A rare presentation of an ACTH-producing high grade large cell neuroendocrine carcinoma with Cushing's syndrome

Francis Essien[1], Christine Persaud[1], David Dado[1], Joshua Tate[1], and George Shahin[1]

[1]Keesler Air Force Base

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) was first proposed by Travis et al. in 1991 and subsequently classified as high grade neuroendocrine carcinoma (HGNEC) by the world health organization. It is a rare tumor with unclear clinicopathologic features. Herein, we describe a rare case of LCNEC with a unique Cushing's presentation.

Introduction:

Neuroendocrine tumors (NET) are a highly aggressive heterogeneous group of neoplasms that arise from a combination of neural and hormonal cell types. They most commonly arise from the lungs, small intestine, appendix, and pancreas and less frequently from the thyroid, parathyroid, pituitary and adrenal glands. There are several different classifications based on differentiation of tumor cells in comparison to neighboring non-neoplastic cells, however, in general tumors that are well differentiated are low grade and those with poor differentiation are high grade. Large cell neuroendocrine carcinoma was first proposed by Travis et al. in 1991 and subsequently classified as high grade neuroendocrine carcinoma (HGNEC) by the World Health Organization (WHO) International Histological Classification of Tumours. HGNEC is a rare tumor with unclear clinicopathologic features. Patients typically present with widespread metastatic disease and the prognosis is poor given the high mortality rate. Herein, we describe a rare case of pancreatic HGNEC, large cell type, associated with a Cushing's syndrome presentation.

Case Report:

A 61 year old female presented to her primary care physician in late December 2020 with increasing right leg/ankle pain unresponsive to conservative therapy, elevated blood pressure, and concerns of new hirsutism. Subsequent MRI of her right leg revealed infiltrative enhancing lesion of the distal tibia concerning for metastatic foci (Figure 1, 2). Follow up PET/CT demonstrated diffuse metastatic disease (Figure 3, 4). An MRI brain was notable for diffuse boney metastasis without overt evidence of intraparenchymal disease. Initially this was thought to be an adrenal gland primary tumor due to noted hirsutism and elevate cortisol, however a full hormonal assessment was completed (Table 1). Ultimately, the results revealed both an elevated cortisol and elevated ACTH, favoring a non-adrenal and suspected pancreatic origin HGNEC (fluorodeoxyglucose [FDG] avid mass seen on PET), given the association of ACTH producing NET arising from islet tumor cells.

In February 2021, the patient had a biopsy of a subcutaneous breast lesion with initial pathology demonstrating malignant infiltrative proliferation within soft tissues that features pleomorphic nests of cells, nucleoli with salt-and-pepper chromatin, higher nuclear:cytoplasmic ratios, and greater than 40 mitoses per 2 mm E^E2 (Image 1, 2). Immunohistochemical stains were performed and positive for Lu-5, CK-7 (patchy), TTF-1, chromogranin, synaptophysin and negative for CK20, SOX10, GATA-3, and p40. These findings were consistent with HGNEC.

Due to the aggressive nature and high burden of her disease, the patient was admitted to the hospital upon receipt of her pathology results. Hematology/Oncology and Endocrinology were consulted. She was initiated on cytotoxic chemotherapy with carboplatin and etoposide. The patient was also initiated on ketoconazole to inhibit steroidogenesis in setting of ectopic ACTH production/Cushing's syndrome. The patient tolerated chemotherapy administration well without evidence of tumor lysis syndrome. On day 5, however, she developed an ileus requiring placement of a nasogastric tube. Labs demonstrated severe cytopenias with absolute neutrophil count (ANC) < 600. On day 7, she began to experience respiratory distress with imaging notable for diffuse bilateral pulmonary opacities with a pleural effusion. The patient was intubated due to impending respiratory failure. Bronchoscopy and thoracentesis were performed at that time. She was initiated on empiric antimicrobials, daily filgastrim, and stress dose hydrocortisone given concern for relative adrenal insufficiency. Infectious workup including blood cultures, urine cultures, cerebral spinal fluid studies, and BAL returned negative. Unfortunately, the patient continued to deteriorate with development of multi-organ failure and decreasing neurologic response despite sedation holds. In March 2021, the patient was transitioned to comfort care, terminally extubated, and passed shortly thereafter.

Discussion:

Pancreatic neuroendocrine tumors (P-NETs) are rare with ectopic (ACTH) secretion syndrome an even rarer clinical manifestation with only a few cases reported in the literature. The most common ectopic ACTH-producing tumors are thoracic (bronchial and thymic) and gastroenteropancreatic (NET), followed by medullary thyroid carcinoma, small cell lung cancer, and pheochromocytoma[1]. These tumors are clinically distinct from the more common, well differentiated, low or intermediate grade neuroendocrine tumors. There are limited cases of HGNEC diagnosed and reported in the literature, thus there is not standardized staging, classification or treatment regimens at this time. Travis et al. first reported this in 1991 after examining a case series of pulmonary cancers in 35 patients and acknowledged this as a distinct subtype of pulmonary cancer. This classification was sustained until 2015 when it was sub classified as a neuroendocrine carcinoma by the WHO International Classification of Tumours.

