CASE REPORT

Mixed endocrine-glandular carcinoma of cecum

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Summary Colorectal mixed endocrine-glandular neoplasms, a subtype of neuroendocrine tumors, are mainly diagnosed based on pathological characterization. The rarity and unusual presentation of mixed endocrine tumors makes their prognosis relatively poor, and an optimal management strategy for the tumors has yet to be devised. Here, we report a case of cecal mixed adenocarcinoma and neuroendocrine carcinoma with ileal tumor seeding, lymph nodes, and left iliac crest metastasis. After undergoing right hemicolectomy, target therapy, chemotherapy, and radiotherapy for adenocarcinoma, the patient survived for more than 15 months and remains alive at the time of writing.

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1. Introduction

Colorectal mixed endocrine-glandular neoplasms, which are rare and heterogeneous in composition, are a type of neuroendocrine tumor. These tumors are composed of at least two populations and account for at least 30% of all tumor cases. Because the prognosis of mixed endocrine-glandular neoplasms of the colon and rectum is poor, diagnosing these tumors immediately is crucial for enabling patients to benefit from treatment with alternative cytotoxic chemotherapeutic agents.

2. Case report

A 52-year-old woman with no major systemic disease was admitted to an emergency room because of right lower abdominal pain for 3 days. The patient history revealed that she experienced left iliac pain for approximately 3 months and right lower abdominal pain 3 days before entering the emergency room. In our emergency room, epigastric tenderness was noted. Blood test results were: white blood cell count, $11.1 \times 10^9/L$; neutrophils, 82.4%; C-reactive protein, 0.37 mg/dL; glutamyl oxaloacetic transaminase, 26 U/L; Na, 139 meq/L; and K, 4.3 meq/L. An X-
ray of the kidney, ureter, and bladder showed mild increased bowel gas in the central abdomen. An abdominal sonogram revealed the presence of ascites and suggested diverticulitis or appendicitis. Abdominal computed tomography revealed an irregular eccentric mass, with dimensions of approximately 4.3 cm × 3.2 cm, in the cecum with ileocecal valve involvement and blurring of the surrounding pericolic fat plane, metastatic lymphadenopathies in the mesenteric cavity and intercavo-aortic space with the largest lymphadenopathy being approximately 1.6 cm × 2.4 cm, and a suspicious osteolytic lesion in the left iliac crest. The patient then received right hemicolectomy, and a polypoid tumor, approximately 6 cm × 5 cm in size, was detected along with near obstruction in the cecum, several enlarged and hard lymph nodes in the mesenteric root, dilatation of the small intestine, and tumor seeding in the terminal ileum. Pathology revealed a mixed adenocarcinoma and neuroendocrine tumor (Fig. 1) with terminal ileum seeding and regional lymph node metastasis (8/12), including angiolymphatic and neural/perineural invasion. The neuroendocrine tumor was classified as G2 grade, and the adencarcinomatous parts were poorly differentiated. An immunohistochemical study showed positive staining for the epidermal growth factor receptor (1+, 30%), cytokeratin (Fig. 2), synaptophysin (Fig. 3), and Ki-67 (15%). The American Joint Committee on Cancer 7 staging was pT3N1M1. In addition, a whole-body bone scan performed using technetium-99m methylene diophosphate revealed bone metastasis through the left anterior iliac crest to the upper aspect of the left acetabulum. After the operation, a full course (1 course 2 weeks; 12 courses) of target therapy and chemotherapy using bevacizumab–FOLFIRI was administered, and radiotherapy (3000 cGy/10 frs) was administered to the left iliac crest. Thereafter, the patient was followed up at our outpatient department regularly and received no medication.

3. Discussion

Neuroendocrine cells are distributed throughout the human body, including organs such as the gastrointestinal tract, pancreas, lung, thyroid, and adrenal glands. The largest population of neuroendocrine cells is located in the gastrointestinal tract. However, neuroendocrine tumors of the colon and rectum are rare. The reported incidence of these tumors is between 0.1% and 3.9% of all colorectal malignancies.3

