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A case report of colon neuroendocrine carcinoma complicated with bone metastasis

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Abstract: Most of the previous literature on neuroendocrine carcinoma mainly comes from the study of small cell lung cancer, and the research data of colon neuroendocrine carcinoma is very little. This paper reports a case of colon neuroendocrine carcinoma complicated with bone metastasis. The patient complained of right abdominal pain and distension without obvious cause, accompanied by nausea, vomiting, and reduced frequency of stool. The initial colonoscopy and pathological examination indicated poorly differentiated ascending colon cancer. Neuroendocrine carcinoma of the colon (NEC) with bone metastasis was diagnosed after a further pathological consultation.

Keywords: Neuroendocrine carcinoma; Tumor metastasis; Immunohistochemistry; diagnosis.

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1. Introduction

Neuroendocrine tumors refer to tumors originating from neuroendocrine cells and peptideric neurons, which can occur in various tissues and organs throughout the body, among which gastrointestinal and pancreatic nerve cell endocrine tumors are the most common [1]. Rare cases of ascending colon with bone metastasis have been reported. The prognosis varies depending on the location and type of primary tumor. According to the SEER database analysis of neuroendocrine carcinoma, the median survival time of patients with primary colon neuroendocrine carcinoma is only 5.9 months, which is shorter than that of primary lung neuroendocrine carcinoma (7.6 months) [2-3]. Moreover, in the SEER database of colorectal neuroendocrine carcinoma, the 5-year survival rate of patients with metastasis is only 6% [4]. Therefore, it is very important to identify the location of the primary tumor and determine the occurrence of metastasis in the primary tumor for the diagnosis and prognosis of neuroendocrine tumors. This paper reports a case admitted to the Department of Surgery of our hospital. The primary diagnosis was ascending colon cancer complicated with bone metastasis, and the postoperative pathological diagnosis was colon neuroendocrine carcinoma.

A 70-year-old female patient complained of abdominal pain and distension for more than 2 months. The patient developed right side abdominal pain and distension, accompanied by nausea and vomiting, and reduced frequency of bowel movements more than 2 months ago without obvious inducement, about once every 3 days. Not accompanied by cold and fever, acid belching, hematemesis, black stool, chest tightness, chest pain, cough and sputum, frequent urination, dizziness and fatigue. 5 days ago, he underwent colonoscopy and pathologic examination in a local hospital, indicating elevated colon cancer and poor differentiation. PET-CT: Increased metabolism of the ascending colon mass was considered as intestinal cancer, with enlargement of the right pelvic wall, retroperitoneum, right mesentery, greater omentum, hepatogastric space, and posterior mediastinal para-esophageal lymph nodes, and increased metabolism was considered as metastasis. Multiple bone destruction in the whole body with increased metabolism was considered bone metastasis, and incomplete intestinal obstruction was considered cT4N3M1IV. Admitted to hospital for further treatment. Since onset, the patient has had poor appetite, normal urination, stool as described above, and weight loss of 7.5kg. She has no family history of tumor. After admission for physical examination, the abdomen was flat and soft, without gastrointestinal type and peristaltic wave, and the abdominal muscle was soft. A tough mass about 5cmx6cm in size could be found in the right lower abdomen, with clear boundary, reasonable motion, and no abdominal tenderness or rebound pain. The liver and spleen were not touched, the bowel sounds were 2-3 times/min, and there was no edema in both lower limbs. Auxiliary examination: The local hospital performed colonoscopy and pathological examination, indicating elevated colon cancer, poor differentiation.PET-CT: The increased metabolism of the ascending colon mass was considered as intestinal cancer, accompanied by enlargement of the right pelvic wall, retroperitoneum, right mesentery, greater omentum, hepatogastric space, and posterior mediastinal para-esophageal lymph nodes, and increased metabolism was considered as metastasis. Multiple bone destruction in the whole body with

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increased metabolism was considered bone metastasis, and incomplete intestinal obstruction was considered cT4N3M1IV. Laboratory test: CEA19.76ng/ml; CA19-94582.15U/ml, NSE18.85ng/ml. Improved pathological consultation: (ascending colon biopsy) malignant tumor, combined with morphology and immunohistochemical results, consistent with neuroendocrine carcinoma (NEC). Immunohistochemical examination: tumor cells CK (+), CK8/18 (+), Syn (+), CgA (local focal cell cytoplasmic spot +), CD56 (+), INSM1 (+), KI67 (hot spot about 70%), SSTR2 (-),P53 (+, mutant), RB (+), HER2 (0),MLH1 (+),MSH2 (+),MSH6 (+),PMS2 (+),CD117 (-),PD-L1(Neg) (-),PD-L1(22C3) (CPS about 20) gene test: Somatic mutations (wild type) were detected in exons 2, 3 and 4 of KRAS and NRAS genes in the samples. V600E mutation (mutant) was detected in the BRAF gene in the sample.SRI: The thickening of the intestinal wall of the terminal ileum, ileocecal part and ascending colon showed mild uptake of DOTATATE, which was consistent with the changes of neuroendocrine carcinoma in combination with pathology and PET-CT of an external hospital (18F-FDG), and multiple enlarged lymph nodes around the lesion, right mesentery and retroperitoneum, paraaorta, and right pelvic cavity. Some of them showed mild uptake of DOTATATE, and metastasis was considered. C4, T5, T9, L3, local DOTATATE uptake in the right first costal head, left acetabulum, and right sciatic bone was mild, and multiple bone metastases were considered. Treatment regimen: octreotide acetate microspheres 30mg subcutaneous, EP regimen: cisplatin + etoposide.

