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CASE REPORT

Multiple clear-cell sarcomas of small intestine with parotid gland metastasis: A case report

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Abstract

Clear-cell sarcoma is a rare, malignant soft tissue tumor that displays melanocytic differentiation with a distinct molecular profile. It is rarely localized in the gastrointestinal tract. Herein we reported a case of multiple synchronous clear-cell sarcomas of the gastrointestinal tract with parotid gland metastasis. A 51-year-old male patient presented with a growing painless mass under the right ear. A preoperative positron emission tomography/computed tomography showed multiple intestinal masses and a mass in the right parotid with increased glucose uptake, and he underwent operative treatment with resection of three tumors in the jejunum and ileum and then received a right parotidectomy. Postoperative pathological examination showed that cells in the intestinal tumor were consistent with clear-cell sarcoma of the gastrointestinal tract, and the malignant cells in the parotid gland were similar to the intestinal tumor. Immunohistochemical studies revealed positive expression of HMB-45, Melan-A, and S-100. EWSR1 gene fusion transcripts were undetectable by

fluorescence *in situ* hybridization.

Key words: Clear-cell sarcomas; Clear-cell sarcomas of the gastrointestinal tract; Parotid gland metastasis; Immunohistochemistry

Core tip: Over the past 13 years, only 53 cases of clear-cell sarcomas of the gastrointestinal tract (CCS-GI) have been reported in the world. Most of the literature on CCS-GI describes a single tumor at diagnosis; our presentation is the third report of simultaneous tumors during the diagnosis to date and is the first case of CCS-GI with metastasis to the parotid gland. We also reviewed the literature on CCS-GI. Because of the high rarity, more cases need to be accumulated for further analysis.

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INTRODUCTION

Clear-cell sarcoma (CCS) is a rare tumor of unknown origin that was first described by Enzinger[1] in 1965. CCS shows a predilection for the tendons or aponeuroses in the extremities in young adults aged 20-40 years[2]. Ekfors *et al*[3] described the first clear-cell sarcoma of the gastrointestinal tract (CCS-GI) in 1993, which occurred in the duodenum. Only a few cases[4] of CCS-GI have been reported. CCS-GI has specific histopathological, immunohistochemical, and genetic features. Here, we present a case of three synchronous clear-cell sarcomas in the jejunum and ileum with parotid gland metastasis.

CASE REPORT

Patient details

A 51-year-old male presented with a two-year history of a growing painless mass under the right ear, initially with a size of a soybean. The mass grew noticeably in the last six months. There was a one-year history of night sweat and frequent stool (three to four times a day). There was no history of fever, weakness, dysphagia, dyspnea, cough, hoarseness, jaundice, vomiting, melena, hematochezia, abdominal pain, abdominal distension or significant weight loss. The patient had a 5-year medical history of hypertension and he was a hepatitis-B carrier of 30 years and a smoker of 40 pack-years. There was no family history of cancer.

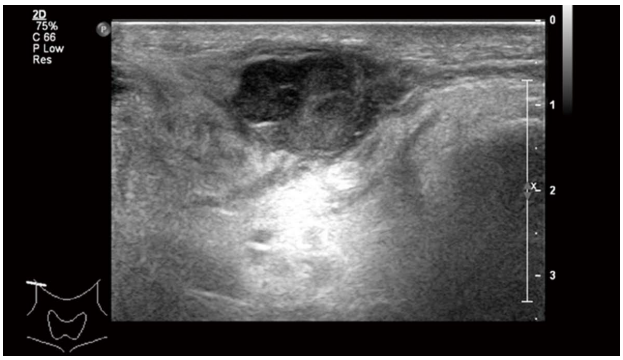

Figure 1 Ultrasonogram of the neck showed a 15 mm × 27 mm mass in the right parotid gland.

