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Phenotypic Appraisal of Collision Tumors of Thyroid – Initial Experience of a Rare Entity at a Cancer Centre in South India

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Introduction: Collision tumours (CT) of the thyroid refer to the coexistence of two or more independent, histologically distinct malignant tumours. Though the presence of multifocal differentiated thyroid carcinomas is common, it is extremely rare for the thyroid to harbour more than one type of malignancy simultaneously.
Methods: An extensive literature search of PubMed databases identified very few cases indicating the tumour rarity. To the best of our knowledge, this is the first documentation of a case series including various combinations of CT in the thyroid. Our main aim is to explore the phenotypic characteristics of CT in the thyroid with an aim of revealing unique features associated with this rare entity.
Results: Of a total of 138 thyroid cancers treated during the eight-year period, five (3.62%) were diagnosed as CT. All were females with a median age of 50 years. Papillary Thyroid Carcinoma (PTC) was the major component (80%) in collision with medullary (MC), follicular, and hurthle cell carcinomas. Both cases with papillary microcarcinoma showed vascular emboli and patients with a combination of MC and PTC had nodal metastasis. 80% of patients had a survival of more than 2.5 years and are alive without disease at present. Our study showed features like female predominance and PTC as the most common component with good overall survival. Metastatic and survival rates were consistent with matched singleton pathology.
Conclusion: Insight into the genomic and proteomic pathways of this entity is the need of the hour.

Introduction

Thyroid carcinoma, the most common endocrine malignancy worldwide, accounts for 1–5% of all carcinomas in females and less than 2% in males [1,2]. In the last few decades, thyroid carcinoma incidence has continuously and sharply increased worldwide [1,2]. Thyroid neoplasms are broadly classified as follicular cell differentiated and C cell/ parafollicular cell differentiated. Follicular cell differentiated carcinomas include well differentiated carcinomas like papillary carcinoma and follicular carcinoma, undifferentiated/ anaplastic thyroid carcinoma and poorly differentiated / insular thyroid carcinomas which is intermediate between the two. Medullary thyroid carcinoma is a C cell differentiated neoplasm. Majority of these differentiated thyroid carcinomas are composed

of a single cell population.

Our area of interest is the “collision tumor” which is defined as simultaneous occurrence of two distinct neoplasms derived from different cells of origin and is a recognized, albeit rare, entity [3,4]. Collision tumors at any site are histologically distinct and morphologically independent malignant tumors that coexist geographically [5]. Collision tumors of thyroid represent the presence of two intimately associated but histomorphologically different malignant neoplasms in thyroid gland [6]. Although differentiated malignancies of the thyroid with multifocality are no longer considered a rare event, it is extremely uncommon for the gland to harbor more than one histologic type of malignancy at the same time [7]. The usual patterns of this dual pathology include combinations of papillary with medullary carcinoma or papillary with squamous cell carcinoma [5, 6].

We undertook an extensive literature search of the PubMed data bases from 1985- the year collision tumor of thyroid was first described [5]. Till date only 36 cases of collision tumors identified in 30 different publications. All these were case reports and to the best of our knowledge, this is the first documentation of a case series including various combinations of collision tumors in Thyroid gland. In this study we explore the phenotypic characteristics of this rare tumor with an aim of revealing the unique features associated with this entity in our population.

Materials and Methods

This study was based on a retrospective review of all patients with histopathological diagnosis of collision tumors of thyroid gland treated at our centre during the period spanning from Jan 2012 – Dec 2019 (8 years). Demographic and treatment data was obtained from the patients’ medical records archived at the department of Carcinoma Registry. Principal focus during analysis of each patient’s record was placed on- a) clinical presenting symptoms b) investigations c) treatment d) follow up details. Haematoxylin and Eosin stained histopathology slides were analyzed for histomorphological characteristics and aid of Immunohistochemistry (IHC) was sought whenever needed.

Results

Of a total number of 138 thyroid carcinoma cases diagnosed during the study period, five (3.6%) presented as collision tumors. All five patients were females with median age of 48 years (range 40 to 60). None of the patients recalled history of irradiation or contributed to occupational/ family history. The most common presenting complaint was swelling in the midline/ front of neck within a duration ranging from 1 month to 2 years. The patients’ clinical and pathological characteristics are described in Table 1.

