Int J Clin Exp Pathol 2016;9(8):8694-8701
www.ijcep.com /ISSN:1936-2625/IJCEP0026833

Case Report

Genetic alterations and expression of epithelial-mesenchymal transition markers in gastric sarcomatoid carcinoma: report of a case and review of literature

Huan Wang[1], Hui-Feng Jiang[2], Si-Bo Meng[1], Jing Hao[3]

[1]Department of Medical Oncology, Qilu Hospital of Shandong University, Qingdao 266000, China; [2]Department of Pathology, Qilu Hospital of Shandong University, Qingdao 266000, China; [3]Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan 250012, China

Received February 27, 2016; Accepted May 22, 2016; Epub August 1, 2016; Published August 15, 2016

Abstract: Sarcomatoid carcinoma arising from stomach is rare and its molecular alterations are largely unknown. We reported one case of gastric sarcomatoid carcinoma in a 69-year-old man who was hospitalized for upper abdominal discomfort and melena. Endoscopic examination revealed an infiltrative and ulcerated mass in the body of stomach. A huge gastric mass was also evident on CT scan. Histologically, the tumor was composed of diffuse undifferentiated cells with high mitotic activity and pleomorphism. Immunohistochemisty revealed intense and diffuse staining for vimentin and p53, focal staining for cytokeratin and loss of cadherin and β-catenin in tumor cells indicative of epithelial-mesenchymal transition. Differential diagnosis was excluded by negative expression of CD56, CgA, CD3, CD20, CD10, bcl-6, S-100, CD117, CD34, desmin, SMA and HMB45. Mutations of nine genes could be found by next generation sequencing including *TP53, ETV1, SOX21, GATA6, FAT1, NORCH2NL, MED12, SRC* and *NSD1*. In addition, four genes were shown to have amplification, including *SOX2, GATA2, RPTOR* and *CCND1*, while *RB1* exhibited loss of gene copy number. The patient was diagnosed as sarcomatoid carcinoma and given one cycle of chemotherapy with oxalipatin and S-1. One month later, the tumor progressed rapidly with ascitis and liver metastasis and the patient died for suspected disseminated intravascular coagulation (DIC).

Keywords: Sarcomatoid carcinoma/genetics, stomach neoplasms, epithelial mesenchymal transition, next generation sequencing

Introduction

Sarcomatoid carcinoma of the stomach is an extremely rare biphasic tumor which consists of both epithelial and mesenchymal elements. There have been more than 50 cases reported so far who were recently reviewed by Cirocchi to have a poor prognosis of median survival to be only 6.5 months in spite of surgery and chemotherapy [1]. In order to understand and develop new tailored therapeutics to improve the prognosis for this rare disease, it is essential to explore its oncogenic mechanisms. Herein, we presented a case of gastric sarcomatoid carcinoma and analyzed its molecular characteristics by next-generation sequencing (NGS) of 416 cancer-related genes together with epithelial-mesenchymal transition (EMT) markers by immunohistochemistry staining.

Case report

Clinical history

A 69- year-old man was admitted to our division reporting a history of epigastric discomfort with intermittent melena and weight loss (10 kilos over 3 months). The physical examination revealed emaciation, marked pallor and a 10 cm mass in epigastric region. Routine laboratory parameters were found to be normal except for leukocytosis, anemia and hypoalbuminemia, white blood cell (WBC) 15.91×10^9/L, hemoglobin 82 g/L, and albumin 34 g/L. The levels of tumor markers, carcinoembryonic antigen (CEA) and carbohydrate anti-gen (CA 19-9) were 0.81 ng/ml and 7.68 ng/ml, respectively (normal CEA <5 ng/ml, CA 19-9 <37 ng/ml).

