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A rare case of neuroendocrine carcinoma of the endometrium metastatic to the thyroid

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1. Introduction

Neuroendocrine tumors (NETs) represent a heterogenous group of malignancies that originate from the neuroendocrine cell system and occur primarily in the lung but can also be found in the gastrointestinal and genitourinary tracts (Schlechtweg et al., 2019; Matsumoto et al., 2019). Within the realm of gynecologic malignancies, neuroendocrine tumors are rare entities, but are most commonly seen originating from the uterine cervix—neuroendocrine tumors of the endometrium (NECE) are the least frequently occurring and represent only 0.8% of endometrial cancers (Schlechtweg et al., 2019; Matsumoto et al., 2019).

Data regarding the clinical course and optimal treatment regimens for NECE are detailed primarily in small case series. Patients with NECE typically present with stage III–IV disease and often exhibit lymphovascular space invasion (Howitt et al., 2017; Koo et al., 2014). Early lymphatic and hematogenous spread leads to metastases most commonly to the lymph nodes with reports of distant metastases to the lungs and brain (Matsumoto, 2019). Here we present a rare case of a neuroendocrine cancer endometrial cancer with metastases to the thyroid.

2. Case

The patient is a 74yo Caribbean Black nulligravid female who initially presented for a 5-month history of postmenopausal bleeding for which endometrial sampling revealed a poorly differentiated high-grade uterine carcinoma. Initial physical exam was notable only for an 18 week-sized uterus. CT scan revealed multiple soft tissue densities in the thyroid, the largest measuring 2.5 cm; an enlarged uterus with an 8.7 cm heterogeneous endometrial mass; and bulky retroperitoneal lymphadenopathy (Fig. 1). Thyroid function tests were normal.

The extent of disease was felt to be amenable to primary surgical resection, so the patient was taken to the operating room for surgical staging. The uterus was noted to be 16 cm with tumor invasion into the bladder and extending to the left adnexa and parametrium extending to the pelvic sidewall. The left ureter was encased in tumor with subsequent hydroureter. Multiple enlarged pelvic and para-aortic lymph nodes were noted, ranging in size from 3 to 5 cm. Tumor nodules were also present in the sigmoid mesentery with invasion into the colon. Her disease was ultimately deemed to be unresectable by two surgeons; only tissue biopsies were obtained.

Patient underwent a thyroid biopsy postoperatively (Fig. 2). Both specimens were consistent with neuroendocrine carcinoma of the endometrium (Figs. 3 and 4). Immunohistochemistry analysis was significant for high expression of PD-L1. The patient was lost to follow-up in the immediate postoperative period. She received one cycle of etoposide and cisplatin after returning to care but expired shortly after her first cycle, only 4 months after her initial diagnosis.

3. Discussion

Our case presented above is one of few reports of a uterine primary cancer with metastases to the thyroid at initial presentation and possibly the first from a neuroendocrine subtype. Patients with disease metastatic to the thyroid can have varying presentations, from an asymptomatic, incidental finding on imaging to an enlarging, firm, thyroid mass. Metastasis to the thyroid is more typically diagnosed in the recurrent setting and approximately 20% of cases have synchronous presentations (Chung et al., 2012). In clinical series, renal cell carcinoma is the most common primary, while in autopsy series, lung is more prevalent (Nakhjavani et al., 1997). Of the reported cases of metastases to the thyroid, gynecologic cancers comprise only 3% of cases (Nixon et al.,