Histological details	CASE 1		CASE 2		CASE 3		CASE 4		CASE 5	
Histological type	Follicular carcinoma + Papillarymicrocarcinoma(Image-2a& 2b)		Hurthle cell carcinoma + Follicular variant of papillary carcinoma		Medullary carcinoma + Papillary carcinoma (Image-1a & 1b)		Medullary carcinoma + Papillary microcarcinoma		Follicular carcinoma, widely invasive+ Medullary carcinoma	
Tumor size (cm)	3.5x3	0.6x0.5	5.8x4.9	1.8x1.7	2.6x2.5	1.5x1.1	2x2	0.5x0.5	5.5x4.5	2x2
Tumor site	Right lobe-Lower pole	Left lobe-Upper pole	Right lobe-Upper pole	Left lobe-Lower pole	Right lobe-Lower pole	Right lobe-Upper pole	Right lobe-lower pole	Left lobe-Lower pole	Left lobe Lower pole	Left lobe Upper pole
Backgrou	Nil	follicular	Multi	Multi	Lymphocy	Nil	Lymphocy	Nil	Nil	Lymphocy

nd		adenoma	Nodular Goitre	Nodular Goitre	tic thyroiditis		tic thyroiditis			tic thyroiditis
Predominant pattern	Follicles	Papillary	Trabeculae, nests, sheets	Follicles, papillary	Nest, trabecule, solid	Papillary, follicular	Nest, sheets, islands	Papillary, follicular	Follicles	Nests, sheets
Lympho Vascular Emboli	Present	Nil	Present	Nil	Nil	Nil	Present	Nil	Present	Nil
Capsular invasion	Present	Nil	Present	nil	Nil	Nil	Nil	Nil	Present	Nil
Peri-neural Invasion	Nil	Nil	Nil	Nil	Nil	Nil	Seen in spinal accessory nerve	Nil	Nil	Nil
Extra Thyroidal Extension	Nil	Nil		Nil	Nil	Nil	Present	Nil	Nil	Nil
Pathological stage	pT2No	pT1aN 0	pT2 No	pT1aN0	pT2N1a	pT1a	pT2 N1b	pT1a	pT3N0	pT1 N1a
Lymph Node involvement	Nil		Nil		2/8 LN shows metastatic deposits of medullary carcinoma in right level IIA		11/27 LN shows metastatic deposits of medullary carcinoma in right level II,III		Nil	
ENE	Nil		Nil		Present		Present		Nil	
Prognostic stage	Stage I		Stage I		Stage I		Stage I		Stage II	
Treatment	Total thyroidectomy + Radioiodine Ablation		Total thyroidectomy + Radioiodine Ablation		Total thyroidectomy + Radioiodine Ablation		Total thyroidectomy + Radioiodine Ablation		Total thyroidectomy + Radioiodine Ablation	
Overall Survival	34		29		43		46		6	
(months)										
Disease Free Survival	33		29		40		44		2	
(months)										

Table 1. Case Series Discussing the Clinico-pathological Characteristics of Collusion Tumors in Thyroid.

Preoperative Fine Needle Aspiration Cytology was done in all cases. Medullary Carcinoma was diagnosed by FNAC in all cases. Two different lesions were diagnosed in two cases in which the lesions were in separate lobes and measured more than 1cm in maximum dimension.

Lesions occurred in separate lobes in 60% cases. No definite predilection for lobe noted. Papillary Carcinoma formed the most common histologic component (n=4) Histological variants included classic type (n=1), follicular variant (n=1) and papillary microcarcinoma (n=2) . Most common observed in our study is Medullary and papillary carcinoma (Figure 1a and 1b) is the most common tumor combination observed (40%). Lymphovascularemboli were present in two cases of follicular carcinoma and one case each of Medullary and Hurthle cell carcinoma. Perineural invasion and ExtraThyroid Extension seen in one case diagnosed as Medullary carcinoma. Nodal metastasis was seen in two cases- both were from Medullary carcinoma with Extranodal extension in one of the cases. All cases had undergone Total thyroidectomy and Radio iodine ablation. At present 80 % cases are alive without disease while one person succumbed to death.

Discussion

The criteria for multiple primary tumors was first established by Bilroth in 1879 and later simplified by Warren and Gates [8,9]. To call an entity as collision tumor, three conditions must be met: (1) each tumor must demonstrate a definite picture of malignancy, (2) each tumor must be distinct, and (3) the possibility that one was a metastatic lesion from the othermust be excluded. While collision tumor refers to coexistence of two or more independent tumors that are histologically distinct, it must be differentiated from mixed and composite tumors of thyroid which show parafollicular and follicular derived cellular elements. Mixed tumor is a single tumor with a common cell of origin, i.e.; tumor cells show expression of both thyroglobulin and calcitonin. Composite tumor on the other hand is a single tumor, with two discrete cellular populations – thyroglobulin positive and calcitonin positive [7,10].

