

Case Report

Synchronous poorly-differentiated neuroendocrine carcinoma and gastrointestinal stromal tumor of the stomach: a case report with immunohistochemical and molecular genetic analyses of KIT and PDGFRA

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Abstract: Although the stomach is the most common location for gastrointestinal stromal tumor (GIST) with co-primary tumors, the synchronous appearance of a poorly differentiated neuroendocrine carcinoma (NEC) and GIST in the stomach is extremely rare. To the best of our knowledge, this is the first case of gastric GIST coexisting with gastric NEC to be reported in the literature. The current study reports the case of a 71-year-old male with gastric poorly differentiated NEC and GIST discovered incidentally during surgical treatment of the NEC. Immunohistochemistry analysis showed that the NEC tumor cells were positive for CK (cytokeratin), CD57, synaptophysin, chromogranin, CD117 (KIT protein), Dog-1 (discovered on GIST-1 protein) and CD34. The synchronous GIST immunophenotype showed positivity for CD117, Dog-1 and CD34 (100%), whereas staining for CK, SMA, desmin and S100 was negative. Ki-67 labeling of proliferating cells was 90% in NEC and 1% in GIST. An accurate diagnosis was confirmed by immunohistochemical findings. Furthermore, genetic analysis using PCR direct sequencing identified no mutations in the KIT (exons 9, 11, 13 and 17) and PDGFRA (exons 12 and 18) genes. The patient developed lymph node metastases and underwent cisplatin-based chemotherapy after the operation. This is the first documented case of synchronous gastric GIST and NEC with the examination of protein expression and gene mutations in KIT and PDGFRA, which will help to further understand the etiology and pathogenesis of NEC coexisting with GIST in a gastric location.

Keywords: Synchronous tumor, neuroendocrine, carcinoma, GIST, gastric

Clinical summary

A 71-year-old male presented at our hospital with a 30-day history of increasingly dull stomachache. The upper gastrointestinal endoscopies performed revealed a 6.0-cm ulcerative mass in the antrum of the stomach. Biopsy confirmed poorly differentiated carcinoma of the stomach. The patient expected further evaluation and surgical treatment. When a distal subtotal gastrectomy (with subsequent reconstruction of the gastrointestinal tract) was performed, a 1.3-cm mass was detected on the anterior wall of stomach close to the fundus

ventriculi, and tumor resection from the anterior wall of the stomach was therefore performed.

Microscopically, the large mass in the antrum of the stomach consisted of medium-sized tumor cells with dark nuclei of a round or oval shape, which formed solid sheets and nests (**Figure 1A**). A total of 29 to 35 lymph nodes were involved in metastasis of the carcinoma. Neoplastic cells were diffuse and strongly decorated with antibodies against cytokeratin (CK), CD57, synaptophysin and chromogranin. These cells showed weak staining for CD117 but with

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focally strong immunoreactivity (10% of tumor cells), as well as focally strong staining (1% of tumor cells) with a background of negative immunoreactivity for Dog-1 (discovered on GIST-1 protein). The proliferation index, as measured with a Ki67/MIB-1 immunostain, was approximately 90% (**Figure 1E-N**). Histology of the mass on the anterior wall of the stomach showed the lesion to be completely excised, and the tumor consisted of relatively bland spindle-shaped cells that were immunopositive for CD117, Dog-1 and CD34 (100%) (**Figure 1B-D**) but negative for CK, SMA, Desmin and S-100; no detectable mitoses were seen. Consequently, a diagnosis of neuroendocrine carcinoma (NEC) grade 3 [Ki67 index > 20%, based on the 2010 World Health Organization (WHO) classification for gastroenteropancreatic neuroendocrine neoplasms] coexisting with low-risk gastrointestinal stromal tumor (GIST) (based on criteria of the Armed Forces Institute of Pathology) was established. Molecular genetic analysis for the KIT (exons 9, 11, 13 and 17) and PDGFRA (platelet-derived growth factor receptor- α (PDGFRA), exons 12 and 18) genes was performed in paraffin specimens using the PCR direct sequencing method. The analysis identified no mutations in the KIT and PDGFRA genes. After recovering from the operation, the patient was sent to the oncology department to receive cisplatin-based chemotherapy.

