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Case Report

Ectopic ACTH Syndrome Emerging at a Late Stage of a Mixed Histology Neuroendocrine Neoplasm

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Abstract

A 66-year-old patient followed for a 3-year history of metastatic Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm (MiNEN) with a Neuroendocrine Carcinoma (NEC) and adenocarcinoma component originating from the vulva, presented to the emergency for dyspnea, and fatigue. Upon clinical examination, we found widespread hyperpigmentation, a moon-face appearance, hirsutism, a buffalo hump and muscle atrophy.

Laboratory investigations revealed severe hypokalemia (2.3 mmol/L), elevated serum cortisol (1812 nmol/L) and Adrenocorticotropic Hormone (ACTH) (194 ng/L) levels. Urinary free cortisol (UFC) was 21-folding the upper limit of the reference range (3614.0 nmol/24h), and cortisol was not suppressed after the 1mg-dexamethasone suppression test confirming the ACTH-dependent Cushing's syndrome.

Thoraco-abdominal Computed Tomography (CT) scan demonstrated progressive neoplastic disease in the liver, kidney, lymph nodes, peritoneum and lung. A Magnetic Resonance Imaging (MRI) of the brain indicated multifocal metastatic infiltration but no evidence of pituitary adenoma.

Interestingly, despite a previously negative ^{68}Ga-DOTATATE Positron Emission Tomography (PET)/CT performed one year prior, there was lymphatic, pulmonary, peritoneal and osseous moderate somatostatin receptor (SSTR) expression, suggesting the presence of a differentiated neuroendocrine component.

After the work-up, the patient was admitted to a supportive care facility. Hypercortisolism symptoms were effectively managed with an adrenal enzyme inhibitor (ketoconazole) in combination with Somatostatin (SST) analogues. Unfortunately, the patient was too frail to benefit from Peptide Receptor Radionuclide Therapy (PRRT).

This redifferentiation phenomenon in neuroendocrine tumors should be further investigated, as patients might be, under certain conditions, eligible for PRRT. Therefore, we suggest that newly occurring paraneoplastic syndromes in NEC patients should always be evaluated by ^{68}Ga-DOTATATE PET/CT.

Keywords: Ectopic adrenocorticotropic hormone secretion; ^{68}Ga-DOTATATE PET/CT; Mixed neuroendocrine non-neuroendocrine neoplasm; Neuroendocrine carcinoma; Peptide receptor radionuclide therapy; Somatostatin receptor

Abbreviation: ACTH: Adrenocorticotropic Hormone; CT: Computed Tomography; EAS: Ectopic Adrenocorticotropic Hormone Secretion; MiNEN: Mixed Neuroendocrine Non-Neuroendocrine Neoplasm; MRI: Magnetic Resonance Imaging; NF1: Neurofibromatosis Type I; NEN: Neuroendocrine Neoplasm; NET: Neuroendocrine Tumors; NV: Normal Value; PET: Positron Emission Tomography; PRRT: Peptide Receptor Radionuclide Therapy; SST: Somatostatin; SSTR: Somatostatin Receptor; UFC: Urinary Free Cortisol

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Introduction

Neuroendocrine Neoplasms (NENs) are a heterogeneous group of malignancies arising from different anatomic sites. In the latest WHO guidelines 2019, NENs are separated into well-differentiated Neuroendocrine Tumors (NETs) and poorly differentiated Neuroendocrine Carcinomas (NECs), as these two types of neuroendocrine neoplasms differ substantially in their clinical behavior, evolution, management and molecular underpinnings [1,2].

Furthermore, NETs are graded as G1, G2 or G3 based on the mitotic rate and Ki67 labelling index [2]. NECs have a relatively high Ki67 index, greater than 20% in essentially all cases and commonly above 50% in the large cell variant and close to 90% in the small cell variant [3].

All NENs can cause paraneoplastic syndromes like ectopic Adrenocorticotropic Hormone (ACTH) secretion (EAS). EAS is a rare form of ACTH-dependent Cushing's syndrome associated with intense hypercortisolism and requiring complex treatment strategies [4-8].

EAS is caused by unregulated ACTH and/or CRH secretion by NENs of varying anatomical locations, degrees of histological differentiation and proliferation. These tumors typically lead to severe cortisol hypersecretion by the adrenal cortex. EAS can be due to well-differentiated tumors, grade I and II NETs with a favorable prognosis or to more aggressive grade III NET and NEC with a worse prognosis [8,9].

Early recognition and rapid management are crucial due to the severity of hypercortisolism. Unfortunately, given the rarity and heterogeneity of the disease, there are no established evidence-based recommendations [7,10].