Several hypotheses have been suggested as mechanisms for collision tumors. The simplest is that the two primary tumors occurred in continuity by a chance/ accidental ‘‘meeting.’’ Two different tumors may develop contiguously because the region is altered by the same carcinogenic stimuli. Another hypothesis is that of “neoplastic coercion” the presence of the first tumor alters the microenvironment, making the development of the second adjacent tumor more likely. The third theory “pluripotent precursor cell” theory put forward by Lax et al proposed that they arise from a single pluripotent precursor cell suggests a common stem cell of origin for the two tumors [7][11-13].

Our case series showed the presence of papillary thyroid carcinoma in majority of cases in collision with Medullary (n=2; Figure 1) following by Follicular cell (n=1; Figure 2), and Hurthle cell carcinomas (n=1).

Figure 1. Collision Tumor of Thyroid with a) Medullary Carcinoma b) Papillary Carcinoma. Haematoxylin and Eosin stain. 40 x magnifications.

Figure 2. Collision Tumor of Thyroid with a) Follicular Carcinoma b) Papillary Microcarcinoma. Haematoxylin and Eosin stain. 40 x magnifications.

A single case of medullary carcinoma with follicular carcinoma was also present. Literature review suggests that, most common collision tumors of the thyroid are that of medullary and papillary carcinomas which was true in our case. These are also the most common singleton tumors of the thyroid. The next most common combination as per literature review was Squamous cell carcinoma (SCC) and papillary carcinomas, all of which had metastasized at presentation [6]. But none of our cases had SCC. A population-based study has placed the incidence of differentiated thyroid carcinoma and medullary carcinoma coexistence at 12.3% of all medullary carcinomas. This coincidence was found to be increasing in collision tumors [14].

Specific case reports have alluded to risk factors for the development of collision tumors of the thyroid. Darwish et al suggests that lymphocytic infiltration, present in some forms of thyroiditis, may predispose a patient to the condition [15]. This was quite acceptable because three (60%) of our cases had a lymphocytic thyroiditis background. Furthermore, in the case of medullary and papillary collision, the risk is thought to be increased by multiple endocrine neoplastic syndromes. Ultimately, there is simply not enough data, evidence, or understanding to support or exclude any one hypothesis [15,16].

When compared to similar studies, we could understand those collision tumors are more common in

females at an age range of 28-84, with an increasing incidence during middle age. This goes in concordance with our study.

Another striking feature is the absence of known risk factors associated with the neoplasms. None of the patients had an exposure to ionizing radiation, familial history or iodine insufficiency. In our study, both cases with papillary microcarcinoma showed LymphoVascular Invasion and patients with a combination of medullary and papillary carcinoma showed lymph node metastasis with extranodal extension. Yet, none of these cases showed recurrence. Only case that showed recurrence was a widely invasive follicular carcinoma with medullary carcinoma and unfortunately that was the only patient who succumbed to death emphasizing the significance of angioinvasion.

On literature review, little information about the survival details are found, owing to rarity of the disease, It is seen that half of the collision tumors did not mention the survival, another half were alive at the time of study and only very few patients died. This highlights the fact that even though collision tumors behave more aggressively than singleton tumors, looking at the body of information, we find that metastatic and survival rates are consistent with matched singleton pathology and no unusual difference in the prognosis of patient was appreciated [17]. We could not find any case reports of collision tumors mentioning the survival outcome.

The treatment of collision tumors poses a unique challenge. As practiced across all oncology, treatment should be developed in a multidisciplinary framework with a patient centered approach. Intrinsically, the most aggressive singleton tumor identified should inform treatment. In the vast majority of cases found in the literature, the authors adopted multimodal treatment with surgery and adjuvant therapy, which was how themultidisciplinary board meeting of our tertiary carcinoma centre also decided to take forward with all the cases [18].

In conclusion, collision tumors of the thyroid are extremely rare. They present both a diagnostic and treatment challenge. There has been limited research into their etiology and patient management. Here, we present a series of this rare entity and would like to ponder upon the genetic and proteomic pathways associated with.

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