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Case Report

A bump in the dark: A case of an esophageal cancer metastasis to the thyroid gland in a patient with an underlying non-invasive follicular thyroid neoplasm with papillary features

Aryesh Ramlal[l*], R Daya[1,2], S Bulbulia[1,2], Z Bayat[1,2]

[1]Department of Internal Medicine, Helen Joseph Hospital, Rossmore, Johannesburg, South Africa

[2]Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa

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ABSTRACT

Differentiated thyroid cancer is the commonest endocrine malignancy in Africa. Other entities such as metastatic disease to the thyroid gland are rare and poorly understood. In keeping with global statistics, the most common thyroid malignancy in South Africa is papillary thyroid carcinoma. With regards to metastatic disease; renal, lung and breast cancers remain the most common types to metastasize to the thyroid gland. The thyroid gland has intrinsic protective mechanisms to prevent the anchorage of metastatic tissue. However, certain disease states may predispose the gland to metastases. Metastatic disease may be synchronous or metachronous. This case study describes a patient with a primary tumor of the thyroid (non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)), co-existing with metastatic esophageal cancer. To our knowledge, this is the first described case of these two tumors colliding with no prior data on the management and diagnosis of such a case. Further research is needed to adequately define and treat these unique tumors.

Keywords: Thyroid gland, Papillary thyroid carcinoma, Esophageal cancer

INTRODUCTION

Thyroid cancer remains the most common endocrine cancer in Africa, with a prevalence of 7.3% to 15% reported in literature.1 Papillary Thyroid Carcinoma (PTC) accounts for 80% of all thyroid malignancies globally. A surgical series from a South African tertiary center showed a local prevalence of 65% of PTC.Noninvasive Follicular Thyroid Neoplasm with Papillary Features (NIFTP) is a specific variant of papillary thyroid cancer and accounts for approximately 9.1% of PTC cases. The diagnosis of NIFTP is usually only made on histology post operatively; however, there are certain sonographic and biochemical markers which may raise the suspicion of its' diagnosis. Metastatic disease to the thyroid gland remains a rare entity; accounting for 1.15% to 1.9% of thyroid malignancies. Most case studies of secondary thyroid malignancies have been reported from the USA (around 44%); with the second highest number of cases reported from Asia and Europe combined. There is a paucity of data from Africa regarding metastasis to the thyroid gland. The most common primary tumors involved in metastatic disease to the thyroid include renal cell carcinoma (23.7%), lung adenocarcinoma (21.4%), invasive breast cancer of a non-specific type (10.7%), esophageal squamous cell carcinoma (7%) and colon adenocarcinoma (6.8%).

The most common primary tumor within the western context is renal cell carcinoma, compared to eastern countries where esophageal and gastric tumors are more common.

[*]**Corresponding author.** Ramlall A, E-mail: aryeshbramlall@gmail.com

Classically, collision tumors are defined as the coexistence of two neoplasms with distinct cell lineages that co-exist within the same organ, without any admixture of the tissue. Other variants or subtypes include metastatic disease of a neoplasm from one organ that "collides" with a secondary neoplasm in another organ or the presence of metastatic disease from two different neoplasms in a single organ or lymph node. Collision tumors are rare in the thyroid gland with only 33 cases reported in English literature as of 2015. Only a handful of collision tumors involving metastatic disease to the thyroid gland and a primary thyroid malignancy have been described (Chagi et al, 2019).

Cases of metastatic disease to the thyroid gland can either be synchronous or metachronous. Metachronous disease is defined when the secondary tumor is found more than 6 months after the primary tumor, whereas synchronous cases (such as our patient) are found within 6 months of the primary tumor being diagnosed. Esophageal cancers along with head and neck tumors and lung adenocarcinoma are typically known to present synchronously due to their aggressive spread. Conversely, indolent cancers such as renal cell carcinoma typically present in a metachronous manner (Zajkowska et al, 2020).

Herein, we describe an unusual case where both metastatic esophageal cancer and a non- invasive follicular thyroid neoplasm with papillary features were found co-existing in the thyroid gland together (Nguyen et al, 2022).