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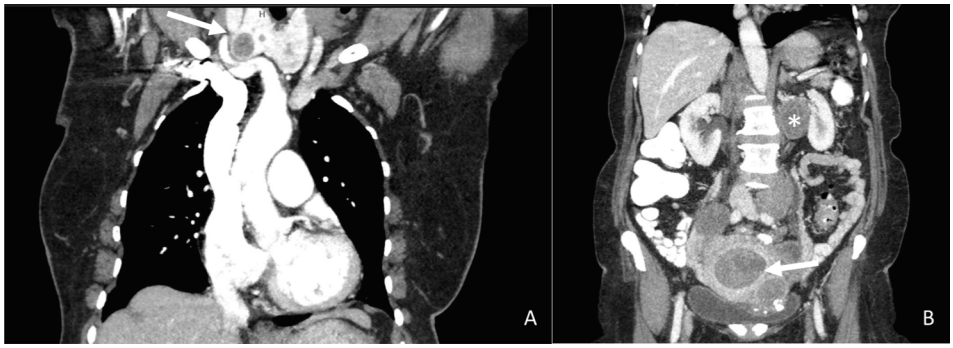

Fig. 1. Contrast enhanced computer tomography (CT) of the chest performed at time of diagnosis showing (A) multiple soft tissue densities in the thyroid (arrow) and (B) an enlarged uterus with heterogenous endometrial mass (arrow) and bulky retroperitoneal lymphadenopathy (asterisk).

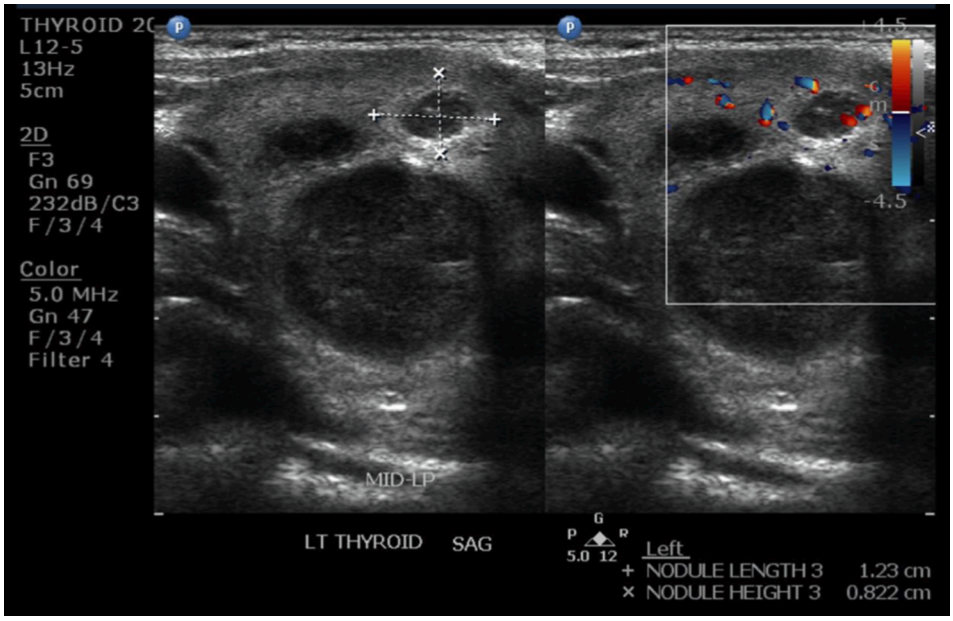

Fig. 2. Thyroid ultrasound performed postoperatively revealing multiple thyroid nodules, biopsy confirmed metastatic neuroendocrine carcinoma of the endometrium.

2017). Previously reported is a case of uterine leiomyosarcoma with recurrence in the thyroid—this patient had an overall survival of 71 months (Leath et al., 2002). In a case series of 43 patients with a malignancy metastatic to the thyroid, three patients were of uterine origin: two endometrioid and one leiomyosarcoma with mean time to diagnosis of metastasis of 132 months (Nakhjavani et al., 1997).

Prognosis and treatment of patients with thyroid metastases depends on the primary tumor and extent of metastatic disease. In primary tumors amenable to curative treatment and with isolated thyroid metastases, surgical management can be considered with a reported 5-year overall survival of 42% (Chung et al., 2012). When thyroid metastases present in the background of widely metastatic disease, reported outcomes are poor. In one meta-analysis of 31 cases of colorectal cancer with thyroid metastases, most patients had multiple other sites of metastases and only a 50% 1-year survival (Lievre et al., 2006). In the current case, our patient had multiple sites of abdominopelvic metastases which were not amenable to primary surgical resection, reflecting the aggressive nature of NECE.