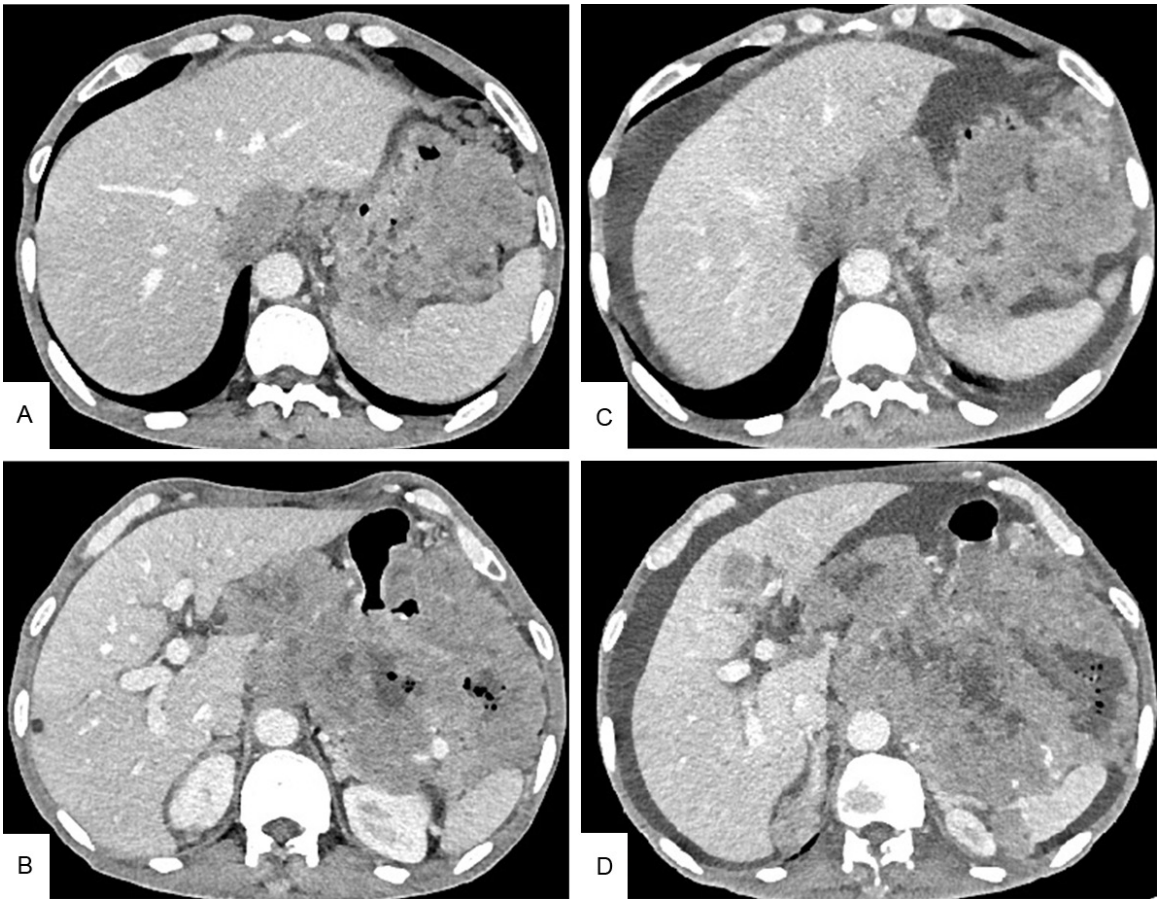

Figure 1. A, B: Abdominal CT scan showed diffuse wall thickening and stiffness of the gastric body to form a huge mass at diagnosis (2014-12-6). C, D: The mass of gastric body enlarged with liver metastasis and ascitis after one cycle of chemotherapy (2015-1-8).

