ACTH-Secreting Neuroendocrine Carcinoma of the Cecum: Case Report and Review of the Literature

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Abstract

Adrenocorticotropic hormone-secreting neuroendocrine tumors of the colon are rare. We describe a case of _BRAF V600E_ and _TP53_ mutations detected with next-generation sequencing (NGS) and performed a comprehensive literature review. Eighteen cases were found with an unadjusted mortality rate of 77.7% and median survival from presentation of 63 days. NGS may be important to identify these rare tumors.
Background: Approximately 30% of neuroendocrine tumors (NETs) present with secretory syndromes or develop one during the course of the disease. Cushing syndrome caused by a gastrointestinal tract NET is rare, with limited published information. We describe a patient with florid Cushing syndrome due to ectopic adrenocorticotropic hormone (ACTH) from a NET of colonic origin. A literature review was conducted to describe the spectrum of this clinical and pathologic entity as reported in the scientific literature. **Patient and Methods:** Next-generation sequencing and microsatellite instability testing was carried out on the tumor from our case. A preliminary PubMed search was conducted using the following terms under the publication type "Case Reports": "Cushing" AND "colon," "neuro-endocrine" AND "colon" and "neuroendocrine AND Cushing AND "colon." A manual search was performed to review all references for inclusion and relevant clinical, biochemical and pathologic data was abstracted. **Results:** Mutations in _BRAF V600E_ and _TP53_ were detected in our case. We retrieved 18 previously reported cases of Cushing syndrome associated with a NET of colonic origin, none of which had next-generation sequencing performed. Median age at diagnosis was 54.5 years (range, 24-74 years), with equal gender distribution. ACTH was detected by immunohis-tochemistry in the primary tumor and/or metastatic lesion in 61.5%. Review of the reports suggested that ectopic ACTH secretion from a colonic tumor might be more common in mixed glandular and NETs, including mixed adenocarcinoma—neuroendocrine carcinoma. Among studies reporting outcomes, the unadjusted mortality rate was 77.7%, with median overall survival from presentation of 63 days (range, 17-380 days). **Conclusion:** Cushing syndrome associated with ectopic ACTH from tumors of colonic origin is a rare phenomenon with poor outcomes and can be associated with pure NETs, adenocarcinomas, and mixed-phenotype tumors, including mixed adenocarcinoma—neuroendocrine carcinoma.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous and complex group of neoplasms that can present with wide-ranging clinical symptomatologies.[1-4] While still uncommon, both the incidence and prevalence of NETs have risen over the past 2 decades.[5,6] NETs can arise from multiple anatomic locations, but the gastrointestinal

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tract remains the most common site of origin.[1,5] Approximately 30% of patients present with secretory syndromes or develop one during the course of the disease. These syndromes lead to a variety of biochemical and metabolic abnormalities that affect multiple domains, potentially influencing prognosis.[2,7-9] Cushing syndrome caused by a gastrointestinal NET is exceedingly rare, with only a few cases reported in the literature.[10-26]

We describe a patient with florid Cushing syndrome due to ectopic adrenocorticotropic hormone (ACTH) from a neuroendocrine carcinoma (NEC) of colonic origin. A literature review was conducted to describe the spectrum of this clinical and pathologic entity.

Methods

Molecular Analysis

The tumor sample from our case was sequenced using the Illumina TruSight 15 Amplicon panel (Illumina, San Diego, CA), with next-generation sequencing data analyzed with the standard Nova Scotia Health Authority Bioinformatics Pipeline.[27] In brief, sequencing reads were aligned with BWA-MEM, then processed with the Genome Analysis Toolkit and Picard, with variants identified with an ensemble variant calling approach (MuTech, Free-Bayes, VarDict, Pindel, Platypus, Scalpel). Variants were annotated using snpEff and vcfanno and were filtered for population level polymorphisms using data from the ExAc database. Known pathogenic/clinically relevant mutations were highlighted according to the COSMIC and ClinVar databases, with additional variants stratified by protein impacts by snpEff. Microsatellite instability (MSI) PCR analysis was performed using the MSI testing kit from Promega (Madison, WI) as previously described.[28]

Literature Review

A preliminary search was performed in PubMed for all published articles using the following terms under the publication type "case reports": "Cushing" AND "colon," "neuroendocrine" AND "colon" and "neuroendocrine AND Cushing AND "colon." An extensive manual search was then performed to review all references for inclusion, and relevant clinical, biochemical, and pathologic data was abstracted.