We present an exceptionally rare case of a 66-year-old patient without any notable medical history, presenting with a paraneoplastic EAS, emerging three years following the initial diagnosis of a MiNEN with an NEC and adenocarcinoma component.

Case Presentation

History of the Neoplastic Disease

In July 2020, a 62-year-old patient, without any notable medical history developed a lesion on her right vulva. Subsequently, a partial right vulvectomy with sentinel lymph node was performed.

An anatomopathological examination showed a MiNEN composed predominantly of a neuroendocrine component, with a 35% adenocarcinoma component. The neuroendocrine component expressed Keratin 7 and 20 weakly, and focal expression of Chromogranin, Synaptophysin and CD56 was observed. The adenocarcinoma component exhibited expression of Keratin 7, CDX2, and P16. There was no expression of GATA3 or P63 in the entire tumor. Furthermore, lymph node metastases from the adenocarcinoma component were observed.

Next-generation sequencing on the tumor tissue revealed a mutation in the Neurofibromatosis type I (*NF*1) gene (F250Lfs*31). Due to the high frequency of this mutation (65%), we investigated for a germline mutation in normal tissue to rule out Neurofibromatosis Type I Syndrome; ultimately, we only found a NF1 mutation in the tumoral tissue. Furthermore, we found *CDK8* amplification, *CKS1B* amplification, *FLT3* amplification, *MCL1* amplification *NTRK1* amplification, *RB1* loss exons 4-5 and *TP53* R333fs*12. The tumour was microsatellite stable, and the tumour mutational burden was estimated at 2 Muts/Mb.

After surgery, the patient received four cycles of adjuvant cisplatin/etoposide chemotherapy, followed by radiotherapy administered to the vulva and the inguinal-pelvic region, completed in January 2021.

In August 2021, a recurrence was detected in the lungs and the lower pole of the left kidney. This lesion was biopsied in October 2021, confirming the diagnosis of an undifferentiated neuroendocrine carcinoma with a Ki67 index at 90% expressing Chromogranin and Synaptophysin.

From November 2021 to August 2022, the patient was treated with carboplatin AUC 2 combined with etoposide 100 mg a day with eventual disease progression after ten cycles. From September 2022, the patient received then capecitabine 625 mg/m^2 with temozolomide 100mg/m^2 followed on November 23 2022, by everolimus 5 mg a day. Subsequently, a therapy with fluorouracil at a dose of 2400 mg/m2 and irinotecan at 180 mg/m2 every three weeks was initiated, with the first cycle administered in February 2023. After five cycles of chemotherapy, on June 2023, the patient was transitioned to metronomic capecitabine while awaiting inclusion in a phase I clinical trial.

In August 2023, the patient went to the emergency department for worsening dyspnea, fatigue and abdominal pain. She reported experiencing a gradual increase in fatigue over the past month and worsening difficulty in walking due to muscle weakness. Additionally, she described an exacerbation of dyspnea accompanied by a dry cough.

Clinical Examination

Upon clinical examination, we found widespread hyperpigmentation of the skin, a moon-face appearance, hirsutism, and the presence of a buffalo hump. Furthermore, muscle atrophy was evident, along with a slight lower extremity oedema.

Laboratory Investigations

Laboratory investigations (Table 1) revealed severe hypokalemia [2.3 mmol/L (reference range: 3.4 to 4.4 mmol/L)], increased urinary potassium excretion, elevated serum cortisol [1812 nmol/L (reference range: 63 to 535 nmol/L)] and Adrenocorticotropic Hormone (ACTH) [194 ng/L (reference range: 0 to 47 ng/L)] levels. Urinary free cortisol (UFC) was markedly elevated [3614.0 nmol/24h (reference range: 30 to 145 nmol/24 h)]. Cortisol was not suppressed after the 1mg-dexamethasone suppression test.

Radiological Investigations

Thoraco-abdominal Computed Tomography (CT) scan (Figure 1) demonstrated progressive neoplastic disease in the liver, kidney, lymph nodes peritoneum and a notable progression of pulmonary metastases, including nearly complete infiltration of the right lower lobe and full involvement of the left upper lobe. MRI of the brain indicated multifocal metastatic infiltration but no evidence of pituitary adenoma. Interestingly, despite a previously negative ^{68}Ga-DOTATATE PET/CT scan performed one year prior (Figure 2), there was lymphatic, pulmonary, peritoneal and osseous moderate Somatostatin Receptor (SSTR) expression, suggesting the presence of a differentiated neuroendocrine component.

Table 1: Laboratory investigations.