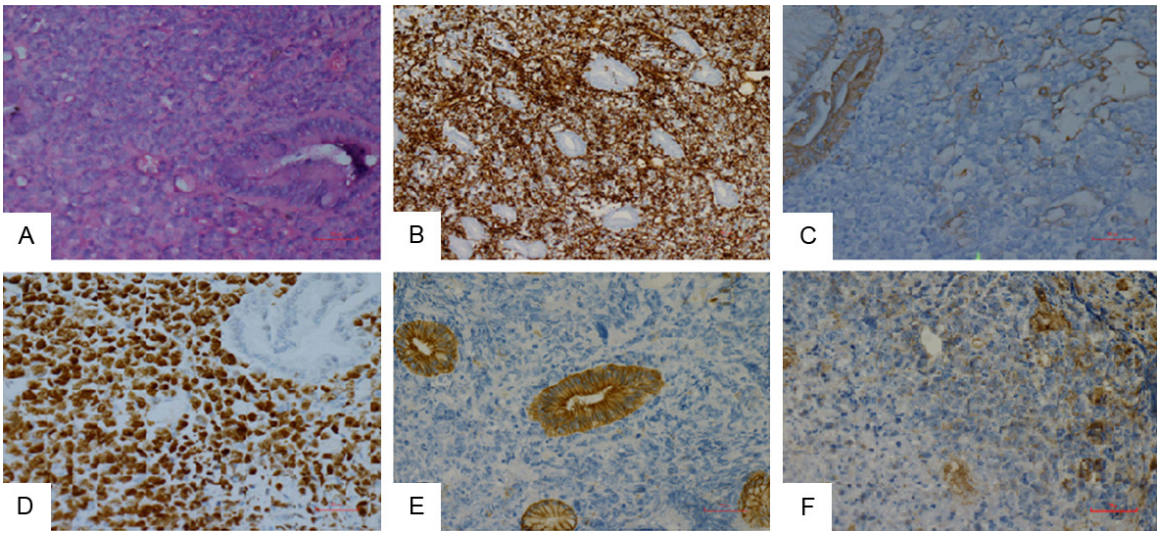

Figure 2. Immunohistochemical staining of EMT-related proteins and TP53 in gastric sarcomatoid carcinoma. HE staining, the tumor was composed of diffuse undifferentiated cells with pleomorphism (A); Diffuse staining of vimentin (B); Focal staining of CKpan (C); Diffuse and intense staining of p53 (D); Negative staining of E-cadherin (E) and β-catenin (F).

Table 1. Genetic alterations in analyzed 416 genes by NGS

Genes	Nucleotide variation	Protein variation	Mutation frequency	Point mutation impact (COSMIC)	Gene function (reference)
TP53	c.G638A	p.R213Q	58%	Loss of function (never reported in gastric neoplamas)	Oncosuppressor, up-regulating both cell cycle arrest and apoptotic factors [2]
ETV1	c.A113G	p.D38G	52%	Unknown (never reported)	Oncogene, promote cell proliferation, motility and invasion [3]
SOX21	c.C56T	p.S19L	43%	Unknown (never reported)	Oncosuppressor, inhibit tumor growth and promote differentiation [4]
GATA6	c.G151A	p. E51K	41%	Unknown (never reported)	Oncogene, regulation of tissue development and promote EMT [5]
FAT1	c.A1105G	p. K369E	39%	Unknown (never reported)	Oncosuppressor, encode a cadherin-like protein and inhibit tumor growth [6]
SRC	c.A913T	p.M305L	6%	Unknown (never reported)	Oncogene, tumorigenesis and acquisition of the invasive phenotype [7]
NSD1	c.T548C	p.I183T	6%	Unknown (never reported)	Regulation of chromatin structure and function [8]
NOTCH2NL	c.G427A	p.D143N	5%	Unknown (reported in skin tumor)	repressing transcriptional activities of Notch proteins [9]
MED12	c.C6226T	p.Q2076X	1%	Unknown (never reported)	transcriptional regulation of the RNA polymerase II complex and maintain gene stability [10]

