

Synchronous incidental gastrointestinal stromal and epithelial malignant tumors

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CONCLUSION: Incidental GIST may occur synchronously with other tumors and has a high prevalence in males. Surgery is its best treatment modality.

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Key words: Gastrointestinal stromal tumor; Multitumor; Synchronous tumor

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Abstract

AIM: To investigate the incidence of incidental gastrointestinal stromal tumor (GIST) and its etiopathogenesis.

METHODS: From January 1, 2000 to December 31, 2007, 13 804 cases of gastrointestinal epithelial malignant tumor (EMT) and 521 cases of pancreatic adenocarcinoma (PAC) were successfully treated with surgery at the Department of General Surgery and the Department of Thoracic Surgery, West China Hospital, Sichuan University, China. The clinical and pathologic data of 311 cases of primary GIST, including 257 cases with clinical GIST and 54 cases of incidental GIST were analyzed.

RESULTS: Of the 311 patients, 54 had incidental GIST, accounting for 17.4%. Of these tumors, 27 were found in 1.13% patients with esophageal squamous cell carcinoma (ESCC), 22 in 0.53% patients with gastric adenocarcinoma (GAC), 2 in 0.38% patients with PAC, 2 in 0.03% patients with colorectal adenocarcinoma, and 1 in one patient with GAC accompanying ESCC, respectively. Patients with incidental GIST presented symptoms indistinguishable from those with EMT. All incidental GIST lesions were small in size, and the majority had a low mitotic activity while only 1.9% (5/257) of clinical GIST lesions had a high risk.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of gastrointestinal (GI) tract, probably arising from precursor interstitial cells of Cajal. Significant advances have been made in symptomatic GIST in the last two decades^[1,2]. However, little is known about the incidental GIST detected during examinations or surgery for other reasons. Its clinicopathologic characteristics are unclear. Many cases of synchronous or asynchronous GIST with other tumors have been reported as single cases^[3-6]. We discovered 54 cases of incidental GIST during surgery for epithelial malignant tumor (EMT). This study was to investigate the incidence of incidental GIST and its etiopathogenesis.

MATERIALS AND METHODS

Patients

From January 1, 2000 to December 31, 2007, 13 804 cases of gastrointestinal EMT and 521 cases of pancreatic adenocarcinoma (PAC) were successfully treated with surgery at the Department of General

Table 1 Location of 54 incidental GIST lesions and their corresponding EMT

EMT	Patients (n)	Median age	Gender (M/F)	Incidental GIST site (No. of patients)							
				Gastric cardia	Gastric fundus	Gastric body	Gastric antrum	Esophagus	Terminal ileum	Colon	Omentum
GAC	22	64.5 (45-79)	19/3	1	7	13	1	-	-	-	-
ESCC	27	63 (44-77)	24/3	1	3	19	1	2	-	-	1
GAC + ESCC	1	79	1/0	-	-	1	-	-	-	-	-
CRA	2	57.5 (54-61)	2/0	-	-	-	-	-	1	1	-
PAC	2	67.5 (65-70)	2/0	-	1	1	-	-	-	-	-
Total	54	63 (44-79)	48/6	2	11	34	2	2	1	1	1

GIST: Gastrointestinal stromal tumor; EMT: Epithelial malignant tumor; GAC: Gastric adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; CRA: Colorectal adenocarcinoma; PAC: Pancreatic adenocarcinoma.

Surgery and the Department of Thoracic Surgery, West China Hospital, Sichuan University, China. Gastrointestinal EMT cases included 2382 cases of esophageal squamous cell carcinoma (ESCC), 35 cases of esophageal adenocarcinoma (EAC), 4168 cases of gastric adenocarcinoma (GAC), 329 cases of small intestinal adenocarcinoma (SAC), and 6890 cases of colorectal adenocarcinoma (CRA). During this period, 311 cases of primary GIST (121 females, 190 males) were identified in our center, including 257 cases of clinical GIST and 54 cases of incidental GIST.

