

Malignant gastric carcinoids with liver metastasis

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BACKGROUND: Malignant gastric carcinoids are often accompanied with liver metastasis synchronously or metachronously. Because of the slow growth rate of carcinoids, patients with metastatic tumors can undergo resection for potential cure or for symptom palliation. This study was designed to evaluate the clinicopathologic characteristics and the diagnosis and management of malignant gastric carcinoids.

METHODS: Seven patients with malignant gastric carcinoids admitted to our hospital between 1990 and 2002 were followed up and reviewed retrospectively.

RESULTS: Liver metastases were found in all the patients, of whom 3 had lesions simultaneously and the other 4 had lesions postoperatively. More than 2 lesions were found in all these patients, except a solitary liver lesion in one. Follow-up showed two patients died within 2 months, three patients in 20, 25 and 32 months after operation respectively, and the other two have been surviving for more than 5 and 3 years respectively.

CONCLUSIONS: Malignant gastric carcinoids have a high metastatic tendency to the liver. Surgical treatment in combination with other therapeutic approaches can significantly prolong the survival rate of the patients.

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KEY WORDS: stomach; carcinoid; liver metastasis; surgery

Introduction

Gastric carcinoid arising from enterochromaffin-like (ECL) cells is rare. Reported clinical data show that it accounts for 0.3% of all malignant gastric tumors and 2% of all carcinoids.^[1,2] The incidence of this tumor has increased recently, representing

improved diagnostic techniques, increased endoscopic surveillance, or a real change in incidence.^[3,4] According to the differences in biological behavior and prognosis, gastric carcinoids are usually classified into three types.^[5,6] Type 1 is associated with hypergastrinaemia and chronic atrophic gastritis, type 2 occurs in patients with multiple endocrine neoplasia, and type 3 is sporadic. Type 1 is usually benign whereas type 3 is highly malignant, and often associated with liver metastasis synchronously or metachronously.

Seven patients with malignant gastric carcinoids were treated at our hospital between 1990 and 2002. Among them, 3 patients had liver metastases synchronously and the other 4 metachronously.

Methods

Patients

In the 7 patients with malignant gastric carcinoid, 5 were men and 2 women. Their mean age was 59 years (range, 17 to 67 years). Their clinical manifestations included gastric hemorrhage (5 patients), pain in the upper abdomen (3), and carcinoid syndromes (2) such as chronic diarrhea and flushing. Patients 4 and 6 were once subjected to histological diagnosis by needle biopsy. Pathologically, tumors of 6 patients who underwent tumor resection were ulcerated infiltrative. The tumor size was more than 2 cm in 6 patients, and less than 2 cm in one patient. Among the 7 patients, 3 had liver metastasis simultaneously, and the other 4 in 6, 16, 22 and 34 months after operation respectively (Table).

Treatments

Among the 7 patients, 6 were subjected to operation. Patient 1 underwent a radical distal subtotal gastrectomy, and was subsequently found to have liver metastasis half a year later. A hepatic artery infusion pump for regular chemotherapy was placed subcutaneously. Patient 2 underwent a total gastrectomy and received intravenous chemotherapy regularly. Patient 3 underwent a palliative proximal subtotal gastrectomy and received regular chemotherapy from the infusion pump postoperatively as did in patient 1. Patient 4 underwent a radical distal subtotal gastrectomy and partial transverse mesocolonecto-

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Table. Clinicopathological data of 7 patients with gastric carcinoid tumors

Case No.	Tumor location	Size (cm)	Depth of penetration	Nodal involvement	Distant metastases	Immunohistochemical stain		
						CGA	NSE	5-HT
1	Antrum	2.5	Muscularis propria	Lesser curvature (1)	Diffuse liver metastases 6 months later	++	-	-
2	Antrum Body	4.0 3.0	Serosa	Lesser curvature (1)	Left lobe and posterior abdomen 16 months later	+++	+	++
3*	Cardia	3.5	Through the serosa	Lesser curvature (3)	Diffuse liver metastases	+	++	-
4	Body	6.0	Through the serosa	Right cardiac (2)	Diffuse liver metastases 22 months later	+++	+	-
5*	Body	1.8	Muscularis propria	Left gastric artery (2)	3 metastatic tumors in liver	++	++	-
6	Fundus and body	Extensive (gastroscopy)	No operation		3 liver metastases (the largest 9-10 cm)	+++	++	-
7	Antrum and body	5.0	Invading transverse colon	Lesser curvature (2), greater (2)	Multiple metastases in right lobe 34 months later (the largest 10 cm)	++	++	

