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# Unusual suspects: pulmonary opportunistic infections masquerading as tumor metastasis in a patient with adrenocorticotropic hormone-producing pancreatic neuroendocrine cancer

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***Abstract:*** Pancreatic neuroendocrine tumors (p-NETs) are a rare group of neoplasms but with increasing incidence. The atypical complications that arise in the setting of functional endocrine tumors are underreported and therefore have not received sufficient attention and the necessary mention in the oncology literature. The clinical implications of these complications pose management challenges starting with the difficulty in establishing diagnosis, accurate staging and optimal treatment of the primary process. We present the case of a middle-aged woman diagnosed with adrenocorticotropic hormone-producing carcinoma arising from the pancreas whose case was complicated by excessive uncontrolled hypercortisolism and reactivation of pulmonary opportunistic infections that confounded her management. We believe that this case illustration will be of value to practicing oncologists and other groups of physicians who are called upon to participate in the multidisciplinary treatment of these relatively rare but highly challenging cases.

***Keywords:*** cancer, neuroendocrine, *Nocardia*, pancreas, pneumocystis

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## Introduction

Pancreatic neuroendocrine tumors (p-NETs) are a rare group of neoplasms but with increasing incidence. When functional, these tumors secrete a wide array of peptide hormones, most commonly insulin, followed by gastrin, glucagon, somatostatin, and vasoactive intestinal peptide. Adrenocorticotropic hormone (ACTH)-producing tumors are very rare, aggressive, and present diagnostic and management challenges with resultant poor prognosis [Kondo *et al*. 2010]. The hypercortisolism produced by ACTH-producing p-NETs leads to significant immune suppression, which may predispose patients to the development of opportunistic infections or reactivation of previously dormant infections. The diagnostic and therapeutic challenges encountered in the management of ACTH-producing p-NETs, including the potential infectious complications, deserve greater awareness by oncologists. This is because of the increasing incidence which leads to greater involvement of oncologists in the management of these rare but challenging tumors. We present the case of a 48-year-old Caucasian woman diagnosed with an ACTH-producing p-NET to illustrate the significant challenges encountered in the management of this condition.

## Case description

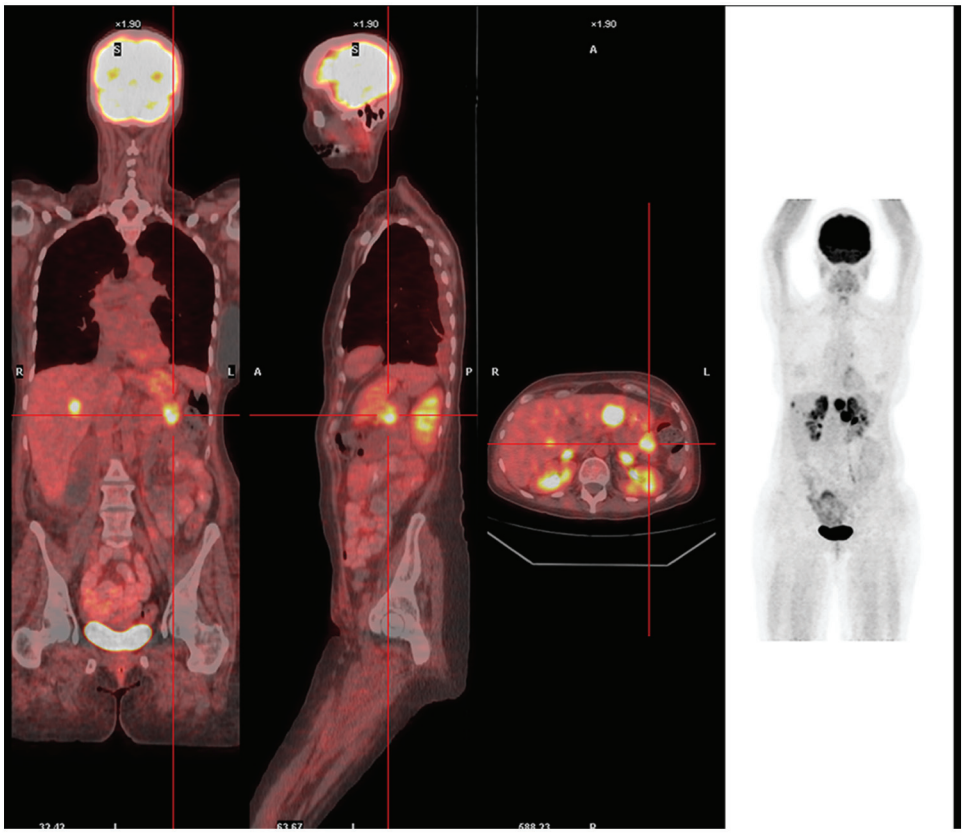
A previously healthy 48 year-old Caucasian woman presented to her family physician with a 1-month history of progressive lower extremity swelling accompanied by fatigue, generalized muscle weakness, increased facial hair, and weight gain. Apart from her known penicillin allergy and a diagnosis

