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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Primary gastric tumors in infants and children: 15 cases of 20-year report

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Abstract
Purpose Primary gastric tumors in infants and children are rare, and their diagnosis and treatment have not been standardized to date. The objective of the present retrospective study was to analyze the clinical characteristics of these tumors and explore possible improvements in their diagnosis and treatment.
Methods The study included 15 children with a diagnosis of primary gastric tumor confirmed by pathology. Clinical manifestations, diagnostic methods and treatment were analyzed retrospectively, and postoperative conditions were assessed in follow-up evaluations.
Results There were nine boys and six girls aged 8 months to 13 years. The main presenting symptoms were abdominal pain, melena, fever of undetermined origin and pallor. Children were assessed by ultrasound, CT and upper gastrointestinal barium meal or gastroscopy and showed abdominal blockage or polypoid space-occupying lesions. All patients underwent surgery as initial treatment, and four patients received postoperative chemotherapy. During the follow-up period from 3 to 92 months, four cases were lost, one patient died of metastatic disease, two patients showed recurrence, and the remaining patients were alive without recurrence or progression.
Conclusions Owing to the atypical and often asymptomatic presentation of primary gastric tumors, careful evaluation using imaging modalities is critical in suspicious cases. Most primary gastric tumors in infants and children are benign or borderline. The prognosis, except in gastric carcinoma, is excellent with close follow-up when complete resection is achieved.

Keywords Child · Stomach neoplasm · Diagnosis · Treatment

Introduction

Primary gastric tumors in infants and children are clinically rare. However, unlike primary gastric tumors in adults, tumors that develop during infancy or childhood include a wide range of pathological types that are different from those in adulthood (Curtis et al. 2008; Wang and Chetty 2012a). Owing to the rarity of the disease, most cases are reported on an individual basis and a systematic analysis of the disease is lacking. Therefore, a strategy for the diagnosis and treatment of this disease has not been established to date. Advances in diagnostic technology have resulted in an increase in the incidence of primary gastric tumors in recent years. In the present study, cases reported in the last 5 years accounted for 67 % of all reported cases (10/15). Here, we performed a retrospective study of infants and children with primary gastric tumors to summarize the clinical features of this disease and to explore diagnostic and therapeutic approaches. Our results provide important insight into management strategies for patients with these challenging diseases.

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Materials and methods

Patients

A retrospective study was conducted at Children's Hospital of Fudan University. The medical records and pathology reports of 15 patients with primary gastric tumors were obtained from the case management system in the medical record room by retrieving all cases of gastric space-occupying lesions between March 1993 and March 2014. All eligible patients were identified by pathological diagnosis. Metastatic gastric tumors, stomach gastric polyposis and gastric ulcer diseases were excluded. Clinical data of these patients, including sex, age, onset characteristics, diagnostic methods and treatment, were recorded and analyzed.

In addition, all children were followed up through clinic visits at 1, 3 and 6 months and 2 years after surgery. In these visits, the patients were evaluated by physical examination and imaging tests, including postoperative gastroscopy and/or gastrointestinal contrast radiography and/or abdominal CT. Serum alpha-fetoprotein (AFP) levels were tested in patients with gastric teratoma or germ cell tumors. Patients who failed to visit on time or those who had been followed up for more than 2 years were contacted by telephone calls or letters. Follow-up information obtained in this manner included data on children's health and the results of tests performed in other hospitals.

Results

Patient characteristics

The clinical details of the 15 patients are summarized in Table 1. The 15 patients included 9 boys and 6 girls aged 8 months to 13 years (median 6.5 years). Two children were diagnosed during infancy (<1 year old), two in the early childhood (1–3 years old), five in the preschool period (3–6 years old), one in the school-age period (6–10 years of age) and five during adolescence (older than 10 years of age).

The main complaints of most patients were abdominal pain (26.7 %), fever (46.7 %) and melena (26.7 %). In addition, two patients with adenoma had pigmentation in the mucosa and skin associated with Peutz–Jeghers syndrome. In four patients, a hard lumpy mass was detected in the left central abdomen on palpation, and two patients presented with periumbilical tenderness. Eleven cases showed paleness at their first visit.