Case Presentation

A 66-year-old previously healthy man presented with a 2-month history of progressive proximal muscle weakness, anorexia, and dysgeusia resulting in a 30-pound weight loss and heart palpitations. Physical examination revealed generalized cachexia and symmetric upper and lower proximal myopathy. There was no hyperpigmentation noted, and overt Cushingoid features were absent. Initial blood work demonstrated hypokalemia (2.3 mmol/L; reference range, 3.4-5.0 mmol/L) and new-onset hyperglycemia, with glucose levels up to 19.3 mmol/L. His hemoglobin A1C measured 2 years previously was 5.5% but at presentation was 7.0%. Subsequent blood work confirmed ACTH-dependent Cushing syndrome with elevated serum cortisol and ACTH (Table 1). Blood work assessing the remainder of his pituitary axis was noncontributory and consistent with mild sick euthyroid syndrome and central hypogonadism (data not shown).

Investigations included computed tomographic scan of chest, abdomen, and pelvis, which revealed an area of colonic thickening

Table 1 Blood Work Results Leading to Diagnosis of Cushing Syndrome

Laboratory Parameter	Results	Reference Range
Serum AM cortisol	3357 nmol/L	120-550 nmol/L
24-hour urine free cortisol	32,802 nmol/TV	12-486 nmol/TV
ACTH level	131 pmol/L	2.3-10.1 pmol/L
Potassium level	2.3 mmol/L	3.4-5.0 mmol/L
Serum cortisol after initiation of treatment	343 nmol/L	120-550 nmol/L

along the ileocecal valve (Figure 1) and multiple hepatic lesions, with the largest measuring 11 cm (Figure 2). Bilateral adrenal glands appeared hyperplastic with no detectable mass. Magnetic resonance imaging of the sella turcica revealed a normal pituitary gland and stalk with no evidence of a macroadenoma. On the basis of the computed tomographic findings, a colonoscopy was performed, which revealed an ulcerated cecal mass (Figure 3), which was sampled via biopsy.

Histologic examination of the cecal mass showed sheets of poorly differentiated malignant cells, with nuclear pleomorphism, prominent nucleoli, and frequent mitoses (Figure 4). Synaptophysin expression detected by immunohistochemistry (IHC) indicated that the tumor had neuroendocrine differentiation. Other immunohistochemical markers showed that the tumor was positive for CK8/18 and CKAE1/3 and negative for CK7, CK20, CDX2, TTF1, PAX8, chromogranin, and ACTH. The Ki-67 index was 90%, and the morphology was considered to be compatible with large-cell NEC. There were also fragments of tubular adenoma without high-grade dysplasia in the biopsy sample, indicating that the tumor had a

Figure 1 Contrast-Enhanced CT Showing Peripheral Wall Thickening (Arrow). Shown is Right Colon Across From Ileocecal Valve. Bilateral Adrenal Glands Were Hyperplastic Without Discernable Mass or Nodule

Abbreviation: CT = computed tomography.

108.1 mm

Abbreviation: CT = computed tomography.

glandular component. No adenocarcinoma component was detected in the biopsy sample, arguing against a mixed adenoneuroendocrine carcinoma (MANEC).

The patient was admitted to the hospital with worsening symptomatologies, including refractory hypokalemia despite aggressive oral replacement, progressive proximal myopathy, and hypertension. Therapy was initiated with ketoconazole, mitotane, metyrapone, and spironolactone. Metformin and gliclazide were initiated for hyperglycemia, and amlodipine was started for hypertension.