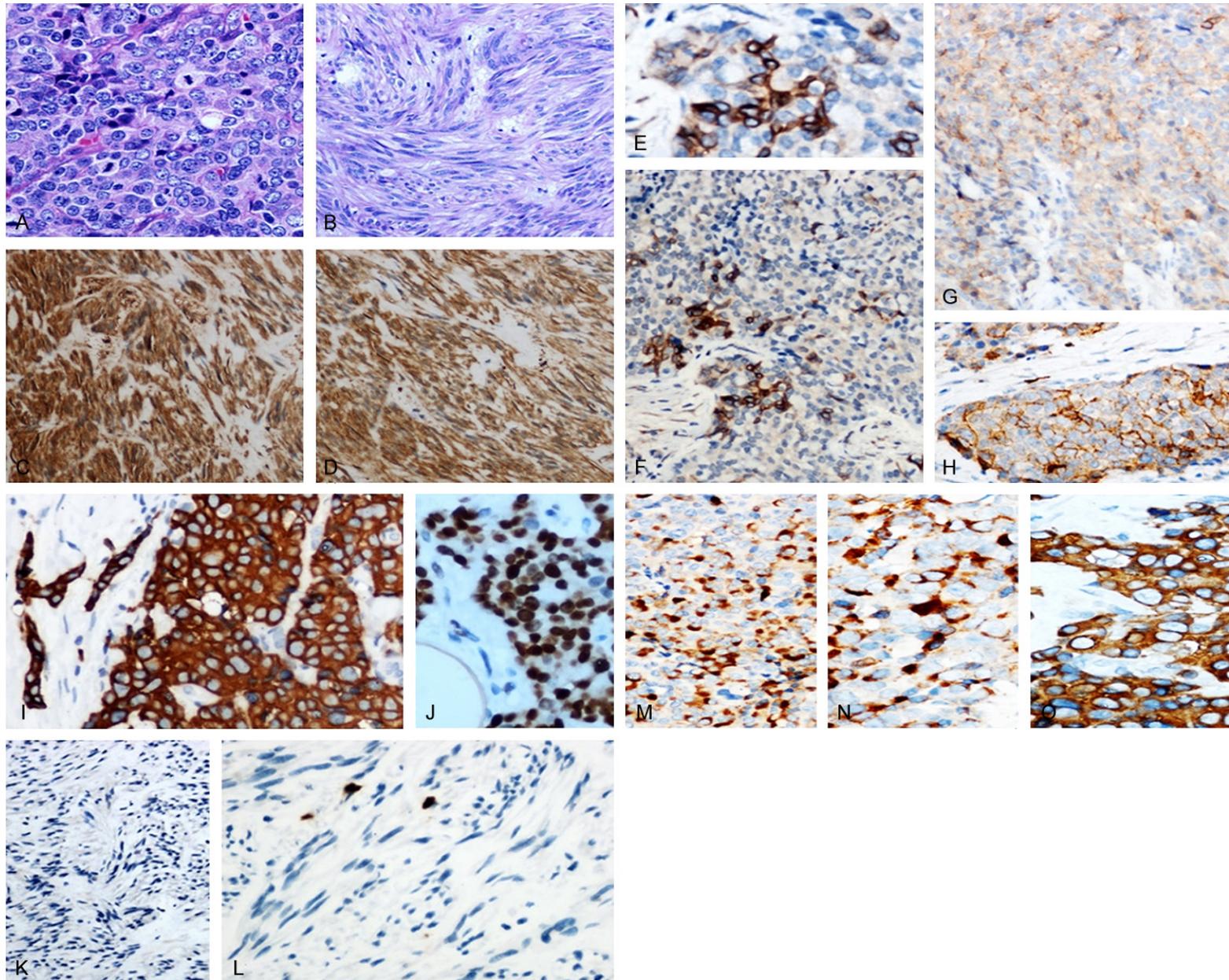
Discussion

GISTs are the most common mesenchymal neoplasia in the gastrointestinal tract, but almost one-third of GISTs are discovered incidentally during investigative or therapeutic procedures for unrelated diseases [1]. Incidental GIST lesions are generally small in size, and the majority show a low mitotic activity [2], as presented in this case. Approximately 15% of synchronous GISTs and other primary tumors are discovered as coincidental findings [2-5], and the stomach is the most common location for GIST with co-primary tumors (50%) [4]. Agaimy A [1] conducted a review of the literature and their own records for cases with sporadic GISTs and other malignancies, which revealed 518 cancers in 486 GIST patients among 4,813 cases with informative data. The major types of other primary tumors accompanying GIST were gastrointestinal carcinomas (47%), lymphoma/

