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Original research

Coexistence of gastrointestinal stromal tumours (GIST) and malignant neoplasms of different origin: Prognostic implications

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ABSTRACT

Background: Over the past decade, several changes occurred in diagnostics, treatment and understanding of pathogenesis of gastrointestinal stromal tumours (GIST). However, their coexistence with other malignancies of different histogenetic origin remains a challenging issue.
Methods: Patients diagnosed with GIST in a 10-years period were identified retrospectively and clinical history and findings thoroughly explored for the presence of associated other malignancies. Follow up data were obtained and analysed for prognostic impact of the concurrent malignancy and/or GIST.
Results: Thirty seven (27 males, 10 females) of 86 GIST-patients (43%) had another malignancy. Mean age was 70 years. Associated malignancies were gastrointestinal ($n = 29$; 69%), renal-/urological ($n = 5$; 12%), haematological ($n = 4$; 9.5%), cutaneous ($n = 3$; 7%) and thyroid ($n = 1$; 2.5%) in origin. Majority of GISTs occurred in stomach (65%) and small intestine (30.6%) and most (78%) were asymptomatic incidental findings during diagnostic or therapeutic procedures for associated malignancies. GIST size ranged from 0.1 cm to 9 cm (mean, 2.2 cm) and all of them had a low (<5/50HPFs) or no mitotic activity. Thirty-one tumours (84%) were of no/very low/low risk and 6 were of intermediate risk. During follow-up (range 3–160 months, mean; 60 months), one patient suffered from distant metastases of GIST. Seven patients (19%) died of associated malignancies and three patients (8%) of other non-tumour-associated cause, but none died of GIST.
Conclusion: Coexistence of GIST with other malignancies is higher than previously reported and should draw attention of clinicians towards these incidental findings. Prognosis in these patients is usually determined by other malignancy and not significantly influenced by GIST. Therefore treatment algorithms should be focused on prognostically relevant malignancy.
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1. Introduction

Gastrointestinal stromal tumours (GIST) represent the most common mesenchymal tumours of the digestive tract. GIST are thought to derive from or differentiate similar to the gastrointestinal pacemaker cells, the interstitial cells of Cajal or their multipotential mesenchymal precursor cells [1,2]. GIST may be composed either of spindle, epithelioid, or pleomorphic cells or a variable combination thereof [3]. Most GISTs are initiated by oncogenic mutations involving the receptor tyrosine kinase proto-oncogenes c-kit and the platelet-derived growth factor receptor alpha (PDGFRA) gene [4,5]. Their clinical symptoms depend on the tumour size and the localisation. In some cases GIST represent incidental findings either during surgery, at autopsy or during other diagnostic procedures for unrelated diseases. Metastases arise predominantly in the liver or in the peritoneum, but rarely in lymph nodes, bones, lungs and other rare sites [6]. A prognostic classification of GIST into four [7] or five [8] risk categories is based on tumour size, mitotic activity and/or site. Their therapeutic options include surgery and treatment with imatinib mesylate (Glivec, Novartis, Basel, Switzerland), a competitive inhibitor of tyrosine kinases (BCR-ABL, ARG, KIT, PDGFRa and PDGFRb) [9,10]. A majority of patients respond to imatinib mesylate or achieve durable tumour growth stabilisation allowing a R0-resection, but some initially responsive patients experience tumour progress because of secondary drug resistance [11]. Unusual phenotypic changes may occur in GIST after neoadjuvant imatinib treatment [12].

The management of GIST has dramatically altered over the last years as a consequence of several achievements on the part of

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their diagnosis, treatment and understanding of their biology. Although several studies have documented the relatively common synchronous or asynchronous coexistence of GIST with other unrelated malignant neoplasms, still little is known on the significance and prognostic impact of their association with other malignancies of different anatomic localisation and histogenetic derivation. With increased awareness of the disease, nowadays the coexistence of GIST with other malignancies is more often detected than initially considered. Most of these cases have been documented as single case reports but several case series and reviews also exist on this topic [13]. This phenomenon remains still a special and challenging situation during multimodal therapy.

We report our experience from a single institution with patients diagnosed with GIST and a second neoplasm occurring in a synchronous or asynchronous setting.

2. Material and methods

2.1. Patients, malignancies and follow up

At our institution, 86 patients with GIST were treated within a period of 10 years (between January 2000 and December 2009). The analysis encompassed those patients, who were identified with another type of malignant neoplasia. The time point of GIST diagnosis with regard to the diagnosis of the other malignancies was defined as either synchronous (during staging or surgical therapy of the diagnosed cancer) or non-synchronous (before the diagnosis of the other-type of cancer or after its treatment). GIST diagnosis was verified according to current diagnosis criteria [8]. Immunohistochemical staining was performed with CD117, CD34, desmin, and S100 as previously. Mitoses were counted in 50 high-power fields (HPFs). One HPF corresponded to an area of 0.238.mm^2. The risk category was defined by assessing the tumour size and mitotic count following the consensus guidelines of the National Institutes of Health-(NIH-NCI) workshop and the Miettinen's criteria [7,8].

Associated malignant neoplasms were classified according to current World Health Organisation (WHO) classification of malignant neoplasm, the UICC criteria and TNM classification [14,15]. Neurofibromatosis type 1 (NF-1) and Carney triad-associated tumours or familial GIST were excluded from this study. Clinical and histopathological records were reviewed and data from cooperating hospitals and general practitioners were included. Patient, age, sex, tumour localization, morphological variant (spindle-cell, epithelioid, mixed), malignant potential (risk classification) and selected immunohistochemical parameters were assessed. The mean follow up of patients was 60 months (range: 3–160 months).