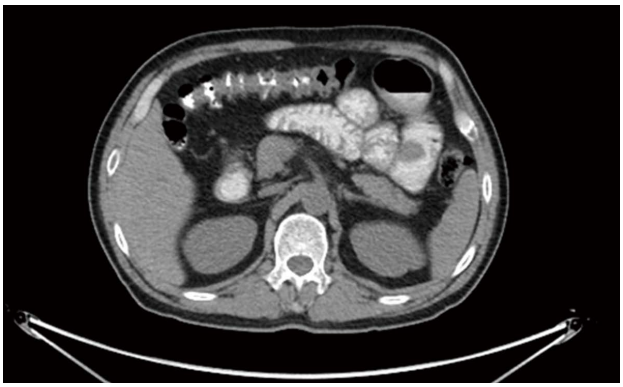

Figure 2 positron emission tomography/computed tomography showed a 36 mm × 33 mm intestinal mass with multiple peripheral lymph nodes in the right midabdomen.

On palpation, a 20 mm × 20 mm relatively well-defined and soft mass with no tenderness was observed along with multiple enlarged cervical nodules. Abdominal examination did not reveal any organomegaly or palpable lumps.

Ultrasonography of the neck two months ago revealed a relatively undefined hypoechoic mass measuring approximately 15 mm × 27 mm in its greatest dimension in the right parotid gland and submandibular gland (Figure 1) along with multiple enlarged right supraclavicular and upper cervical lymph nodes. A needle biopsy of the mass was performed and the pathologic report found malignant tumor cells. The patient was recommended for surgery for the mass in the parotid gland. The preoperative blood routine examination showed that the HGB was 106 g/L. Therefore, the patient underwent positron emission tomography/computed tomography (PET/CT). A 36 mm × 33 mm intestinal mass with increased glucose uptake, and multiple peripheral lymph nodes in the right mid-abdomen were found (Figure 2), and the maximum standard uptake value (SUV) was 6.6. An intestinal lesion with increased glucose uptake in the right hypogastrium was also seen and the SUV was 7.0. The mass in the right parotid and peripheral lymph nodes also showed increased glucose uptake, and

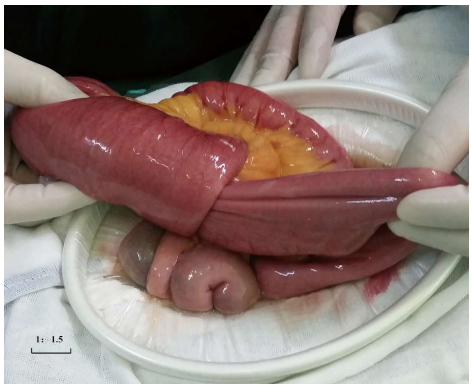

Figure 3 Intussusception was observed 80 cm distal to the duodenojejunal junction and the involved bowels were swollen and expanded.

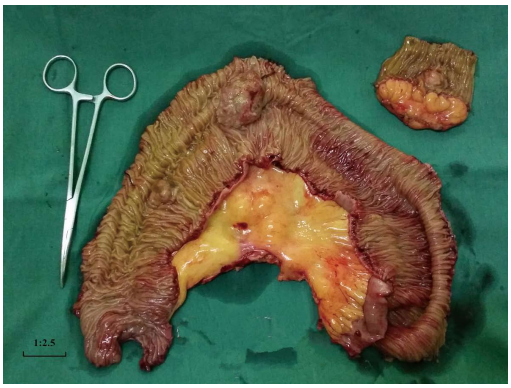

Figure 4 Involved bowels with the masses and mesentery were resected with a proximal 10 cm and distal 10 cm margin.

the SUV was 10.3. Preoperative tumor makers, such as CA125, CA15-3, CA19-9,CA72-4, AFP, cyfra21-1, NSE,SCC, CEA, and ProGRP, did not show abnormal expression.