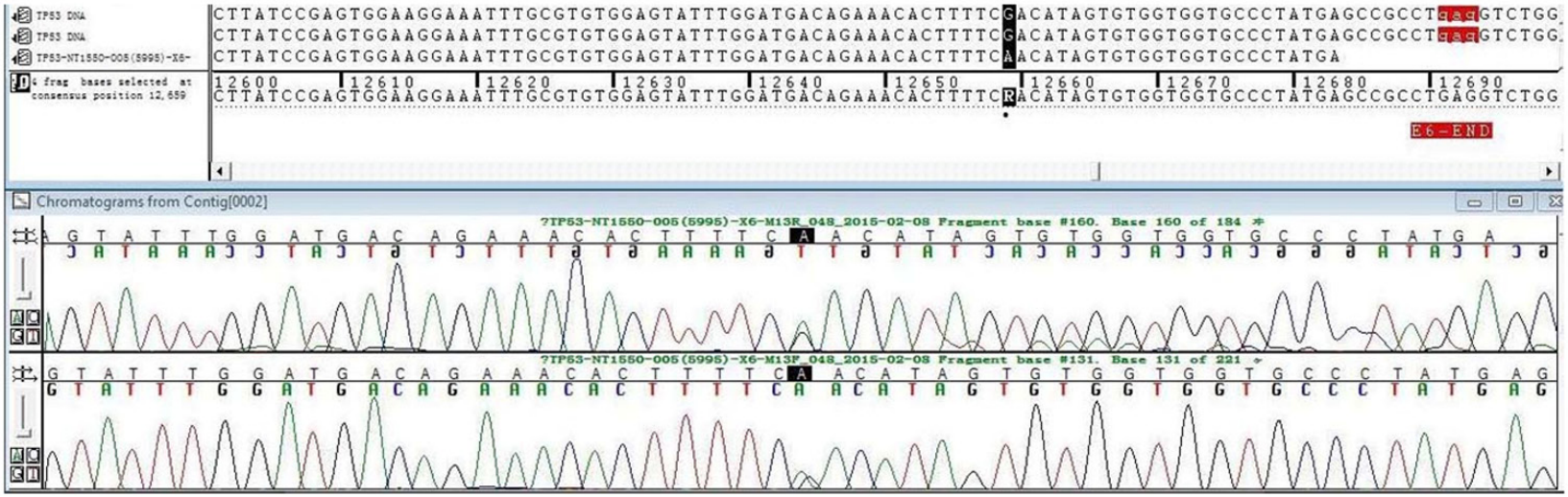

Figure 3. Point mutation G638A of *TP53* gene discovered by NGS was validated by Sanger sequencing in a case of gastric sarcomatoid carcinoma.

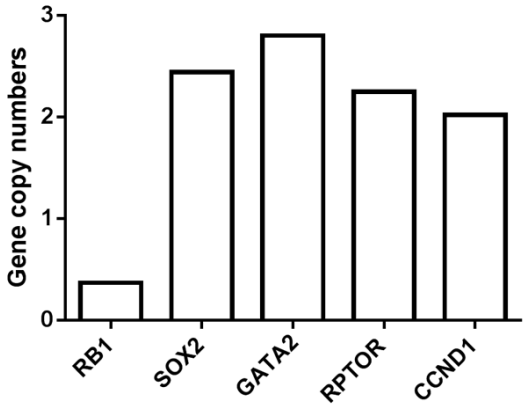

Figure 4. Gene copy number variations in one case of gastric sarcomotid carcinoma.

Endoscopic examination revealed a huge ulcerative lesion that infiltrated the posterior wall of the stomach and part of fundus. The abdominal computed tomography scan showed diffuse wall thickening of the gastric body to form a huge unevenly contrasted mass with a diameter of 18 cm, which infiltrated through serosa to the pancreas (**Figure 1A**, **1B**). An endoscopically taken biopsy revealed the diagnosis of sarcomatoid carcinoma by pathological and immunostaining findings (**Figure 2A**, **2B**).

The patient received one cycle of chemotherapy with oxaliplatin (150 mg) and S-1 (80 mg/day, 14 days). 25 days later, the patient was hospitalized again for the deterioration of abdominal distension and malaise. The physical examination revealed shifting dullness of abdomen. Blood tests showed severe anemia with hemoglobin concentration of 79 g/L, leukocytosis (21.46×10^9/L), and low albumin level (25.7 g/L). Platelet count was 165×10^9/L. Abdominal enhanced CT scan showed that the enlargement of gastric tumor, liver metastasis and peritoneal effusion (**Figure 1C**, **1D**), indicative of rapid progression. Best supportive care was then given to the man due to his bad conditions. To make illness even worse, widespread petechia could be seen around the umbilicus 2 days after hospitalization and blood tests revealed a rapid decrease of platelet count (94×10^9/L) and coagulation abnormality (Promthrombin time 18.30 s, Fibronogen 1.96 g/L and D-dimer 1.60 mg/L). Disseminated intravascular coagulation (DIC) was suspected to occur secondary to cancer and the man died soon in spite of fresh blood plasma and red blood cell transfusion. The total survival time from diagnosis was only one month.

Pathological findings and expression of EMT markers

Histologically, the tumor was composed of diffuse undifferentiated cells with high mitotic activity (Ki67 labeling as high as 90%) and pleomorphism (**Figure 2A**). No carcinomatous component was recognized. Immunohistochemistry staining revealed focal positivity for pancytokeratin Cam5.2, diffuse positivity for vimentin and p53 (**Figure 2B-D**), but negativity for CD3, CD20, HMB45, SMA (-), S-100, CD21, Bcl-6, CD10, CD3, CgA, CD56, CD117 and CD34. As for EMT markers, loss of E-cadherin and β-catenin was evident (**Figure 2E**, **2F**) together with diffuse and intense staining of vimentin (**Figure 2B**). So these immunohistochemical findings led to a diagnosis of Sarcomatoid carcinoma of the stomach.

Genetic analysis by NGS

Genomic DNA was extracted from FFPE tissues with QIAamp DNA mini kit (Qiagen, Heidelberg, Germany). Fragment DNA was generated with Bioruptr (Diagenode, Bioruptor UCD-200) and Libraries were constructed with the KAPA Hyper DNA Library Prep Kit, (KAPA Biosystem, KK8504). Dual-indexed sequencing libraries were PCR amplified with KAPA HiFi Hot start-ready Mix (KAPA, KK2602) for 4-5 cycles, then cleaned up by 1× purification Beads (Corning, AxyPrep Fragment Seclect-I kit, 14223162). The 5'-biotinylated probe solution was provided as capture probes. The baits target 416 cancer-related genes (Geneseeq Techonology Inc.). Illumina HiSeq 4000 was used for 75×75 paired-end sequencing (80-100 per flowcell).