* : presenting with carcinoid syndrome; CGA; chromogranin A; NSE; neuro-specific enolase; 5-HT; 5-hydroxytryptamine.

my, followed by regular intravenous chemotherapy. Patient 5 underwent distal subtotal gastrectomy and liver tumor resection, followed by regular intravenous chemotherapy. Five months later, a liver metastatic tumor recurred and was treated by transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI). Patient 6 was discharged from the hospital without any treatment. Patient 7 underwent a distal subtotal gastrectomy and resection of the transverse colon, followed by intravenous chemotherapy, and 34 months later, multiple liver tumors were found and treated by TACE. Chemotherapeutic reagents used for these patients were 5-fluorouracil in combination cisplatin (DDP).

Results

In the 7 patients, 3 had metastatic lesions of the liver simultaneously and the other 4 postoperatively. These patients had more than 2 metastatic lesions, except one who had one hepatic solitary lesion. Follow-up showed patients 1, 2 and 4 survived for 32, 20 and 25 months respectively. Patient 3 died of complications within 50 days after operation. Patients 5 and 7 have been surviving for more than 5 and 3 years respectively. Patient 6 died in 2 months after diagnosis.

Discussion

Clinicopathological characteristics of malignant gastric carcinoids

Malignant carcinoids, generally sporadic, often occur in men at age from 50 to 60 years without specific symptoms in early stage. The patients with typical carcinoid

syndrome are uncommon, but some patients, especially those with liver metastasis, usually present atypical carcinoid syndrome such as flush, diarrhea, cardiac valvular fibrosis and others. Of 9 cases reported by San et al,^[7] 5 were malignant; 2 of the 5 cases presented carcinoid syndrome. In this study, 2 of 3 patients with synchronous liver metastasis had carcinoid syndrome. Clinically, patients with malignant gastric carcinoids often accompany some symptoms such as loss of appetite, and upper gastrointestinal bleeding.^[8] Pathologically carcinoid should be distinguished from low-differentiated adenocarcinoma. Typical carcinoid tumor consists of uniform small or middle size tumor cells that array as patches, funicular or cluster shape, unclearly marginated cytoplasm, and round, regular nuclei. Sometimes chrysanthemum structure and acinous gland structure can be found. The tumor cells in mitotic phase are absent or very few. Gastric carcinoids belong to pregut carcinoids. Because the concentration of amine is low in carcinoid tumor cells, the cells are usually negative to argentaffin staining and positive to argyrophil staining. In some cases, electron microscope or immunochemistry assay should be used in order to confirm the diagnosis. Under an electron microscope, there are some specific dense core granules, which appear to be argyrophil but rarely argentaffin or even no reaction in the cytoplasm.^[9] Gastric carcinoids show a wide distribution of granule size, with significantly greater diameters than those in rectal carcinoids.^[10] In immunochemistry assay, the tumor cells are usually positive for chromogranin A (CGA) and neuro-specific enolase (NSE), but often negative for 5-HT.^[9,11] In our study, all the cases were positive for CGA and 6 positive for NSE, but only 1 was positive for 5-HT.

The common pathological types of malignant gastric carcinoids are ulcerating infiltration, to which all

seven cases in this study belonged. Lin et al^[12] reported that 4 of 5 patients with malignant gastric carcinoids with large ulcerating lesions had liver metastases synchronously, indicating that this type of malignant gastric carcinoid is easy to metastasize to the liver or other distal organs. Others^[13] reported that patients with sporadic carcinoid tumors had usually solitary tumors located within the corpus of the fundus, with a metastasis rate of 16.7%. It is difficult to determine the malignancy of gastric carcinoid tumor only by morphological characteristics because the tumor cells are not typical and few mitotic phases can be found. Some factors are important to judge this malignancy such as size, penetration of the muscularis propria, and distant metastasis. The real malignant mark of gastric carcinoid should be metastasis or invasion to the structure nearby, not histological features. Metastasis, atypical histology, serosal involvement, and size larger than 2 cm are adverse prognostic factors.^[14] When the tumor is limited within the mucosa, it is difficult to evaluate whether it is benign or malignant. The rate of metastasis is usually high and the liver is mostly involved when the tumor is larger than 2 cm in diameter. In our study, liver metastasis had occurred in 3 patients when diagnosed, whereas in the other four patients it occurred postoperatively, also suggesting that the carcinoid had a high tendency to liver metastasis. Over expression of p21 and reduced staining of E-cadherin are correlated with malignant behavior. These two parameters may be useful as prognostic indicators for gastrointestinal carcinoid tumors.^[15]