Methods

Hospital records of patients with incidental GIST were reviewed. Each patient was followed up by telephone or mail. Histopathologic features of primary GIST were evaluated by two experienced pathologists, blinded to their respective findings and patient outcomes, at the Department of Pathology, West China Hospital. The largest diameter of tumor was recorded. In patients with multiple GIST lesions, only the largest GIST lesion was included in pathological analysis. The risk category for GIST was defined by assessing the tumor size and mitotic count following the consensus guidelines of the National Institutes of Health-(NIH-NCI) workshop^[7]. In addition to the assessment of CD117 in tumor cells, reactions with CD34, SMA, and S-100 proteins were also studied. Immunohistochemical examination of these proteins was performed on tumor tissues embedded in paraffin with DAKO (Glostrup, Denmark) antibodies according to the manufacturer's instructions.

Statistical analysis

Categorical variables were compared by χ^2 test or by Fisher's exact test where applicable. Survival analysis was performed using the Kaplan-Meier method. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 311 patients, 54 had incidental GIST, accounting for 17.4%. Among these tumors, 27 were found in 1.13% patients with ESCC, 22 in 0.53% patients with GAC, 2 in 0.38% patients with PAC, 2 in 0.03% patients with CAC, and 1 in one patient with GAC accompanying ESCC,

respectively.

The median age of the 54 cases of incidental GIST was 63 years (range, 44-79 years). Interestingly, 48 of them (88.9%) were males, and 6 (11.1%) were females ($P < 0.001$). The patients presented symptoms of EMT without specific clinical manifestations indicative of GIST. Among the 54 patients, only a submucous lesion in gastric fundus, 2.5 cm in diameter, was preoperatively detected in 1 patient with GAC by gastroscopy, and a single-lesion was postoperatively detected in 4 patients by specimen examination. A total of 58 incidental GIST lesions were discovered in the 54 patients, including 51 single-lesions, 2 double-lesions, and 1 triple-lesion. A total of 90.7% incidental GIST lesions occurred in stomach, 3.6% in esophagus, 1.9% in terminal ileum, 1.9% in colon and 1.9% in omentum, respectively. The most common sites were the gastric fundus and body. In our series, 4 cases with a unique coexistence style (esophageal GIST + ESCC: 2, gastric GIST + ESCC + GAC: 1, colonic GIST + CRA: 1) have not been reported previously. The location of 54 incidental GIST lesions and their corresponding EMT lesions are shown in Table 1.

Of the incidental GIST lesions, 37 (68.5%) were of spindle-cell morphology, 9 (16.7%) epithelioid morphology, and 8 (14.8%) a mixed histological type. Immunohistochemical staining showed that 50 cases (92.6%) and 52 cases (96.3%) of incidental GIST were positive for CD117 and CD34, respectively. None of them was proven to have a metastasis of GIST, while 29 cases were confirmed with metastasis derived from EMT. Incidental GIST was small in size. The majority (90.7%) had a low mitotic activity and a very low risk, while only 1.9% cases of clinical GIST had a very low risk ($P < 0.001$), and 38.5% had a high risk with a marked mitotic activity (Table 2).

All the GAC patients received radical excision (distal gastrectomy for 3, proximal gastrectomy for 2, total gastrectomy for 12, esophagogastrectomy for 5). All the ESCC patients including the patient with triple tumors underwent esophagogastrectomy. The two PAC patients underwent duodenopancreatectomy and distal pancreatectomy, respectively, with local gastrectomy. Right and left hemicolectomy was performed for the two CRA patients, respectively. Thirty-four out of the 54 patients received either adjuvant chemotherapy and/or radiotherapy after operation. None of them received oral Imatinib mesylate (Glivec) treatment. On September

Table 2 Distribution of gender, age, tumor site, tumor size, and risk in 311 patients with GIST