Table 1 Clinical details and tumor characteristics

No.	Gender	Age	Initial symptom	Pathology	Maximum diameter of tumors (cm)	Metastasis
1	M	11 years	Paleness, melena	Leiomyosarcoma	3.5	No
2	F	10 years	Abdominal pain	Leiomyosarcoma	3	No
3	M	11 years	Abdominal pain	Adenocarcinoma (poorly differentiated)	4	Liver and left supraclavicular lymph nodes
4	F	3 years	Melena	Mixed germ cell tumor	10	Adjacent organs and peritoneal lymph node
5	M	12 years	Bloody stool	Gastric epitheliomesenchymal biphasic tumor	7	No
6	M	4 years	Fever, melena	Inflammatory myofibroblastic tumor	6.5	No
7	F	5 years	Abdominal pain, Low fever	Inflammatory myofibroblastic tumor	6.5	No
8	M	8 m	Recurrent fever	Inflammatory myofibroblastic tumor	6	No
9	F	1 years	Paleness, recurrent fever	Inflammatory myofibroblastic tumor	10	Invasion of the pancreatic tail
10	F	6 years	Paleness, fever	Inflammatory myofibroblastic tumor	5	No
11	M	9 m	Recurrent fever	Immature teratoma (grade I)	10	No
12	M	8 years	Abdominal pain	Vascular tumor	4	No
13	F	3 years	Recurrent melena	Adenoma	6	No
14	M	6 years	Paleness	Adenoma	8	No
15	M	13 years	Paleness, low fever	Stromal tumor	7	No

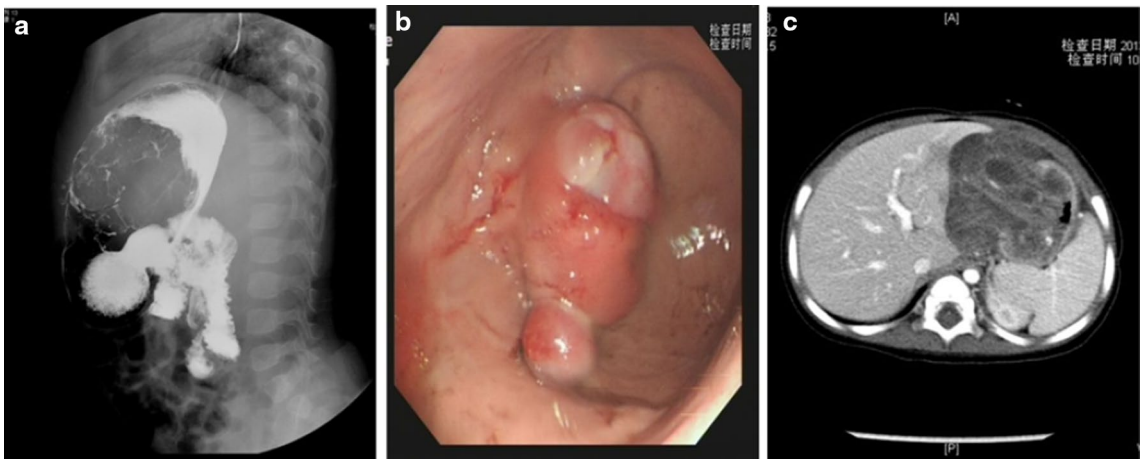

Fig. 1 Imaging findings of gastric tumors. **a** UGI showed a huge filling defect in the stomach (patient number 11). **b** Gastroscopy was characterized by a mass in the gastric mucosa (patient number 10). **c** CT showed abnormal density in the upper left abdomen (patient number 11)

Laboratory examination and imaging findings

Abnormally elevated AFP was detected in two germ cell tumors (216.2 and 681.1 ng/mL). Other common tumor markers such as CEA, CA-125, CA-199, NSE and VMA were normal or slightly higher than normal. Significantly decreased levels of hemoglobin (Hb) (<90 g/L) were observed in twelve cases (80 %), and four of these patients had severe anemia (<60 g/L).

Ultrasound examination was performed in twelve patients. Among these, nine showed a positive sign in the left upper quadrant described as a low echo area or uneven lesions; two were false-negative cases, suggesting the abdomen without space-occupying; one case was misdiagnosed as a liver lesion. Among 10 patients who underwent upper gastrointestinal barium radiography (UGI), nine had a positive result, showing an irregular filling defect in the stomach (Fig. 1); one case was misdiagnosed as antral gastritis. Of 13 cases undergoing gastroscopy who were characterized by a mass in the gastric mucosa or depressed lesions under the gastroscopy (Fig. 1), three underwent biopsy, which was negative for tumor cells and revealed mild mucositis. Thirteen cases underwent computed tomography (CT) examination, and all of them showed abnormal density in the upper left abdomen (Fig. 1).