Laboratory investigations			
Hemoglobin	14,5	g/dL	12 - 16
Platelets	143.000	/µL	150.000 - 440.000
White Blood Cells	11470	/µL	3.500 - 11.000
Lymphocytes	530	/µL	1.200 - 3.500
C- reactive Protein	68,8	mg/L	< 5
Kalium	2,3	mmol/L	3.4 - 4.4
Chlore	91	mmol/L	98 - 107
Natrium	139	mmol/L	136 - 145
Urea	29,9	mg/dL	16.6 - 48.5
Creatinine	0,76	mg/dL	0.5 - 0.9
g-GT	544	Ui/L	6 - 42
Lactate dehydrogenase	507	Ui/L	135 - 214
Total bilirubin	0.7	mg/dL	< 1.2
Serum cortisol (morning)	1764	nmol/L	63 - 535
ACTH (morning)	194	ng/L	0 - 47
Serum cortisol (after 1 mg dexamethasone)	1812	nmol/L	63 - 535
Arterial Blood Gaz Analysis			
pH	7.55		7.35 - 7.45
pCO2	50	mmHg	32 - 45
pO2	44	mmHg	75 - 104
Natrium	138	mmol/L	136 - 145
Kalium	2,6	mmol/L	3.4 - 4.4
Chlore	86	mmol/L	136 - 145
Glucose	318	mg/dL	70 - 100
Lactate	1,5	mmol/L	0.7 - 2.0
Oxygen-Saturation	84	%	95 - 98 %
Urinary investigations			
Urinary Potassium	159	mmol/g creatinine	8 - 129
Urinary free cortisol	3614.0	nmol/24h	30 to 145

Table 2: ACTH and cortisol monitoring during treatment titration.

Date	ACTH (ng/L) (NV : 0 - 47)	Morning plasma cortisol (nmol/L) (NV : 63 - 535)	UFC (nmoL/24h) (NV : 30 to 145)
23-01-23	9	411	/
02-08-23	190	1762	/
03-08-23	**Initiation of treatment with Ketoconazole**		
08-08-23	/	/	3614
14-08-23	210	1020	/
20-08-23	/	/	1265
21-08-23	182	911	/
27-08-23	/	/	1253
28-08-23	209	681	/
01-09-23	**Initiation of treatment with SST analogues**		
04-09-23	239	/	/

Management

We initiated treatment with ketoconazole (an adrenal enzyme inhibitor), which was gradually increased to 200 mg three times per day with good tolerability and biological response (Table 2). In addition, the patient received SST analogues.

Moderate SSTR expression demonstrated by ^{68}Ga-DOTATATE PET/CT and the frail clinical condition of the patient were serious drawbacks to considering PRRT as an additional therapeutic modality. After effective management of the hypercortisolism symptoms, the patient was admitted to a supportive care facility to continue the ketoconazole titration to optimize further the control of hypercortisolism linked to the EAS.

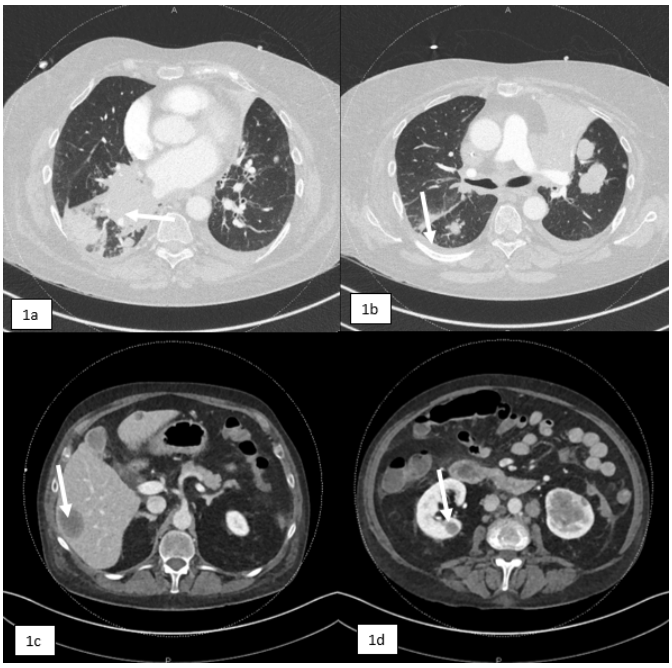

Figure 1: Thoraco-abdominal computed tomography.
In the thoracic region, we did not find a pulmonary embolism. There was a clear progression of pulmonary metastases. There was an almost complete involvement of the right lower lobe and the left upper lobe (arrow 1a.). Minor pleural effusions appeared (arrow 1b.).
In the abdominal region, a known left renal metastasis and retroperitoneal lymph nodes were progressing. There was also progression in previously identified hepatic metastases (arrow 1c.). Progression was observed in retroperitoneal para-aortic adenopathy and in the left renal metastasis (arrow 1d.), invading the local retroperitoneal fat.

