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CASE REPORT

Gastric adenocarcinoma with rhabdoid morphology

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Abstract Extrarenal rhabdoid tumors (ERRTs) are very rare neoplasms and have been reported in a range of organs, including sixteen cases in the stomach. We describe a woman aged 86 years who had an advanced gastric tumor with lymph node metastasis. The tumor mostly showed a diffuse arrangement with a small glandular region. The tumor cells were non-cohesive and had polygonal morphology with eccentric vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm, i.e. they showed rhabdoid features. Immunohistochemically, the rhabdoid tumor cells were strongly positive for cytokeratins and vimentin. However, a candidate tumor suppressor gene of rhabdoid tumors, the *INI1* gene, showed no mutations or loss of expression in the tumor cells. Although ERRTs typically have an aggressive clinical course, the patient was still alive without any evidence of recurrence or metastasis at 26 months after surgery. The rhabdoid features of the present case seemed to be a variant of gastric adenocarcinoma.

Keywords Adenocarcinoma · *INI1* · Rhabdoid

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Introduction

Extrarenal rhabdoid tumor (ERRT) has been described in many sites, including the liver, skin, central nervous system, orbit, mediastinum, peritoneal cavity, and urinary bladder [1–10]. To date, sixteen cases of gastric ERRTs [11–17] have been reported.

Here, we present a rare case of a primary gastric adenocarcinoma showing rhabdoid features.

Case presentation

An 86-year-old woman who was diagnosed with a left incarcerated obturator hernia underwent radical surgery. During postoperative imaging procedures, a gastric tumor was detected. Endoscopic examination revealed a mass on the posterior wall of the gastric body. Biopsy of the mass revealed a moderately differentiated tubular adenocarcinoma. The patient's history and family history were unremarkable. Laboratory data on admission showed serum levels of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) of 433.9 U/ml and 4.5 ng/ml, respectively. No tumoral lesion was found in any other organs. About 1 month after the above surgery, the patient underwent en-bloc distal gastrectomy with Billroth-I reconstruction and regional lymph node dissection. After the operation, the serum CA19-9 level was 26.6 U/ml and CEA was 2.8 ng/ml. The patient was still alive without any evidence of recurrence or metastasis at 26 months after the gastrectomy.

Pathological findings

The tumor was located in the posterior wall of the gastric body. The gross features showed an ulcerating infiltrative

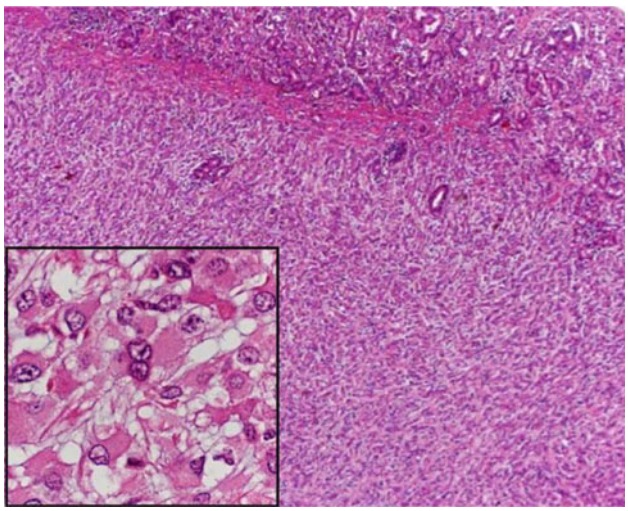

Fig. 1 At low magnification (H&E, ×40), the gastric tumor mostly shows a solid pattern. The surface portion of the tumor is partially consistent with moderately differentiated tubular adenocarcinoma. At high magnification (*inset*, H&E, ×600), tumor cells in the *solid area* have vesicular nuclei and abundant eosinophilic cytoplasm. Some cells show rhabdoid features with eccentric nuclei and intracytoplasmic paranuclear inclusions

type that was 5.4 cm in diameter. The tumor had invaded the subserosal portion of the gastric wall. The tumor cells had grown in a diffuse arrangement, with glandular structures (<10%) on the surface of the tumor, corresponding to moderately differentiated tubular adenocarcinoma (H&E staining; Fig. 1). However, most of the tumor cells were non-cohesive, with a polygonal morphology, showing rhabdoid features, with eccentric vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Fig. 1, inset). Some paranuclear inclusions were also noted in the cytoplasm. There were numerous mitotic figures. We also noted a morphological transition between the two components. The stroma of the tumor was scanty and supported by delicate fibrovascular components. Periodic acid-Schiff staining showed mucin in the glandular tumor cells, but not in the rhabdoid tumor cells. Four of the 21 regional lymph nodes showed metastases that consisted of rhabdoid cells, but not glandular cells.