GIST	Patients (n)	Gender (M/F)	Median age in yr (range)	Tumor site (No. of patients)	Tumor size (cm)			Risk patients, n (%)
					Median	Mean	Range	
Incidental GISTs	54	48/6	63 (44-79)	Gastric (49), esophagus(2), ileum(1), colon (1), omentum (1)	0.8	0.9	0.2-2.5	VL: 49 (90.7); L: 5 (9.3)
Clinical GISTs	257	142/115	57 (22-87)	Gastric (147), duodenum (10), jejunum-ileum (57), colon (25), rectum (3), anal canal (3), mesenterium (6), omentum (4), pancreatic (2)	7.5	6.2	1.5-30.0	VL: 5 (1.9); L: 86 (33.5); Int: 67 (26.1); H: 99 (38.5)
Total	311	190/121	61 (22-87)	Gastric (196), esophagus(2), duodenum (10), jejunum-ileum (58), colon (26), rectum (3) anal canal (3), mesenterium (6), omentum (5), pancreas (2)	6.3	5.5	0.2-30.0	VL: 54 (17.4); L: 91 (29.3); Int: 67 (21.5); H: 99 (31.8)

Risk was determined as previously described^[7]. VL: Very low risk; L: Low risk; Int: Intermediate risk; H: High risk.

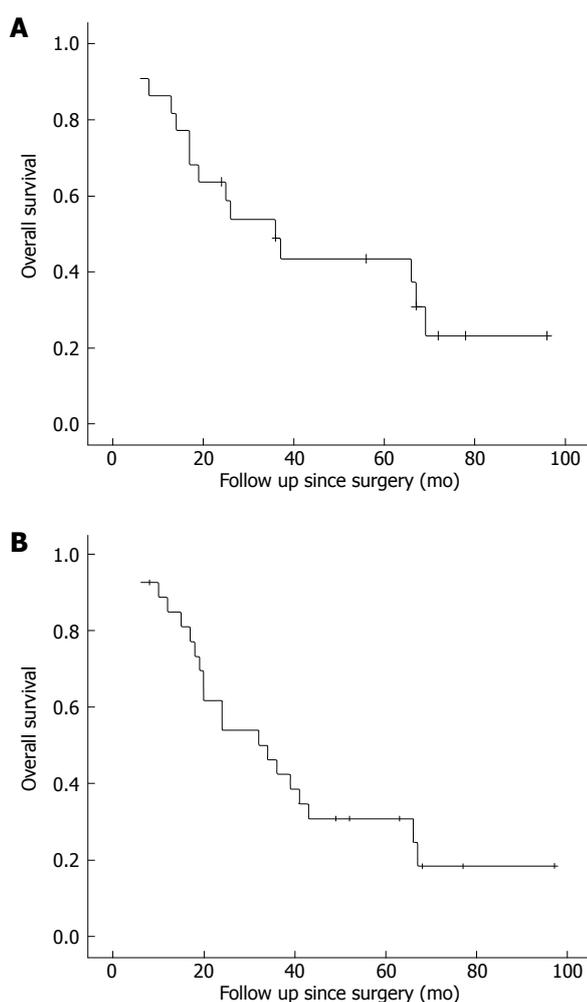


Figure 1 Kaplan-Meier survival curves. A: 22 patients with GIST accompanying GAC; B: 27 patients with GIST accompanying ESCC.

1, 2008, four of the patients were alive while 50 died of recurrence or distal metastasis of other malignancies. The remaining two patients died of other causes. Recurrent GIST was not found during the survival period of all dead patients, and the follow-up time of the remaining four. The overall 5-year survival rate of the 22 patients with GAC and incidental GIST was 31.8%, with a median survival time of 36 mo (Figure 1A). The 5-year survival rate of the 27 patients with ESCC and incidental GIST was 22.2%, with a median survival time of 32 mo (Figure 1B). The average survival time of the

two PAC and two CRA patients was 26 mo and 52 mo, respectively, and the survival time of the patients with triple tumors was 47 mo.