of mood disorder 2 years previously, she had no significant medical or surgical history while there was a family history of prostate and breast cancer in her father and mother respectively. The patient was initiated on a short course of diuretics several weeks before presentation by her family physician. The patient denied tobacco use but admitted infrequent alcohol consumption. Physical exam revealed a well built woman with no obvious distress. Other pertinent findings included cushingoid facies, lower extremity pitting edema, skin striae and multiple ecchymoses on her arms. Laboratory evaluation revealed a low serum potassium level of 3.1 mEq/liter (3.6–5.1), suppressed thyroid-stimulating hormone of 0.05 μIU/ml (0.34–5.6), normal free thyroxine (T4) of 0.7 ηg/dl (0.5–1.6) but suppressed total and free T3 of 39 ηg/dl (59–174) and 1.4 pg/dl (2.4–4.2) respectively. The hypokalemia was initially ascribed to recent diuretic use but the abnormal thyroid function tests were concerning for secondary causes of hypothyroidism and necessitated referral to the endocrinology clinic. Full endocrinology workup showed elevated serum and urinary cortisol of 106.2 μg/dl (6.7–22.6) and 16,340 μg/day (<45) respectively, elevated ACTH of 296 pg/ml (5–27) and glucose of 207 mg/dl (65–110), along with a low potassium despite discontinuation of furosemide. A negative dexamethasone suppression test and normal pituitary gland on brain magnetic resonance imaging scan supported a preliminary diagnosis of ectopic ACTH-secreting tumor. Due to high cortisol/ACTH levels, hypokalemia and rapid onset of symptoms, the patient underwent a whole body 18-fluorodeoxyglucose ($^{18}$FDG) positron emission tomography (PET) scan [Figure 1 (a, b)] as well as an octreotide single-photon emission computed tomography (SPECT) scan (Figure 2). The octreoscan SPECT scan showed excellent target to background radiotracer uptake whereas the $^{18}$FDG-PET scan showed other areas of abnormal uptake, suggesting additional areas of metastatic disease possibly because of the increased sensitivity of PET imaging.

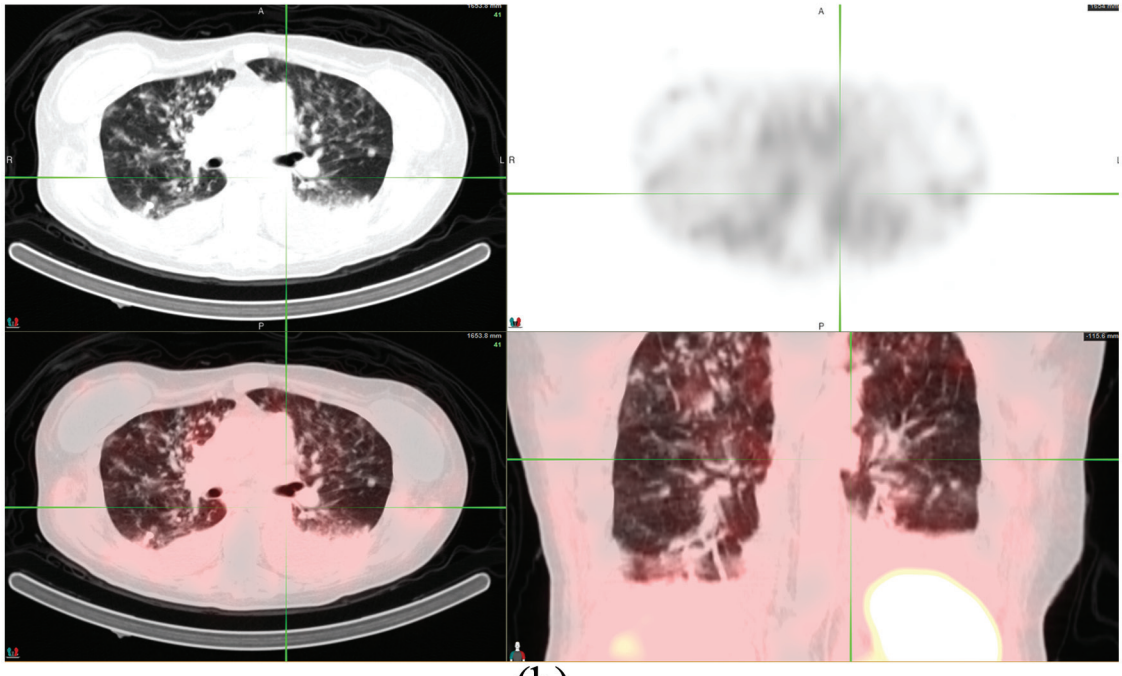
Histopathological confirmation of high-grade neuroendocrine carcinoma was obtained via image-guided biopsy of the PET-positive nodule in the liver (Figure 3(a, b)]. The overall clinicopathological and radiological findings were deemed consistent with a high-grade p-NET with hepatic and pulmonary metastases.