We next performed immunohistochemical analysis, using antibodies from Dako (Glostrup, Denmark), except for anti-low molecular cytokeratin and INI1 (CAM5.2 and 25/BAF47, respectively), which were from Becton–Dickinson Biosciences (Franklin Lakes, NJ, USA). Antibodies for α-fetoprotein (AFP), human chorionic gonadotropin (hCG), c-Kit, S-100 protein, and myoglobin were rabbit polyclonal and the others were mouse monoclonal. The tumor sections were stained immunohistochemically using the streptavidin–biotin-peroxidase complex (SAB) method, as previously described [18]. The immunohistochemical studies showed strong reactivity for pan-cytokeratin (Fig. 2a, left), low-molecular weight cytokeratin (CAM5.2), cytokeratin 7, and epithelial membrane antigen (EMA), with the strongest staining being paranuclear and corresponding to the inclusions shown in the H&E-stained sections. Immunohistochemistry also showed that the rhabdoid cells were positive for vimentin (Fig. 2a, right) and negative for E-cadherin (Fig. 2b), CEA, and CA19-9. In contrast, cells in the moderately differentiated component were negative for vimentin and positive for E-cadherin (Fig. 2b), CEA, and CA19-9. All of the tumor cells were negative for AFP, hCG, desmin, myoglobin, smooth muscle actin, S-100 protein, CD34, and c-Kit. The rate of Ki-67-positive tumor cells in the glandular and rhabdoid components was 46.4 and 82.8%, respectively (Fig. 2c). We confirmed immunoreactivity for the protein products of the *INI1* gene in the nuclei of rhabdoid cells, carcinomatous cells, and non-tumoral foveolar cells (Fig. 2d). Table 1 summarizes the immunoprofiling of the cancer cells.

Mutation analysis

We examined whether mutations in the *INI1* gene were present, using DNA extracted from paraffin sections of the tumor, as previously described [19]. We used primer pairs that were previously reported to detect exons 1–9 of the *IN11* gene [20]. For exon 8, we constructed an original primer for nested polymerase chain reaction (PCR) (5′-agggcacagacaggggccaaagc-3′ and 5′-cctgtgggcagagcccag gac-3′). Each exon extracted from the primary tumor and lymph node metastasis was detected by PCR. The PCR products were directly sequenced and the sequences were compared with those held in the GenBank database (accession no. U04847). However, no mutations were detected (data not shown).

Discussion

Extrarenal rhabdoid tumors (ERRTs) are exceedingly rare in the stomach, and only 16 cases have been reported to date. These cases, as well as the present case, are summarized in Table 2. Ueyama et al. [11] reported that only four gastric tumors, of 5437 cases of gastric adenocarcinoma, showed rhabdoid features. These tumors consisted of either poorly differentiated or non-cohesive round to polygonal cells, and co-expressed keratins and vimentin [11–13]. The presence of a few glandular structures might suggest an adenocarcinoma cell origin, as in our case. Moreover, immunohistochemical profiling revealed an absence of features that could assign this tumor to a specific category, such as myogenic, neural, glial, or

