Synchronous incidental gastrointestinal stromal and epithelial malignant tumors

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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, Chengdu 610041, Sichuan Province, 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.

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

Key words: Gastrointestinal stromal tumor; Multitumor; Synchronous tumor

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 gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol 2009; 15(16): 2027-2031 Available from: URL: http://www.wjgnet.com/1007-9327/15/2027.asp DOI: http://dx.doi.org/10.3748/wjg.15.2027

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
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[1]. 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 \( \chi^2 \) 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, 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.

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

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

GIST: Gastrointestinal stromal tumor; EMT: Epithelial malignant tumor; GAC: Gastric adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; CRA: Colorectal adenocarcinoma; PAC: Pancreatic adenocarcinoma.
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%)\(^\text{[8]}\). 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, plasmacytoma, neuroblastoma, somatostatinoma, chronic lymphatic leukemia, lipoma and ectopic pancreas\(^\text{[4,9-13]}\). Synchronous incidental GIST and non-tumorous diseases have been reported, such as ulcerative colitis, Meckel’s diverticulum, rapidly progressiv glomerulonephritis, HIV carriers, and Crohn’s disease\(^\text{[5,14-17]}\). Sanchez et al\(^\text{[18]}\) 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\(^\text{[19]}\) 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\(^\text{[20]}\). Especially, incidental GIST has also been detected in 0.2% of all autopsies, accounting for 10% of all patients with primary GIST\(^\text{[21]}\). 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.

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

### 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 (%) |
|---------------|--------------|--------------|--------------------------|-----------------------------|-----------------|----------------------|
|               |              |              |                          |                             |                 |                      |
| Incidental GISTs | 54           | 48/6         | 63 (44-79)               | Gastric (49), esophagus(2), ileum(1), colon(1), omentum (1) | 0.8             | 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             | 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             | VL: 54 (17.4); L: 91 (29.3); Int: 67 (21.5); H: 99 (31.8) |

Risk was determined as previously described\(^\text{[7]}\). VL: Very low risk; L: Low risk; Int: Intermediate risk; H: High risk.
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. GI epithelial malignant tumors (EMT) refer to a tumor arising from the surface cells of the GI tract. The incidence of incidental GIST coexisting with other GI tumors is much higher than expected. Surgeons are advised to be alert against possible primary GIST accompanying other tumors.

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 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 males 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 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.

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, germine mutations, and exposure to ionizing radiation. 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.
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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