The patient initially started treatment with oral ketoconazole in an attempt to control her hypercortisolic state in preparation for adrenal gland ablation and systemic chemotherapy. She subsequently required subcutaneous octreotide and spironolactone due to suboptimal ACTH control, worsening muscle weakness and refractory hypokalemia. In spite of maximum outpatient medical therapy and supportive care, her cortisol level remained elevated and she progressively deteriorated and required inpatient care. On admission to the hospital, she was short of breath but without fever, cough or leukocytosis. Repeat imaging studies showed bilateral pulmonary nodules and bilateral effusion which indicated worsening pulmonary tumor burden but granulomatous disease could not be excluded. She also had *Escherichia coli* urinary tract infection for which she was started on oral trimethoprim and sulfamethoxazole. The patient's clinical state rapidly deteriorated and she was transferred to the intensive care unit due to progressive respiratory distress and high oxygen requirement. Immediate diagnostic bronchoscopy was deferred because her condition was ascribed to metastatic lung involvement and out of concern that she may become ventilator dependent post bronchoscopy. The patient received chemotherapy (cisplatin/etoposide) in an attempt to control her hypercortisolic state and presumed worsening tumor burden in the lungs. Following a short period of apparent clinical and biochemical improvement, the patient required intubation and mechanical ventilation for increased work of breathing. She was started on empiric broad-spectrum antibiotics (vancomycin, meropenem, amikacin and metronidazole) due to severe neutropenia. However, she deteriorated into multiorgan failure and required vasopressors for septic shock. The patient's family agreed to pursue comfort measures only due to the overall poor prognosis and she died within 48 hours of intubation and after 9 days in hospital. Microbiology cultures initially grew Gram-negative rods in the blood with a final speciation showing *E. coli* and *Nocardia* spp. after the patient had died.

Follow-up limited autopsy revealed a p-NET with metastasis to the liver as demonstrated by the PET scan but no other site of metastatic involvement was found. Gross examination of the lung at autopsy showed severe necrotizing bronchopneumonia suspected due to opportunistic infections [Figure 3(c, d)]. *Nocardia* and *Pneumocystis jirovechi* pneumonia (PJP) were confirmed on subsequent histological examination [Figure 3(e, f)]. The final cause of death was determined to be respiratory



(a)



(b)

**Figure 1.** 18-Fluorodeoxyglucose positron emission tomography and computed tomography scan images at the time of initial diagnosis revealed abnormal radiotracer uptake in the tail of the pancreas and liver (a). A repeat scan approximately 6 weeks later at the time of hospital admission showed multiple bilateral hypermetabolic pulmonary nodules (b).

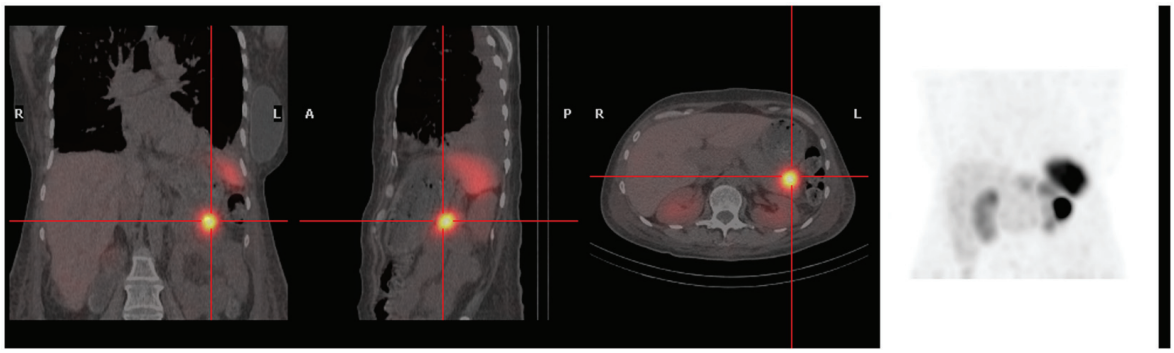



**Figure 2.** In contrast to findings on 18-fluorodeoxyglucose positron emission tomography scan, octreotide scan only showed significant tracer accumulation in the tail of the pancreas but not in the liver or the lung.

failure from necrotizing pneumonia caused by opportunistic infections because the patient was in an immunocompromised state induced by profound uncontrolled hypercortisolism.

