Case Report

Genomic profiling of high-grade large-cell neuroendocrine carcinoma of the colon

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Abstract: High-grade neuroendocrine carcinoma (HGNEC) of the colon is a rare and aggressive cancer that has a poor prognosis. Currently no standard treatment exists, and published case series report an overall survival of approximately one year with treatment. Typically patients receive treatment similar to that recommended for small-cell lung cancer, extrapolating from the similarity in cancer biology. Here we report a case of HGNEC of the colon with genomic profiling that identified a *KRAS* G12D mutation and a *PI3K* mutation that has not yet been reported in the literature for this tumor type.

Keywords: Colon cancer; genomic profiling; neuroendocrine carcinoma

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Case presentation

A 70-year-old man with an unremarkable medical history and no history of smoking presented to his primary care physician with intermittent abdominal cramping, mild abdominal bloating, and a dry cough that had begun approximately 2 months prior. Four months later, the patient developed persistent abdominal pain and dyspepsia. His Eastern Cooperative Oncology Group (ECOG) performance score at this time was 0. His family history revealed that his mother had lung cancer of an uncertain etiology. A subsequent colonoscopy showed a flat ulcerated mass of the colon at the hepatic flexure. Pathologic examination revealed a tubulovillous adenoma with high-grade neuroendocrine carcinoma (HGNEC). A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed a mass in the cecum measuring 5.3×3.7 cm and several small, suspicious regional mesenteric lymph nodes. Magnetic resonance imaging (MRI) of the brain was unremarkable.

The patient underwent a right hemicolectomy with a terminal ileum resection and lymph node and omentum sampling. The resulting pathologic examination revealed a 6.0-cm pT4a tumor that was described as a high-grade carcinoma with a syncytial growth pattern, a high nucleus/cytoplasm (N/C) ratio, numerous mitoses and apoptotic cells, and large nuclei with coarse chromatin but without prominent nucleoli. The Ki-67 proliferation index was reported to be 90%. Cells showed uniform granular cytoplasmic positivity for synaptophysin (weak to intermediate in >75% of the cells), but no reactivity to chromogranin. Thyroid transcription factor-1 (TTF-1) expression was negative, and there was no loss of mismatch repair antigen expression (MLH1, MSH2, MSH6, or PMS2). All surgical margins were negative (R0 resection). There was no perineural invasion, but lymphovascular invasion was present. None of the 25 lymph nodes sampled had malignant involvement. Omental sampling of two nodules revealed no evidence of malignancy. The results of microsatellite instability testing were negative. Final pathologic diagnosis was stage T4aN0M0 large-cell high-grade neuroendocrine carcinoma of the colon.

The patient was treated with adjuvant carboplatin and etoposide and completed four cycles of therapy without dose adjustment, but his third cycle was delayed because he developed atrial flutter. Three months after completing chemotherapy, restaging CT scans revealed a new 3.9-cm

liver mass and new nodules in the peritoneum. Liver mass biopsy confirmed metastatic disease. At this time, tissue from the original tumor was sent for molecular profiling.

Molecular profiling with a PathGroup SmartGenomics™ (Brentwood, TN, USA) Cytogenomic Array revealed a complex karyotype that included the loss of 1, 2p, 3p, 4, 9, 11q, 15q, 16p, 16q, 21, 22, and Y; and the gain of 8, 12, 13, 14, 16p, 16q, 17, 18, 19, 20p, and 20q. Next-Generation Sequencing performed by AKESOgen (Norcross, GA, USA) using a thirty-five gene panel revealed a *KRAS* G12D point mutation and a *PIK3* R1 frameshift deletion mutation.

The patient was then started on single-agent topotecan every 2 weeks, but he had evidence of progression after three cycles. At this time he presented to our institution for a second opinion. He declined pursuit of a clinical trial and was started on single-agent paclitaxel because of the reported success in relapsed refractory small cell lung cancer (1,2). The patient died 14 months after his initial diagnosis.

Discussion

Extrapulmonary, high-grade neuroendocrine carcinomas are an uncommon subtype of carcinoma and are clinically distinct from the more common, well-differentiated, low- or intermediate-grade neuroendocrine tumors. High-grade NECs (HGNECs) are found primarily in the lung but are also rarely found in other locations, including the cervix, kidney, bladder, prostate, pharynx, larynx, colon, rectum, esophagus, gallbladder, and stomach (3-5). HGNECs account for less than 1% of all colorectal cancers, tend to have an aggressive course, and are associated with a poor prognosis. Clinically these tumors behave in a pattern similar to small-cell carcinoma or large-cell neuroendocrine carcinoma of the lung (3). The largest case series, which contained 126 HGNECs of the colon and rectum and included those with localized disease and metastatic disease at presentation, reported a median overall survival (OS) of 13.2 months and a 3-year OS of 8.7% for all patients (6). This was consistent with prior case series reported over the past two decades (7-9).

