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Original Article

Chondroid gastrointestinal stromal tumor in the stomach with early adenocarcinoma

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Abstract: Objective: To explore the pathologic features of gastric chondroid gastrointestinal stromal tumors. Methods: The clinicopathologic data of one case of gastric chondroid gastrointestinal stromal tumor were collected and the features were analyzed by literature review. Results: The male patient was 64 years old and had suffered from upper abdominal fullness discomfort without obvious cause for 5 years. Gastroscopic examination showed a rough area located in the lesser curvature of the gastric antrum, measuring 6 cm × 4 cm. CT scan showed the stomach wall was unevenly thick at the gastric antrum and stomach outlet. Multiple enlarged lymph nodes were seen nearby. The biopsy pathology showed adenocarcinoma of gastric antrum. The patient underwent laparoscopic gastrectomy and gastric chondroid gastrointestinal stromal tumor was found with adenocarcinoma of the stomach. Asp842Val mutation was found in the PDGFRα 18 exon. Conclusion: Gastric chondroid gastrointestinal stromal tumors are rare and low risk. Tumor cells express CD117 and Asp842Val mutation in the PDGFRα 18 exon revealed by genetic sequencing suggesting this kind of tumor might be resistant to imatinib.

Keywords: Gastrointestinal stromal tumor, chondroid, early adenocarcinoma

Introduction

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors in the gastrointestinal tract and is thought tooriginate from Cajal cells [1, 2]. The mutation of c-kit gene and/or platelet-derived growth factor receptor alpha (PDGFRα) gene is the mechanism of tumorigenesis [3]. About sixty percent of GISTs arise from the stomach and thirty percent from small intestine. Only ten percent of GIST are found in rectum, colon and esophagus [4]. Microscopically, GIST has diverse histologic manifestations and spindle or epithelioid cells often appear in the tumor. Here we report one case of chondroid GIST in the stomach accompanied by adenocarcinoma simultaneously. The clinicopathologic features of this tumor are reviewed in the literature.

Materials and methods

Clinical data collected

In our study, one case diagnosed as chondroid GIST in the stomach with early adenocarcinoma was obtained from Department of Pathology, Yantai Yuhuangding Hospital. The clinical data including following-up information were collected.

Sample process

Tissue samples were immersed in 10% buffered formalin for complete fixation. Subsequently, tissue dehydration and paraffin embedding were carried out. 3-5 μm sections were cut from tissue blocks for hematoxylin and eosin (H&E) staining.

Immunohistochemical staining

EnVision two-step method was adopted by an automatic immunostainer (VENTANA) for immunohistochemical staining and DAB chromogen. Each slice was stained with known positive tissues as the positive control, while negative controls replaced the first antibody with PBS. All the antibodies were bought from Beijing Zhongshan Jinqiao Biological Technology Co., Ltd. Information on antibodies is included in **Table 1**.

Table 1. Results of antibodies employed in immunohistochemistry

Antibody	Clone	Dilution	Result
Anti CD34	QBEnd/10	1:100	+
Anti CD117	2E4	1:100	+
Anti Dog-1	SP31	1:100	+
Anti S-100	4C.9	1:100	-
Anti SMA	1A4	1:100	-
Anti H-caldesmon	H-CALD	1:100	+
Anti Ki67	MIB-1	1:100	+2%
Anti INI-1	MRQ-27	1:100	+
Anti Cytokeratin	AE1/AE3	1:100	-
Anti Desmin	D33	1:100	-
Anti HMB45	HMB45	1:100	-
Anti Syn	SP11	1:100	-
Anti NSE	E27	1:100	-
Anti EMA	E29	1:100	-
Anti MelanA	A103	1:100	-

Molecular detection

Exon 9, 11, and 13 of c-kit and exon 12, and 18 of PDGFRα gene were sequenced by PCR amplification to analyze gene mutation. Using Primer and Olig software, primers were designed and synthesized according to c-kit and PDGFRα gene sequences. Primer sequences are shown in **Table 2**.