## Discussion

Epidemiological data show an increased incidence of neuroendocrine tumors, with US prevalence exceeding 100,000 cases based on recent Surveillance, Epidemiology and End Results database analysis [Modlin *et al.* 2007; Yao *et al.* 2008]. Carcinoid and neuroendocrine tumors of the pancreas constitute the most frequently diagnosed subtypes of neuroendocrine tumors. Approximately 3% of all primary pancreatic malignancies are p-NETs [Strosberg *et al.* 2011]. While approximately half of all p-NETs are functional tumors [Alexakis and Neoptolemos, 2008], only 1.2% of functional p-NETs secrete ACTH [Ito *et al.* 2007]. Clinical experience informing the optimal management of this very rare subtype of neuroendocrine tumors is therefore limited to specialized centers. This case report illustrates the management challenges posed by this rare tumor.

The diagnosis of this case was somewhat fortuitous given that the patient was initially referred to the endocrinologist out of concern for a thyroid disorder. However, appropriate workup led to the correct diagnosis of an ACTH-producing p-NET, thus highlighting the importance of a multidisciplinary team of experts in the management of this disease. The use of $^{18}$FDG-PET imaging in oncology has revolutionized diagnostic and staging accuracy for a wide variety of cancers. In a head-to-head comparative study of $^{18}$FDG-PET, $^{111}$In-diethylenetriaminepentaacetic acid-octreotide somatostatin receptor scintigraphy (SRS) and $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy in 96 patients with neuroendocrine tumors, SRS had the best overall sensitivity (89%) followed by $^{18}$FDG-PET (58%) and $^{123}$I-MIBG scintigraphy (52%). Of significant relevance to the case under discussion was the fact that $^{18}$FDG-PET showed superior sensitivity in diagnosing high-grade neuroendocrine tumors, especially those arising from the pancreas. Indeed, 7 out of 11 SRS-negative patients had positive findings on PET imaging. Moreover, $^{18}$FDG-PET had the highest sensitivity (92% *versus* 69% for SRS and 46% with $^{123}$I-MIBG) for tumors with high malignant potential as measured by high proliferative index [Binderup *et al.* 2010]. This is consistent with our observation in this case when $^{18}$FDG-PET imaging facilitated the histological diagnosis by revealing metastatic involvement in the liver, which was not obvious on the SRS scan. However, the increased sensitivity of PET imaging also produced a false-positive finding in the lung which potentially confounded the overall management of this case.

Pulmonary nocardiosis is a common opportunistic infection in immunocompromised patients [Minero *et al.* 2009]. While delayed diagnosis of nocardiosis is not uncommon, it is a treatable disease that is responsive to standard antibiotic therapy such as trimethoprim sulfamethoxazole, linezolid and carbapenems. Invasive disease in the immunocompromised host is frequently associated with steroid therapy and carries a high mortality [Martinez Tomas *et al.* 2007; Minero *et al.* 2009]. Similarly, PJP has been well described to complicate the immunocompromised state as seen in Cushing's disease. It is arguable whether or not antemortem recognition of these infections could have changed the outcome in our case given the high mortality reported in other cases in which opportunistic infection was established and