Mutations of nine genes could be found including *TP53, ETV1, SOX21, GATA6, FAT1, NORCH2NL, MED12, SRC* and *NSD1* (**Table1**) [2-10]. Of note, the first five genes had high mutation frequency and *TP53* mutation (exon 6, G638A) was validated by Sanger sequencing (**Figure 3**). In addition, gain of copy numbers could be seen in the genes of SOX2, GATA2, RPTOR and CCND1, while RB1 exhibited loss of gene copy number (**Figure 4**).

A literature review of gastric sarcomatoid carcinoma excluding gastric carcinosarcoma

In order to characterize the clinical features of true gastric sarcomatoid carcinoma, we dogged

Table 2. A review of gastric sarcomatoid carcinom diagnosed on both histological and immunohistological characteristics

No	Year	Ref.	Age	Sex	Location	D (cm)	EGDS	Symptoms	T	N	M	Vimentin	CK	EMA	CAM5.2	Treatment	Outcome
1	1990	11	78	M	fundus	5	polypoid	Epigastric pain	T2	N0	M0	+	-	-	-	Resection and chemo-therapy for recurrence	45 m, dead
2	1990	11	57	F	GEJ	5	polypoid	swallowing pain	T4	Nx	kidney, lung, ovary, pleura, peritoneum	+	focal+	-	NA	Esophagogastrectomy, jejunostomy and sple-nectomy	6 m, dead
3	1990	11	47	F	GEJ	5	Infiltrative ulcerative	Epigastric distension	T4	N+	ovary	+	focal+	-	NA	Gastrectomy, bilateral salpingooophorectomy and chemotherapy	8 m, alive wd
4	1993	12	63	M	Body, antrum	11	NA	NA	T4a	Nx	liver	+	NA	-	+	gastric cancer resection	2 m, dead
5	1993	12	60	M	body	8	NA	NA	T3	Nx	M0	+	NA	-	focal+	gastric cancer resection	49 m, alive fd
6	1993	12	68	M	antrum	3	NA	NA	T1b	Nx	M0	focal+	NA	focal+	focal+	gastric cancer resection	60 m, alive fd
7	1993	12	74	F	body, antrum	12	NA	NA	T4	Nx	liver	focal+	NA	+	focal+	gastric cancer resection	1 m, dead
8	1993	12	55	M	antrum	8	NA	NA	T4	Nx	M0	+	NA	-	+	gastric cancer resection	3 m, dead
9	1993	12	58	M	body, antrum	13	NA	NA	T3	Nx	M0	focal+	NA	focal+	focal+	gastric cancer resection	6 m, dead
10	2002	13	53	M	antrum	3.5	polypoid	hematemesis	T3	Nx	liver	+	-	-	NA	Subtotal gastric cancer and liver wedge resection	8 m, alive fd
11	2007	14	70	F	Cardia, body	21	Infiltrative ulcerative	Epigastric discomfort	T4	Nx	M0	+	NA	NA	+	palliative gastric resection with chemotherapy	16 days, dead
12	2007	15	62	F	body	15	polypoid	Epigastric pain	T3	N+	liver	+	-	-	NA	gastric cancer resection	12 m, dead
13	2012	1	62	F	fundus	20	polypoid	Epigastric pain	T4	N+	liver	+	-	+	NA	Gastrectomy and RFA for liver metastasis	4 m, dead
14	2013	16	76	M	cardia	4	polypoid	melana	Tx	Nx	M0	+	+	+	NA	Gastrectomy of remnant stomach	7 m, alive fd
15	2013	17	80	F	fundus	7.5	polypoid	Epigastric pain	T2	N+	M0	+	-	NA	NA	palliative gastric resection with omentectomy	3 m, alive fd
16	2013	18	51	F	antrum	12	Infiltrative ulcerative	Epigastric pain	T4	N+	peritoneum	+	+	+	NA	palliative gastric resection with chemotherapy	NA
17	2015	19	49	M	antrum, body	14	polypoid	melana	T4	N+	M0	+	focal+	NA	NA	resection of distal stom-ach, gallbladder and right hemicolon	2 m, alive fd