DISCUSSION

In our series, incidental GIST occurred simultaneously with EMT in 17.4% (54/311) of the GIST patients, which is higher than the reported incidence (14%)^[8]. However, assessment of the actual incidence of incidental GIST with EMT is difficult, because the data are only based on patients who have been surgically treated, whereas EMT patients managed with non-surgical measures are unaccounted for. Moreover, during examination or surgery, identification of GIST is incidental rather than intentional, and many lesions are missed as a result.

Notably, in addition to those with EMT, many synchronous and asynchronous cases of GIST with non-epithelial tumors have been reported, such as osteosarcoma, Burkitt's lymphoma, plasmocytoma, neuroblastoma, somatostatinoma, chronic lymphatic leukemia, lipoma and ectopic pancreas^[4,9-13]. Synchronous incidental GIST and non-tumorous diseases have been reported, such as ulcerative colitis, Meckel's diverticulum, rapidly progressive glomerulonephritis, HIV carriers, and Crohn's disease^[5,14-17]. Sanchez *et al*^[18] reported that incidental gastric GIST is found in 0.8% of patients undergoing laparoscopic Roux-en-Y gastric bypass surgery for obesity. Kawanowa *et al*^[19] showed that microscopic GIST can be found in 35% of stomach-resected patients with gastric cancer. It has been shown that microscopic GIST can be found in 10% of patients undergoing surgery for esophageal carcinoma^[20]. Especially, incidental GIST has also been detected in 0.2% of all autopsies, accounting for 10% of all patients with primary GIST^[21]. These findings suggest that incidental GIST may occur synchronously with other diseases more frequently than expected, and the incidence of incidental GIST might be much higher than that of clinical GIST.

Particular attention has been paid to clinical GIST because of its striking symptoms such as gastrointestinal bleeding, pain, dyspepsia, abdominal mass and obstruction^[22,23]. On the contrary, incidental GIST may emerge asymptotically, and even if symptomatically, the symptoms may often be vague and nonspecific^[18]. In our study, all the 54 patients presented symptoms

indistinguishable from those of EMT, which might have been overlooked because of the progressing symptoms of EMT such as severe dysphagia, weight loss, abdominal pain and anemia. The size of incidental GIST was small, and the majority (90.7%) of them had a very low risk. Also, only a few reports are available on incidental GIST with a high risk^[21,24,25]. In this study, only 1.9% of clinical GIST lesions had a very low risk, and 38.5% had a high risk, indicating that GIST is malignant. Perhaps, incidental GIST might have emerged later than EMT, or their development may have been depressed by EMT through mechanisms which are yet to be studied.

Generally, the preoperative detection rate of incidental tumors is very low. In this study, except for two patients with PAC, the other patients received endoscopic examinations preoperatively, yet only one GIST lesion was found. Difficulty in detecting the lesion might be attributed to its small size and intramural location. Incidental GIST, if detected at CT or MRI, is often mistaken for metastatic lymph nodes derived from EMT. Therefore, radiological examination is minimally helpful for its diagnosis. As a result, the endoscopist and surgeon should take the major responsibility of detecting incidental GIST. Incidental GIST occurs most commonly in stomach, esophagus, small bowel, colon and omentum. Consistent with the reported findings^[19], incidental GIST was observed in gastric fundus and body in the present study. Careful assessment of the hotspot (i.e. the upper portion of stomach) is important for both endoscopist and surgeon.

Interestingly, we found that there was a significant difference of the incidence of incidental GIST in male and female patients. Because of the unclear pathogenesis of incidental GIST, we cannot explain this finding. Further studies are needed on the gene expression in primary tumor cells from male and female patients and signal transduction may also provide us with some clues to this question.