With initiation of antiadrenal therapy and improvement in hypercortisolemia, the biochemical abnormalities, diabetes, and hypertension resolved. Unfortunately, the rapid reduction in serum cortisol levels resulted in symptoms of adrenal insufficiency despite block-and-replace strategies with hydrocortisone. Further

investigations were planned, including a positron emission tomography scan, octreotide scan, and biopsy of liver lesions. However, the patient's health declined precipitously, and with the support of his family, he made the decision to stop all active treatment, including antiadrenal therapy. He died 35 days after his initial presentation, and the family declined an autopsy request. Two pathogenic mutations were identified on posthumous next-generation sequencing: Chr17:7577121 G > A, *TP53*, c.817C > T, p.R273C and Chr7:140453136 A > T, *BRAF*, c.1799T > A, p.V600E. MSI testing results documented it to be microsatellite stable.

Discussion

The vast majority of colorectal NETs present with advanced stage disease and are nonfunctional.[2,9,29] Carcinoid syndrome, the most common hypersecretory syndrome associated with NETs, was estimated to occur in only 10% of colorectal NETs in a large population-based study.[8] Ectopic ACTH secretion by NETs accounts for only 5% to 10% of cases of ACTH-dependent Cushing syndrome and is far less common than ACTH secretion from pituitary sources or Cushing disease.[23] Thoracic NETs originating from bronchial and thymic sources represent the most common sources of NET-associated ectopic ACTH secretion.[30,31] While difficult to estimate given the rarity, Kamp et al[30] attempted to determine the prevalence of NET-associated Cushing syndrome in a multicenter European series of 918 patients. They reported 29 patients (3.2%) with ectopic ACTH secretion, and none was from a colorectal source.

Table 2 presents the results of our literature review, which retrieved 18 previously reported cases of ectopic Cushing syndrome associated with a NET of colorectal origin. Data completeness and quality among these reports were variable. Among those that reported age at diagnosis, the median was 54.5 years (range, 24-74 years), with 55.6% (10/18) of cases occurring after the fifth decade. Gender distribution was equal. Fifteen reports specified the site of origin within the colon, with the most common being sigmoid (n = 6), followed by the ascending colon (n = 4). Left-sided lesions were slightly more common (n = 8) than right-sided lesions. More than