Diagnosis of gastric carcinoids with liver metastasis

Gastric carcinoids are considered to arise from the fundic mucosa of the stomach and have a tendency to infiltrate into the submucosa in early stage. Often there is a mass under the mucosa with protrusion or ulcer, so deep biopsy is necessary when endoscopy is performed. The typical appearances of endoscopy include irregular erythema, excavation, or ulcer on the mucosa.^[16] In our study, CT scan revealed gastric tumor in one patient, which was not found by endoscopy. Endoscopic ultrasonography (EUS) is the best method for visualizing submucosal lesions and preoperative staging, but it is still inadequate to differentiate benign from malignant submucosal tumors.^[17,18]

Malignant gastric carcinoids are often accompanied with liver metastasis. In our study, all 7 patients had synchronous or metachronous liver metastatic lesions. Generally, most patients with malignant gastric carcinoid have multiple liver metastatic lesions. So routine ultrasonography (US) and CT scans for the liver are necessary. Fine needle aspiration cytology under ultrasonography or CT should be made in some cases.^[19] Angiography has a superiority for demonstrating hepatic metastasis, and intraoperative ultrasonography can raise the detective rate of the liver occupying lesions.^[20] Since

somatostatin receptor scintigraphy (SRS) is a noninvasive method for identifying patients with gastric carcinoids with a reasonable sensitivity and a high specificity, it is useful to identify receptor-positive metastasis that may be treated by somatostatin analogues, but SRS is not superior to CT or US in localization of primary carcinoid tumors or liver metastasis.^[21, 22] The pentagastrin provocative test is a useful diagnostic aid, which induces facial flushing, gastrointestinal symptoms, and elevation of circulating 5-HT.^[23] Plasma chromogranin A is usually increased in patients with gastric carcinoids, it appears to be a valuable tumor marker for all types of gastric carcinoid, but has a relatively low specificity.^[24,25]

Treatment of malignant gastric carcinoids

Radical gastrectomy is the main approach for malignant gastric carcinoids. Primary tumors should be resected to eliminate endocrinopathies resulting from the carcinoid, improve the effect of chemotherapy, and get rid of possible complications of obstruction and bleeding caused by tumor lesions. Even if there are liver metastases, surgical treatment combined with adjuvant treatment can also prolong patients' life or even cure the disease.^[26,27] Liver metastasis implies a major problem in patients with carcinoid tumors, in whom liver surgery can be performed safely with long-term survival and amelioration of symptoms.^[28-30] If the metastatic lesions are located near the margin or in one lobe of the liver, local excision or partial hepatectomy can be performed. If there is multiple metastases involving more than one segment of the liver, TACE or hepatic artery ligation may be the effective approach.^[31] Radiofrequency ablation can be effective in dealing with liver metastasis.^[32] Percutaneous cryoablation or PEI combined with TACE is a treatment of choice for liver tumors unsuitable for surgery.^[33] With regular TACE and PEI treatment, one patient (patient 5) in this study has been surviving for 5 years. Streptozocin in combination with 5-FU or DDP is most effective for the treatment of gastric carcinoid.^[34,35] Administration of somatostatin analogues (e.g. octreotide) can ameliorate carcinoid syndrome consisting of flush and diarrhea and also inhibit the tumor. Interferon- α has some anti-tumor and immunoregulatory effects on the carcinoid and has cooperative effect with octreotide.^[24,36,37] Liver transplantation may be a potential therapeutic approach for some highly selected patients with unresectable hepatic metastases,^[38-40] but radiotherapy has hardly effect on carcinoid tumor.

The 5-year survival rate of patients with gastric carcinoid is reported to be 46% to 63%.^[4,27] In patients with regional and distant metastasis of the tumor, however, the 5-year survival rate is 40% and 10% respectively.^[41]

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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