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Case Report
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# A Case Report of Synchronous Metastatic Neuroendocrine Tumor and Papillary Thyroid Cancer in the Setting of Lynch Syndrome

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## Abstract

**Introduction:** This case report presents a patient with Lynch syndrome with primary neuroendocrine lung cancer and synchronous papillary thyroid cancer with focal metastasis of neuroendocrine cells of the thyroid. One year after diagnosis, this patient then had an incidental finding of focal ovarian neuroendocrine cells after risk-reducing bilateral oophorectomy for Lynch syndrome.

**Method:** 52-year-old female who was found to have metabolically active lesions of the left lower lung and right thyroid lobe. The biopsies of the thyroid and left lung were remarkable for papillary thyroid carcinoma and grade 1 well-differentiated neuroendocrine tumor, respectively. Patient underwent complete left pneumonectomy and subsequent total thyroidectomy; a focal metastasis of neuroendocrine cancer was found on the thyroid pathology. Genetic testing was positive for Lynch syndrome. After one year of surgical and medical treatments, patient underwent risk-reducing laparoscopic bilateral oophorectomy for Lynch syndrome. Pathology was remarkable for two foci of neuroendocrine tumor on one of the ovaries.

**Discussion:** To our knowledge, this is a rare case presentation that has not been reported in the literature and it proposes several suggestions. In the setting of metastatic neuroendocrine lung cancer to the thyroid and ovary and synchronous papillary thyroid cancer, a post-menopausal patient may benefit from an empiric oophorectomy. It also suggests the need for further investigation on the differentiating characteristics between primary and metastatic neuroendocrine ovarian cancer. Lastly, it also suggests a need for further exploration on Lynch syndrome and its role in neuroendocrine and thyroid cancer development.

**Keywords: Lynch syndrome; Thyroidectomy; Lung cancer; Hypothyroidism**

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## Introduction

Lynch syndrome is an autosomal dominant genetic condition that results from mutation(s) in the mismatch DNA repair genes, which can predispose patients to a variety of cancers, including but not exclusive to colon, endometrial, ovarian, stomach, small bowel, renal pelvis, biliary tract, and brain cancers. Lynch syndrome commonly involves germ line mutations of MLH1, MSH2, MSH6, PMS2, and EPCAM. The cumulative lifetime risk of ovarian cancer is approximately 12% in individuals with Lynch syndrome. In the setting of Lynch syndrome, ovarian cancer is known to be histologically epithelial typically endometrioid [1].

Neuroendocrine Tumors (NETs) are an uncommon group of heterogeneous tumors arising from neuro endocrine cells. Their incidence ranges between 1-5 per 100,000 patients, which is more frequently seen in lungs, rectum, small bowel, stomach, and pancreas. NETs make up 2% of all gynecologic malignancies but may also be metastatic from other sites; differential diagnoses of ovarian NETs include germ cell tumors, sex-cord and granulosa cancers, other gynecologic cancers, and metastatic neoplasms [2].

Thyroid cancer is not typically found under the spectrum of cancers in Lynch syndrome. Specifically, the authors only found three cases of patients who developed papillary thyroid cancer in the setting of Lynch syndrome.

This case report presents a patient with Lynch syndrome who had a pathologically confirmed primary neuro endocrine lung cancer and synchronous papillary thyroid cancer with focal metastasis of neuro endocrine cells of the thyroid; then, she subsequently was found to have an incidental finding of focal ovarian neuro endocrine cells after risk-reducing bilateral oophorectomy.

## Case Presentation

The patient is a 52-year-old female with medical history of hypothyroidism, type II diabetes mellitus, dyslipidemia, gastric reflux, and obesity with known history of a 2.7 cm × 2.1 cm left lower lung nodule in 2017 who was lost to follow up. Five years later, the patient underwent a CT scan with contrast of the thorax that showed multiple irregular, non-calcified nodular densities within the left infrahilar and lower lobe with the largest nodule measuring 4.6 cm. A month later, a PET CT scan was performed and was remarkable for a metabolically active solid lesion in the left hilum measuring 3.4 cm × 2.8 cm, which extended into the left hilar region and lower lobe, and another metabolically active lesion was noted in the right thyroid lobe measuring 2.8 cm × 4.0 cm. A fine needle aspiration biopsy of the right mid-thyroid nodule was performed and was remarkable for papillary thyroid carcinoma.

Subsequently, a needle core lung biopsy was remarkable for Grade 1 well-differentiated neuroendocrine tumor, which stained positive for pan- Cytokeratin, TTF1, INSM1, chromogranin, and synaptophysin. A PET CT Dotatate scan was performed after the lung biopsy and showed no evidence of metastases.

Two months after the cancer diagnoses, the patient underwent a complete left pneumonectomy. Pathology of the lung showed stage III A pT3N1 atypical neuroendocrine tumor grade 2, which focally involved the visceral pleura and lymphovascular invasion. Per National Comprehensive Cancer Network, no further adjuvant treatment was recommended at this time. Two months later, the patient underwent a total thyroidectomy. The pathology of the thyroid showed a 4 cm papillary thyroid carcinoma of the right thyroid and isthmus and a 1 mm focus of neuroendocrine tumor that was presumed to be metastatic.

Shortly after the thyroidectomy, genetic testing results were remarkable for PMS2 gene mutation indicating Lynch syndrome. Since the patient was diagnosed with an atypical neuroendocrine tumor with metastatic disease to the thyroid, it was recommended to start the patient on octreotide injections 30 mg every 4 weeks and surveillance imaging every 3 to 6 months to help monitor for progression of the cancer. A year after the thyroidectomy and octreotide injections, the patient had two PET CT Dotatate scans that were negative for further malignancy.