CASE PRESENTATION

A 52-year female of African descent presented with a 3-month history of progressive dysphagia (initially solids and now to liquids) with an associated history of chronic post-prandial vomiting and loss of weight of 15 kg. The patient also reported a long-standing history of dyspepsia and heartburn in keeping with Gastro-Esophageal Reflux Disease (GERD). There was no history of hematemesis, chronic cough or recurrent pneumonias to suggest aspiration. On further medical history, she was known to be living with Human Immunodeficiency Virus (HIV) currently on a fixed dose anti-retroviral combination containing Tenofovir, Lamivudine and Dolutegravir (TLD). Her Cluster of Differentiation 4 (CD4) count at diagnosis was 447 with a recent lower than detectable viral load. She denied smoking or alcohol use and had no family history of malignancy (Abdullah et al, 2022).

On physical examination, the patient was dehydrated, sarcopenic and pale with no appreciable lymphadenopathy or jaundice. The patient weighed 52 kg and had a height of 157 cm resulting in a Body Mass Index (BMI) of 21 kg/m^2. There was no palpable goiter or other ophthalmic or dermatological manifestations of thyroid disease. An absence of retrosternal dullness and a negative Pemberton's sign was also noted. There was no appreciable abdominal organomegaly. The patient's cardiovascular, respiratory and neurological examinations were unremarkable (Tessler et al, 2017).

The patient's biochemistry showed a hypokalemic, hypochloremic alkalosis, as well as a mild normocytic normochromic anemia of 11.4 g/dL (reference 11.6-16.4 g/dL). A thyroid function test showed a normal Thyroid Stimulating Hormone (TSH) of 0.37 mIU/L (0.35- 5.50 mIU/L), a normal free thyroxine (T4) of 19.9 pmol/L (11.5-22.7 pmol/L) and a normal free triiodothyronine (T3) of 3.2 pmol/L (3.1-6.8 pmol/L). In keeping with her poor nutritional status, the patient had a low serum albumin of 23 g/L (35-52 h/L). Pre-operatively the patient had a corrected calcium of 2.43 mmol/L (2.15-2.50 mmol/L) with an associated magnesium of 0.93 mmol/L (0.63-1.05 mmol/L) and an inorganic phosphate of 1.19 mmol/L (0.78- 1.42 mmol/L) (Table 1).

Table 1. Patient's biochemical results.

Laboratory test	**Result**	**Reference range**
Hemoglobin	11.4 g/dL	11.6-16.4 g/dL.
Mean corpuscular volume	91.4 fL	78.9-98.5 fL
Hematocrit	0.340 L	0.340-0..480 L
Total white cell count	7.32×10^9/L	$3.90\text{-}12.60 \times 10^9$ /L
Platelets	430×10^9/L	$186\text{-}454 \times 10^9$/L
Sodium	140 mmol/L	136-145 mmol/L
Potassium	2.7 mmol/L	3.5-5.1 mmol/L
Chloride	90 mmol/L	98-107 mmol/L
Bicarbonate	>40 mmol/L	23-29 mmol/L
Urea	2.5 mmol/L	2.1-7.1 mmol/L
Creatinine	52 umol/L	49-90 umol/L

Thyroid stimulating hormone	0.37 mIU/L	0.35-5.50 mIU/L
Thyroxine	19.9 pmol/L	11.5-22.7 pmol/L
Triiodothyronine	3.2 pmol/L	3.1-6.8 pmol/L
Corrected calcium	2.43 mmol/L	2.15-2.50 mmol/L
Magnesium	0.93 mmol/L	0.63-1.05 mmol/L
Phosphate	1.19 mmol/L	0.78-1.42 mmol/L

From the above clinical presentation, the primary concern was for an esophageal malignancy. The risk factors in this patient included her positive retroviral status, ethnicity, age and a history of chronic GERD. A differential to the above included intrinsic disease of the upper gastro-intestinal tract (opportunistic infections such as candida or viral esophagitis, esophageal strictures, esophageal motility disorders, peptic ulcer disease or gastric malignancy with gastric outlet obstruction) or extrinsic compressive diseases to the upper GI tract (mediastinal malformations or masses). In an HIV positive patient compression from localized lymphadenopathy secondary to tuberculosis or lymphoma was also considered.

A neck ultrasound was then performed, which showed a nodule measuring 10.8 × 10.8 mm in the left inferior thyroid lobe with hypo-echogenicity, irregular margins and no associated lymphadenopathy. The nodule was therefore classified as a Thyroid Imaging Reporting and Data Systems (TIRADS) Grade 4B5. Ultrasound-guided fine-needle aspiration of the nodule revealed features suspicious for a papillary thyroid carcinoma (Fakhar et al, 2021).