Treatment

The patient underwent an exploratory laparotomy and the excision of multiple intestinal neoplasms. Operative exploration showed no ascites, pelvic, periaortic, peritoneal, omental deposits, or liver metastasis. No tumors were palpated in the cavity of the stomach, duodenum, colon, rectum, or the mesentery root. Three masses were found at the jejunum and ileum. Intra-operatively, the first tumor was present in the jejunum, located at 80 cm distal to the duodenojejunal junction. Intussusception was observed at the point, and the involved bowels were swollen and expanded (Figure 3). The second tumor was at the end of the intussusception (approximately at the fourth loop of intestine). The third tumor was present in the ileum, located at 80 cm proximal to the ileocecal junction. These three tumors of varying sizes invaded the serosa, and the surface of the serosa had shrunk and was depressed. Multiple enlarged lymph nodes were observed in the intestinal mesentery. Following serial ligation of the mesenteric vessels, resection of the involved bowels, along with the masses and mesentery, was performed, with a proximal margin of 10 cm and a distal margin of 10 cm. The first and second tumors were removed together in one segment of the intestine (Figure 4). Then, a primary anastomosis formed. The patient recovered gradually and then underwent right parotidectomy with retention of the facial nerve, followed by right cervical lymph node dissection 17 d after abdominal surgery because the pathology of the parotid gland neoplasms was undetermined.

Postoperative pathology

Intestinal neoplasms: Upon gross examination, the specimen consisted of two segments of the small intestine: the longer one was approximately 26 cm with attached mesentery, and the other segment was 7.8 cm with attached mesentery. Two tumors were on the longer segment of intestine, one (2.5 cm × 2.2 cm × 1 cm) was at 11 cm from one margin and the other (6.5cm × 5.5cm × 4 cm) was at 19 cm from the same margin. A 2.5 cm × 1.9 cm × 1 cm tumor was on the other segment of the small intestine. The cut surface of the three tumors had hard, obscure borders that were white to tan in appearance.

Microscopically, the jejunum and ileum tissues were infiltrated with malignant cells, which was consistent with CCS-GI (a type of gastrointestinal neural ectoderm tumor, GNET) based on morphology and immunohistochemistry (Figure 5A). The tumors had invaded the mucosal and muscular layers. There was no focal necrosis, vessel invasion or nerve invasion. The mitotic index exceeded 20/10 HPFs, and the tumor was grade G3 according to the FNCLL (French Fédération Nationale des Centres de Lutte Contre le Cancer) system.

Lymph node metastases (1/29) without invasion of the outer lymph node capsule: (1) peripheral lymph nodes of the jejunum: 1/26; and (2) peripheral lymph nodes of the ileum, 0/3.

Immunohistochemistry: S100 (3+), Vim (3+), GFAP (-), HMB-45 (2+), Melan-A (2+), Melanomapan (1+), CD56 (2+), Syn (-), CgA (-), AE1/AE3 (-), CD138 (-), CD19 (-), CD20 (-), CD3 (-), CD38 (-), CD79a (-), Ki-67 (+40%), LCA (-), MUM1 (-), CD117 (lesion+), CD34 (-), DOG1 (-), CD10 (-), Calponin (-), P63 (-), EBER (-).

Gene detection: EWSR1 gene fusion transcripts were undetectable by fluorescence *in situ* hybridization (FISH).

Parotid gland neoplasms: Upon gross examination, a 1-cm diameter nodule was found in a 5.5 cm × 3 cm × 2 cm area of tissue; the cut surface of the nodule had a tough, grey-to-yellow appearance.

