Case Report

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Metastatic neuroendocrine tumor of the esophagus with features of medullary thyroid carcinoma

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Summary **A 41-year-old female presented with a pedunculated mass in the upper esophagus and bilateral lymphadenopathy. Biopsies suggested a neuroendocrine tumor, possibly carcinoid, and ensuing imaging revealed cervical lymph node metastases. The esophageal mass was removed endoscopically and discovered by pathologists to closely resemble medullary thyroid carcinoma (MTC) on immunohistochemistry staining. Following surgery, further work up demonstrated very high serum calcitonin levels, suggestive of medullary thyroid carcinoma, however the thyroid gland was normal on ultrasound. The patient underwent a neck dissection to remove the lymph node metastases and subsequently her calcitonin levels dropped to 0 ng/mL, indicating remission. It appears that the primary tumor was not in the thyroid, but in the cervical esophagus. The thyroid has appeared normal on multiple ultrasounds without any detectable nodules or masses. This is quite a unique case because this patient presented with a tumor resembling medullary carcinoma of the thyroid that presented as a pedunculated mass in the cervical esophagus. The actual final diagnosis of this mass in the cervical esophagus was neuroendocrine tumor (NET), consistent with a carcinoid tumor, not ectopic MTC. This case report highlights that calcitonin-secreting tumors outside the thyroid should not lead to erroneous recommendations for thyroidectomy.**

Keywords: Esophageal neuroendocrine carcinoma, esophageal carcinoid, neuroendocrine tumors, esophageal neoplasm, calcitonin

1. Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare heterogeneous group of tumors that can involve any part of the gastrointestinal tract (*1*). Esophageal neuroendocrine tumors are exceedingly rare and are the rarest of the GEP-NETs, representing approximately 1% of all neuroendocrine tumors (*1*). GEP-NETs originate from diffuse neuroendocrine cells which are unique in their ability to synthesize and secrete neuropeptides and hormones, the most common of which are synaptophysin, chromogranin and CD56 (*1*). Esophageal neuroendocrine tumors are found more commonly in men, in the sixth decade of life (*2,3*). Our research objective in presenting this case study was to describe a unique esophageal neuroendocrine tumor that was found in a young, female patient that secreted calcitonin, in addition to the neuropeptides chromogranin and synaptophysin that are commonly found in esophageal neuroendocrine tumors.

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2. Case Report

A 41-year old African American female with a chief

complaint of fatigue was being evaluated for chronic iron deficiency anemia. Past medical history was significant for iron deficiency anemia and menorrhagia due to uterine leiomyomas. She had a surgical history of inguinal herniorrhaphy and her only medications included iron supplementation and naproxen. On a review of symptoms, she was asymptomatic except for mild dysphagia with an occasional feeling of food sticking while swallowing. She denied weight loss, odynophagia, hemoptysis, and hematemesis. There were no focal changes and no shortness of breath. She denied any history of smoking, excessive alcohol use, or any radiation exposure. Her family history was significant for two first-degree relatives with colon cancer and one first-degree relative with breast cancer. Due to the strong family history of colon cancer, she underwent screening with upper and lower endoscopy as a preventive measure. Colonoscopy was unremarkable but upper endoscopy revealed a large pedunculated polyp at the pharyngoesophageal junction. A biopsy was taken of the polyp and was interpreted as a well-differentiated and low-grade NET, consistent with a carcinoid tumor. The discovery of this rare GI tumor and the strong family history of multiple GI tumors prompted a referral to a medical genetics specialist, however the evaluation was non-contributory. Further evaluation of the esophagus was necessary to find the primary site and the first echelon lymphatic basins in the mediastinum and neck. Ensuing work-up included CT scans of the abdomen and pelvis, which were negative for distant disease. Chest CT revealed the pedunculated mass on the anterior wall of the cervical esophagus (Figure 1). Octreotide scan was non-contributory, however the flurodeoxyglucose (FDG) PET/CT displayed the metabolically active esophageal lesion as well as two active bilateral neck lymph nodes (Figure 2A and 2B).