3. Results

3.1. GIST-associated malignancies

The 86 GIST patients included 50 men and 36 women with an age range of 35–91 (mean age was 64.8 years and 67.4 years for men and women, respectively). There was a slight male predominance in our series (M:F = 1.4:1). Thirty-seven patients (43%) were identified with non-GIST malignancy. Five of the 37 patients (13.5%) suffered from more than one other malignancy in addition to GIST. Among the 37 patients were 27 men (73%) and 10 women (27%) with a mean age of 70 years (range 56–86). Male predominance was even higher in the group with other malignancies (2.7:1). The mean age was 68 years (range: 60–80) and 75 years (range: 56–86) for men and women, respectively. Thus, mean age was higher in the group with associated malignancies than those without (70 yrs vs. 65.7 yrs). The most common localisation of GIST was the stomach (24 cases, 65%) (Fig. 1a), followed by the small intestine (11 cases, 30.6%) (Fig. 1b), oesophagus (1 case, 2.7%) and rectum (1 case, 2.7%). Small intestinal GISTs were located in the duodenum ($n = 3$), jejunum ($n = 2$) and ileum ($n = 6$) (Table 1). Of the 42 identified associated non-GIST neoplasms, the majority (69%) was located in the gastrointestinal and hepato-pancreato-biliary tract (7 gastric carcinomas, 5 rectal adenocarcinomas, 4 esophageal carcinomas, 4 pancreatic adenocarcinomas, 3 colon carcinomas, 2 carcinomas of the papilla of Vater, 1 hepatocellular carcinoma). The remaining cases were represented by pharyngeal carcinomas ($n = 2$), plasma cell myeloma ($n = 2$), malignant melanoma ($n = 2$), squamous cell skin carcinoma ($n = 1$), prostatic adenocarcinoma ($n = 3$), urothelial carcinoma ($n = 1$), renal cell carcinoma ($n = 1$), neuroendocrine tumour in colon ($n = 1$), thyroid carcinoma ($n = 1$) and anaplastic T-non-Hodgkin lymphoma ($n = 2$) (Table 2). In twenty-nine patients (78%), detection of the GIST and the second tumour was simultaneous. In five patients of them there were two non-GIST malignancies either preceding ($n = 4$) or following ($n = 1$) the diagnosis of GIST. The mean time interval between previous additional malignancy and GIST was 97 months (range: 40–156 months). In six patients (16%) GIST was found during follow-up for a known other malignancy and in two patients (5.5%), the second malignancy was detected after the diagnosis of GIST. In one patient, two separate GIST were found in the same organ (stomach). The chronology of GIST diagnosis is detailed in Table 2. GIST were almost always an incidental finding either during the diagnostic procedures for other tumours (5 cases, 14%) or during surgery (24 cases, 65%). Only 8 GIST (21%) presented with clinical symptoms (abdominal pain, bleeding); four of them were not synchronous with other malignancies.

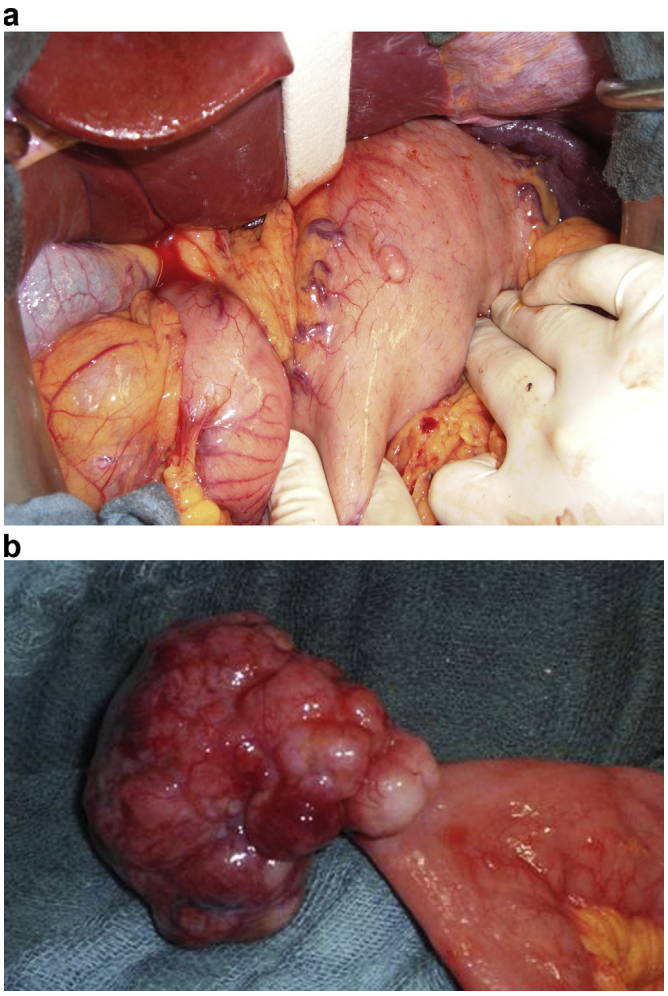

Fig. 1. a. Typical appearance of a GIST of very low risk localisated in the stomach during surgery for adenocarcinoma of eosophagus. b. Typical extramural appearance of an incidentally identified GIST of the small intestine during surgery for ductal adenocarcinoma of pancreas.

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