Microscopically, the parotid gland tissues were infiltrated with malignant cells, which was consistent with CCS morphology and immunohistochemistry and morphologically similar to the previously assessed

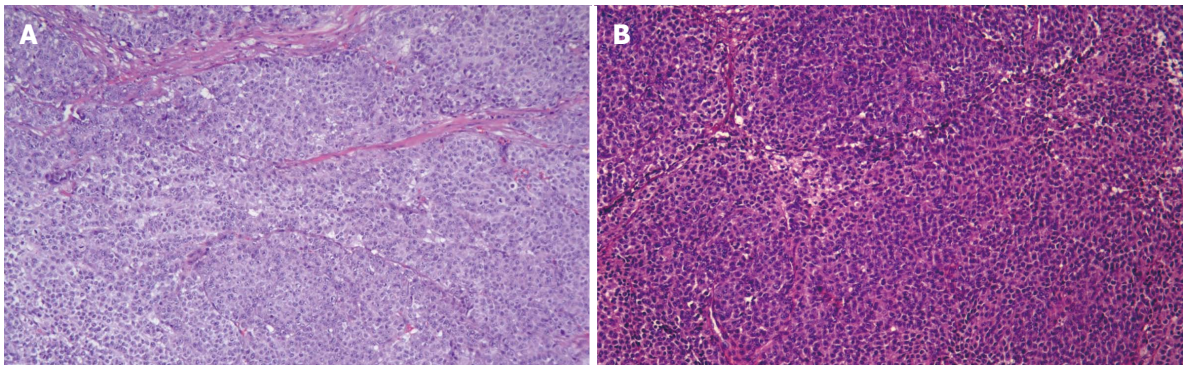

Figure 5 Microscopic observation of intestinal neoplasms and parotid gland neoplasms. A: Microphotography shows that polygonal malignant cells of intestinal neoplasms were separated by fibrous tissues, arranging in sheets and nests, with eosinophilic or clear cytoplasm and there was no exact necrosis, vessel invasion and nerve invasion. Nucleolus was obvious and the mitotic index exceeded 20/10 HPF (Hematoxylin-Eosin G × 10); B: Malignant cells of parotid gland neoplasms were similar to the intestinal tumor by microphotography (Hematoxylin-Eosin G × 10).

intestinal tumor (Figure 5B). Lymph tissues were found in the tumor and at the tumor edge, which may be metastatic lesions.

No lymph node metastases (0/30): (1) right cervical lymph nodes, level Ⅱ, 0/10; (2) right cervical lymph nodes, level Ⅲ, 0/12; (3) right cervical lymph nodes, level V, 0/5; (4) peripheral lymph nodes of the superficial lobe of the right parotid gland, 0/2; and (5) peripheral lymph nodes of the caudate lobe of the right parotid gland and tumor, 0/1.

Immunohistochemistry: S100 (3+), Melan-A (3+), Melanomapan (3+), HMB-45 (3+), AE1/AE3 (-), CK18 (-), Calponin (-), P63 (-), SMA (-).

Follow-up

Twenty days after the surgery on the parotid gland, the patient underwent CT imaging of the neck, thorax and abdominopelvic area, and no recurrence or metastasis was observed. He then started with 6 cycles of chemotherapy using an EI regimen (epirubicin 100 mg + ifosfamide 2 g D1-4+mesna 0.4 g 0 h, 4 h, and 8 h after the ifosfamide D1-4). At the time that this article was written, the patient was on the first cycle of the chemotherapy.

DISCUSSION

CCS-GI is so rare that only 53 cases (including our case) have been reported in the literature to date (Table 1)[3,5-39]. Most of the literature on CCS-GI describes the diagnosis of a single tumor; only two case reports[25,38] have described the diagnosis of two simultaneous tumors to date. CCS-GI often involves the ileum and jejunum, stomach and colon[4-7,9-12,14-35,38,39]. Because of the aggressive clinical course, regional and distant metastases are common in CCS-GI at presentation[5-7,9,10,15,17,21,25,27,29,31,37,39]. The lymph nodes, liver, and mesentery are the most common locations of the metastases at the time of presentation. The patient in our report had three synchronous masses in the jejunum and ileum, with metastasis to the parotid gland, and he attended the hospital mainly due to the swollen parotid gland. The presence of lymph nodes both inside and outside of the parotid gland makes it a common site of metastasis for head and neck neoplasms[40], but it is a very rare metastatic site for gastrointestinal tumors. In the limited literature on CCS-GI, this is the first case of CCS-GI with metastasis to the parotid gland.