2. Discussion

Neuroendocrine tumors are tumors originating from neuroendocrine cells and peptide-capable neurons, which can occur in any tissues and organs of the body, and the gastrointestinal and pancreatic neuroendocrine tumors (GEP-NEN) are the most common. According to the latest classification and nomenclature of digestive system neuroendocrine tumors by WHO (2019), neuroendocrine tumors (NEN) can be classified into highly differentiated neuroendocrine tumors (NET) based on the nuclear mitotic image and Ki-67 index of tumor cells. Poorly differentiated neuroendocrine carcinoma (NEC) and mixed neuroendocrino-non-neuroendocrine tumor (MiNEN) [5-6]. MiNEN is a mixed epithelial tumor composed of neuroendocrine and non-neuroendocrine components with at least 30% of each of the two components. According to histological morphology, Mi-NEN can be divided into three types: mixed cancer, collision cancer and duplex cancer [7]. Mixed cancer refers to two components mixed together, the two have no clear dividing line; Collision cancer is when the two components are adjacent but clearly delimited; Bisexual cancer refers to tumor cells with both of the above components. Studies on the tissue origin of gastrointestinal MiNEN are mainly divided into the following four theories: ① Origin theory of pluripotent stem cells: Thompson et al. found that endocrine cells had the same clonal origin as other intestinal cell lineages in mice by in situ hybridization, suggesting that gastrointestinal endocrine cells and other gastrointestinal epithelial cells were derived from endodermal pluripotent stem cells. In the process of tumor occurrence and development, neuroendocrine cells and epithelial cells derived from endodermal pluripotent stem cells. Bidirectional differentiation may be influenced by the body's microenvironment and gene stability, which is related to tumor heterogeneity [8]. ② Double primary theory: Furlan et al. conducted a genetic analysis on a case of rectal collision tumor and found that the neuroendocrine and non-neuroendocrine components detected completely different alleles, suggesting that the collision tumor was cloned by two independent tumors. This theory focuses on collision tumors, suggesting that they may originate from two simultaneous carcinogenic events [9]. ③ Adenocarcinoma origin theory: Vanacker et al. conducted second-generation sequencing of two components of colorectal MiNEN in 1 case, and the results showed that SMARCA4 gene mutation only occurred in the neuroendocrine carcinoma component (R849W), while the deletion/repeat mutation form had no significant difference between adenocarcinoma and neuroendocrine carcinoma. Therefore, the missense mutation of SMARCA4 gene is the cause of the transformation of adenocarcinoma into neuroendocrine carcinoma. According to this theory, neuroendocrine components are derived from adenocarcinoma, and the adenocarcinoma phenotype gradually transforms into neuroendocrine phenotype in the process of chromosome and gene mutation [10]. ④ Neuroendocrine carcinoma theory: Ishii et al. reported a case of multiple liver metastases of rectal neuroendocrine tumor, and found that the primary rectal tumor and liver metastases were negative for CK19, while the tumors with bile duct cell carcinoma growth pattern in liver metastases were diffuse positive for CK19. Therefore, it is believed that tumors with the growth pattern of cholangiocarcinoma contain adenocarcinoma components, and the carcinogenesis of adjacent bile duct epithelial cells may be caused by neuroendocrine tumors, and the components of adenocarcinoma may come from neuroendocrine tumors [11]. Although the above theories can explain some immunological, pathological and molecular biological features from different perspectives, most of them lack direct evidence and still

need further exploration.

Colorectal NEC is relatively rare clinically, and its incidence is less than 1% of all colorectal malignancies [12-13]. The clinical symptoms of colorectal NEC are similar to colorectal adenocarcinoma, so it is easy to be missed and misdiagnosed clinically [14]. NEC in the digestive system is mostly found by gastroenteroscopy, and its morphology is not easily distinguishaed from adenocarcinoma. Immunohistochemical detection of NEC specific markers such as neuron-specific enolization (NSE), CgA, Syn, etc. is required for differential diagnosis. CgA and Syn are required tests for the diagnosis of NEN, and CgA is recognized as the most valuable marker of NEN. NET diffuse strongly positive expression of CgA, Syn, NEC diffuse expression of Syn, but weak expression of CgA. In this case, the pathological examination showed that the tumor cells were nested or lamellar infiltrating growth, with little cytoplasm, irregular nuclei, and easy to see mitotic images. Immunohistochemistry showed Syn (+), (local small focal cell cytoplasmic dot +), which was consistent with neuroendocrine carcinoma. Colorectal NEC is highly malignant and aggressive, and about 70% to 80% of patients have distant metastasis at the time of visit [16]. The prognosis is closely related to the size, differentiation, depth of invasion and distant metastasis of the tumor. This patient was accompanied by multiple bone metastases. As the biological behavior of NEC is similar to that of small cell lung cancer, chemotherapy mainly adopts platinum-based combination chemotherapy regimen. Currently, cisplatin combined with etoposide is the commonly used chemotherapy regimen [15], with an effective rate of 69%. A phase II study by Hainsworth et al. [17] showed that, The effective rate of carboplatin and etoposide combined with paclitaxel on NEC was 67.9%. The EP regimen for this patient was cisplatin plus etoposide. In addition, targeted therapy and biotherapy are helpful in prolonging median survival time and improving prognosis.

In summary, this case is currently diagnosed as stage IV neuroendocrine carcinoma of the ascending colon. Since the patient's primary lesion was located in the ascending colon with bone metastasis, surgery was not suitable, so chemotherapy was considered as the main treatment. At present, platinum-based chemotherapy combined with etoposide or irinotecan is the first-line chemotherapy regimen. Although chemotherapy combined with immunotherapy has been widely used in lung neuroendocrine carcinoma, the treatment data in colon neuroendocrine carcinoma are limited and further research is needed.

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