EGDS: esophagogastroduodenoscopy; GEJ, gastroesophageal junction; NA, non-available. N+, lymphnode positive; RFA, radiofrenquency ablation; wd, with disease; fd, free of disease; m, month.

into the PubMed database from 1980 to 2015 and excluded the cases of carcinosarcoma on the basis of the following definitions. Keywords used were Gastric Sarcomatoid Carcinoma OR Gastric Carcinosarcoma OR Spindle cell carcinoma, Stomach OR Stomach neoplasms, Vimentin positive. Only those sarcomatous component stains positive, at least focally, for at least one epithelial marker could be diagnosed as true sarcomatoid carcinoma. By contrast, when the sarcomatous components do not express epithelial markers or reveal typical specialized differentiation, such as the obvious striation of rhabdomyosarcoma or osteoid production by malignant neoplastic cells, the diagnosis should be carcinosarcoma. In total, we found 18 cases of gastric sarcomatoid carcinoma (including our report) (**Table 2**) [11-19]. Females (8 cases) were similarly affected as males (10 cases). The median age was 62 years (range, 47-80) and median tumor diameter was 9.5 cm. It could arise from all areas of the stomach and it did not occur more frequently in any one area. 8 cases were polypoid and 4 cases were ulcerated in appearance. Most of cases were in advanced stage at diagnosis. 10 cases had T4, 7 cases had lymphnodes metastasis, 9 cases had distant metastasis and liver was the most often metastatic site. Although 17 patients had a surgical procedure and in most cases curative surgery was performed, the median survival was only 6.5 m. Of note, 3 patients survived as long as 45 m, 49 m and 60 m respectively, which might be due to their early tumor stage at diagnosis (T1b to T3, N0 or Nx, M0).

Discussion

Sarcomatoid carcinoma arising from stomach is a rare tumor of unclear etiology and pathogenesis. Sarcomatoid carcinoma and carcinosarcoma were often mixed up and most cases reported in literature did not make such a distinction. Only those sarcomatous component stains positive, at least focally, for at least one epithelial marker could be diagnosed as true sarcomatoid carcinoma, for sarcomatoid carcinoma was considered to develop through a "conversion theory" (known as epithelial-to-mesenchymal metaplastic transformation [20]. In the present case, loss of membrane E-cadherin and β-catenin indicated the occurrence of EMT and validated the conversion theory. Based on the above histological and immunohistochemical characteristics, we found more than half of 13 cases in the review by Cirocchi [1] should be diagnosed as carcinosarcoma, while the others could be classified as sarcomatoid carcinoma or undefined. Whether such distinction is of clinical value remains unknown. However, both of them seem to have dismal prognosis. Besides, few cases of gastric sarcomatoid carcinoma have been reported on their response to chemotherapy [14], the case we reported here was extremely aggressive and refractory to chemotherapy. Thus we need a comprehensive dissection of the molecular mechanisms underlying the initiation and progression of this disease and then develop novel therapeutic strategies to specifically target it.

Next-generation sequencing (NGS) is a powerful technology for elucidating the pathogenesis of human cancer and identifying potential therapeutic targets. As far as we know, this is the first case report analyzing its genetic alterations by NGS in gastric sarcomatoid carcinoma. For the sarcomatoid carcinomas from lung [21] and urinary tract [22], they shared the similar molecular characteristics as carcinomas, thus basically, sarcomatoid carcinoma was considered to be a special type of carcinoma. However, there have not been similar comparative study of genetic variations on gastric sarcomatoid carcinoma with carcinomas. The case presented here was found to have a high mutation load and nine genes were detected to have a point mutation. Of note, five genes had high mutation frequency which included *TP53, ETV1, SOX21, GATA6, FAT1* and might be the candidate driver mutated genes in this case. Except for *TP53*, the other four gene mutations were uncommon in gastric cancer [23] which might result from the fact that gastric cancer is a highly heterogeneous disease and each patient has distinct genetic and molecular profile. Most of these point mutations in this case have not been observed in COSMIC database and their functional data were still lacking except *TP53*. However, considering the important roles in tumor growth and invasion of these four genes (*ETV1, SOX21, GATA6, FAT1*) [3-6], we could postulate that they contributed to the aggressiveness of this case. In addition, four genes (*TP53, ETV1, GATA6, FAT1*) were all involved in EMT [5, 6, 24, 25] and might contribute to EMT phenotype and chemotherapy resistance in the

present case. Unfortunately, the functional roles of these mutated genes are sparse and the road to targeted therapy against them are still long.