CCS-GI shows specific histopathological, immunohistochemical, ultrastructural, and genetic features[2,4]. In 2010, Kosemehmetoglu *et al*[41] first divided CCS-GI into two subtypes according to its histomorphology: (1) CCS-like gastrointestinal tumor (CCSLGT); and (2) CCS of soft tissue (CCS-ST). However, there has been disagreement about whether these subtypes are two independent entities[31]. In 2003, Zambrano *et al*[10] reported 6 cases of CCSLGTs. They found that the CCSLGTs were at least focally positive for the S100 protein, but most did not express melanocytic markers such as HMB-45 or Melan-A. Meanwhile, Huang *et al*[36] found that certain CCS-STs were positive for the S100 protein and most could express melanocytic markers such as HMB-45 or Melan-A. Several reports found that > 90% of cases of CCS were associated with the reciprocal translocation t (12; 22) (q13; q12), resulting in fusion of the EWSR1 gene, located at 22q12, and the ATF1 gene, located at 12q13[2,41-46]. To date, these translocations have never been observed in malignant melanoma[13,22,43-46], which has a very similar histologic appearance to CCS[20]. Immunohistochemical staining of CCS reveals positivity for the S100 protein as well as melanocyte-specific markers, with this combination of staining allowing for CCS to be distinguished from malignant melanoma histologically. In our case, the tumor was consistent with CCS-GI based on morphology, was positive for the S100 protein, and expressed melanocytic markers such as HMB-45 and Melan-A, but EWSR1 gene fusion transcripts were undetectable by FISH.

Currently the most effective treatment for CCS-GI is extensive resection of the tumor and peripheral lymph nodes; chemotherapy and radiotherapy appear to have little effect[31]. The clinical behavior of CCS-GI seems to

Table 1 Clinical, pathological, immunohistochemical and genetic features of clear-cell sarcoma of the gastrointestinal tract in previously reported cases