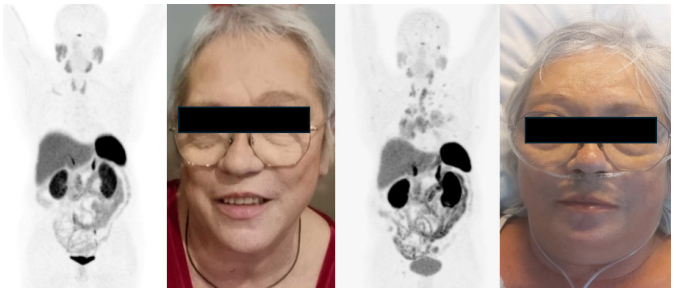

Figure 2: ^{68}Ga-DOTATATE PET/ CT and clinic of the patient.
Negative ^{68}Ga-DOTATATE PET/CT scan in July 2022, one year before hospital admission, with the patient not showing any signs of Cushing syndrome (2.a).
In August 2023, upon hospital admission, there was a reappearance of low to moderate somatostatin receptor expression at the lymphatic, pulmonary, peritoneal, and osseous levels (arrow), suggesting the presence of a differentiated neuroendocrine component (2.b). At this moment, the patient exhibited all the signs of Cushing syndrome.

Furthermore, a dose of 20 grey was delivered to the brain in 5 sessions using 6 MV photon beams from the linear accelerator, with a palliative intent.

Unfortunately, due to her progressive disease, the patient died several weeks later.

Discussion

Interestingly, in this case, is that the patient initially presented with a MiNEN containing a neuroendocrine carcinoma component, which typically does not express somatostatin receptors in contrast to well-differentiated NET [11].

In our case, the tumor has been biopsied twice, and we

found twice an undifferentiated neuroendocrine tumour with an elevated Ki-67 index that was estimated at 90%. Additionally, underlying genomic alterations in *RB1* and *TP53* are typical of poorly differentiated NEC and are generally not found in well-differentiated NET G3.

Furthermore, NETs do not typically transform into poorly differentiated NECs or vice versa. Once a specific neuroendocrine neoplasm is diagnosed, recurrences or metastases usually exhibit the same histological characteristics (NET or NEC) as the primary tumor [12]. However, progression from a lower grade (G1 or G2) NET to a NET G3 can be seen within an individual tumor or between topographically or temporally separate metastasis [12-13]. Yang et al. presented a study where Ki-67 labelling indices of metastatic well-differentiated NETs were assessed; they concluded that nearly one-half of the tumors showed intertumoral heterogeneity sufficient to change the grade from low to intermediate [14].

The natural history of neuroendocrine tumors involves a genome-wide loss of DNA methylation as an epigenetic event, accompanied by an increase in the Ki-67 index, which plays an essential role in tumour development and progression [12]. Progression might be characterized in certain instances by an increase in the rate of cell proliferation or other alterations like nuclear abnormalities and the emergence of notable necrosis [13].

After chemotherapy treatments, NET and NEC can change their Ki-67 index and even become hypermutated [15, 16].

Vyas et al. highlighted that chemotherapy can cause treatment-related alterations in NEC, occasionally leading to a decrease in the Ki-67 index, resulting in a Ki-67 index below 10%, either locally or diffuse (probably related to a cytotoxic effect toward the most aggressive part of the disease) stressing out that this reduction in proliferative rate is of uncertain clinical significance and should not be taken as evidence of a lower grade NET component of the neoplasm [17].

Besides, several case reports have described the re-expression of somatostatin receptors in patients exposed to everolimus and capecitabine/temozolomide. However, these cases were observed in NET patients [18-20].

Curiously, in our case, the patient was also treated after the first 68Ga-DOTATATE PET/CT with capecitabine/temozolomide, followed by everolimus. One could hypothesize that both phenomena described above have occurred. Firstly, the most aggressive part of the NEC, more sensitive to chemotherapy, has been eradicated, leading to the emergence of a less aggressive, more differentiated neuroendocrine tumor. Then, capecitabine/temozolomide and everolimus induced a redifferentiation with re-expression of SSTR.

To the best of our knowledge, this is the first case of re-expression of SSTR in a NEC that has been described, occurring on the later stages of the disease course. This redifferentiation phenomenon in neuroendocrine carcinoma should be further investigated, as patients might be, under certain conditions, eligible for PRRT.