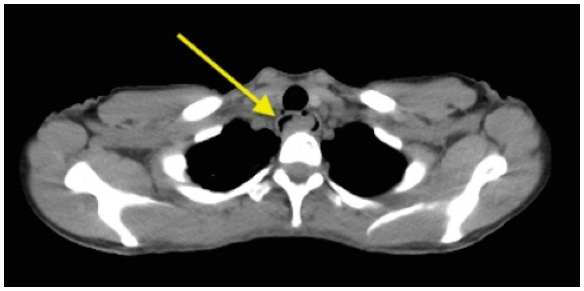

Figure 1. Chest CT showing the mass on the anterior wall of the cervical esophagus.

Follow-up included endoscopic evaluation and possible removal. Pre-operative metabolic panel revealed mild hypocalcemia at 8.0 mg/dL but no contraindications to surgery. During the surgery, the tumor was visualized endoscopically which showed a very mobile pedunculated mass on a stalk that was pedicled within the anterior esophagus, close to the tracheal party wall just left of the midline. The mass was excised transorally and sent for permanent histology (Figure 3A and 3B). Additional deep tissue and mucosal biopsies were taken which showed negative margins. An additional biopsy of the lymph node on the left side of the neck was taken for permanent histology. Post-operatively, the patient recovered well with no complications.

Shortly after, we received the pathology interpretation of immunohistochemistry staining, which became a turning point in our observations. We previously thought we were managing an esophageal carcinoid tumor, a rarity itself, however the pathology results informed us that the tumor actually had features of medullary thyroid carcinoma (MTC) since calcitonin staining was positive. This peculiar finding incited further evaluation. Supportive of the pathologist's interpretation, serum calcitonin levels were in fact markedly elevated at 570 pg/mL (Normal is < 5.0 pg/mL), which implied metastatic disease especially since this was measured two months post-operatively. At this point, the possibility of completely missing a primary medullary carcinoma from the thyroid was considered, however, the ensuing thyroid and neck ultrasound did not show any thyroid nodules but did show three level II nodes on the right and two level II nodes on the left. Thyroid hormone levels were also normal. Serum chromogranin A and serotonin were normal, which disfavors carcinoids, and the 24-hour urine metanephrines were negative, ruling out a concurrent pheochromocytoma. Serum CEA levels were negative as well, which are usually positive in MTC. A PET scan showed mild uptake in bilateral neck lymph nodes

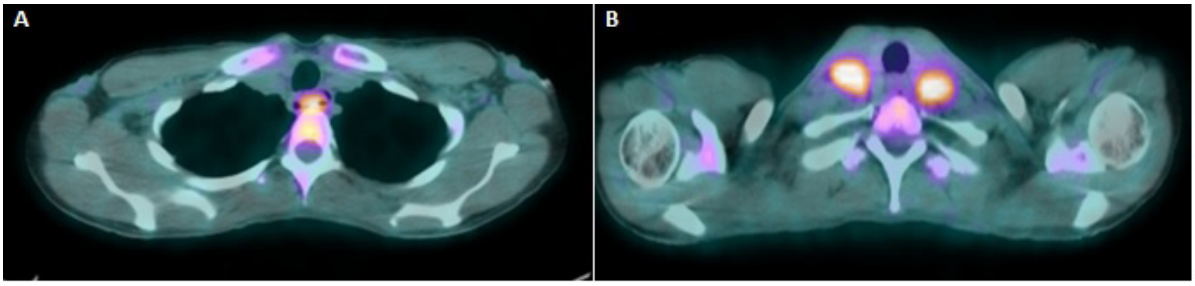

Figure 2. PET/CT displaying. (A) metabolically active mass in the upper cervical esophagus (2.5 × 1 cm with standardized uptake value (SUV) of 3.23); **(B)** bilateral cervical lymph node metastases.