Given the rarity of NECE, there currently is no prospective data on the optimal treatment regimen. Surgery is typically the basis of treatment followed by adjuvant chemotherapy with or without radiation. Combination platinum-etoposide chemotherapy, as was used in this case, has been the cornerstone for neuroendocrine tumors across various disease sites. A phase II trial evaluating the use of carboplatin, paclitaxel and etoposide in 67 patients with advanced-stage, poorly differentiated neuroendocrine carcinomas reported a 15% complete response rate (Hainsworth et al., 2006). Median 3-year survival was 24%. Our patient, however, succumbed to her disease one month after her first cycle of chemotherapy and only 4 months after her diagnosis.

Immunohistochemistry analysis and molecular tumor profiling have become integral for treatment planning in gynecologic malignancies. NECE exhibits loss of expression of mismatch repair proteins in up to 44% of cases, with loss of MLH1/PMS2 being the most common (Pocrnich et al., 2016). Our patient's immunohistochemistry analysis was significant for MMR proficiency but high PD-L1 expression, suggesting future treatment options if this patient survived. Pembrolizumab, a monoclonal antibody against PD-L1, has been utilized across multiple solid tumors with varying response rates. In KEYNOTE-28 where PD-L1 positive patients were treated with pembrolizumab, carcinoid and pancreatic neuroendocrine tumors demonstrated an overall response rate of 6.3%. The median duration of response was not reached after 24 months (Mehnert et al., 2017). As part of KEYNOTE-158, a sub-analysis of 107 patients with NETs noted a 3.7% overall response rate (Strosberg et al., 2020). Responses were noted only in patients negative for PD-L1. Sixty patients (56.1%) had stable disease, regardless of PD-L1 status. Of note, 40.2% of patients received $\geq$3 prior lines of chemotherapy. There