The incidence of P-NETs is difficult to categorize due to the fact that most international cancer registries do not collect information on tumor grade, but available data suggests that high grade neoplasms are rare. Registries from Netherlands, United States and Norway suggests an annual incidence between 0.2-0.5 per 100,000 inhabitants[1 2, 3]. Within the last few decades the incidence is noted to be increasing, but this may coincide with the changes in the nomenclature and classification, resulting in more awareness. Unlike its lung cohort, the risk factors for P-NETs are not well elucidated and more data is being compiled. The largest case series reported a medium overall survival (OS) of 13.2 months and a 3 year OS of 8.7% for all patients[1,2]. Histopathologically, HGNEC has an architecture consistent with neuroendocrine differentiation. The cells are arranged in an organoid, trabecular or palisading pattern, with prominent necrosis. Evidence of neuroendocrine differentiation is demonstrated by immunoreactivity for chromogranin and synaptophysin[3]. The mitotic rate tends to be considerably larger than what is seen in atypical carcinoid cells with WHO criteria stating cut off above $>10/2$ mm2[3]. Our patient had a mitoses rate greater than 40 mitosis per 2 mm E^E.

These tumors have an aggressive natural history constituted by early, rapid widespread metastasis. HGNECs are very difficult malignancies to diagnose due to the subtle presentation[1]. Ectopic adrenocorticotropic hormone (ACTH) secretion syndrome is a rare clinical manifestation, but is responsible for 15% of all cases of Cushing syndrome[4,5]. This has been previously well documented in the subset of small cell carcinoma of the lung, but not the pancreatic subset. However, pancreatic islet tumors constitute 1 of the 4 histological subsets (small cell, pheochromocytoma, and carcinoid tumors) of ectopic ACTH-producing tumors and therefore, this possibility can be extrapolated to the neuroendocrine tumor[2]. Most patients present with a number of cushingoid features to include facial plethora, ecchymoses, muscle weakness, hypertension and laboratory derangements such as severe hypokalemia and glucose intolerance. Our patient presented with clinical features of hirsutism, virilization, hypokalemia and metabolic alkalosis.

The treatment for metastatic P-NETs is difficult to determine due to the general lack of data from prospective

trials. Some patients present with potentially resectable metastatic disease and hence may benefit from a combination of chemotherapy and surgical resection. For patients who do not meet this criteria, such as our patient, recommendations are to treat in similar fashion to its cohort, small cell carcinoma. Chemotherapy regimens use in this setting are platinum-based (cisplatin or carboplatin) with etoposide[2,3]. This regimen has been well established in several retrospective studies as a first line treatment. Recently there have been experimentation with several classes of drugs to include rapamycin (mTOR) inhibitors such as Everolimus, Temozolomide and Capecitabine[2]. Various treatments are being explored with aim for DNA synthesis interruption by alkylation, pyrimidine analogs or platinum exposure. Recently there has been exploration into molecularly therapies with sunitinib and PD-1 inhibitor Pembrolizumab. Preliminary data suggests that HGNEC are less responsive but if there are high levels of mutations or microsatellite instability, then immunotherapies such as Pembrolizumab should be considered early in the course of the disease[6]. In our patient, she had multiple complications due to mineralocorticoid excess including severe electrolyte/metabolic derangements, as well as elevated cardiac markers, which increased risk of complications due to cisplatin therapy. Therefore, it was elected to proceed with carboplatin in the palliative setting.

Hormonal hypersecretion plays a large role in tumor morbidity and mortality depending on the type of hormone. Cushing syndrome is a result of excess cortisol release, which can be caused by a number of etiologies to include ectopic ACTH production, as seen in our patient. This can result in a number of systemic issues to include hypertension, myopathy, and osteoporosis, poor wound healing and psychiatric disturbance[4]. The serum ACTH and cortisol were both very elevated in our patient. In order to control the excessive amount of tumor driven hormone release there are three classes of drugs available for use to include steroidogenesis inhibitors, neuromodulators of ACTH release and glucocorticoid receptor-blocking agents[5]. Current guidelines suggest steroidogenesis inhibitor mitotane as first line in combination with chemotherapy[7]. Due to limitations in the Tricare network, many steroidogenesis inhibitors are not readily available including mitotane, metyrapone, and mifepristone. Ketoconazole, used in our patient, works through inhibition of 17-20 desmolase, blockade of 17-hydroxylase, and inhibition of 21- and/or 11-hydroxylase[8]. Time to peak concentration is around 2 hours[9], therefore even though it might take several weeks to achieve full inhibition, Ketoconazole should have a readily available effect.

This case highlights several important clinical implications. Firstly, HGNEC is a rare neoplasm that is often difficult to differentiate. Treatment, while available, is limited and associated with poor outcomes. Secondly, treatment should consist of a multidisciplinary discussion in order to facilitate an effective plan of action for patients with this disease process. Thirdly, although mitotane is the first line adrenolytic therapy, not every facility may have this readily available[10]. Lastly, the past decade has seen a shift of focus from empiric therapeutic trials to pathological and molecular profiling–based studies that may help define and select patient subtypes that could benefit from subtype-specific treatment.

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