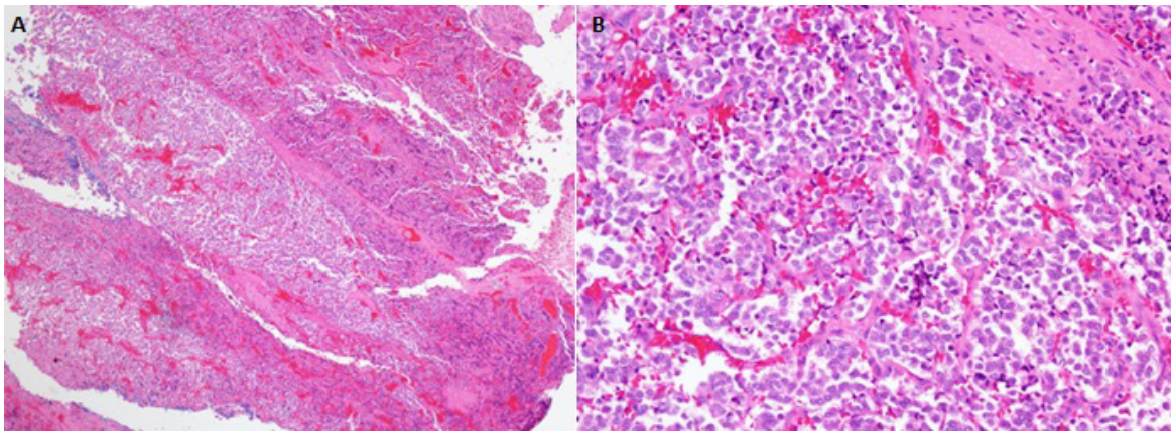

Figure 3. Pedunculated esophageal mass at (A) 4×, (B) 20×.

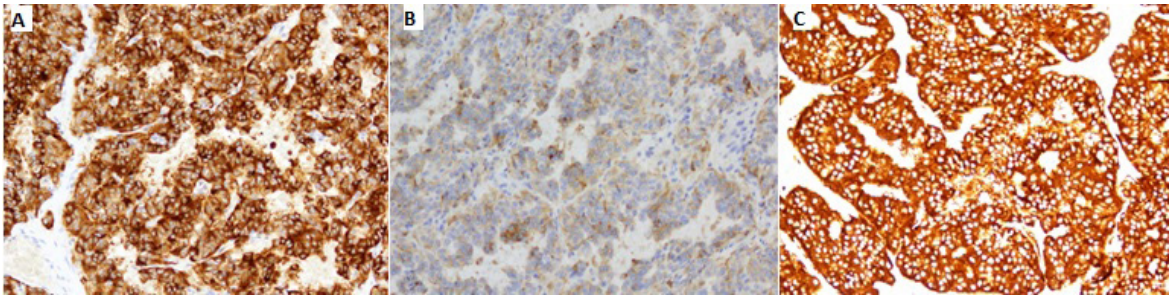

Figure 4. Left neck dissection lymph node at 20× showing positive immunohistochemistry staining for (A) Calcitonin; **(B)** Chromogranin; and **(C)** Synaptophysin.

and subsequent fine needle aspiration on the right was interpreted as neuroendocrine carcinoma, which was identical on the left. However, no lesions were present in the thyroid. The patient was still doing very well and had no symptoms except for mild bilateral lymphadenopathy on physical exam. At this point, the next step in management was puzzling because high calcitonin levels usually advocates for removing the thyroid gland, yet this patient had a normal thyroid on imaging. The only reasonable explanation was that the primary tumor was from the esophagus.

The patient had surgery for the second time where she underwent a bilateral neck dissection to remove the metastatic spread to the lymph nodes. The thyroid gland was left untouched. 3/30 excised nodes demonstrated the previous diagnosis of metastatic well-differentiated neuroendocrine carcinoma with features of medullary thyroid carcinoma. Immunohistochemistry was positive for calcitonin (Figure 4A), chromogranin (Figure 4B) and synaptophysin (Figure 4C), which are suggestive of medullary thyroid carcinoma, and negative for CEA, serotonin, and P53. Ki-67 stain showed 3% of cells in a proliferative phase. The patient did very well post-operatively without any complications. Although the diagnosis was labeled as neuroendocrine tumor, the pathologists continued to be suspicious for medullary thyroid carcinoma. Thyroid ultrasounds and PET scans failed to reveal any thyroid disease. Following the second surgery, serum calcitonin levels normalized which proves that the cancer was fully resected and that the primary was most likely from the esophagus. It was decided that adjuvant radiation therapy was not needed.

The patient's disease was indolent and caught early. She has remained healthy without evidence of recurrence. After two years of follow-up, the patient's only complaints have been acid reflux and occasional fatigue. Since she presented with low-neck metastases, she has received surveillance chest CTs watching for interval changes, which have all been negative. Since part of the differential diagnosis indicated possible medullary thyroid carcinoma based on pathology, the patient has had regularly scheduled thyroid ultrasounds and calcitonin levels which all have remained negative. Due to the very unusual nature of this case, we will continue to follow-up with this patient indefinitely to screen for recurrence and occult MTC.