Pathological diagnosis and gastric tumor characteristics (Table 1)

All 15 cases were identified by pathological diagnosis, which revealed nine pathological types. Four cases were benign tumors, including one gastric immature teratoma (level I), one gastric vascular tumor and two gastric adenomas. There were six borderline tumors, including gastric inflammatory myofibroblastic tumor in five cases and gastric epitheliomesenchymal biphasic tumor in one case. There were four malignant tumors, including one gastric mixed germ cell tumor (with an endodermal sinus pattern and a predominant immature teratoma component), one gastric adenocarcinoma and two gastric leiomyosarcoma. Special types of tumors included gastric stromal tumors (epithelioid cell type) in one case, with an intermediate-risk classification [according to the latest National Institute of Health risk classification (CSCO 2013)].

The maximum diameter of tumors ranged from 3 to 10 cm (mean, 6.4 cm), and it was <5 cm in four cases and >5 cm in 11 cases. The tumor site was the gastric antrum in five cases and the gastric body in 10 cases. Twelve (12/15) tumors were limited to the stomach. Among the remaining three cases (3/15), the mixed germ cell tumor had extensive adhesions to adjacent organs and peritoneal lymph node metastasis; one gastric adenocarcinoma had metastasized to the liver and left supraclavicular lymph nodes, and one inflammatory myofibroblastic tumor showed invasion of the pancreatic tail.

Treatment and follow-up results (Table 2)

All 15 patients were treated surgically. Of the four benign tumors, one patient with a benign teratoma underwent tumor resection and partial gastrectomy, one patient with a gastric vascular tumor underwent tumorectomy under laparoscopy, and two patients with gastric adenoma underwent polyp resection after failing to remove polyps under the gastroscope. Of the six borderline tumors, five patients with inflammatory myofibroblastic tumors underwent tumor resection and partial gastrectomy; one patient with gastric epitheliomesenchymal biphasic tumor underwent subtotal gastrectomy plus gastroduodenal anastomosis. Among the four malignant tumors, one patient with

Table 2 Treatment and outcome of 15 patients

Pathology	Operative procedure	Postoperative chemotherapy	Follow-up and outcome
Leiomyosarcoma	Subtotal gastrectomy, gastrointestinal anastomosis	1/2 Chemotherapy	2/2 Lost
Adenocarcinoma	Palliative tumor resection	No	Death 3 months after diagnosis
Mixed germ cell tumor	Subtotal gastrectomy, gastroesophagostomy, retroperitoneal lymph nodes removal	Chemotherapy	Event-free survival 42-month follow-up
Gastric epitheliomesenchymal biphasic tumor	Subtotal gastrectomy, gastroduodenostomy	No	Event-free survival, 8-month follow-up
Inflammatory myofibroblastic tumor	Tumor resection, partial gastrectomy	No	4/5 Patients survive with event free, 92-, 17-, 8-, 3-month follow-up (1 patient lost)
Immature teratoma (grade I)	Tumor resection, partial gastrectomy	No	Event-free survival, 11-month follow-up
Vascular tumor	Tumor resection under laparoscopy	No	Event-free survival, 20-month follow-up
Adenoma	Tumor resection	No	2/2 Patients relapse 3 and 7 months after operation
Stromal tumor	Subtotal gastrectomy, gastroduodenostomy	Imatinib	Lost

adenocarcinoma underwent palliative tumor resection, considering the metastases to the liver and left supraclavicular lymph nodes, and three patients (two cases of leiomyosarcoma and one case of mixed germ cell tumor) underwent subtotal gastrectomy plus gastrointestinal tract reconstruction (gastrojejunostomy, gastroduodenostomy or gastroesophagostomy). The margin of the resected specimen was free of tumor cells. Other tumors (the gastric stromal tumor) underwent subtotal gastrectomy plus gastroduodenal anastomosis. None of the 15 patents with gastric tumors received lymph node dissection, and just enlarged lymph nodes around the tumor were removed.

Two of the four malignant tumor cases received postoperative chemotherapy, one was a leiomyosarcoma treated with 2 cycles of the Johnson maintenance plan (including vincristine, cyclophosphamide and actinomycin-D), and the other one was a mixed germ cell tumor treated with the maintenance JEB scheme (including carboplatin, etoposide and bleomycin) for four cycles. The remaining two patients with leiomyosarcoma and adenocarcinoma did not receive chemotherapy because of parent refusal. One patient with a gastric stromal tumor was maintained on imatinib for 2 years.

Follow-up time ranged from 3 to 92 months. Four cases were lost to follow-up (Table 2). One patient with gastric adenocarcinoma died from disseminated disease 3 months after the initial diagnosis. Two patients had tumor recurrence detected by gastroscopy at 3 and 7 months after surgery. The remaining eight cases that were followed up to the end were in good condition and had no discomfort such as abdominal pain, abdominal distention, nausea, vomiting, dark stools or unexplained fever. Repeat GI, gastroscopy and CT scans of the abdomen revealed no abnormal signs. AFP levels in the two germ cell tumors returned to normal 1 month after surgery and showed no fluctuations in the follow-up period. Of the gastric malignant tumors, one patient died (1/4) and one case was followed up for 3.5 years without recurrence. Of the gastric benign and borderline tumors, two cases recurred, and the others had no recurrence or progression.