In addition to high load of genes mutation in this case, five genes exhibited copy number variation. Except GATA2, copy number variations of the other four genes (*CCND1, SOX2, RPTOR* and *Rb1*) have been reported in gastric neoplasms of COSMIC database with a low frequency. Of note, copy number gain of *CCND1* and *SOX2* genes which encode cyclin D1 and stem cell factor Sox2 respectively, as well as copy number loss of Rb1 could synergistically promote cancer cell proliferation [26-28]. Besides, *GATA2* was considered to be a potential metastasis-driving gene [29], which might contribute to the rapid liver metastasis in this case.

By far, there are no specific treatment guidelines due to the limited number of cases of gastric sarcomatoid carcinoma. However, early diagnosis and radical surgery with adjuvant chemotherapy may be an important approach to improve the dismal prognosis. Since most cases will relapse and metastasize, new targeted therapies should be developed, which warrants whole-genome sequencing and comprehensive molecular profiling in more cases in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jing Hao, Department of Medical Oncology, Qilu Hospital of Shandong University, Wenhua West Road 107, Jinan 250012, China. Tel: 86-0531-82169841; Fax: 86-0531-86927544; E-mail: hedi0084@hotmail.com

References

[1] Cirocchi R, Trastulli S, Desiderio J, Grassi V, Barillaro I, Santoro A, Boselli C, Avenia N, Noya G and DE Sol A. Gastric carcinosarcoma: A case report and review of the literature. Oncol Lett 2012; 4: 53-57.

[2] Pan Y and Haines DS. Identification of a tumor-derived p53 mutant with novel transactivating selectivity. Oncogene 2000; 19: 3095-3100.

[3] Oh S, Shin S and Janknecht R. ETV1, 4 and 5: an oncogenic subfamily of ETS transcription factors. Biochim Biophys Acta 2012; 1826: 1-12.

[4] Caglayan D, Lundin E, Kastemar M, Westermark B and Ferletta M. Sox21 inhibits glioma progression in vivo by forming complexes with Sox2 and stimulating aberrant differentiation. Int J Cancer 2013; 133: 1345-1356.

[5] Song Y, Tian T, Fu X, Wang W, Li S, Shi T, Suo A, Ruan Z, Guo H and Yao Y. GATA6 is overexpressed in breast cancer and promotes breast cancer cell epithelial-mesenchymal transition by upregulating slug expression. Exp Mol Pathol 2015; 99: 617-627.

[6] Morris LG, Kaufman AM, Gong Y, Ramaswami D, Walsh LA, Turcan S, Eng S, Kannan K, Zou Y, Peng L, Banuchi VE, Paty P, Zeng Z, Vakiani E, Solit D, Singh B, Ganly I, Liau L, Cloughesy TC, Mischel PS, Mellinghoff IK and Chan TA. Recurrent somatic mutation of FAT1 in multiple human cancers leads to aberrant Wnt activation. Nat Genet 2013; 45: 253-261.

[7] Alper O and Bowden ET. Novel insights into c-Src. Curr Pharm Des 2005; 11: 1119-1130.

[8] Vougiouklakis T, Hamamoto R, Nakamura Y and Saloura V. The NSD family of protein methyltransferases in human cancer. Epigenomics 2015; 7: 863-874.

[9] Duan Z, Li FQ, Wechsler J, Meade-White K, Williams K, Benson KF and Horwitz M. A novel notch protein, N2N, targeted by neutrophil elastase and implicated in hereditary neutropenia. Mol Cell Biol 2004; 24: 58-70.

[10] Mittal P, Shin YH, Yatsenko SA, Castro CA, Surti U and Rajkovic A. Med12 gain-of-function mutation causes leiomyomas and genomic instability. J Clin Invest 2015; 125: 3280-3284.

[11] Robey-Cafferty SS, Grignon DJ, Ro JY, Cleary KR, Ayala AG, Ordonez NG and Mackay B. Sarcomatoid carcinoma of the stomach. A report of three cases with immunohistochemical and ultrastructural observations. Cancer 1990; 65: 1601-1606.

[12] Ueyama T, Nagai E, Yao T and Tsuneyoshi M. Vimentin-positive gastric carcinomas with rhabdoid features. A clinicopathologic and immunohistochemical study. Am J Surg Pathol 1993; 17: 813-819.

[13] Kayaselcuk F, Tuncer I, Toyganozu Y, Bal N and Ozgur G. Carcinosarcoma of the stomach. Pathol Oncol Res 2002; 8: 275-277.