Ref.	Age (yr)/ sex	Location	Maximum diameter of tumor(cm)	S-100	HMB-45	Melan-A	Genetic findings	Outcome
Alpers *et al*[5]	26/F	Jejunum	1.5	ND	ND	ND	ND	Liver mets
Ekfors *et al*[3]	38/M	Duodenum	3.0	Positive	Positive	ND	ND	Not given
Donner *et al*[6]	37/M	Ileum	6.5	Positive	Negative	ND	t(12;22)(q13;q12-13)	Liver mets at 24 and 36 mo
Fukuda *et al*[7]	74/M	Colon	3.0	Positive	Positive	ND	EWSR1-ATF1 by RT-PCR	Liver mets at 9 mo
Hu *et al*[8]	10/M	Rectum	5.0	Positive	Positive	ND	ND	NA
Pauwels *et al*[9]	30/M	Stomach	4.0	Positive	Negative	ND	t(12;22)(q13;q12)	LN and peritoneal mets at diagnosis
Zambrano *et al*[10]	15/F	Jejunum	5.0	Positive	Negative	Negative	t(12;22)(q13;q12)	DOD 16 mo
	21/F	Jejunum	4.0	Positive	Negative	Negative	ND	DOD 12 mo
	35/F	Ileum	3.5	Positive	Negative	Negative	ND	Liver mets at 12 mo
	37/F	Ileum	4.5	Positive	Negative	Negative	ND	NA
	32/M	Ileum	5.0	Positive	Negative	Negative	ND	NA
	13/M	Stomach	6.7	Positive	Negative	Negative	ND	Local recurrence at 12 mo;2nd Local recurrence at 36 mo
Achten *et al*[11]	57/M	Jejunum	6.5	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA
Venkataraman *et al*[12]	21/F	Ileum	7.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA
Covinsky *et al*[13]	47/F	Pancreas	NA	Positive	Positive	Positive	EWSR1-ATF1 by RT-PCR and FISH	NED 24 mo
	85/F	Mesentery	NA	Positive	Positive	Positive	EWSR1-ATF1 by RT-PCR and FISH	DOD 1 mo
Taminelli *et al*[14]	35/M	Ileum	1.8	Positive	Negative	Positive	EWSR1-ATF1/ by RT-PCR	DOD 15 mo
Friedrichs *et al*[15]	41/M	Jejunum	8.7	Positive	Negative	Negative	EWSR1 rearrangement by FISH	Liver mets at 6 mo
Huang *et al*[16]	40/M	Stomach	3.0	Positive	Negative	Positive	ND	NED 9 mo
Antonescu *et al*[17]	81/F	Colon	7.5	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	Mets to liver and peritoneum at 60 mo
	42/F	Ileum	5.7	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	NA
	42/F	Ileum	3.5	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	Peritoneal and liver mets at diagnosis
	51/F	Jejunum	NA	Positive	Negative	Negative	EWSR1 rearrangement by FISH	Peritoneal and liver mets; AWD
	18/F	Jejunum	NA	Positive	Negative	Negative	EWSR1-ATF1 by RT-PCR	Local recurrence
Granville *et al*[18]	16/M	Ileum	5.0	Positive	Negative	ND	EWSR1-ATF1 by RT-PCR; t(12;22)(q13;q12)	DOD 15 mo
Comin *et al*[19]	31/F	Ileum	2.8	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA
Lyle *et al*[20]	46/M	Jejunum	11.0	Positive	Positive	Positive	EWSR1 rearrangement by FISH; EWSR1-ATF1 by RT-PCR	NED 7 mo
	49/M	Cecum	10.5	Positive	Positive	Positive	EWSR1 rearrangement by FISH; EWSR1-ATF1 by RT-PCR	DOD 12 mo
	60/M	Jejunum	10.0	Positive	Positive	Positive	EWSR1-ATF1 by RT-PCR	DOD 28 mo
	62/M	Ileum	4.0	Positive	Positive	Positive	EWSR1 rearrangement by FISH; EWSR1-ATF1 by RT-PCR	DOD 12 mo
Abdulkader *et al*[21]	37/M	Jejunum	8.2	Positive	Negative	ND	EWSR1 rearrangement by FISH	Liver mets at 2 mo
Lagmay *et al*[22]	10/F	Stomach	7.8	Positive	Negative	Negative	EWSR1 rearrangement by FISH; EWSR1-ATF1 by RT-PCR	NED 4 mo
Joo *et al*[23]	60/M	Ileum	2.4	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA

	46/M	Jejunum	6.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA
Terazawa *et al*[24]	Early 20s/F	Ileum	3.0	Positive	ND	ND	EWSR1-ATF1 by RT-PCR	NED at 24 mo
Shenjere *et al*[25]	53/F	Ileum	5.0	Positive	Negative	Negative	EWSR1-ATF1 by RT-PCR	Regional LN mets at diagnosis/ NED at 7 mo
	26/F	Small and large bowel[1]	13.5/10.1	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	NA
	66/M	Ileum	2.5	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	Regional LN mets at diagnosis/NED
Balkaransingh *et al*[26]	15/M	Ileum	NA	ND	ND	ND	EWSR1 rearrangement by FISH	NA
Yang *et al*[27]	15/M	Ileum	4.0	Positive	ND	ND	EWSR1 rearrangement by FISH	Liver mets at 12 mo
Suárez-Vilela *et al*[28]	36/F	Jejunum	1.5	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NA
D'Amico *et al*[29]	69/F	Ileum	4.0	Positive	Negative	ND	EWSR1 rearrangement by FISH	Liver mets at 2 mo
Lasithiotakis *et al*[30]	49/F	Jejunum	3.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NED 20 mo
Huang *et al*[31]	45/F	Colon	4.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	Liver mets at 20 mo
Mallick *et al*[32]	45/M	Jejunum	4.4	Positive	Negative	Negative	ND	NA
Kong *et al*[33]	17/M	Stomach	6.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NED 10 mo
Liu *et al*[34]	76/M	Jejunum	2.5	Positive	Negative	Negative	EWSR1-ATF1 by RT-PCR	NA
Thway *et al*[35]	36/M	Ileum	3.0	Positive	Negative	Negative	EWSR1-CREB1 by RT-PCR	DOD 7 mo
Huang *et al*[36]	36/M	Pancreas	4.0	Positive	Positive	Positive	EWSR1 rearrangement by FISH	Liver mets at 10 mo
Yegen *et al*[37]	25/F	Ileum	3.2	Positive	Negative	Negative	EWSR1 rearrangement by FISH	Liver mets at diagnosis and at 15 mo. Ovarian mets and peritoneal dissemination at 47 mo
Moslim *et al*[38]	57/M	Duodenum and Jejunum[2]	5.5/7.5	Positive	Negative	Positive	EWSR1 rearrangement by FISH	NED 30 mo and then DOD 4 mo later
Chen *et al*[39]	29/F	Jejunum	6.0	Positive	Negative	Negative	EWSR1 rearrangement by FISH	NED 17 mo
Our case	51/M	Duodenum and Jejunum[3]	6.5/2.5/2.5	Positive	Positive	Positive	EWSR1 rearrangement undetectable by FISH	NED up to date