3. Discussion

Neuroendocrine tumors (NETs) consist of a broad spectrum of heterogeneous tumors originating from the diffuse endocrine system. They share certain features such as similar appearance, presence of secretory granules, and production of various hormones through an amine precursor uptake and decarboxylation (APUD) mechanism (*4*). Despite these similarities, there are substantial differences in clinical behavior, often attributed to the site of origin. NETs most commonly

arise in the small intestine but can develop in the lung, pancreas, and other areas, each with different incidences and presentations. NETs are challenging to diagnose and the lack of inclusive knowledge has led to periodic changes in classification systems (*4*). One of the difficulties is that the current understanding of NETs has accumulated from different directions, causing use of extraneous terminology. In an effort to simplify this, NETs are currently classified under two groupings, the pancreatic NETs and the carcinoids (*5*).

The determination of NETs is made by the morphology and the presence of neuroendocrine biomarkers. Biomarker workup is useful for screening and diagnosis, but since there is no standardized panel established, the serum markers to investigate should be tailored to the patient's clinical presentation. The general immunohistochemical markers indicating neuroendocrine differentiation are synaptophysin, chromogranin and CD56 (*6*). In the current World Health Organization (WHO) classification system, NETs are graded using the Ki-67 proliferative index and mitotic rate. There is not a standard staging criterion for TMN classification, but use of either the AJCC or ENETs systems is acceptable. NETs presenting with mixed or unusual histotypes are treated with focusing on the most aggressive component that is present. Since medullary thyroid carcinoma was in our differential diagnosis, it was obligatory to rule out this aggressive malignancy. Another challenge with NETs is that patients' symptoms are rarely linked to the correct diagnosis initially, which leads to a delay in proper treatment. For example, many gastrointestinal carcinoids are initially misdiagnosed as irritable bowel syndrome, lactose intolerance, or celiac sprue (*4*). In addition, many NETs do not become symptomatic until late in the disease course when there is advanced metastases, therefore prognosis can be poor (*5*). Our patient was fortunate that her NET was discovered incidentally on screening upper endoscopy, especially since she already had early metastatic disease at the time of diagnosis.

Since the neuroendocrine system is not as well developed in the esophagus, it is rare for NETs to grow in this region (*4*). NETs in the cervical portion of the esophagus are especially rare and its analysis can be difficult. Generally, most primary esophageal cancers occur in the lower two thirds of the esophagus. While there are many advanced secondary cancers of thyroid and trachea that can extend into the cervical esophagus, isolated malignancies in this region are rare. Some authors group cervical esophageal cancer along with hypopharyngeal cancer, which is fitting due to overlapping embryology and anatomy (*7*). Most primary tumors of the cervical esophagus include SCC and adenocarcinoma. Post-cricoid cancers tend to arise in females and are associated with Plummer-Vinson Syndrome. These patients also present with iron-deficiency anemia and severe GERD. NETs in the esophagus may represent as little as 0.05-2.4% of all esophageal cancers (*8*). Esophageal NETs have a poor prognosis because they are aggressive and often present at advanced stages with metastases. Of the few esophageal NETs reported, most occurred in the distal third of the esophagus in the presence of concurrent Barrett's esophagus (*9*).