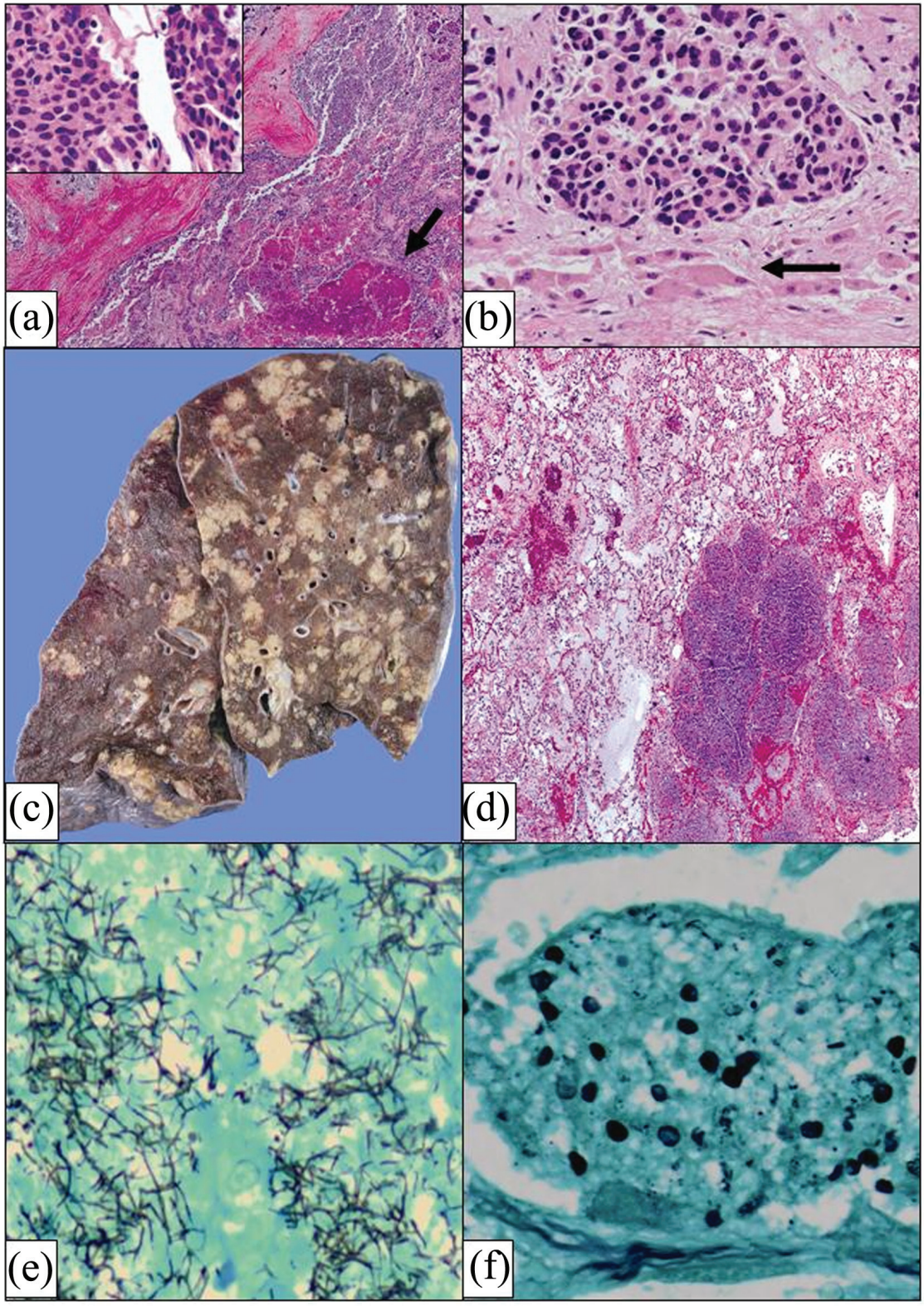



**Figure 3.** Hematoxylin and eosin (H&E) stained section from the pancreatic mass shows a necrotic (arrow), high-grade neuroendocrine carcinoma (inset; higher power view) (a). H&E stained section from metastatic nodule in the liver mass (arrow shows adjacent hepatocytes) showed foci of metastatic neuroendocrine carcinoma (b). Left lung with multiple nodules of necrotizing pneumonia that correspond with the hypermetabolic nodules on PET scan (c). H&E stained section of a representative lung nodule shows a focus of necrotizing bronchopneumonia (40×) (d). Grocott's Methenamine Silver stain shows foci of *Pneumocystis jirovechi* and branching filamentous bacteria consistent with *Nocardia* spp. (e, f).

aggressively treated antemortem [Bakker *et al.* 1998; Kim *et al.* 2000]. The surprising postmortem finding of PJP and nocardiosis highlights the importance and continuing relevance of autopsy examination as a tool for learning and discovery. The continuing decline in the autopsy rate [Limacher *et al.* 2007], however, is disappointing. It is hoped that cases like this will reinforce the need for a judicious application of this tool in spite of the increasing sophistication of noninvasive diagnostic techniques available to the modern clinicians. Although PET scanning has greatly enhanced our diagnostic capability, this challenging case is another reminder that even in a patient with confirmed metastatic disease, not all that glows on a PET scan is cancer.

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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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