[1]Two simultaneous tumors in small and large bowel; [2]Two simultaneous tumors in duodenum and jejunum; [3]Three simultaneous tumors in duodenum and jejunum. AWD: Alive with disease; DOD: Dead of disease; FISH: Fluorescence *in situ* hybridisation; LN: Lymph node; Mets: Metastases; NA: Not acquired; ND: Not done; NED: No evidence of disease; RT: Reverse transcription.

be highly aggressive, with high rates of local recurrence, lymph node or visceral metastases, and death, generally within < 36 mo[41,46]. In the current report, the patient underwent excision of multiple intestinal neoplasms and right parotidectomy before the first cycle of the chemotherapy and no recurrence or metastasis has been observed during the follow-up to date.

In conclusion, CCS-GI is a highly rare soft-tissue sarcoma with distinct morphological, immunohistochemical, and genetic features. This case demonstrates that the parotid gland is a potential metastatic site for CCS-GI. Prior to developing a routine method to diagnose and treat CCS-GI, more cases need to be accumulated for further analysis.

COMMENTS

Case characteristics

A 51-year-old male presented with a two-year history of a growing painless mass lesion under the right ear that had grown noticeably over the past six months and a one-year history of night sweat and frequent stool.

Clinical diagnosis

A relatively well-defined soft mass with no tenderness was observed along with multiple enlarged cervical nodules.

Differential diagnosis

Small intestinal stromal tumors, lymphoma, head and neck neoplasm, sarcomatoid carcinoma.

Laboratory diagnosis

The patient's laboratory test had no remarkable findings.

Imaging diagnosis

Positron emission tomography/computed tomography showed an intestinal mass with involvement of multiple peripheral lymph nodes and mass in the right parotid.

Pathological diagnosis

The intestinal neoplasms and parotid gland neoplasm were consistent with

CCS based on morphology and immunohistochemistry.

Treatment
The patient underwent curative resection and postoperative chemotherapy.

Related reports
Only 53 cases of clear-cell sarcomas of the gastrointestinal tract (CCS-GI) have been reported in the literature to date, and CCS-GI shows distinct morphological, immunohistochemical, and genetic features.

Term explanation
CCS-GI is a highly rare soft tissue sarcoma.

Experiences and lessons
The present case report is the third instance of diagnosis of simultaneous multiple CCS-GIs to date and the first case of CCS-GI with metastasis to the parotid gland.

Peer-review
The authors have described a case of multiple clear-cell sarcomas of the small intestine with parotid gland metastasis. The article highlights the morphological, immunohistochemical, and genetic features of the tumors.

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