Discussion

Gastric tumors developing during infancy or childhood show a wide range of pathological types that differ from those in adults. In addition, some tumors that are often encountered in other sites rarely occur in the stomach (Anilkumar et al. 2013; Mehta et al. 2013; Sugandhi et al. 2012; Wang and Chetty 2012b). According to the current literature and clinical experience, benign tumors of the stomach include leiomyoma, benign teratoma, hemangioma or lymphangioma, adenoma, schwannoma, fibroma and nerve fibroma among others (Attash et al. 2012; GUPTA et al. 1995; Schettini et al. 2007). Borderline tumors of the stomach include inflammatory myofibroblastic tumors and epitheliomesenchymal biphasic tumor among others (Mehta et al. 2013; Miettinen et al. 2009; Shin et al. 2010); malignant tumors of the stomach include adenocarcinoma, leiomyosarcoma, malignant germ cell tumor (GCT), rhabdomyosarcoma, malignant lymphoma and peripheral primitive neuroectodermal tumor among others (Breitfeld and

Meyer 2005; Curtis et al. 2008; Dokucu et al. 2002; Gao 2013).

In adults, most primary gastric tumors originate from epithelial cells of the stomach and tend to be malignant. Benign tumors account for only 2 % of all gastric tumors (Wu 2007). By contrast, in infants and children, most tumors have a mesenchymal origin and the proportion of benign tumors is higher, accounting for more than 60 % of gastric tumors (Gao 2003). In the present study, most of the tumors originated from mesenchymal cells (14/15, 93.3 %), and 10 cases were borderline and benign tumors (10/15, 66.7 %), which is consistent with the literature reports. Similar to metastasis in adults, the most common types of metastasis in infants and children with gastric malignant tumors were lymph node metastasis and direct invasion to adjacent tissues in our study, and this is also consistent with the current literature.

In our series, primary gastric tumors tended to occur in the preschool period and adolescence, with 67 % of tumors occurring in these periods, and all tumors were located in the gastric body or gastric antrum. Because of the atypical symptoms and even asymptomatic presentation in some cases, most tumors were large or had metastasized at the time of detection. Initial symptoms included abdominal pain, melena or melana. Presentation can include signs of gastrointestinal obstruction or abdominal mass on palpation when the tumor is large. The initial symptoms can also be nonspecific, such as nausea, vomiting, constipation and diarrhea, or nongastrointestinal signs such as persistent fever, anemia and weight loss. Therefore, a careful and comprehensive history and physical examination are necessary, and a potential diagnosis of gastric tumor should be considered in children.

In suspicious cases, auxiliary tests are necessary to confirm or exclude gastric tumors. Although laboratory tests are not specific indicators, abnormally low hemoglobin or a positive fecal occult blood test needs further evaluation. Gastric teratomas, particularly when malignant, can be associated with abnormally elevated AFP levels; however, in infants younger than 8 months, a physiological increase in AFP needs to be distinguished from pathological changes (Saha 2010). CEA, CA-199 and CA125 were not elevated in our series; however, their value in the diagnosis of gastric tumors in infants and children differs from that in adults.

Imaging examination can provide reliable evidence to support a diagnosis. The detection rate of gastric tumors has increased significantly with recent developments in imaging technology. Ultrasound, CT, UGI and gastroscopy, when used alone or in combination with, have the ability to detect gastric lesions. Each method has its advantages and disadvantages for the diagnosis of gastric space-occupying lesions. Ultrasound is included in routine examinations because it is noninvasive and convenient. UGI has high sensitivity for the detection of gastric lesions, but it is not accurate for detecting tumors at the fundus of the stomach or submucosal exogenous tumors. Gastroscopy is an important examination for patients with upper gastrointestinal symptoms. It can accurately confirm the location of the mass in the gastric wall, and it can be used to collect biopsy samples for pathological diagnosis. Abdominal CT facilitates the accurate detection of masses and determining whether the tumor has invaded adjacent organs or is associated with lymph node metastases. Therefore, the complementation of these methods would offer higher diagnostic power.

Surgical resection is the primary treatment for gastric tumors. However, the types of surgery differ from those in adults and consist of complete tumor resection without digestive tract reconstruction or abdominal lymph node dissection. In the present study, only swollen lymph nodes were removed.