A contrast-enhanced Computed Tomography (CT) of the neck and chest was then requested revealing multiple bilateral thyroid nodules with no significant local lymphadenopathy (Tang et al, 2022).

Upper gastrointestinal endoscopy was performed. Biopsy taken during the procedure confirmed an invasive moderately differentiated keratinizing squamous cell carcinoma of the esophagus. The tumor was obstructive extending from the 29 cm till the 35 cm mark. The patient subsequently had an esophageal dilatation done while awaiting further workup. The patient was planned for neo-adjuvant chemotherapy and radiotherapy prior to surgical intervention for the management of her esophageal cancer.

With regards to the patient's thyroid malignancy, a multi-disciplinary discussion involving the departments of endocrinology, radiology, surgery, anesthetics and anatomical pathology was held. The decision made was for the patient to undergo a total thyroidectomy as the procedure was seen as curative and impactful in the patient's morbidity and quality of life (Yumoto et al, 2019).

Macroscopic examination of the thyroid gland revealed a multi-nodular goiter weighing 20 g, with an asymmetrically enlarged left lobe compared to the right. Histological examination revealed an encapsulated nodule measuring 10.0 mm × 8.0 mm × 7.0 mm composed of small, well-formed follicles. Nuclear features of papillary thyroid carcinoma were seen in the form of nuclear enlargement, crowding and overlapping (Figure 1). Some nuclei had irregular contours. No capsular or vascular invasion was identified. These features were consistent with a non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP).

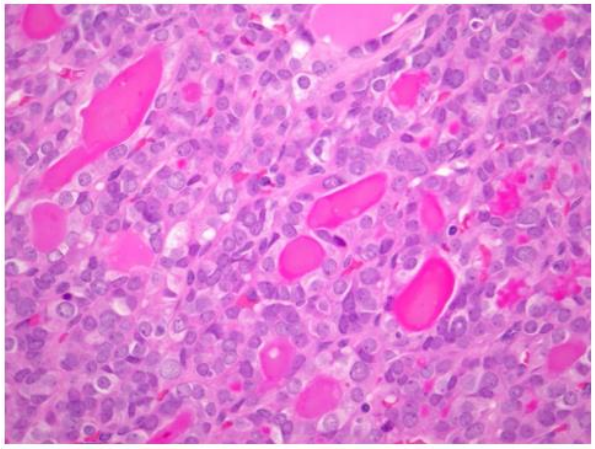

Figure 1. Haematoxylin and Eosin; 400X Histological examination of an encapsulated thyroid nodule: Nuclear features of papillary thyroid carcinoma are seen. There is nuclear enlargement, crowding and overlapping. Some nuclei have irregular membranes. Nuclear clearing with chromatin margination is focally seen.

Unusually, a small focus of invasive moderately differentiated, keratinizing squamous cell carcinoma was identified in the adjacent, non-neoplastic thyroid parenchyma (Figures 2 and 3). The squamous cells were large and polygonal with brightly eosinophilic cytoplasm, large nuclei and prominent nucleoli. In light of the concomitant history of esophageal carcinoma, the focus most likely represented metastatic disease to the thyroid. This was further confirmed by sequencing done on the tissue, confirming the presence of esophageal tissue in the thyroid gland (Bojoga et al, 2021).

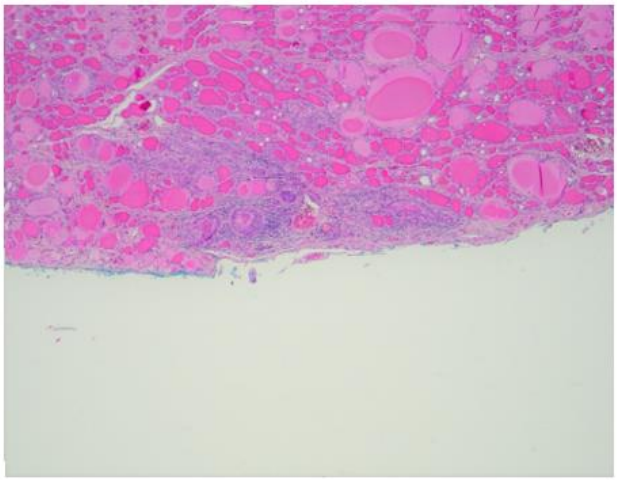

Figure 2. Haematoxylin and Eosin; 40X A small focus of invasive squamous cell carcinoma.