After one year of treatment, the patient underwent risk-reducing laparoscopic bilateral oophorectomy for Lynch syndrome. Of note, the patient is status post total laparoscopic hysterectomy and bilateral salpingectomy for fibroids. The pathology of the ovaries was remarkable for two foci of neuroendocrine tumor (size 0.2 cm and 0.1 cm) on one ovary. The patient's most recent PET CT Dotatate scan after the bilateral oophorectomy was negative for any malignancy. At this time, the patient has continued receiving octreotide injections and surveillance imaging.

## Discussion

To our knowledge, this is the first case report that presents a patient with Lynch syndrome with history of synchronous papillary thyroid and neuroendocrine lung cancers with focal neuroendocrine metastases to the thyroid and ovary.

This case presentation suggests two different hypotheses. The first and most likely hypothesis is that this was a primary neuroendocrine tumor of the lung that metastasized to the thyroid and ovary. The second hypothesis is this is a primary ovarian neuroendocrine tumor in the setting of Lynch syndrome.

For the first hypothesis: NETs that metastasize to the ovary are uncommon with limited information in the literature. Kristen E. Limbach, et al performed a retrospective study that showed 11.2% of patients with well-differentiated lung and gastroenteropancreatic NETs developed neuroendocrine ovarian metastases. The study also reported that 29.6% of neuroendocrine ovarian metastases were not visible on imaging and 8.3% were not visible intraoperatively [3]. Given this information, it may be possible that the ovarian metastases were undetectable on the PET CT Dotatate scans. The authors of this paper suggest that a postmenopausal patient with history of primary neuroendocrine tumor of the lung with focal thyroid metastasis may benefit from an empiric bilateral oophorectomy, given the incidental finding of focal metastases of the ovary that was undetected with imaging.

The second hypothesis of the neuroendocrine tumor being primary ovarian in the setting of Lynch syndrome cannot be completely ruled out. One study found that 53 out of 577 female patients with Lynch syndrome developed ovarian cancer; of the 53 patients, one singular recorded case of and plastic neuroendocrine tumor was noted to be associated with MSH2. N.A.J Ryan, et al suggests that there may be a rare genetic association between Lynch syndrome and neuroendocrine cancer [4]. Additionally, there has been a small amount of case reports regarding an association with neuroendocrine tumors and Lynch syndrome. For example, S. Sorscher, et al reported a patient with a deleterious germ line mutation in the MLH-1 gene that had a neuroendocrine tumor in the liver and a distinct gastric adenocarcinoma that both lacked MLH-1 expression, suggesting that Lynch syndrome may predispose neuroendocrine tumor development [5]. Furthermore, the histology of ovarian cancers is commonly found to be epithelial in Lynch syndrome; theoretically, epithelial cells can differentiate to neuroendocrine cells, though there is not much evidence found in the literature to support this theory.

It is difficult to differentiate whether this is primarily ovarian versus ovarian metastases because the characteristics of the ovarian tumor described in our case differs from those described in the literature. Although ovarian NETs are rare, primary disease often arises within cystic teratomas or dermoid tumors [6]. In a statistical evaluation of 329 reported ovarian carcinoid cases worldwide, 57% of primary ovarian NETs coexisted with cystic teratoma or dermoid tumors. The primary ovarian NETs that were not associated with the germ cell tumors were significantly smaller, less likely to metastasize to the liver, less likely to have carcinoid syndrome, and the five year survival rates were modestly better [7]. Jonathan Strosberg, et al performed a clinicopathologic analysis of seventeen patients with metastatic carcinoid tumors to the ovary. They found that metastatic NETs are most commonly associated with intestinal primary tumors, present bilaterally, originate in the small intestine, and are associated with peritoneal carcinomatosis [8]. In this case report, the ovarian findings were focal and unilateral with the absence of teratoma, dermoid tumor, or peritoneal carcinomatosis. These findings are

inconsistent with information available in the literature, which suggests the need for further exploration on how to differentiate between primary versus metastatic neuroendocrine tumor(s) of the ovary.

Another interesting component of this case is that the patient also had papillary thyroid cancer with a 1 mm focus of neuroendocrine metastasis. Thyroid cancer is not traditionally considered part of Lynch syndrome; however, there are a few cases that present thyroid cancer and Lynch syndrome together. There are two reported cases of patients with Lynch syndrome who developed and a plastic and undifferentiated thyroid cancer in the absence of MLH-2 and MLH-2/MSH-6 expression, respectively [9]. Alternatively, Pelizzo MR, et al presented two patients who developed papillary thyroid cancer in the presence of Lynch syndrome, specifically associated with MSH-2 mutation [10]. Unfortunately, we do not have genetic analysis on the thyroid and lung tissue because genetic testing was performed after the complete left pneumonectomy and total thyroidectomy. However, this information suggests that patients with thyroid cancer may have some association with MMR genetic mutations. Patients may benefit from earlier genetic screening and counseling, given the aggressive nature of certain thyroid tumors.

## Conclusion

Ultimately, the occurrence of Lynch syndrome, papillary thyroid cancer, and metastatic NETs in a single individual is extremely rare. To our knowledge, there are no reported cases of ovarian neuroendocrine tumor in the setting of Lynch syndrome and papillary thyroid cancer. We present a unique case report that presents suggestions. One, postmenopausal patients with synchronous papillary thyroid cancer and known metastatic neuro endocrine lung cancer may benefit from an empiric bilateral oophorectomy. It also suggests the need to further investigate the different characteristics of primary versus metastatic neuro endocrine cancer of the ovaries. Lastly, this case also emphasizes the importance of further understanding the pathogenesis of Lynch syndrome and its role in the development of neuro endocrine and thyroid cancers.

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