In infants and children with benign and borderline gastric tumors, treatment usually consists of tumor resection and stomach wall repair (Yaji et al. 2013). Recent advances in endoscopic instruments and techniques have challenged traditional laparotomy. An increasing number of case reports describe the successful treatment of gastric benign tumors under endoscopy. Endoscopic resection of gastric tubular adenoma is possible if the lesion is small and the pedicle is not wide. In the present study, the masses were too big, and two cases were treated by laparotomy to avoid bleeding and incomplete resection. In cases of villous adenoma, which has a higher potential for malignant transformation than that of tubular adenoma, laparotomy is strongly recommended (Gao 2003). Successful resection of stomach cavernous hemangioma under endoscopy has also been reported without complications or recurrence after removal (Garcia-Hernandez et al. 2012). However, endoscopic resection is currently not used as a routine operation except in cases of adenoma, and more experience needs to be gained.

In cases of malignant gastric tumors, subtotal gastrectomy with large tumor-free margins and digestive tract reconstruction is the standard procedure (Pauser and Grimm 2008; Son et al. 2014; Subbiah et al. 2011). Total gastrectomy is not usually performed because of its impact on the growth and development of children. If the tumor has invaded the surrounding organs and in cases of distant metastasis, surgery does not improve the prognosis, and palliative resection is performed when necessary to relieve symptoms.

Malignant gastric tumors in infants and children have unique biological characteristics that are different from those in adults; however, chemotherapy and radiotherapy are still largely based on principles used in adults (Harting et al. 2004) and data in the literature. For gastric adenocarcinoma, preoperative or postoperative adjuvant

chemoradiation is commonly used, and platinum-based chemotherapy combined with paclitaxel, doxorubicin or fluorouracil has been the standard frontline regimen (Schneider et al. 2012; Subbiah et al. 2011; Varadhachary and Ajani 2005). Nevertheless, the prognosis remains poor, especially in cases ineligible for tumor removal or those with adjacent tissues involved (Curtis et al. 2008). In a case report, all 5 patients analyzed showed disease progression despite postoperative chemotherapy, and the median time to disease progression was 4 months (Subbiah et al. 2011). In the present study, one patient died of disseminated metastases 1 month after surgery without chemotherapy. Leiomyosarcoma is not sensitive to chemotherapy, and Hidek et al. reported that it has a favorable prognosis even in cases showing aggressive histologic appearance. Case reports indicate good long-term results with no adjuvant therapy (Pauser and Grimm 2008; Yamamoto et al. 2004). Therefore, adjuvant therapy is not necessary when complete resection of the tumor is achieved (Yamamoto et al. 2004). Although teratoma in the presence of immature neuroepithelial elements is regarded as malignant, the prognosis of gastric teratoma is excellent after complete excision, and additional therapies such as chemotherapy and radiotherapy are not necessary (Anilkumar et al. 2013; Saha 2010; Yaji et al. 2013). Saha et al. suggested that it is safer to treat all patients with extragonadal immature teratomas by surgical excision followed by close observation, withholding chemotherapy until there is evidence of disease recurrence (Saha 2010). The recommended treatment for extragonadal malignant GCT is cisplatin-based chemotherapy. Mixed GCTs have been reported to be more aggressive. Ait et al. recommended four-cycle chemotherapy of bleomycin, etoposide and cisplatin (BEP) as the initial therapy, rather than surgery or radiation therapy (Ait et al. 2012). In our series, the patients with mixed GCTs were followed up for more than 3 years with no local recurrence or distant metastasis.

The GST expert consensus in 2013 suggested that the objective of surgery is to achieve RO resection for limited GST. Notably, tumors are often brittle, and surgeons need to avoid tumor rupture and intraoperative spread. In addition, intraoperative frozen biopsy is not recommended as a routine procedure (CSCO 2013). Gastric stromal tumors are not sensitive to radiotherapy and chemotherapy, although imatinib may be effective in CD-117-positive patients (Egloff et al. 2005).

Because of its rarity, the diagnosis and treatment of infants and children with primary gastric tumors remain a significant challenge. Owing to its atypical symptoms and even a potential asymptomatic presentation, suspicious cases need to be evaluated with the aid of imaging tests. Most primary gastric tumors in infants and children are benign or borderline tumors. The prognosis of gastric tumors is excellent when complete resection is achieved, except in cases of gastric carcinoma; therefore, total gastrectomy is not recommended. However, gastric borderline and malignant tumors and villous adenoma have a risk of recurrence, and close follow-up is needed in these cases.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical standards Our investigation of 15 patients has been approved by the appropriate ethics committee. All persons gave their informed consent prior to their inclusion in the study.

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