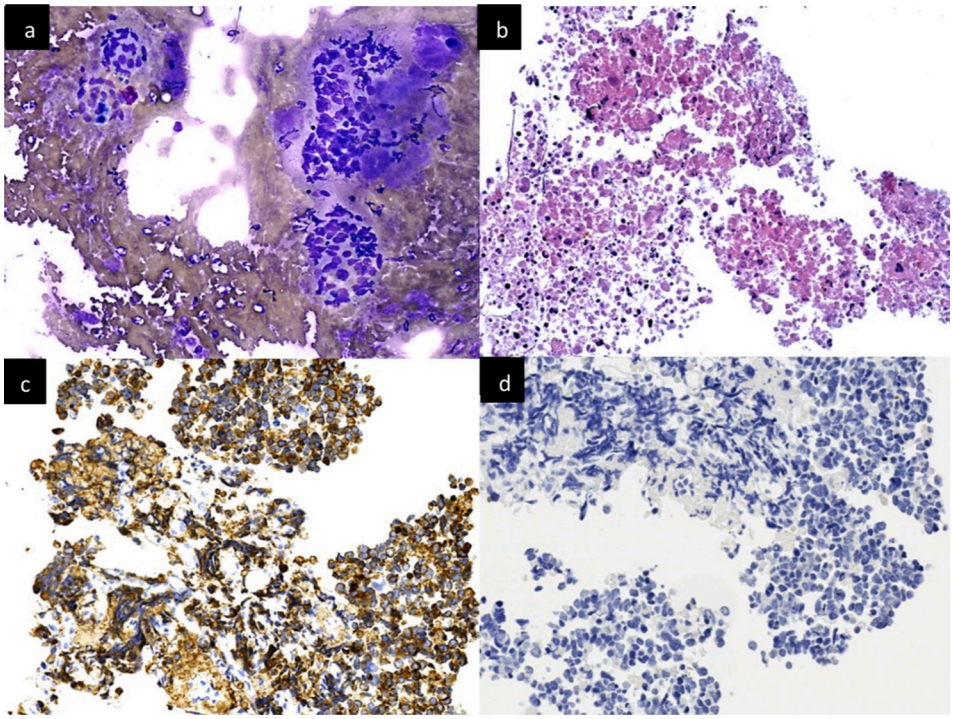

Fig. 3. Fine Needle Aspiration (FNA) of thyroid lesions demonstrate nests of high-grade tumor cells in Diff-Quick stained smears (a) and H&E stained cell block with abundant tumor necrosis (b); positive neuroendocrine markers including synaptophysin (c) confirms the neuroendocrine differentiation of these thyroid lesions and negative TTF-1 stain (d) excludes a thyroid primary (200X magnification).

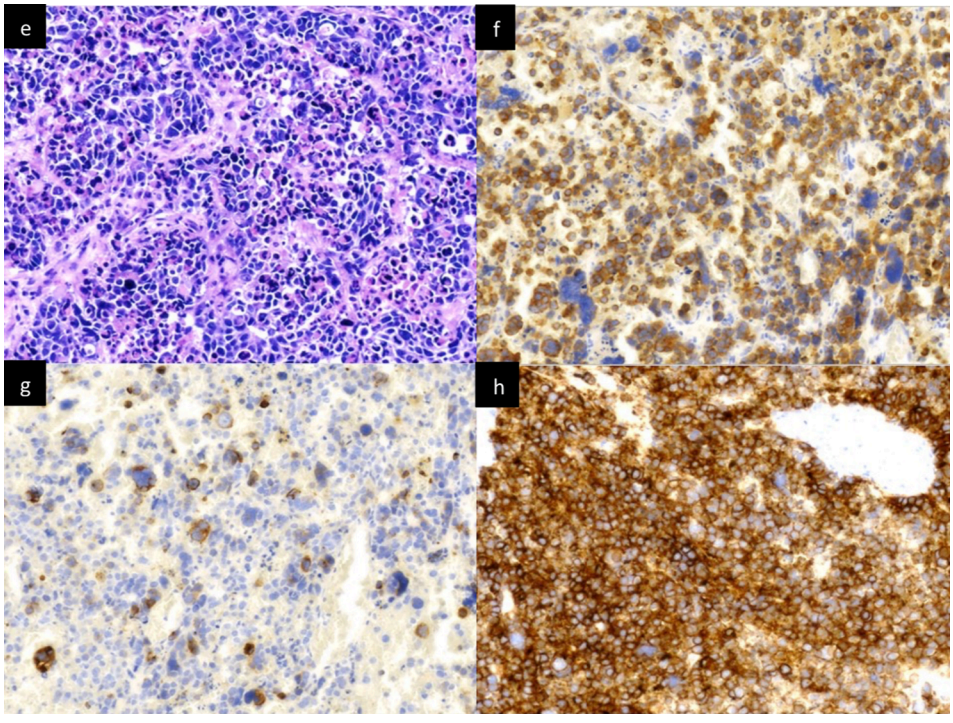

Fig. 4. Histologic examination of left ovary and lymph nodes show high grade tumor with typical organoid/nested growth pattern (e); Immunohistochemical staining shows the tumor cells are immunoreactive to synaptophysin (f), chromogranin (g) and CD56 (h); all three neuroendocrine markers. (200X magnification).

appears to be a small subset of NET patients that derive durable response and disease control on pembrolizumab regardless of PD-L1 status.

4. Conclusion

Neuroendocrine carcinoma of the endometrium is known to be a rare and aggressive subtype of endometrial cancer, as demonstrated by our report of NECE with thyroid metastases at initial presentation. Tumor

testing for targeted therapies and immunotherapy should be performed.

Informed consent statement

Informed consent could not be obtained from the patient as she expired prior to the writing of this manuscript and has no living relatives or designated next of kin.

CRediT authorship contribution statement

Nancy Zhou: Conceptualization, Writing - original draft. **Nicolette Reese:** Writing - original draft, Data curation. **Shah Giashuddin:** Pathology review. **Margaux J. Kanis:** Conceptualization, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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