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GASTROINTESTINAL STROMAL TUMOURS – CLINICAL EXPERIENCE

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A b s t r a c t

Gastrointestinal stromal tumours (GIST) belong to less frequent tumours of connective tissue in the gastrointestinal tract. Increasing concern about elaboration of sorting, evaluation of cell origin diagnosing, and prognosis has been reported in recent 30 years. According to similar microscopic findings, GIST and leiomyosarcomas were confused. The use of electron microscope and particularly of immunohistochemical methods led to the understanding that GIST could have myogenic attributes of neutral character and even mixed (neuronal and muscular) matter or undifferentiated. At the present time the GIST is suspect of being originated in the Cajal cells, which are considered to be pacemaker cells in the intestine.

A surgical resection of the tumour is nowadays the only effective treatment, because of non-effectiveness of radiotherapy and systemic chemotherapy. However, imatinib mesylate is said to be promising. Fourteen patients underwent surgery at the First Department of Surgery of St. Anne's Faculty Hospital between 1996 and 2006. Most of the tumours were localised in the stomach (52.7 %).

A metastasis placed in the mesenterium was recorded in a patient with a primary GIST tumour also placed in the mesenterium, whose diameter exceeded 200 mm.

K e y w o r d s

Gastrointestinal stromal tumour, Cell of Cajal, R0 resection, Imatinib mesylate, c-kit

A b b r e v i a t i o n s u s e d

GIST, gastrointestinal stromal tumour; ICC, interstitial cell of Cajal; SONO, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; M2A, capsule endoscopy

INTRODUCTION

Gastrointestinal stromal tumour (GIST) is the designation for a most important group of gastrointestinal mesenchymal tumours that histologically, immunohistochemically and genetically differ from typical leiomyomas and schwannomas (*8,11*). GISTs are often more cellular than typical oesophageal leiomyomas and typically lack cytoplasmic eosinophilia. They are almost invariably positive for CD 34, negative for S-100 protein, negative for desmin, and positive for muscle actins. GISTs typically express c-kit (CD 117) (*9,10,14,17,19*). At present, GISTs are defined as spindle cells or epithelioid mesenchymal tumours that express c-kit.

In 1987, Saul and co-workers described a possible cell of origin for these tumours. These cells are interstitial cells of Cajal (ICC), which has a pace-making function in the bowel. C-kit (CD 117) is a marker for these cells. Immunohistochemical analysis revealed expression of c-kit in 82 % of the gastrointestinal stromal tumours (*3,15,16*).

The biological behaviour of gastrointestinal stromal tumours can be difficult to predict. At present, there has been considerable discussion regarding diagnostic modality, prognosis, and management of treatment. To define the biological potential and the risk of malignancy, systems have been reported using many parameters, e.g. Lewin's grading system (*1,8,13*).

Patients with gastrointestinal stromal tumours generally lack specific symptoms. Many patients have gastrointestinal bleeding or non-specific symptoms. Patients are often asymptomatic at first presentation (*2,8*). Diagnostic modalities include endoscopy (gastrofibroscopy, enteroscopy, M2A, colonoscopy), sonography (SONO), endosonography, computed tomography, and magnetic resonance (MRI). In many cases endoscopy is negative due to intramural localisation (*5*). Gastrointestinal stromal tumours are most often found in the upper digestive tract – stomach 40–70 %, oesophagus 5 %. In the lower digestive tract – small intestine 20–40 %, colorectal 5–15 %. GISTs have been found in omentum, mesenterium, and retroperitoneum – 5 %. (*6*)

In the treatment of GISTs surgery is the only real modality. *Langer et al.* (*8*) in a recent study indicates that the resection status strongly influences the outcome. Responses to radiotherapy or systemic chemotherapy are poor (*7,8,13*). In one study only 7 % patients with GISTs or sarcomas responded to chemotherapy (combination of doxorubicin and dacarbazine) (*20*). Radiotherapy is also problematic because GISTs are usually mobile. Low tolerance of intra-abdominal organs does not allow curative doses of radiotherapy (*6*).

MATERIAL AND METHODS

We have performed a retrospective analysis of the history of 14 patients with gastrointestinal stromal tumours treated from 1996 to 2003 in the Department of Surgery. The tumours were reviewed in the Department of Pathology, St. Anne's Faculty Hospital, Brno, to establish the diagnosis and to assess potential clinical behaviour. Primary tumours could be removed in 11 cases.

RESULTS

There were 10 men and 4 women. Mean age at diagnosis of 57.9 years, range 38–79. Eight of these patients (57.2 %) had GIST in the stomach, three (21.5 %) in the jejunum, one (7.1 %) in the retroperitoneum, one (7.1 %) in the mesenterium, and one (7.1 %) had stromal tumour in the rectum. In all cases consequent diagnostic modalities were used – sonography, endosonography, endoscopy, CT.