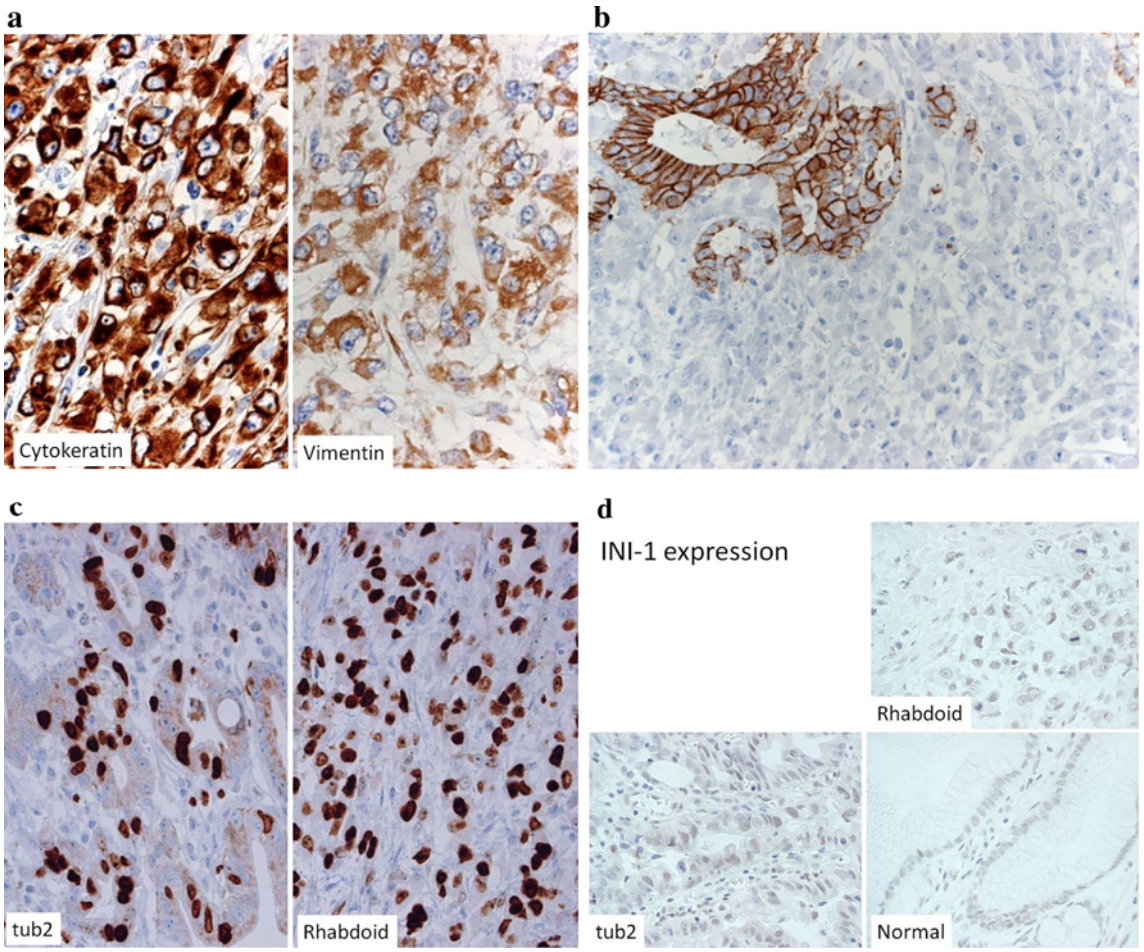

Fig. 2 **a** The tumor cells show intracytoplasmic immunostaining for cytokeratin (AE1/AE3) (*left*) and vimentin (*right*) (×600). **b** E-cadherin is strongly expressed in the glandular components (*left*) of the tumor, but not in the rhabdoid components (*right*) (×600). **c** Immunoreactivity for Ki67 in the nucleus of tubular adenocarcinoma (*tub2*) and rhabdoid cells (×600). **d** Immunoreactivity for INI1 in the nucleus of *rhabdoid* cells, tubular adenocarcinoma (*tub2*), and normal foveolar cells (*Normal*) (×600). Some stromal cells in each portion are also weakly stained

interstitial cells of Cajal. Additionally, the high Ki-67 labeling index and the loss of E-cadherin expression suggested that the tumor cells had extremely high proliferative potential and had lost the cohesive function of the E-cadherin system.

ERRTs, similar to classical RTs, are very aggressive, with very poor prognoses [1]. It is of note that eight of the above reported seventeen patients died within 6 months after surgery (Table 2). All of these patients were thought to have had distant metastasis at the time of the surgery. In the present patient, metastatic tumors were noted in four of a total of 21 regional lymph nodes, although the patient was still alive with no evidence of recurrence or metastasis 26 months after surgery. Accordingly, it seems that patients with gastric ERRT can be cured by sufficient resection, even if they have lymph node metastasis.

Cytogenetic studies have discovered a mutation of the *Hsnf5/INI1* gene, located on chromosomal band 22q11.2, in renal RT and ERRT [21]. Accordingly, the *INI1* gene seems to be a tumor suppressor involved in both RT and ERRT. In the present case, we found no mutations in the *INI* gene, and no abnormal protein expression. These findings suggest two possibilities. First, there may have been no mutations of the *INI* gene in this tumor. Although INI1 protein was recognized by immunohistochemistry, its expression tended to be weaker in the tumor tissue than in the surrounding normal epithelium. Second, because of post-translational changes, such as phosphorylation, the functions of the INI1 protein may have been abnormal. Hoot et al. [22] reported that *INI1* gene mutations were not present in five of 19 RTs and one of eight ERRTs in children. ERRT, in addition to *INI* gene mutations, might also be caused by the loss of INI protein function or by other, still unknown factors.

