorly in the lobe. it was less suspicious with defined borders, therefore, was graded 3.

Fine Needle Aspiration of the left thyroid nodule, a follicular lesion of undermined significance was reported.

A complete thyroidectomy of the gland was carried out in an operating theatre while the patient was under general anesthesia. No reported complications were recorded after the surgery.

Upon grossing, Right lobe measured 3.5x2.0x1.0 cm the left lobe's size was 5x2.5x2cm. Cuts of thyroid showed a mass in the right lobe 3.5x2.5x1.5 cm in size and one in the left lobe 1.2x1x1cm. Slides from the lesion in the right lobe, a neoplasm composed of papillae with a fibrovascular core was interpreted. Figure 4. Cells show nuclear enlargement and membrane irregularity and chromatin with few psammoma bodies. Figure 5. Adjacent thyroid shows lymphocytic thyroiditis. Moreover, the left lobe displayed a capsulated tumor, it constituted oncocytes arranged in a follicular pattern with focal area of capsular infiltration. Figure 6. At last, a diagnosis of PTC and oncocytic carcinoma was made (Table 2).

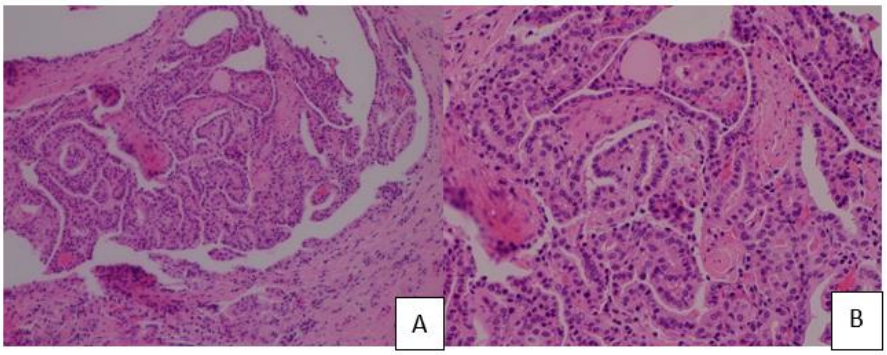

Figure 4. A) *Papillary carcinoma composed of complex, branching, randomly oriented papillae with fibrovascular cores.* ***B)*** *Cells showing ground glass nuclei, Orphan Annie nuclei with irregular nuclear contour, nuclear grooves and nuclear pseudoinclusions*

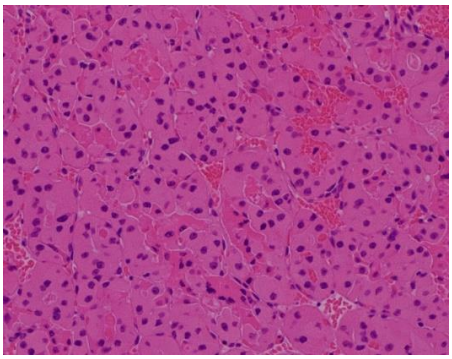

Figure 5. *Tumour cells are arranged as follicles with cells which are large in size, with distinct cell borders, deeply eosinophilic and granular cytoplasm, large nucleus with prominent nucleolus (oncocytes)*

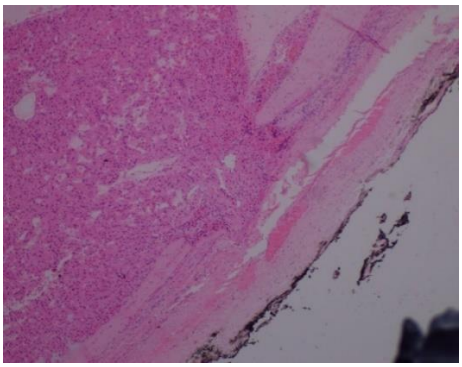

Figure 6. *Oncocytes showing capsular infiltration*

According to the 2015 guidelines of the American Thyroid Association for MTC, the primary treatment is total thyroidectomy, with the extent of lymph node dissection determined by the clinical stage.[10] For Patient One, the pathology findings revealed a pT3b pN0 M0 tumor in the right lobe, indicating a locally advanced tumor without lymph node or distant metastasis, and a pT1a pN1a M0 tumor in the left lobe, suggesting a small tumor with regional lymph node involvement but no distant metastasis. In contrast, Patient Two presented with early-stage disease, with the right lobe staged as pT1b pN0 (a tumor size between 1-2 cm without lymph node involvement) and the left lobe as pT2 pN0 (a tumor size between 2-4 cm, also without lymph node involvement).