Figure 3 Colonoscopy Revealing Ulcerated Cecal Mass (A and B)
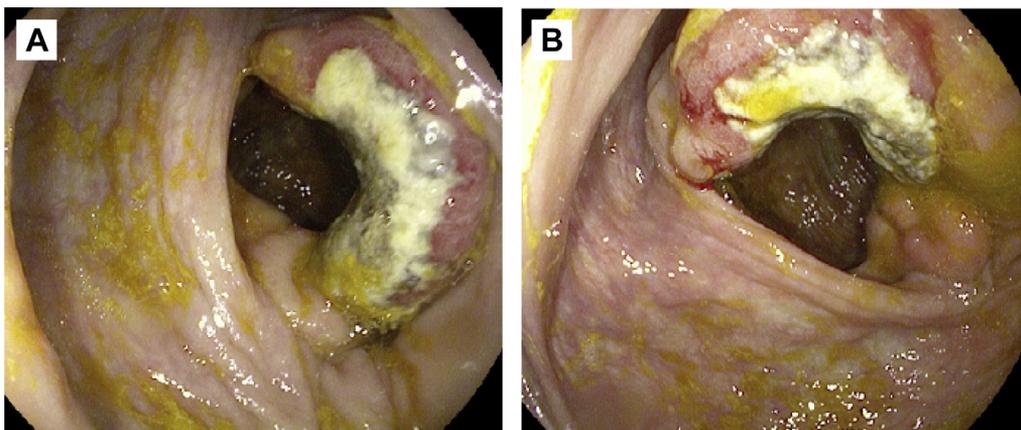
Figure 4 Histologic Examinations of Cecal Mass. (A) Colonic Mucosa Was Infiltrated by Sheets of Malignant Cells (H&E; Original Magnification, 100×). (B) High Magnification Revealed Large Malignant Cells, Many With Prominent Nucleoli (H&E; Original Magnification, 400×). (C) Separate Tissue Fragment in Tumor Biopsy Sample Demonstrated Neoplastic Glandular (Adenomatous) Component in Tumor (H&E; Original Magnification, 40×). (D) Tumor Cells Were Strongly and Diffusely Positive for Neuroendocrine Marker Synaptophysin (Synaptophysin IHC; Original Magnification, 100×). (E) Proliferation Marker Ki-67 Was Positive in Over 90% of Malignant Cells (Ki-67 IHC; Original Magnification, 100×). (F) Tumor Was Negative for ACTH (ACTH IHC; Original Magnification, 100×)
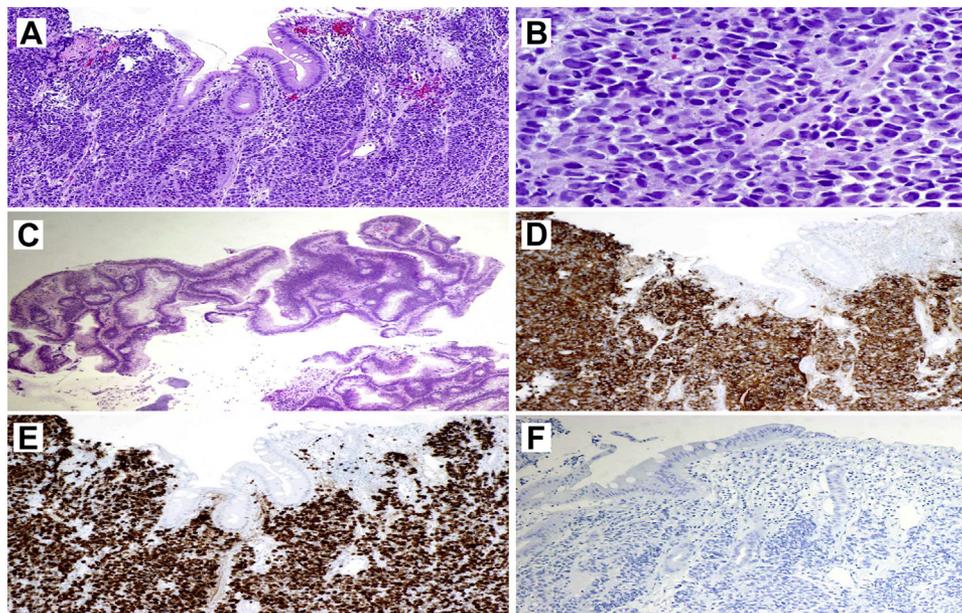
Abbreviations: ACTH = adrenocorticotropic hormone; H&E = hematoxylin and eosin; IHC = immunohistochemistry.

two thirds of patients had documented liver metastases (13/18, 68.4%). Among those reporting outcomes, the unadjusted mortality rate was 77.7%, with a median overall survival from presentation of 63 days (range, 17-380 days).

ACTH was detected by IHC in the primary tumor and/or metastatic lesion in 8 (61.5%) of 13 cases (Table 2). Interestingly, ACTH could not be detected by IHC in the tumor biopsy sample of our patient. The ACTH IHC protocol used was developed and validated for pituitary tumors, but theoretically the antibody should detect ACTH of any origin as long as the peptide structure is intact. Sampling may have been an issue, as the sample was small and there can be variable expression of antigens within tumors assessed by IHC. Furthermore, IHC is not a completely sensitive or specific test for the functional status of a NET; nor is it essential for the diagnosis of functionality.[32] Kamp et al[30] noted that ACTH IHC was positive in 13 of 18 patients in their series of ectopic ACTH associated with a variety of NETs. Isidori et al[22] also reported a negative ACTH stain in 41.6% of their bronchial NET-associated Cushing syndrome cases.