Results

Clinical data

The 64-year-old male suffered from upper abdominal fullness discomfort for five years without any obvious cause. The discomfort occurred as intermittent episodes from time to time and were exacerbated after meals and reduced after defecation. The patient had nausea, anorexia, and occasional vomiting of stomach contents. He did not receive any treatment until the above symptoms worsened for one month and he was sent to hospital for further medical examination. Gastroscopic examination showed a rough area which was about 6 cm × 4 cm at the lesser curvature and the gastric antrum. The following biopsy pathology showed gastric adenocarcinoma. CT scan revealed that the gastric wall in the gastric antrum and stomach horn was unevenly thickened. Multiple enlarged lymph nodes were seen around the lesion (**Figure 1**). The patient underwent laparoscopic gastrectomy subsequently and did not receive further treatment after surgery. The total follow-up period was nineteen months. The recent repeat CT scan revealed no recurring or residual lesion during the post-surgical course.

Gross examination

The sample was resection of the distal stomach with omentum. The greater curve was 13 cm and lesser curve was 8 cm. There was a small curved area at the antrum, measuring 5 cm × 4 cm. Under this mucosal lesion, a gray-white mass was found which measured 2.5 cm × 1.5 cm × 1.8 cm. The cut surface had a hard and gray appearance with obvious boundary (**Figure 2**).

Histologic findings

Microscopically, the glandular structures in the gastric mucosa were disordered and nodular mass was found under the mucosa (**Figure 3A**). The epithelial cells showed severe dysplasia (**Figure 3B**). On a background of hyaline and mucoid degeneration, epithelioid tumor cells were arranged as clustered or flaky chondroid cells in the submucosa (**Figure 3C**). The epithelioid tumor cells were large in volume with light cytoplasm and a small round nucleus (**Figure 3D**). The mitotic count was less than 5/50HPF.

Immunohistochemical staining

Immunohistochemical staining showed submucosal epithelioid tumor cells were positive for DOG-1, CD117, CD34 and INI-1 while negative for HMB45, SMA, MelanA, S-100, synaptophysin, NSE, cytokeratin, desmin, and EMA. Ki67 positive rate was about 2%. During the differential diagnosis of smooth muscle tumors, H-caldesmon, which is considered to be a myogenic-specific marker, was used and positive expression was found in this case (**Figure 4**).

Molecular detections

The 9, 11, 13 exons of the c-kit gene and the 12, 18 exons of the PDGFRα gene were detected for the submucosal tumor. The results showed that the PDGFRα 18 exon had Asp842Val mutation and there was no gene mutation found in c-kit gene 9, 11, 13 exon or PDGFRα gene 12 exon (**Figure 5**).

Table 2. Primer sequences for PCR amplification in this study

Exon		Sequence (5'-3')	Length of fragment (BP)
c-kit exon 9	9F	TCCTAGAGTAAGCCAGGGCTT	284
	9R	TGGTAGACAGAGCCTAAACATCC	
c-kit exon 11	11F	CCAGAGTGCTCTAATGACTG	227
	11R	TGACATGGAAAGCCCCTGTT	
c-kit exon 13	13F	GCTTGACATCAGTTTGCCAG	193
	13R	AAAGGCAGCTTGGACACGGCTTTA	
PDFGRα exon 12	12F	TCCAGTCACTGTGCTGCTTC	260
	12R	GCAAGGGAAAAGGGAGTCTT	
PDFGRα exon 18	18F	ACCATGGATCAGCCAGTCTT	251
	18R	TGAAGGAGGATGAGCCTGACC	

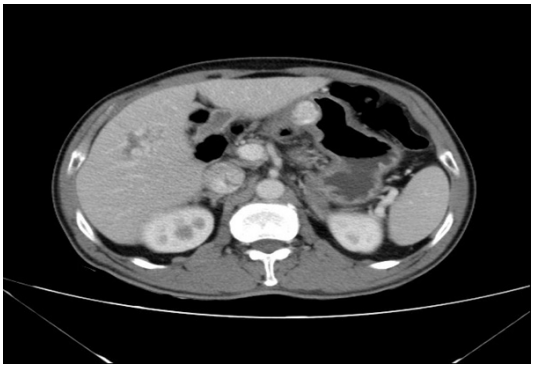

Figure 1. Imaging of the tumor: CT scan shows space-occupying lesions in the stomach wall.