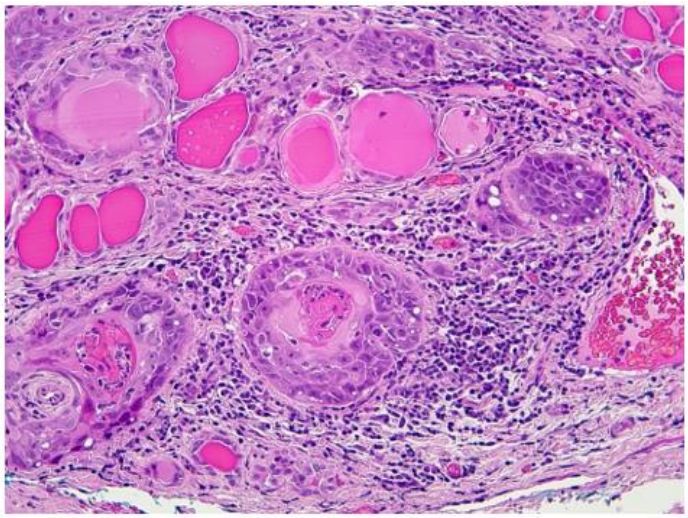

Figure 3. Haematoxylin and Eosin; 200X. The invasive focus has typical squamous morphology. The tumor cells are polygonal with abundant eosinophilic cytoplasm. They have large nuclei with prominent nucleoli. Intercellular bridges and keratin pearls are seen.

Post-total thyroidectomy the patient developed iatrogenic hypoparathyroidism with a parathyroid hormone value of <0.6 pmol/L (1.6-6.0 pmol/L) and a corrected calcium of 2.08 mmol/l (2.15-2.50 mmol/L). She was initiated on calcium and calcitriol and subsequently discharged with normal calcium levels.

The patient was referred to the oncology unit for neo-adjuvant chemotherapy and radiation for her esophageal cancer. Unfortunately, before receiving treatment the patient demised at home 1-month post thyroidectomy. The cause of death remains unknown.

RESULTS AND DISCUSSION

NIFTP is a relatively new histological diagnosis that originated from a revised nomenclature in 2016. Prior to the new nomenclature, all encapsulated follicular variants of PTC were classified into either invasive disease or non-invasive disease. This was defined by whether or not the tumor exhibited features of capsular or vascular invasion. A retrospective study done comparing mortality rates of the non-invasive variant to the invasive variant showed that none of the patients with the non-invasive variant died or developed metastatic disease from this tumor-up to 26 years after being diagnosed. Thus, given the indolent

nature of the non-invasive variant it was re-named non-invasive follicular thyroid neoplasm with papillary features (NIFTP). The diagnosis of NIFTP requires specific histological criteria: Encapsulation or clear demarcation of the tumor, a lack of capsular or vascular invasion, a follicular growth pattern that lacks high grade features (e.g. high mitotic activity) and nuclear features suggestive of papillary thyroid cancer.6 Ancillary genetic tests that show a lack of BRAF V600-E mutations may also be used to support the diagnosis (Jacobson et al, 2008).

As previously mentioned, NIFTP is a post-operative histological diagnosis; however, pre-operative cytology may show features to suggest it. These include: A low level of colloid with abundant small clusters of follicular cells and micro follicles, nuclear atypia and an absence of true papillae. In keeping with these features, our patient's pre-operative cytology showed nuclear atypia in the form of nuclear enlargement and crowding; as well as small amounts of colloid. Unfortunately, NIFTP can fall within any of the 6 categories of the Bethesda system for reporting thyroid cytopathology. Of concern, up to 30% of NIFTP may present as Follicular Lesion of Undermined Significance (FLUS).

With regards to sonographic features of NIFTP, it most commonly presents as round to oval nodules with smooth margins. This may be helpful in differentiating it from invasive variants of follicular PTC; which, often have irregular margins and speculations in keeping with invasive disease. While these features should be of use, 3 studies have currently shown very little success in the pre-operative diagnosis of NIFTP with ultrasound.

This is corroborated by our case, where the thyroid nodule described on ultrasound had irregular margins but histologically was proven to be NIFTP.