DISCUSSION

Collision tumors are made of two or more different recognized cellular populations that are closely located to each other. Those can be either benign or malignant but mostly the mix of one benign and one malignant tumor co-exist, yet, in this paper both patients had two malignant tumors together.[13] These mixed neoplasms are usually seen in the skin, kidneys, GIT, lung and even the ovaries but hardly in the thyroid.[13] There are only a few papers on this subject. In fact, a paper back in 2015 addressed that there are as little as 33 reported cases in the literature at that time.[14] However, many theories have been proposed attempting to explain this phenomenon. One of the most widely accepted ones is the “Stem Cell Theory,” it suggests that a cancerous precursor cell of the thyroid can mature to give rise to different malignant cells.[15] PTC, MTC and Oncocytic carcinoma as mentioned previously, share common driven genetic mutations, therefore, some individuals are more prone to their co-existence.[16]

Clinically, cases mainly present complaining of a lump in the neck which was true for both cases reported in here.[16] Though, some patients experience more serious symptoms. A case series of 8 patients with mixed thyroid tumors described different symptoms patients complained of. These include; dyspnea, palpitation, dizziness, decrease of appetite and pain, certainly, all 8 patients presented with a neck swelling.[17] Collision tumors of the thyroid are challenging to diagnose. Especially when it involves MTC and oncocytic carcinoma where they could be easily missed, this is why there’s a lack of reported cases in literature. However, careful diagnosis is extremely important since the management greatly depends on it.[18]

Most cases of PTC metastasize even though, it generally has a good prognosis. MTC tends to metastasize far easier with worse outcome.[19] This is seen in case 1 as the patient had MTC metastasis to one lymph node. On the other hand, oncocytic carcinoma which is a highly invasive poorly differentiated tumor, is usually the most aggressive, therefore, the treatment of this tumor with radioactive iodine is of limited effectiveness.[20] fortunately, in patient two (PTC and Oncocytic carcinoma) the tumor was still confined to the thyroid and was diagnosed before the cancer had metastasized.

Histologically, PTC has 15 recognized types,[21] the most common are: classical, tall cell, cribriform and follicular.[22] Both the first and second cases displayed the classical variant. Positive imunostains for PTC are: cytokeratin AE1 / AE3, CK7, TTF1, thyroglobulin and PAX8 but calcitonin negative.[23]

MTC also has many histopathological varieties. It is harder to distinguish from other thyroid tumors. However, there is abundance of amyloid due to calcitonin and specific nuclear features that aid in the diagnosis.[24] TTF1, CEA and calcitonin are all expressed in MTC and not Thyroglobulin.[25] In Oncocytic thyroid carcinoma oncocytes are found, these are large eosinophilic cells with a granular cytoplasm and hyperchromatic nuclei. The tumor could also show calcifications which are psammoma like. HCC tend to have a thicker capsule with a solid pattern and higher numbers mitotic figures as opposed to its benign counterpart. Unlike MTC it stains for thyroglobulin together with TFF1 and CK7 markers.

In the discussed cases, both patients have received a complete thyroidectomy. Classically, in patients diagnosed with PTC at a late stage as an adjunct to thyroid removal, to minimize recurrences, and help better patient outcome, such cases with no distant metastasis professionals prescribe levothyroxine supplementation.[26] Active surveillance without surgery has also been suggested in certain cases with smaller lesions <1.5cm and older age groups to avoid post thyroidectomy complications.[22] Similar to PTC, the proper management for MTC is thyroidectomy with neck dissection.[27] Regarding the treatment of collision neoplasms, it had been recommended that the management is based on the most aggressive tumor. For most cases the treatment of choice is total thyroidectomy with appropriate adjunctive treatment.[17]

CONCLUSION

Collision tumors of the thyroid have been gaining more attention in the past few years in literature. Although more cases are being reported, there is still a lack of large-scale and long-term studies to further explore the pathogenesis, genetic background, and management for patients with these tumors. A standardized guideline protocol for treating these mixed pathologies would greatly benefit the clinicians as these present a challenge.

DECLARATIONS

Conflicts of interest and financial disclosures

The author declares that he has no conflict percent and there was no external source of funding for the research in question.

Ethical approval

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of the World Medical Association.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Source of funding

The work was not funded.

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