An interesting observation is the variable histologic classification of ACTH producing colonic tumors with a paucity of pure NETs represented (Table 2). The list includes only one well-differentiated (low grade) NET.[26] There is 1 NET of unclear grade[17] and 3 poorly differentiated NECs (large-cell or small-cell NECs).[13,23,25] There are a striking number of tumors with mixed endocrine or

completely nonneuroendocrine differentiation. Six of 18 cases were reported as having mixed differentiation including a neuroendocrine component,[10,16,18,19,24,25] and 7 cases have no reported neuroendocrine component at all,[11,12,15,20,21,23] with 6 of them reported to be pure adenocarcinomas, which would not be expected to be associated with an endocrinopathy due to ectopic hormone production. Some of these of the cases may have had limited pathologic sampling, and they also may have predated the widespread availability of immunohistochemical markers for neuroendocrine differentiation. This raises the possibility that some of these reported "adenocarcinomas" might have had a neuroendocrine component that was not identified pathologically at the time of reporting. Our case did not have an adenocarcinoma component in the biopsy sample, but we suspect that it was a mixed glandular and NET, based on the presence of an adenomatous component. The findings in our case and the literature review suggest that ACTH secretion from a colonic tumor might be more common in mixed glandular and NETs, including MANEC than pure NETs.

The finding of a *BRAF V600E* mutation is concordant with previous work observing a high frequency of this mutation in poorly differentiated colorectal NECs, with one study documenting a 59% *BRAF V600E* mutation detection rate in colorectal NEC compared to a 5% detection rate for poorly differentiated conventional adenocarcinoma.[33] *BRAF V600E* mutations were documented in both pure colorectal NECs and in those associated with an adenocarcinoma

| Table 2 | Clinical and Pathologic Characteristics of ACTH-Secreting Colorectal NETs Reported in Literature |

Case No.	Study (Year)	Age, Gender	Clinical Presentation	Site of Primary Disease	Metastasis	Pathology	Tissue Sample	Neuroendocrine Stains Reported and Result	ACTH Detected in Tumor Tissue	Death From Disease	Time From Presentation to Death From Disease
1	Miura (1970)[10]	52, M	Melena, hyperpigmentation, hepatomegaly, hyperglycemia, hypokalemia, alkalosis	Ascending	Liver, diaphragm, omentum, duodenum	Mixed small-cell carcinoma and adenocarcinoma, moderately differentiated	Autopsy sample of tumor	Argentaffin negative	RIA positive	Yes	17 days
2	Balsam (1972)[11]	60, M	BRBPR, proximal myopathy, hyperglycemia, hypertension, hepatomegaly, palpable LLQ mass, hypokalemic alkalosis	Sigmoid	Liver	Adenocarcinoma, moderately differentiated	Autopsy sample of tumor	Argentaffin negative	RIA positive	Yes	5 weeks
3	Suda (1977)[12]	45, F	Weight loss, peripheral edema, amenorrhea	Transverse	Liver	Adenocarcinoma, not graded	Autopsy sample of tumor	None	RIA positive	Yes	3 months
4	Stambaugh (1978)[13]	72, M	Unknown	Ascending	Liver, Bone	Adenocarcinoma, poorly differentiated	Surgical resection, biopsy sample of liver and bone	None	RIA positive	Yes	10 weeks
5	Remick (1979)[14]	74, M	Hyperglycemia, confusion, hypokalemic alkalosis, Cushingoid	Anorectal	Bone	Small-cell carcinoma	Surgical resection	None	Not reported	Yes	12.5 months
6	Coates (1986)[15]	33, F	NR	colon, location unclear	NR	Undifferentiated carcinoma	Colon biopsy sample	Neuron-specific enolase negative	Negative ACTH IHC	Yes	1 month
7	Sterling (1993)[16]	25, M	Hypertension, BRBPR, hypokalemia, hepatomegaly	Anorectal	Liver	Mixed squamous and small-cell carcinoma	Anorectal biopsy sample	Chromogranin positive	Positive ACTH IHC	NR	NR
8	Beales (1994)[17]	69, F	Ventricular arrhythmias, hypokalemia, malaise, alkalosis	Ascending	Liver	NET, grade unclear, unclear if NET or small-cell/large-cell NEC	Autopsy sample of tumor	Neuron-specific enolase positive	Positive ACTH IHC	Yes	5 weeks
9	Anthoney (1995)[18]	57, F	Arthritis, hepatomegaly, rectal bleeding, jaundice.	Sigmoid	Liver	Mixed: predominantly moderately differentiated adenocarcinoma with component of neuroendocrine differentiation	Sigmoid biopsy sample	None	Negative ACTH IHC	Yes	~ 5 months
10	Onishi (1996)[19]	62, F	Depression, hypertension, hyperkalemic alkalosis, weight gain, occult gastrointestinal bleeding	Ascending	Liver	Mixed: predominantly undifferentiated carcinoma with areas of adenocarcinoma, squamous, and NEC differentiation	Surgical resection	None	RIA and ACTH IHC positive	Yes	3 months
11	Eggenberger (1999)[20]	51, F	Hyperglycemia, ascites, hepatomegaly, pleural effusion, hypokalemia	Sigmoid	Liver, spleen pleurae, peritoneum	Adenocarcinoma, moderately differentiated	Surgical resection	None	Negative ACTH IHC	Yes	19 months