The classification of low, intermediate, and high-grade neuroendocrine tumors is determined by the mitotic rate or proliferation index. High-grade tumors of the gastrointestinal tract are those with a high mitotic rate, which is defined as >20 mitotic figures per ten high power fields, or a Ki-67 proliferation index >20% (10,11). Tumors are classified as small or large cell; however, there appears to be no difference in prognosis between the two subtypes (12).

Advanced molecular profiling and next-generation, or high-throughput, sequencing is increasingly used for the management of oncology patients. The results of these tests can reveal potential therapeutic targets and are helpful in evaluating patients' eligibility for potential clinical trials.

In the above case, a *KRAS* G12D mutation was detected. This mutation has only been reported in one retrospective case series of colonic neuroendocrine carcinomas that described two patients; however, there is no mention of treatment or response (13). Because our patient had the *KRAS* G12D mutation, he would not be expected to respond to EGFR-targeted therapy, but this is based on extrapolation from studies on colonic adenocarcinoma.

Genetic testing also found that our patient had a frameshift deletion mutation in the *PI3K* gene. To our knowledge, this genetic alteration has not previously been reported in HGNEC of the colon. Tumors with PI3K mutations are currently being studied in clinical trials utilizing PI3K and mTOR inhibitors. The RADIANT-3 trial has shown promising therapeutic activity of mTOR inhibitors in low- to moderately-differentiated advanced pancreatic neuroendocrine tumors; however, this trial did not enroll patients with high-grade disease. Whole-exome sequencing has shown that 6% of small-cell lung cancers have mutations in *PIK3CA*, and 36% of tumors have mutations in molecules in the mTOR pathway, including PIK3CA, PTEN (4%), AKT2 (9%), AKT3 (4%), RICTOR (9%), and mTOR (4%) (14). Two phase II trials of mTOR inhibitors in patients with previously treated small-cell lung cancer were conducted based on identified *PIK3CA* mutations; however, both trials showed minimal single agent activity (15,16).

Due the aggressive behavior of these tumors, consideration should be given to adjuvant chemotherapy with, for example, cisplatin or carboplatin with etoposide. This is based on data from adjuvant treatment of HGNEC of the lung, i.e., small-cell lung cancer (17,18). However, given its rarity, there are no clinical trials for adjuvant chemotherapy following resection of HGNEC of the colon. There are also no radiation guidelines for primary site or prophylactic cranial irradiation, although data suggest a lower incidence of central nervous system metastases with extrapulmonary HGNEC when radiation is used (4). With few guidelines for the treatment of extrapulmonary HGNEC, genomic testing may provide potential therapeutic options and guide treatment strategies.

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Footnote

Conflicts of Interest: We certify that we have no financial affiliation/interest.

References

1. Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998;77:347-51.
2. Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006;26:777-81.
3. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas 2010;39:799-800.
4. Cicin I, Karagol H, Uzunoglu S, et al. Extrapulmonary small-cell carcinoma compared with small-cell lung carcinoma: a retrospective single-center study. Cancer 2007;110:1068-76.
5. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: A Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol 2011;122:190-8.
6. Smith JD, Reidy DL, Goodman KA, et al. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. Ann Surg Oncol 2014;21:2956-62.
7. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Ann Oncol 2013;24:152-60.
8. Bernick PE, Klimstra DS, Shia J, et al. Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum 2004;47:163-9.
9. Staren ED, Gould VE, Warren WH, et al. Neuroendocrine carcinomas of the colon and rectum: a clinicopathologic evaluation. Surgery 1988;104:1080-9.
10. Rindi G, Klöppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007;451:757-62.
11. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013;42:557-77.
12. Shia J, Tang LH, Weiser MR, et al. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol 2008;32:719-31.
13. Karkouche R, Bachet JB, Sandrini J, et al. Colorectal neuroendocrine carcinomas and adenocarcinomas share oncogenic pathways. A clinico-pathologic study of 12 cases. Eur J Gastroenterol Hepatol 2012;24:1430-7.
14. Umemura S, Mimaki S, Makinoshima H, et al. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol 2014;9:1324-31.
15. Pandya KJ, Dahlberg S, Hidalgo M, et al. A randomized, phase II trial of two dose levels of temsirolimus (CCI-779) in patients with extensive-stage small-cell lung cancer who have responding or stable disease after induction chemotherapy: a trial of the Eastern Cooperative Oncology Group (E1500). J Thorac Oncol 2007;2:1036-41.
16. Tarhini A, Kotsakis A, Gooding W, et al. Phase II study of everolimus (RAD001) in previously treated small cell lung cancer. Clin Cancer Res 2010;16:5900-7.
17. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-71.
18. Simon GR, Turrisi A, American College of Chest Physicians. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:324S-39S.

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