Most ERRTs are considered to be biphasic lesions composed of rhabdoid cells and either carcinomatous or

Table 1 Immunoprofiling of the tumor cells

Antibodies	Clone	Commercial source	Dilution	Antigen retrieval	Reactivity of the tumor cells	
					Rhabdoid cells	Glandular cells
Vimentin	Vim 3 B4	DAKO	1/100	MW/EDTA	+	−
Pan-CK	AE1/AE3	DAKO	1/100	Pro	+	+
CK (low molecular)	CAM 5.2	Becton–Dickinson Biosciences	Diluted	Pro	+	+
CK7	OV-TL12/30	DAKO	1/100	Pro	+	+
EMA	E29	DAKO	1/100	Pro	+	+
E-cadherin	NCH-38	DAKO	1/100	MW/CB	−	+
CA 19-9	116-NS-19-9	DAKO	1/50	−	−	+
CEA	II-7	DAKO	1/50	MW/CB	−	+
AFP	Poly (rabbit)	DAKO	1/1000	−	−	−
hCG	Poly (rabbit)	DAKO	1/500	−	−	−
Desmin	D 33	DAKO	1/50	MW/CB	−	−
Myoglobin	Poly (rabbit)	DAKO	1/1000	−	−	−
S-100 protein	Poly (rabbit)	DAKO	1/500	MW/CB	−	−
CD 34	BI-3C5	DAKO	1/50	MW/CB	−	−
c Kit	Poly (rabbit)	DAKO	1/100	MW/CB	−	−
Ki67 LI	MIB-1	DAKO	1/100	MW/CB	82.8%	46.4%
INI	25/BAF 47	Becton–Dickinson Biosciences	1/100	MW/CB	+	+

CK cytokeratin, *CEA* carcinoembryonic antigen, *EDTA* ethylenediaminetetraacetic acid, *EMA* epithelial membrane antigen, *AFP* alpha-feto-protein, *hCG* human chorionic gonadotropin, *LI* labeling index, *MW* microwave, *Pro* protease, *CA* carbohydrate antigen, *CB* citrate buffer

Table 2 Clinicopathological findings in the present patient and 16 previously reported patients with gastric adenocarcinoma with rhabdoid features

Case no.	Reference	Age (years)/sex	Tumor size (cm)	Glandular component	Metastasis	Follow-up (months)	
						DOD	Alive
1	[11, 12]	63/M	11	Present	Liver	2	
2	[11, 12]	60/M	8	Present	(−)		49
3	[11, 12]	68/M	3	Present	(−)		60
4	[11, 12]	58/M	13	Present	(−)	6	
5	[12]	No data	No data	Present	LN		6
6	[12]	No data	No data	Present	LN	5	
7	[12]	No data	No data	Present	LN	No data	
8	[12]	No data	No data	Present	LN	5	
9	[12]	No data	No data	Absent	No data	29	
10	[12]	No data	No data	Absent	LN	9	
11	[12]	No data	No data	Absent	(−)	2	
12	[12]	No data	No data	Present	No data		36
13	[14]	59/F	16	Absent	Liver, lung	4	
14	[15]	73/F	9	Present	Umbilical region	3	
15	[16]	52/M	13	Present	Liver, LN	4	
16	[17]	40/F	12	No data	No data	No data	
17	Present patient	86/F	5.4	Present	LN		26

LN lymph node, *DOD* dead of disease

mesenchymal cells. Parham et al. [1] have suggested that ERRTs are a heterogeneous group of unrelated tumors with cellular morphology similar to that of renal RTs. Moreover, Pinto et al. [15] suggested that the rhabdoid areas probably represent a phenotypic variant of gastric adenocarcinoma. Twelve of the seventeen reported cases of gastric ERRT,

including the present case, exhibited a carcinomatous component (Table 2). The cells with rhabdoid features were positive for vimentin in all 17 cases, and they were positive for cytokeratin or EMA in 16 cases. Although the morphological and immunohistochemical findings for gastric ERRTs are similar to those for renal RT, the findings in our patient support the hypothesis that gastric ERRTs originate from epithelial components.

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