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Large cell neuroendocrine carcinoma of the ileocecal junction with well differentiation adenocarcinoma

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Abstract

Neuroendocrine tumors are unique and rare tumors originating from neuroendocrine cells. Large cell neuroendocrine tumors have been found in almost every organ such as gastrointestinal tract, bronchopulmonary, pancreas, uterine cervix, urinary bladder and salivary gland, but primary sites in gastrointestinal tract and lung are the most frequent. These neoplasms show neuroendocrine differentiation in organizational structure, which requires further confirmation with immunohistochemistry or electron microscope. In immunohistochemistry staining, pure neuroendocrine areas are diffusely stained positive for synaptophysin (Syn), chromogranin (CgA) and CD56.At least two neuroendocrine markers (Syn, CgA or CD56) must be diffusely stained positive to establish a diagnosis for large cell neuroendocrine carcinoma.

We studied a rare case of large cell neuroendocrine tumor that was originated from the ileocecal junction and showed CgA, Syn and CD56 triple-negative. The tumor, however, showed typical morphologic and immunohistochemical features of neuroendocrine differentiation; it also exhibited well differentiation and a significant peritumoral lymphoid reaction. Furthermore, we also found the intracytoplasmic neurosecretory granules through the electron micrograph examination.

CASE REPORT

A 74-year-old Chinese female patient had bowel difficulties associated with abdominal distension for four months. Physical examination detected a hard mass with a diameter about 7 cm in the right lower abdomen, without clear boundary and activity. She had never been seriously ill before and did not take any medications. She had never smoked or consumed alcohol.

Pathological tests showed that cancer antigen (CA) 125 34.8 U/mL and all other blood tests were normal. Computed tomography (CT) scan of the chest was normal but abdominal CT scan confirmed a colon mass of 6.68×5.41 cm, and suspicious liver findings. Further abdominal enhanced

CASE REPORT

CT confirmed the colon wall mass and found no metastatic lesions of liver.

Further examination found a tumor appeared ulcerated type with a volume of 11.0×8.0×3.0 cm located in the ileocecal junction. Intramural growth involved full colon wall of ileocecal junction. The tumor showed a solid gray nodule with necrotic areas near ascending colon and infiltrated full wall of ileocecal, without clearing boundary and no bleeding. In gross specimen, no other abnormal lesions were found.

Histopathological examination showed a tumor composed of different elements. The well-differentiated adenocarcinoma was located in the mucosa-submucosa and the ductal structures were obvious, consisting of about 10% of the tumor. Approximately 90% of the tumor was composed of another histopathological pattern; large tumor cells showed typical oval or molded nucleus with diffuse chromatin, scant cytoplasm and little stoma, more vesicular nucleus and proponent nucleoli (Figure 1A). Tumor cells were arranged in a nested and sheet structure. The mitotic rate was in excess of 10 mitoses per 10 high power fields. The tumor cells had diffuse architecture with necrosis. A small cell component was not present.

In immunohistochemistry, the adenocarcinoma was positive for CK8/18, EMA and CEA, and negative for chromogranin, synaptophysin and CD56. The pure neuroendocrine areas were negative for Syn, CgA and CD56. PGP9.5 and NSE staining were diffusely positive. P53 and vimentin staining were also diffusely positive. CDX2 staining was positive at low frequency and TTF-1 negative in large tumor cells. The Ki-67 labeling index was >80% (Table 1, Figure 1B–G). The electron micrograph examination also showed that the multiple intracytoplasmic neurosecretory granules (Figure 1H).

After taking the morphological and immunohistochemical features and the electron micrograph examination into account, we think this is a large cell neuroendocrine carcinoma (LCNEC) at the ileocecal junction with well differentiation adenocarcinoma.