Table 2	Continued									
Case No.	Study (Year)	Age, Gender	Clinical Presentation	Site of Primary Disease	Metastasis	Pathology	Tissue Sample	Neuroendocrine Stains Reported and Result	ACTH Detected in Tumor Tissue	Death From Disease	Time From Presentation to Death From Disease
12	Gómez de la Torre (2002)[21]	74, M	Diarrhea, anorexia, hypertension, hypokalemic alkalosis, osteoporosis	Sigmoid	Liver	Adenocarcinoma, not graded, arising in villous adenoma	Sigmoid colon biopsy sample	Neuron-specific enolase negative	Negative ACTH IHC	Yes	2 months
13,14	Isidori (2006)[22]	NR	NR	Colon, site not specified	NR	Small-cell carcinoma (both)	Tissue sample done, but not clear if from biopsy or surgery	Chromogranin positive in both tumors	Positive ACTH IHC in first case; negative ACTH IHC in second case	NR	NR
15	Sehgal (2010)[23]	35, F	Abdominal pain, weight gain, peripheral edema, acne, hirsutism, hyperpigmentation, hypertension, Cushingoid, hypokalemia	Cecum	Liver	Adenocarcinoma, poorly differentiated	Surgical resection	None	Positive ACTH IHC	Yes	NR
16	Baldvinsdottir (2014)[24]	72, F	Cushingoid appearance, hypertension, proximal muscle weakness, hyperglycemia, hypokalemia, peripheral edema	Sigmoid	Liver, lymph nodes, lungs	Mixed: adenocarcinoma (not graded) and small-cell carcinoma	Autopsy sample of tumor	Synaptophysin and chromogranin positive in small-cell carcinoma component	Positive ACTH IHC (5% of cells)	Yes	28 days
17	Fujimoto (2016)[25]	48, F	Abdominal distention, low back pain, hypertension, proximal myopathy, palpable abdominal mass, pigmentation, bilateral edema, weight loss, anemia	Sigmoid	Liver, pancreas	NEC, poorly differentiated, mixed small- and large-cell carcinoma	Sigmoid colon biopsy and autopsy samples	Synaptophysin and CD56 positive	Positive ACTH IHC (large cell component only)	Yes	145 days
18	Streuli (in press)[26]	24, M	Weight gain, Cushingoid, hypertension, striae, acne, proximal weakness	Cecum	none	Well-differentiated NET (Ki-67 index = 4%)	Surgical resection	None	Positive ACTH IHC (focal); CRH IHC strongly positive	No	Not applicable

Abbreviations: ACTH = adrenocorticotropic hormone; BRBPR = bright red blood per rectum; CRH = corticosterone-releasing hormone; IHC = immunohistochemistry; LLQ = left lower quadrant; NEC = neuroendocrine carcinoma; NET = neuroendocrine tumor; NR = not reported; RIA = radioimmunoassay.