Current recommendations in the management of NIFTP are the same as thyroid neoplasms with a low incidence of recurrence. Lobectomy is a suitable option; however, as the diagnosis of NIFTP is often made post-operatively most patients would have undergone a total thyroidectomy. Post-operative remnant radio-ablation in lobectomy patients is not recommended. Thyrotropin levels should be kept between 0.5> IU/ml to 2.0 IU/ml post operatively.

Metastatic disease to the thyroid remains a rare phenomenon. Two protective mechanisms prevent metastasis to the thyroid. These include a high vascular flow which prevents anchorage of malignant cells to the thyroid gland, and high oxygen and iodine concentrations which inhibit the growth of malignant cells. Thus, most patients with a secondary thyroid malignancy usually have an underlying diseased thyroid gland. Some predisposing conditions include a multi-nodular goiter (as in the case of our patient), thyroiditis or an active thyroid adenoma.
Due to the highly vascular nature of the thyroid, most metastatic spread is hematogenous. However, direct infiltration from aero-digestive tract tumors can also be considered. Lymphogenous spread to the thyroid gland is rare and most commonly occurs with breast and lung neoplasms.

Esophageal metastasis to the thyroid gland accounts for approximately 7% of metastatic disease to the thyroid, with very little literature available on this phenomenon. Until 2019, only 9 cases of esophageal cancer spread to the thyroid gland had been reported in English literature. All cases were assumed to be lymphogenous in spread; as cervical lymphadenopathy was present in these patients.

With regards to histological findings, 6 out of the 9 cases were confirmed as squamous cell carcinoma (as in the case of our patient); while the remaining 3 showed adenocarcinoma. Out of the 9 patients, 7 of them were male. All patients ranged between the ages of 60-70 years. At the time of compilation, 3 out of 9 of the patients were confirmed deceased with a median survival time of 11 months- post diagnosis of metastatic disease. Currently no literature or cases series have reported cases of esophageal metastasis to the thyroid gland with a concomitant thyroid cancer.

While the sex of our patient differed, her age group and diagnosis of squamous cell carcinoma were in keeping with previous reports.

The pathophysiology of two different tumors occurring within the same organ, such as this one, are based on three theories. The first, is the "stem cell theory" which postulates that the two cell lines arise from a common pluripotent precursor cell. The second theory (neoplastic coercion theory) suggests that the growth of one tumor changes the cellular environment, promoting the growth of the second neoplasm. Finally, "random collision theory" states that the two tumors colliding is purely co-incidental. In the case of the above patient, the second and third theories hold more weight to the underlying pathogenesis. Cases involving metastasis of another neoplasm to the thyroid with an associated primary thyroid neoplasm are relatively scarce, with only 5 cases reported in literature to date. In these cases, the primary sites of the non-thyroid neoplasms included: Metastatic osteolipoma of the thigh, metastatic adenocarcinoma of the lung, metastatic osteosarcoma, tracheal sarcomatoid carcinoma and laryngeal squamous cell carcinoma.

To our knowledge our case is the first description of an NIFTP thyroid tumor with a co- existent esophageal cancer that has been reported.
There are no clear guidelines on the treatment of metastatic disease to the thyroid gland with an associated primary thyroid cancer due to the rarity of this scenario. In general, these cases require multi-disciplinary team care; and, treatment depends on the aggressiveness of the metastatic

tumor: with more aggressive tumors requiring early surgical resection. In our patient's case the requirement for prior neo-adjuvant treatment for her esophageal cancer would have delayed her thyroidectomy; as such, her thyroid malignancy was managed prior to an esophageal resection. Thyroid metastasis is often resistant to radio-ablative therapy and usually requires surgical resection for long-term cure. A total thyroidectomy is advised more often than lobectomy. If the disease presents late, a palliative approach is usually taken.

CONCLUSION

In conclusion, our case presents a unique meeting of two rare events in inconspicuous circumstances. The presentation of both NIFTP and metastatic disease to the thyroid gland has not been described previously. To our knowledge this case is the first description of a NIFTP tumour with co-existent esophageal cancer metastasis as well as the 10^{th} case of co- existing thyroid and esophageal neoplasms. Further data and research is required into this phenomenon and the management thereof.

CONSENT

The patient gave verbal and written consent for this case report.

ETHICS APPROVAL

Ethics approval was granted from the Human Research Ethics Committee (Medical) from the University of the Witwatersrand (M220971), which conforms to the recognized standards as per the Declaration of Helsinki.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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