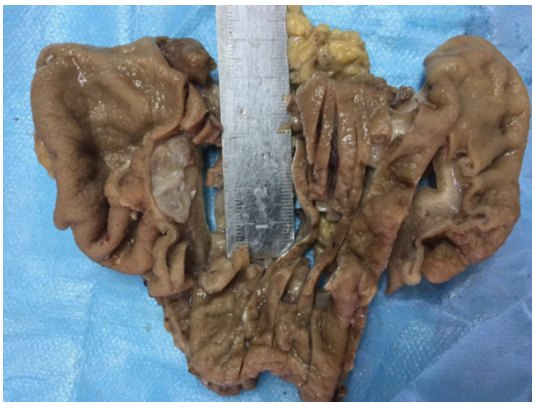

Figure 2. Gross examination shows a gray-white mass in the stomach wall with clear boundaries. The mucosal folds disappeared on the surface of the tumor.

Final diagnosis

On the basis of histologic features, immunohistochemical and molecular findings, a diagnosis was made of chondroid GIST with poorly differentiated adenocarcinoma of the stomach. Gastric adenocarcinoma was confined to the mucosa. Gastric chondroid GIST was low risk. No residual tumor was found in the upper and lower surgical margins of the stomach. There were thirty-two lymph nodes totally detected without tumor metastasis.

Discussion

GIST can exhibit a variety of histologic structures, such as spindle cell type, epithelial cell type, schwannoma type, clear cell type and ring type [5, 6]. Chondroid GIST is rare and according to our Pubmed research for "chondroid gastrointestinal stromal tumor", only three other cases of chondroid GIST have been published in the English literature since Pulcini et al. reported the first case in 2009. It is worth mentioning that our present case combined with early gastric cancer which was the first such report. All the patients and tumor findings are given in **Table 3** [7-9].

Patients with GIST have a peak incidence between 55 and 65 years old in general [10]. The incidence of men and women is almost equal. According to **Table 3**, the series of patients with chondroid GIST had the average age 64.5 years and there was also no gender trend. The site of disease in all patients was in the stomach without exception. Gastrointestinal symptoms were mainly clinical manifestations: three patients had clinical symptoms of upper abdominal discomfort or pain, two had melena, one had vomiting, and one had anemia.

All of the cases in our group showed similar histologic morphology: the tumor was composed of epithelioid cells that were surrounded by the fibrous and myxoid stroma in such a way that chondroid cells were observed. The maximum diameter of the tumor was less than or equal to five cm. The risk rating of the three cases available was low risk. Immunohistochemical markers of GIST usually express CD117, CD34 and Dog-1 [11, 12]. The polymerase chain reaction-

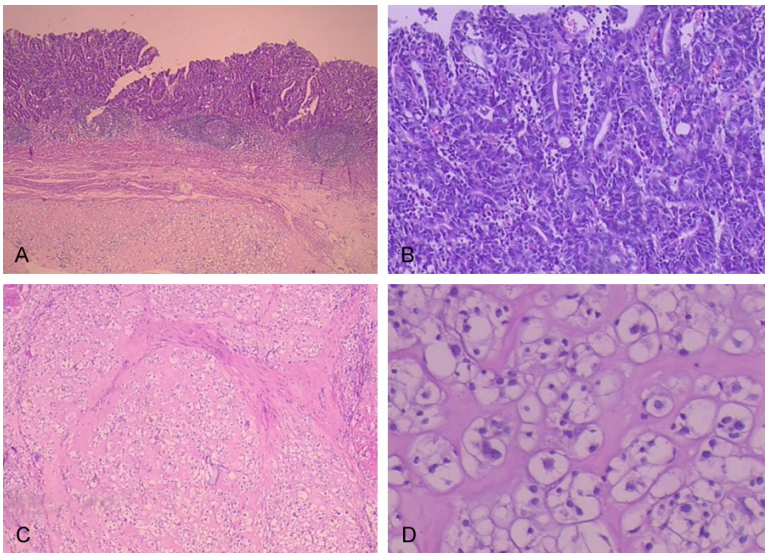

Figure 3. Histologic morphology of GIST and gastric cancer. A. The glandular structure was disordered and nodular mass was found under the mucosa (H&E staining, 4 ×). B. The epithelial cells showed severe dysplasia (H&E staining, 40 ×). C. In a background of hyaline and myxoid degeneration, epithelioid tumor cells are arranged as clustered or flaky chondroid cells (H&E staining, 10 ×). D. The epithelioid tumor cells were large in volume with bright cytoplasm and a small round nucleus (H&E staining, 40 ×).