In the absence of prospective control studies, whether resection of incidental GIST lesions helps to improve the quality of life and/or the survival rate of EMT patients remains unclear. There are two major concerns for incidental GIST if missed during operation for other tumors. First, residual GIST lesions may progress to invasive disease and cause intestinal obstruction and/or life-threatening gastrointestinal hemorrhage because the malignant potential is unpredictable based on gross appearance alone. Second, a residual incidental GIST may be mistaken for the relapse or metastasis of a previously removed neoplasm, which may result in inappropriate treatment of patients in follow-up after operation. Therefore, an en bloc resection with other tumors or an additional local resection with adequate margins has been recommended by surgeons^[6,18,25]. Making surgeons aware of this will help to correct surgical procedures, and ultimately improve the quality of life and avoid inappropriate treatment of patients during follow-up after operation.

Common carcinogenic agents, which result in a simultaneous proliferation of different cell lines (epithelial

and stromal cells), may be involved in the development of incidental GIST as a mere coincidence. In this study, males with primary GIST were more likely to have a synchronous tumor than females ($P < 0.001$). Synchronous tumors may have a high prevalence in males. Simultaneous neoplastic proliferation of epithelial and stromal cells might be stimulated by the same carcinogenic factors, such as *Helicobacter pylori* infections, germline mutations, and exposure to ionizing radiation^[6,24,26,27]. To clarify possible common carcinogenic agents against synchronous tumors, further studies are needed.

In conclusion, incidental GIST coexists with EMT at a higher incidence than expected. Surgeons are advised to be alert against possible primary GIST accompanying other tumors.

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COMMENTS

Background

Gastrointestinal stromal tumor (GIST) is one of the most common tumors in gastrointestinal (GI) tract, probably arising from precursor cells that serve as a pacemaker to trigger gut contraction. It may exist alone with clinical manifestations or coexist with other diseases. The former is usually diagnosed by its clinical presentations and called clinical GIST, while the latter is usually found during examination or surgery for other diseases and called incidental GIST.

Research frontiers

Clinical GIST has been extensively studied in the past twenty years. Many cases of GIST existing alone or coexisting with other diseases have been reported, but GIST coexisting with other GI tumors has only been reported as single cases. It is necessary to conduct a comprehensive study with a large sample size to determine its incidence and features.

Innovations and breakthroughs

For the first time, the authors report an extensive study on incidental GIST coexisting with other GI tumors. This study revealed some important and interesting information regarding incidental GIST coexisting with other GI tumors. Firstly, they found that incidental GIST coexisted most frequently with esophageal and gastric tumor (1.13% and 0.53% respectively), and least with colorectal tumor (0.03%). Secondly, the majority of clinical GISTs had a moderate or a high risk. In contrast, the majority of incidental GISTs had a very low risk. Thirdly, the incidence of incidental GIST was significantly higher in male than in female patients (88.9% vs 11.1%). Finally, this study also provided the statistics for age, survival time and prognosis of studied patients and outlined the other features of incidental GIST, such as the number of lesions, lesion location and cellular morphology, etc.

Applications

The incidence of incidental GIST coexisting with other GI tumors is much higher than expected. However, without specific manifestations, preoperative detection of incidental GIST is difficult. Residual GIST lesions may progress to invasive diseases, cause intestinal obstruction and/or life-threatening gastrointestinal hemorrhage. In addition, residual incidental GIST may be mistaken for the relapse or metastasis of previously removed tumors, resulting in inappropriate treatment of patients during follow-up after operation. A careful inspection for GIST is highly recommended during surgery for GI tumors.

Terminology

GIST is one of the tumors in the GI tract, probably arising from precursor cells that serve as a pacemaker to trigger gut contraction. GI epithelial malignant tumor (EMT) refers to a tumor arising from the surface cells of the GI tract.

Peer review

This article is the first report to present the incidence of incidental GIST accompanying gastrointestinal EMT. In this study, the authors evaluated the

incidental GIST and its clinical significances. The title of the paper reflects the major contents of the article. The abstract gives a clear delineation of the research background. Results and discussion are well organized. The conclusion is reliable and valuable.

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