leukemia (7%), carcinomas of the prostate (9%), breast (7%), kidney (6%), lung (5%), female genital tract (5%), and carcinoid tumors (3%). In the study by Liu YJ [2], which analyzed 54 cases of incidental GIST in 311 patients with GIST-accompanying epithelial malignant tumors in China, the coexistence of non-GIST cancer included esophageal squamous cell carcinoma (50%), gastric adenocarcinoma (42.6%), pancreatic adenocarcinoma (3.8%) and colorectal adenocarcinoma (3.8%), but not a single case of endocrine carcinoma was reported. Although the synchronous appearance of a neuroendocrine tumor and GIST in the stomach has been occasionally reported [6, 7], this is the first documented case of GIST coexisting with a poorly differentiated neuroendocrine carcinoma in gastric location in the English literature.

GISTs stem from interstitial Cajal cells located within the wall of the gastrointestinal tract and show characteristic immunoreactivity for CD117 due to activation of the KIT tyrosine kinase by somatic mutation. In addition, although these neuroendocrine neoplasms arise from cells of the diffuse neuroendocrine system, CD117 expression in NEC has been identified [8, 9], suggesting that NEC and GIST may share oncogenic mechanisms. We evaluated immunoreactivity for CD117 and performed genetic analysis using the PCR direct sequencing method in NEC. The results showed that the tumor cells were positive for CD117 but free of KIT gene mutations (exons 9, 11, 13 and 17), which is consistent with the literature. According to recent studies, with the exception of GIST, CD117 may also be identified in a wide variety of carcinomas [9, 10], but the large size samples studies mainly focused on lung and gastrointestinal NECs. Approximately 25% of gastrointestinal NECs and 70% of pulmonary NECs express CD117 [8, 11-14]. Interestingly, with the exception of one case of metastatic NEC in the pelvis without evidence of a primary tumor that showed KIT overexpression associated with a KIT exon 11 mutation [15], none of the previously reported NECs accompanying GIST showed mutations in KIT exon 9, 11, 13 or 17 or in PDGFRA exon 12 or 18, as typically observed in GISTs [10-12, 16], indicating that there is no correlation between positive immunostaining and the occurrence of activating mutations in KIT and PDGFRA. KIT activation in NEC tumor cells without the acquisition of acti-

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Figure 1. (A) Neuroendocrine carcinoma (NEC) consisting of poorly differentiated tumor cells with many mitosis forming solid sheets and nests and (B) gastrointestinal stromal tumor (GIST) consisting of bland spindle-shaped cells without mitosis (H&E, $\times 400$). (C and D) Strong CD117 and Dog-1 immunoreactions were noted in all tumor cells of the GIST (immunoperoxidase, $\times 400$). Dog-1 staining showed focally strong immunoreactivity (1% of tumor cells) (E) with a background of negative immunoreactivity (F) and CD117 staining showed largely weak staining (G) but focally strong immunoreactivity (10% of tumor cells) (H) in the NEC (immunoperoxidase, $\times 200$ and $\times 400$, respectively). CK staining was strongly positive in NEC cells (I), with a high proliferation rate indicated by Ki67 labeling (J), but was essentially negative in GIST cells (K) with a low Ki67 proliferation index (L) (immunoperoxidase, $\times 400$). CD57 (M), chromogranin (N) and synaptophysin (O) staining demonstrated strong reactivity in NEC cells (immunoperoxidase, $\times 400$).

vating mutations is postulated to be due to autocrine and/or paracrine stimulation of the receptor by its ligand or to cross-activation by other kinases and/or loss of regulatory phosphatase activity.

In summary, this report describes a rare case of the simultaneous occurrence of a GIST with a poorly differentiated NEC in the stomach, the combination of which has not been reported in literature to the best of our knowledge. This gastric NEC expressed KIT and PDGFRA protein but was free of KIT and PDGFRA gene mutation.

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Disclosure of conflict of interest

None.

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