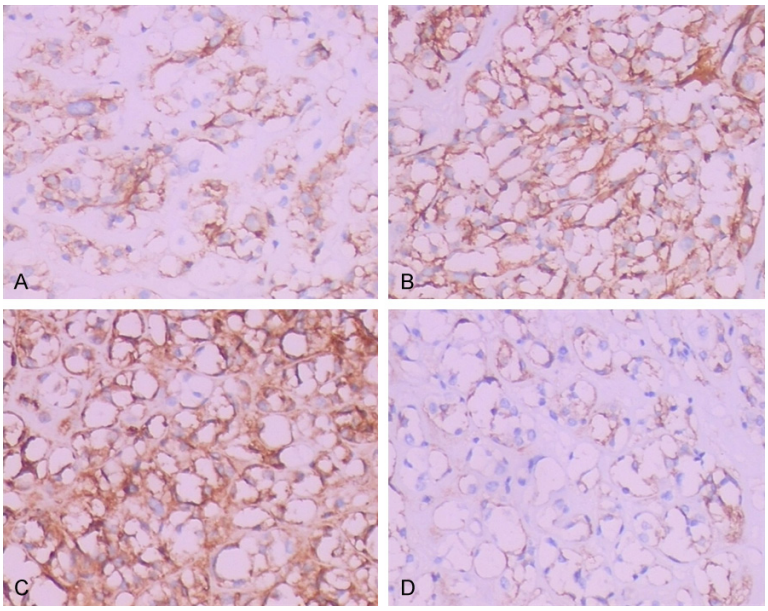

Figure 4. Immunohistochemical staining of the tumor. The tumor cells are positive for (A) CD34, (B) CD117, (C) DOG-1, (D) H-caldesmon (40 ×).

direct sequencing method is usually used to analyze the mutations of c-kit and PDFGRα gene exons in molecular detection for GIST [13]. According to the data available, CD117 was expressed very well in tumor cells of this group. Two cases expressed DOG-1, one case expressed CD34 and one case expressed S-100. In three cases which molecular testing was obtained, Asp842Val mutation in PDGFRα 18 exon was detected in one case, one case found a strong aneusomy in chromosome 1 by FISH and one case without mutation in c-kit and PDGFRα. As far as the latter case without a mutation detected, we believe that it is necessary to add SDHB immunohistochemical marker further to exclude the possibility of SDH-deficient GIST [14, 15]. Asp842Val mutation in the PDGFRα 18 exon suggests that the tumor may be resistant to imatinib [16].

In general, the histologic differential diagnosis of chondroid GIST includes extraskeletal myxoid chondrosarcoma (EMC), PEComa, carcinoma and epithelioid leiomyoma. EMC is a rare malignant soft tissue tumor. Eighty percent of cases occur in the proximal extremities and deep soft tissues of the limbs, and 20% in the trunk. EMC has nothing to do with bone tissue. EMC has an obvious fibrous envelope and the tumor is divided into multiple lobular structures by fibrous tissue. The tumor cells floating in the chondroid matrix are small, round or polygonal. The cytoplasm is rich, the nucleus is round, and the mitotic figures are rare. Clinical manifestations and tumor cells without expression of CD117 and DOG-1 can be differentiated from chondroid GIST [17]. PEComa is called perivascular epithelioid cell tumor. Tumor cells are epithelial-like with clear or eosinophilic cytoplasm. Characteristic expression of HMB45 and MelanA could be helpful