Additionally, we suggest that newly paraneoplastic syndromes occurring in NEC patients should always be evaluated for somatostatin receptor expression by ^{68}Ga-DOTATATE PET/CT.

References

1. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020; 76: 182-8.
2. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018; 31: 1770-86.
3. Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, Capdevila J, Castaño-Pascual Á, Benavent M, et al. Neuroendocrine Tumor Heterogeneity Adds Uncertainty to the World Health Organization 2010. Classification: Real-World Data from the Spanish Tumor Registry (R-GETNE). Oncologist. avr 2018; 23: 422 32.
4. Tang LH, Basturk O, Sue JJ, Klimstra DS. A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. Am J Surg Pathol. 2016; 40: 1192 202.
5. Hayes AR, Grossman AB: The Ectopic Adrenocorticotropic Hormone Syndrome: Rarely Easy, Always Challenging. Endocrinol Metab Clin North Am. 2018, 47: 409–25.
6. Dimitriadis GK, Angelousi A, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Paraneoplastic endocrine syndromes. Endocr Relat Cancer. 2017; 24: R173 90.
7. Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, et al. MANAGEMENT OF ENDOCRINE DISEASE: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol. 2020; 182: R29–58.
8. Hofland J, de Herder WW. Effective strategies for adequate control of hormonal secretion in functioning neuroendocrine neoplasms. Best Practice & Research Clinical Endocrinology & Metabolism. 1 sept 2023; 37: 101787.
9. Wu Y, Xiong G, Zhang H, Wang M, Zhu F, Qin R: Adrenocorticotropic Hormone-Producing Pancreatic Neuroendocrine Neoplasms: A Systematic Review. Endocr Pract. 2021; 27: 152–7.
10. Sharma ST, Nieman LK, Feelders RA: Cushing's syndrome: epidemiology and developments in disease management. Clinical Epidemiology. 2015; 7: 281-293.
11. Refardt J, Hofland J, Wild D, Christ E. Molecular Imaging of Neuroendocrine Neoplasms. J Clin Endocrinol Metab. 2022; 107: e2662-70.
12. Nagy-Mignotte H, Shestaeva O, Vignoud L, Guillem P, Ruckly S, et al. Prognostic impact of paraneoplastic cushing's syndrome in small-cell lung cancer. J Thorac Oncol. 2014; 9: 497–505.
13. Tang LH, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, et al. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. Clin Cancer Res. 2016; 22: 1011-7.
14. Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015; 39: 683-90.
15. Klempner SJ, Hendifar A, Waters KM, Nissen N, Vail E, Tuli R, et al. Exploiting Temozolomide-Induced Hypermutation With Pembrolizumab in a Refractory High-Grade Neuroendocrine Neoplasm: A Proof-of-Concept Case. JCO Precis Oncol. 2020; 4: 614-9.

16. Bourg L de M du, Cohen D, Masliah-Planchon J, Sivakumar S, Rycke O de, Dhome OH, et al. 1182O Temozolomide treatment induces an MMR-dependent hypermutator phenotype in well differentiated pancreatic neuroendocrine tumors. Annals of Oncology. 2023; 34: S701.

17. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol. 2011; 35: 853-60.

18. Vyas M, Tang LH, Rekhtman N, Klimstra DS. Alterations in Ki67 Labeling Following Treatment of Poorly Differentiated Neuroendocrine Carcinomas: A Potential Diagnostic Pitfall. Am J Surg Pathol. janv 2021; 45: 25-34.

19. Sharma P, Basu S. Occurrence of the Redifferentiation-Akin Phenomenon on 68Ga-DOTATATE PET/CT After CAPTEM Chemotherapy in Metastatic Neuroendocrine Tumors with Intermediate MIB1 Index: What Could Be the Molecular Explanation? Journal of Nuclear Medicine Technology. 2020; 48: 290-1.

20. Mileva M, Wimana Z, Flamen P, Karfis I. Everolimus-induced somatostatin receptor overexpression in a rectal neuroendocrine tumor patient may promote somatostatin receptor-guided radionuclide therapy (peptide receptor radiotherapy) as an additional treatment option. World J Nucl Med. 2021; 20: 316-8.

21. Basu S, Ostwal V. Observation on enhanced avidity on somatostatin receptor targeted 68Ga-DOTATATE PET-CT following therapy with everolimus and capecitabine–temozolamide: is redifferentiation akin phenomenon a reality in neuroendocrine tumors? Nuclear Medicine Communications. 2016; 37: 669-71.