Since our patient's cervical tumor stained positive for calcitonin on immunohistochemistry, the possibility of metastatic medullary thyroid carcinoma (MTC) was considered. MTC is the NET of the thyroid gland, which arises from neoplastic parafollicular C cells and is responsible for 5-10% of all thyroid malignancies (*10*). It presents usually in the fourth decade and has a female predominance. Approximately 80% of cases are sporadic and 20% of cases are hereditary, which are part of the multiple endocrine neoplasia (MEN) syndromes due to a mutation of the RET proto-oncogene. An elevated serum calcitonin level is the classic marker for MTC. Calcitonin is useful for detection, staging, post-op management, and prognosis (*11*). Higher levels of calcitonin are associated with greater likelihood of MTC, with values > 100 pg/mL correlating extremely high for MTC, as seen in our patient (*12*). Calcitonin levels > 150 ng/mL are associated with distant metastases. Therefore, systemic imaging of the thorax, liver, and bones is indicated (*13*). However, since our patient's thyroid gland was normal on neck ultrasound, metastatic disease originating from the thyroid gland was very unlikely. This concerning finding raised questions in management because if we were dealing with MTC, then early surgical removal would be necessary, especially since this patient had lymph node metastases, which is already associated with a significantly poorer prognosis (*14*). Normally, survival is dependent upon the adequacy of the initial surgical procedure, accomplished by total thyroidectomy and bilateral lymph node dissection (*13*). Serum calcitonin alone has a high false positive rate corresponding with a low positive predictive value that may lead to unnecessary thyroid surgery (*15*). Serum CEA is a useful marker in clinically evident MTC and the doubling time is useful in postoperative surveillance (*16*). Our patient's CEA was negative in both serum and immunohistochemistry staining, but CEA may have low sensitivity in less aggressive or occult disease, especially in the absence of a thyroid nodule (*15*). Currently, the most accurate method of measuring serum calcitonin is with immunoassays. Calcitonin is somewhat of a heterogeneous hormone and this test can accurately distinguish the epitope associated with MTC. Currently, RET mutation analysis is being used to identify individuals at risk and determine the timing of prophylactic thyroidectomy (*16*). Because our patient's thyroid gland was normal appearing and she did not have a hereditary syndrome, there was no clear indication for thyroidectomy, so the decision was made to preserve it. At this point, the differential diagnosis of

metastatic calcitonin-secreting NETs in the esophagus was debatable.

While there are well known cases of ectopic follicular and papillary thyroid carcinomas, ectopic medullary thyroid carcinoma is exceptionally rare and the mechanism has yet to be described. Ectopic medullary thyroid carcinoma has only been reported twice in the literature, once in a lingual thyroid (*17*) and another in the submandibular region (*18*). Medullary thyroid carcinoma develops from neoplastic parafollicular C cells, which have a separate lineage from the thyroid follicles. Most ectopic thyroid tissue is negative for calcitonin staining on immunohistochemistry, indicating a failure of colonization by the c-cells from neural crest (*19*). Although hypercalcitoninemia is highly indicative of MTC, it is not pathognomonic. It is important to identify other possible etiologies of hypercalcitoninemia. Causes of elevated serum calcitonin include conditions such as hypercalcemias, hypergastrinemias, renal insufficiency, other thyroid disorders, and other NETs. Elevated serum calcitonin can also be observed with prolonged use of certain treatments, such as omeprazole, beta-blockers, glucocorticoids, and potential secretagogues (*20*). Cancers such as bronchogenic carcinoma and small cell lung cancer (SCLC) may secrete high levels of calcitonin. SCLC, in particular, may grow up into the neck making it indistinguishable from primary MTC that has spread down into the mediastinum. This distinction is especially important since SCLC treatment involves chemotherapy (*21*). There are several case reports of NETs in the larynx associated with elevated serum calcitonin levels, closely resembling medullary thyroid carcinoma. These lesions were often supraglottic or glottic. Similar to our case, these were polypoid lesions that arose in the mucosa and submucosa. It was suggested that these calcitonin-secreting laryngeal NETs represented ectopic medullary thyroid carcinomas, but this is uncertain and probably difficult to ascertain because they were classified using different systems (*22*). At any rate, the evidence points to a NET of the esophagus as the diagnosis in this case, as opposed to ectopic MTC, as normal thyroid tissue was not present on histopathology.

4. Conclusion

There are several causes of hypercalcitoniemia, few of which are due to head and neck tumors. This case report underlines that calcitonin-secreting tumors outside of the thyroid should not lead to erroneous recommendations for thyroidectomy. Calcitonin immunoassays are available and should be utilized more frequently when the diagnosis is questionable. This case report further elucidates the need for more comprehensive clarification of neuroendocrine tumors, which can be challenging and diagnosed late. Knowledge of the embryological development of C cell migration or factors promoting differentiation of calcitonin-secreting cells may be key in understanding how anomalies appear clinically and how they should be managed. Certain signals and factors cause neuroendocrine cells to differentiate into the calcitonin secreting cells of the thyroid. Perhaps rest cells of neuroendocrine origin in the esophagus lining led to a calcitonin-secreting tumor, much like that of medullary thyroid carcinoma.

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