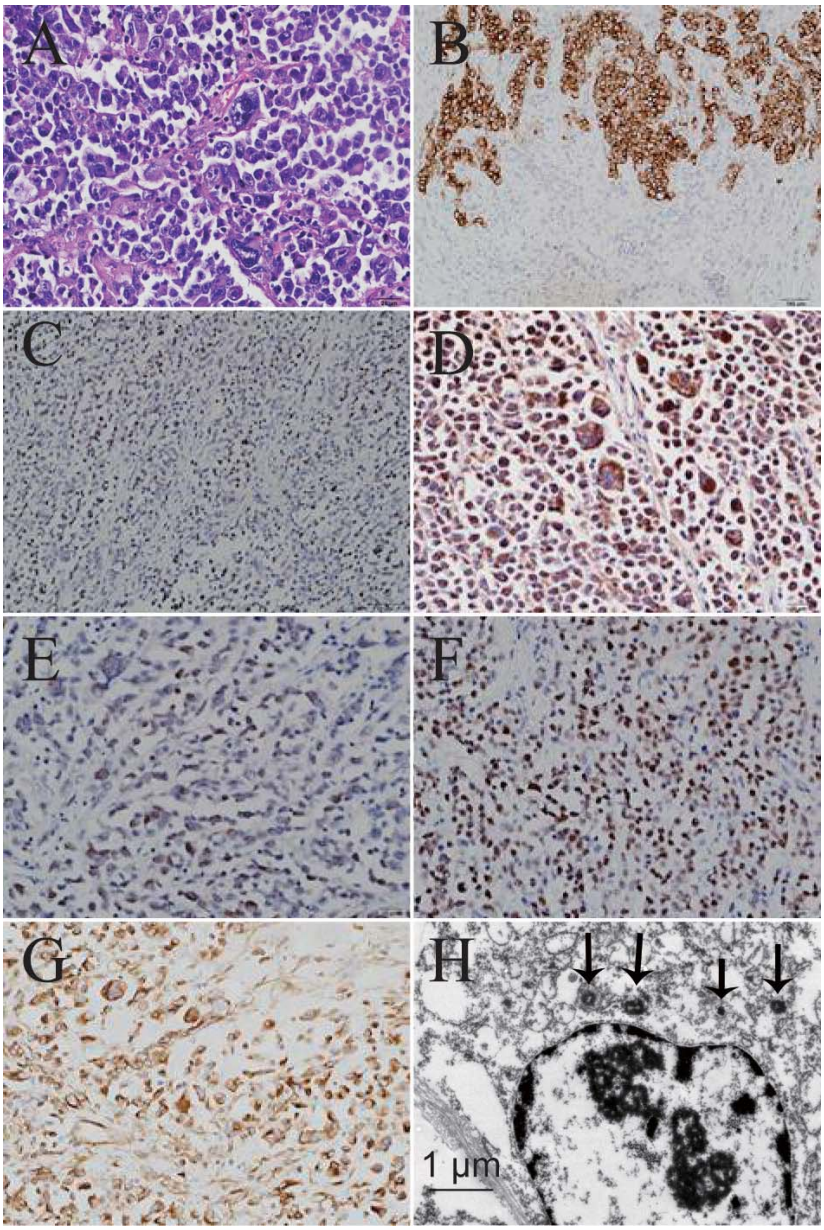

Fig. 1. Histopathological examination of the tumor.

DISCUSSION

Gastrointestinal cancers containing neuroendocrine differentiation are frequent findings but pure large cell neuroendocrine carcinoma together with adenocarcinoma of the ileocecal junction are rare (Lipi *et al.* 2014; Treglia *et al.* 2014). The incidence of neuroendocrine carcinoma cells among colorectal adenocarcinomas has been reported to range from 1.9% to 41.7%, which is mainly well-differentiated carcinoid with organ-like structures(Lee *et al.* 2014; La Rosa *et al.* 2012; Saclarides *et al.* 1994). In this case, two histopathological features were found: pure LCNEC and well-differentiated adenocarcinoma. Various combinations of LCNEC and adenocarcinoma usually do not occur independently of each other, including pure LCNEC on the one side and adenocarcinoma on the other. Based on histopathological analysis, we think that this case is a co-existence of LCNEC and adenocarcinoma, rather than adenocarcinomas with neuroendocrine differentiation.

Among NE markers, chromogranin A (CgA), synaptophysin (Syn) and CD56 are the most reliable ones for diagnosis. According to WHO 2010, diffused staining is considered positive to establish a diagnosis for large cell neuroendocrine carcinoma (McCluggage *et al.* 2010; Ordonez 2000). However, when three molecular markers (CgA, Syn and CD56) were all negative, it is difficult to accurately diagnose neuroendocrine cancer. We failed to detect CgA, Syn and CD56 in neuroendocrine cells. It was reported that CgA and Syn have a relatively good specificity and sensitivity while CD56 has a relatively good sensitivity but less specificity (Chou *et al.* 2012; Ather *et al.* 2008; Mlika *et al.* 2015). Other markers such as NSE and PGP9.5 also showed some similar features to CD56. Therefore, in the pathological practice, more examinations are required, such as morphological characteristics of HE staining and more neuroendocrine markers, such as NSE and PGP9.5 for the diagnosis of CgA, Syn and CD56 triple-negative tumor cells and the electron micrograph examination for neurosecretory granules. In this case, CgA, Syn and CD56 were all negative while NSE and PGP9.5 were diffusely positive in tumor cells. Furthermore, the neurosecretory granules were detected in the cytoplasm. This is how we drew the conclusion that it was a large cell neuroendocrine carcinoma.

Usually, Ki-67 index in well differentiated neuroendocrine cell tumor, such as carcinoid, is relatively low. Thus, Ki-67 index alone is difficult to distinguish small and large cell NECs although Ki-67 is relatively high in large cell carcinoma, about 40% (Tang *et al.* 2012). In this case, Ki-67 index was more than 80%. Together with morphological characteristics, this index can help diagnose large cell neuroendocrine carcinoma.

The possible risk factors involved in the incidence of neuroendocrine tumors were still unknown. The patients had never been seriously ill, had never smoked nor consumed alcohol and did not take any medications. Malignant neuroendocrine tumors (NETs) are rare and solid tumors were sometimes found in children (Allan *et al.* 2013). This case, however, involved a 74-year-old woman. Important makers for neuroendocrine tumors such as Syn, CgA and CD56 were not found while NSE and PGP9.5 were positive.

Neuroendocrine tumor with Syn, CgA and CD56 triple-negative was a rare clinical case. We need to study the histological features and patients' clinical symptom, such as paraneoplastic syndrome. Moreover, there were many diffused neuroendocrine cells in the digestive system. We need to consider the possibilites of neuroendocrine tumors in the tissues with diffused neuroendocrine cells. More than three kinds of the common neuroendocrine makers should be used to avoid misdiagnosis.

After surgery, the patient received three courses of chemotherapy. Since patient responded to chemotherapy vigorously, the patient failed to adhere to the full chemotherapy treatment. In the followed up of this case, metastasis of the liver and lung were not found after two years. In fact, for LCNEC in extrapulmonary organs, chemotherapy was usually useful in the short term, but distant metastasis would be found within a year. Thus, the possibility that LCNEC with Syn, CgA and CD56 triple-negative may have a better prognosis needs further studies.

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