Like primary colorectal adenocarcinomas, most colorectal neuroendocrine tumors are located in the proximal colon.7 In addition, data showed that the frequency of combined adenocarcinoma and neuroendocrine tumors in the proximal colon is high. In accordance with previous reports, our patient’s combined adenocarcinoma and neuroendocrine tumor was located in the cecum. Neuroendocrine tumors behave aggressively and are associated with a prognosis less favorable than that of conventional adenocarcinomas at the same stage; moreover, 80% of the tumors exhibit distant metastases at the time of diagnosis.6 Similar signs were observed in our patient, who exhibited left iliac crest metastasis and lymph node and terminal ileum involvement at the time of diagnosis.
According to the 2000 World Health Organization classification, gastroenteropancreatic neuroendocrine tumors are classified as well-differentiated neuroendocrine tumors, well-differentiated neuroendocrine carcinomas, and poorly-differentiated neuroendocrine carcinomas (small cell carcinomas). However, in 2010, the World Health Organization reclassified gastroenteropancreatic neuroendocrine tumors into neuroendocrine tumors G1, G2, and G3 (large cell type or small cell type). Among these categories, only G3 is neuroendocrine carcinoma.

The systematic application of immunohistochemical techniques to the study of tumors has led to the recognition that neuroendocrine cells occur rather frequently in exocrine neoplasms of the gut. The spectrum of combinations of exocrine and neuroendocrine components is wide, ranging from adenomas or carcinomas with interspersed neuroendocrine cells at one extreme to classical neuroendocrine tumors with a focal exocrine component at the other extreme. In addition, both exocrine and neuroendocrine components can have different morphological features. The features of exocrine components range from adenomas to adenocarcinomas differentiated to various degrees, and the features of neuroendocrine components range from well-differentiated to poorly-differentiated neuroendocrine tumors. Usually, the neuroendocrine component is well-differentiated, and it is easily recognized based on its clear histological features and verified by performing immunodetection by using specific neuroendocrine markers, including chromogranin, synaptophysin, neuron-specific enolase, prostatic acid phosphatase, somatostatin, 5-HT, Ki67, and CD56. However, if the neuroendocrine component is poorly differentiated, then the demonstration of neuroendocrine markers is required to confirm the diagnosis. Because endocrine cells are often inconspicuous and their quantity is not substantial, the diagnosis is made only after the tumors are stained with neuroendocrine cell markers. Our patient had positive neuroendocrine markers, including synaptophysin and Ki67.

Although a wide range of combinations of neuroendocrine and exocrine components are frequently observed in routine practice, mixed exocrine—neuroendocrine carcinomas, recently renamed mixed adenoneuroendocrine carcinomas (MANECs), are rare. By definition, this type of neoplasms contains the two components, each representing at least 30% of the lesion. The patient in this report represented a case of mixed adenocarcinoma and neuroendocrine tumor G2, which may also be described as a mixed adenocarcinoma—neuroendocrine tumor (MANET) or MANEC containing a well-differentiated neuroendocrine tumor component according to a previous study.

Because of the rarity and unusual presentation of MANECs and MANETs, an optimal strategy for managing these tumors has yet to be devised. A previous study recommended that extrapulmonary neuroendocrine carcinomas, particularly small-cell carcinomas of the colon and rectum, be treated with cytotoxic chemotherapeutic regimens similar to those used for small-cell carcinoma of the lung. In a small-scale serial trial evaluating the treatment of metastatic anaplastic neuroendocrine carcinomas of the colon and rectum, the combination of cisplatin and etoposide was associated with a 67% response rate and a median survival of 19 months. However, the efficacy of this chemotherapy regimen in treating colorectal neuroendocrine carcinomas has yet to be validated. According to the literature, the median survival period for patients with neuroendocrine carcinomas of the colon and rectum is 5–11 months, and 1-year survival rates have been reported to be 10–15%. Generally, the more aggressive component of MANECs must be considered before determining a treatment regimen for these patients. It has been suggested that mixed tumors containing a well-differentiated neuroendocrine component and an adenocarcinoma component should be treated in a manner similar to that used to treat adenocarcinoma. MANECs containing a poorly-differentiated neuroendocrine component must be treated as poorly-differentiated neuroendocrine carcinomas. Our patient had a mixed neuroendocrine tumor (G2) and poorly differentiated adenocarcinoma of the cecum with left iliac crest metastasis and lymph node and terminal ileum involvement. Therefore, she was treated as if she had colorectal adenocarcinoma with bone metastasis. After undergoing target therapy using bevacizumab (Avastin), chemotherapy using FOLFIRI, and radiotherapy of the left iliac crest, she has survived for more than 15 months.

References