Symptomatology: Two patients were asymptomatic at first presentation, four resections had unspecified symptoms (abdominal pain, nausea), and seven patients had bleeding. Three patients were examined with anaemia.

Surgical treatment: All patients were treated surgically, twelve by complete resection R0 (no residual tumour), one by R1 (microscopic residual tumour), and one by resection R2 (macroscopic residual tumour) (*17*). Four patients underwent emergency laparotomy for bleeding; in these cases without specific preoperative determination.

Pathology: The mean size of the 12 tumours was 65 mm (from 35 to 200 mm). Metastases were in one case localised in the omentum, while the primary tumour was in the mesenterium (size 200 mm). Eight tumours showed positivity for c-kit (reactivity was made in 10 cases), focal expression of CD 34 was observed in 7 of 10 cases.

DISCUSSION

Many immunohistochemical studies have revealed expression of c-kit and positivity of CD-34. Indication of these markers is a useful tool in the diagnosis of gastrointestinal stromal tumours. C-kit (CD-117) is more constantly expressed in GISTs and is a more valuable factor in the diagnosis (*3,16*). Consequently, it is possible to accept the definition of GISTs – spindle cells or epithelioid mesenchymal tumours that almost invariably express c-kit and are also positive for CD-34. The origin of these tumours was suggested in the intestinal cells of Cajal, which has a pace-making function in the bowels (*17*). GISTs are classified according to their light-microscopic appearance as grades I-III. Grade I – tumours with low cellularity and monomorphic tumour cells and nuclei, grade II – tumours with higher cellularity and little to moderate cellular and nuclear pleiomorphism, and grade III – highly cellular tumours with pronounced cellular and nuclear pleiomorphism (*15,16*).

We have investigated 14 patients with GISTs. Our detections are equivalent with reviews of the literature. A review shows that surgery is one real primary treatment modality (*5,6,7,8,13*). Prognostic features have been suggested to predict the biological behaviour – localisation, size, invasion, growth pattern, mucosal invasion, cell type, cellularity, pleiomorphism, mitotic rate, grade, result of surgery, necrosis, and immunophenotype (*1*).

Lewin's grading-system defines the possible biological potential and the risk of malignancy (*1,8,13*). This grading system might predict the outcome. A further system is Consensus Conference ESMO 2004 (*Table 1)* (*20*). The terminology of "benign and malignant" GISTs is problematic as well. Classification of low- and high-risk tumours better describes their clinical behaviour (*8,12*).

Many patients with GISTs are asymptomatic at first presentation, others had non-specific symptoms: nausea, abdominal pain. Frequent symptoms include anaemia, tiredness or bleeding into the digestive tract. As diagnostic modalities, they are better than endoscopy endosonography, CT, and MRI (*13*). In surgical treatment, R0 resection with wide margins is necessary. Adjuvant or neoadjuvant chemotherapy approaches have failed, but new possibilities of treatment are under research – e.g. imatinib mesylate (*14,20*).

GASTROINTESTINÁLNÍ STROMÁLNÍ TUMORY – KLINICKÉ ZKUŠENOSTI

S o u h r n

Gastrointestinální stromální tumory patří mezi málo časté pojivové nádory zažívacího traktu. Jedná se o heterogenní skupinu zřídka se vyskytujících novotvarů, u kterých v průběhu tří desetiletí vzrůstá zájem o upřesnění třídění, buněčného původu, diagnostiku a prognózu. Pro podobný mikroskopický obraz byly dříve GIST považovány za neoplazmata z hladké svaloviny a byly často klasifikovány jako leiomyomy či leiomyosarkomy. S nástupem elektronové mikroskopie a zejména imunohistochemických metod bylo prokázáno, že GIST mohou mít myogenní rysy, neurální atributy, smíšenou podstatu svalovou a nervovou nebo vykazují nedostatečnou diferenciaci. V současnosti je buněčný původ GIST přisuzován buňkám Cajalovým, které jsou považovány za intestinální pacemaker buňky. V léčení je v současnosti základem R0 resekce tumoru, radioterapie a systémová chemoterapie zatím nevykazují efekt, slibná je léčba s použitím preparátu imatinib mesylate. V letech 1996–2006 podstoupilo operaci na naší klinice 14 pacientů s GIST. Nejvíce tumorů bylo lokalizováno v žaludku (57,2 %), metastázy byly zaznamenány u pacienta s tumorem v oblasti mezenteria. Lokalizace metastáz byla v mezenteriu, velikost primárního tumoru přesáhla 200 mm.

Table 1
Factors of risk behaviour

Risk behaviour	Height of tumour	Mitotic count
-	< 2 cm	< 5/50 HPFs
+	2–5 cm	<5/50 HPFs
++	<5 cm 5–10 cm	6–10/50 HPFs <5/50 HPFs
+++	>5 cm >10 cm all	>5/50 HPFs all >1050 HPFs

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