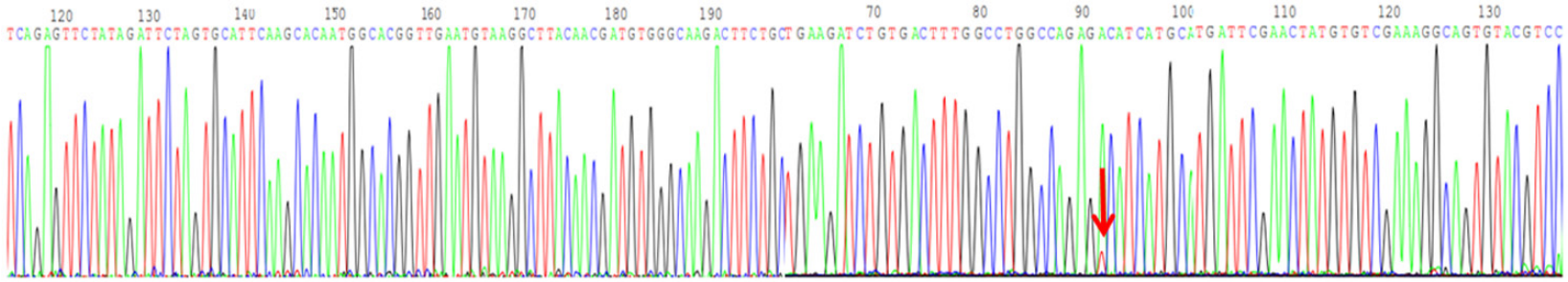

Figure 5. Genetic testing revealed a PDGFRα 18 exon Asp842Val mutation.

Table 3. Clinical data of previously published cases of chondroid GIST

No./Series	Age (years)	Sex	Site of lesion	Clinical Presentation	Size of tumor	Risk	IHC staining	DNA Change	Treatment	Follow-up (Months)	Status
1/Pulcini et al. 2009	79	Female	Stomach	Melena, coffee ground vomiting and abdominal pain	1.5 cm diameter	Low	Positivity for CD117 and negativity for all other antibodies employed	Strong aneusomy was seen in chromosome 1	Upper polar resection of the stomach	8	ANED
2/Sonia B et al. 2012	77	Male	Stomach	Melena and anemia	3.7 cm × 2.5 cm × 2.4 cm	Low	CD117+, PDGFa+, DOG1+, CD99, CD34-, SMA-, desmin-, S-100-, EMA-, CK-, D2-40-	No mutations were detected in the c-kit gene and PDGFa gene	Laparoscopic gastric tumor resection	10	ANED
3/A.M. Musaad et al. 2016	38	Female	Stomach	Persisting epigastric pain	5 cm × 3 cm	NA	CD117+, S-100+, other antibody was not mentioned	NA	Resection of the stomach and received treatment with imatinib	NA	NA
4/Present case	64	Male	Stomach	Upper abdominal fullness discomfort	2.5 cm × 1.5 cm × 1.8 cm	Low	DOG-1+, CD117+, CD34+, SMA-, INI-1+, HMB45-, MelanA-, S-100-, Syn-, NSE-, CK-, Desmin-, EMA-. Ki67 was 2%	Asp842Val mutation in PDGFRα 18 exon	Laparoscopic distal gastrectomy	19	ANED

Abbreviations: ANED, alive with no evidence of disease; NA, not available.

in differential diagnosis [18]. Because our present case is combined with gastric adenocarcinoma, the special histologic type of adenocarcinoma needs to be excluded. Immunohistochemical markers for epithelial cell such as cytokeratin and EMA were useful [19]. Gastric epithelioid leiomyoma is rare and the tumor cells did not express CD34, CD117, and DOG-1 while expressingmyogenic markers such as SMA or Desmin [20]. H-caldesmon seems not to be a smooth muscle-specific marker [21, 22]. Other differential diagnoses, including neuroendocrine tumor, and chondroma should also be considered, and typical morphologic characteristics with proper immunohistochemical markers and molecular detection could help to render a correct diagnosis.

Prognostic assessment of GIST relies on risk rating of tumor after surgery [23]. Three patients followed up in the reported cases were assessed as low risk. They underwent surgical resection without further chemotherapy and targeted therapy. The survival status was good. One patient reported by Musaad et al. had no follow-up information, but the tumor diameter reached five cm and the risk was assessed to be at least moderate. Our present patient is the first reported chondroid GIST with gastric adenocarcinoma. Because this was only early gastric adenocarcinoma, there was no further treatment after surgery.

Conclusion

We report the first chondroid GIST with gastric adenocarcinoma. Gastric chondroid GISTs are rare and most cases are low risk. Asp842Val mutation in the PDGFRα 18 exon, revealed by genetic sequencing, suggested this tumor might be resistant to imatinib.

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Disclosure of conflict of interest

None.

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