component (60% and 82%, respectively), suggesting that this mutation is more common in colon cancer with neuroendocrine differentiation, but this may not be helpful in differentiating pure NEC from MANEC. *BRAF V600E* mutations have prognostic and therapeutic implications for typical colorectal and other carcinomas, but data in colorectal NEC are scant.[34,35] The R273 mutation in *TP53* is a common finding in a wide range of malignancies, including those of the central nervous system, digestive tract, and hematopoietic and lymphoid systems, and is of uncertain clinical significance. The tumor in our case was microsatellite stable, which is similar to the trend in the study by Olevian et al,[33] which documented that 93% of NECs tested were microsatellite stable by PCR or had intact mismatch repair proteins by IHC.

Unlike more common malignancies, functional NETs often present with secretory symptomatology that can develop insidiously before the diagnosis of malignancy and can be associated with significant impact on quality of life and health. The classic example is that of the carcinoid syndrome, typically associated with NETs of small intestinal origin and with symptoms that can predate a diagnosis of malignancy by years. Conversely, our case and review of the available literature suggest that symptoms associated with ACTH-secreting NETs of colorectal origin can develop relatively acutely and progress quickly, with devastating impact on overall health and very poor survival outcomes compared to other NET subtypes or functional syndromes.

Management of NET-associated ectopic ACTH secretion, as in other hormone-secretory syndromes, primarily revolves around source control and addressing the clinical burden associated with excess cortisol.[36,37] Hypercortisolism can be acutely addressed with steroidogenesis inhibitors, such as metyrapone, ketoconazole, mitotane, and etomidate.[37,38] Patients should be carefully monitored in regard to speed and depth of cortisol reduction, as relative adrenal insufficiency can arise and lead to worsening symptoms, as demonstrated in our case. When medical therapy is insufficient, bilateral adrenalectomy may be an option, but this should be discussed in the context of a patient's overall disease and functional status as well as his or her expressed wishes.[30,38] The role of somatostatin analogs in combination with steroid inhibitors is unclear.[37] Surgical excision of a solitary ACTH-secreting primary lesion can be potentially curative. Isidori et al[22] reported 12 cases of unifocal NETs from various primary locations associated with Cushing syndrome and observed complete remission in 83% after excision. A larger series, including all clinical stages of NET-associated ectopic ACTH, reported a complete remission rate of less than 50%.[39]

Conclusion

In a retrospective multicenter study of NET-associated Cushing syndrome, independent predictors of mortality included severity of hypercortisolism ($P < .02$), hypokalemia ($P = .001$), diabetes mellitus ($P = .0146$), and presence of distant metastases ($P < .001$).[31] Prognosis for ACTH-secreting colonic NETs is poor, with short overall survival from diagnosis. Early diagnosis of ectopic ACTH secretion and appropriate treatment of the endocrinopathy may affect outcomes and permit surgical consideration for appropriately selected patients. The findings in our case and the literature review suggest that ACTH secretion from a colonic tumor might be more common in mixed glandular and NETs, including MANEC, than pure NETs. New molecular diagnostic technologies such as NGS may be important to identify potential novel therapeutic avenues for this devastating diagnosis with the aim of improving outcomes.

Clinical Practice Points

- ACTH-secreting neuroendocrine tumors of colonic origin are rare clinical entities, with limited clinical data previously reported.
- We describe a case of ectopic Cushing syndrome due to an ACTH-secreting neuroendocrine tumor of the cecum.
- NGS identified mutations in *BRAF V600E* and *TP53*.
- A literature review produced only 18 other reported cases of this condition. Among those cases reporting outcomes, the unadjusted mortality rate was 77.7%, with a median overall survival from clinical presentation of 63 days (range, 17-380 days).
- NGS may be important to identify novel therapeutic options for this devastating disease with the aim of improving outcomes.

Disclosure

The authors have stated that they have no conflict of interest.

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