[14] Ikeda Y, Kosugi S, Nishikura K, Ohashi M, Kanda T, Kobayashi T and Hatakeyama K. Gastric carcinosarcoma presenting as a huge epigastric mass. Gastric Cancer 2007; 10: 63-68.

[15] Randjelovic T, Filipovic B, Babic D, Cemerikic V and Filipovic B. Carcinosarcoma of the stomach: a case report and review of the literature. World J Gastroenterol 2007; 13: 5533-5536.

[16] Sato A, Oki E, Kohso H, Endo Y, Uchida H, Hiroshige S, Ishida M, Saito G, Matsumoto T,

Takeuchi H, Kusumoto T, Yoshikawa Y and Muto Y. Sarcomatoid carcinoma of the remnant stomach: report of a case. Surg Today 2013; 43: 308-312.

[17] Carboni F, Levi Sandri GB, Valle M, Covello R and Garofalo A. Gastric sarcomatoid carcinoma. J Gastrointest Surg 2013; 17: 2025-2027.

[18] Choi KW, Lee WY, Hong SW, Chang YG, Lee B and Lee HK. Carcinosarcoma of the stomach: a case report. J Gastric Cancer 2013; 13: 69-72.

[19] Zhu CC, Li MR, Lin TL and Zhao G. Sarcomatoid carcinoma of the stomach: A case report and literature review. Oncol Lett 2015; 10: 1385-1389.

[20] Virgilio E, Mercantini P, Tarantino G, Masyuk M, La Gumina G and Ziparo V. Diagnosing sarcomatoid carcinoma and carcinosarcoma of the large bowel: heads or tails? Int J Surg Pathol 2015; 23: 92-93.

[21] Fallet V, Saffroy R, Girard N, Mazieres J, Lantuejoul S, Vieira T, Rouquette I, Thivolet-Bejui F, Ung M, Poulot V, Schlick L, Moro-Sibilot D, Antoine M, Cadranel J, Lemoine A and Wislez M. High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta Panel: exploring therapeutic targets. Ann Oncol 2015; 26: 1748-1753.

[22] Wang X, MacLennan GT, Zhang S, Montironi R, Lopez-Beltran A, Tan PH, Foster S, Baldridge LA and Cheng L. Sarcomatoid carcinoma of the upper urinary tract: clinical outcome and molecular characterization. Hum Pathol 2009; 40: 211-217.

[23] Liang H and Kim YH. Identifying molecular drivers of gastric cancer through next-generation sequencing. Cancer Lett 2013; 340: 241-246.

[24] Chang CJ, Chao CH, Xia W, Yang JY, Xiong Y, Li CW, Yu WH, Rehman SK, Hsu JL, Lee HH, Liu M, Chen CT, Yu D and Hung MC. p53 regulates epithelial-mesenchymal transition and stem cell properties through modulating miRNAs. Nat Cell Biol 2011; 13: 317-323.

[25] Li Z, Zhang L, Ma Z, Yang M, Tang J, Fu Y, Mao Y, Hong X and Zhang Y. ETV1 induces epithelial to mesenchymal transition in human gastric cancer cells through the upregulation of Snail expression. Oncol Rep 2013; 30: 2859-2863.

[26] Hutz K, Mejias-Luque R, Farsakova K, Ogris M, Krebs S, Anton M, Vieth M, Schuller U, Schneider MR, Blum H, Wagner E, Jung A and Gerhard M. The stem cell factor SOX2 regulates the tumorigenic potential in human gastric cancer cells. Carcinogenesis 2014; 35: 942-950.

[27] Seo JH, Jeong ES, Lee KS, Heo SH, Jeong DG and Choi YK. Lentivirus-mediated shRNA targeting of cyclin D1 enhances the chemosensitivity of human gastric cancer to 5-fluorouracil. Int J Oncol 2013; 43: 2007-2014.

[28] Kouraklis G, Katsoulis IE, Theocharis S, Tsourouflis G, Xipolitas N, Glinavou A, Sioka C and Kostakis A. Does the expression of cyclin E, pRb, and p21 correlate with prognosis in gastric adenocarcinoma? Dig Dis Sci 2009; 54: 1015-1020.

[29] Chiang YT, Wang K, Fazli L, Qi RZ, Gleave ME, Collins CC, Gout PW and Wang Y. GATA2 as a potential metastasis-driving gene in prostate cancer. Oncotarget 2014; 5: 451-461.