Originals

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Gastrointestinal Stromal Tumors. A Multicenter Experience*

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The report presents 200 cases of gastrointestinal stromal tumors (GIST). The material originated from six diagnostic centers in Poland and was reclassified according to the current criteria. Among lesions other than GISTs, 14 were identified as smooth muscle tumors and seven as neural tumors. GISTs were located in the stomach (51–63.3% of the investigated series), small intestine (27.4–33.8%), colon (approximately 4.5%), abdominal cavity, i.e. in the peritoneum and omentum (6%), and in the retroperitoneal space (2.5%). A slight predominance of women was noted (53–56%). The age of the patients ranged between 14 and 93 years of life, with the mean age of 62.4 years. Individuals younger than 45 years of age accounted for 10% of the group. In ten patients (five of them less than 45 years of life), multiple tumors were detected, their number ranging from two to less than 20; these individuals constituted 5% of the entire series. Moderately and highly aggressive tumors predominated. In the series, when multiple tumors were excluded, a total of 24 epithelioid GISTs (12%) were observed; of this number, 13 were situated in the stomach, six – in the small intestine, two – in the abdominal cavity and another two in the retroperitoneal space. Synchronic tumors observed in patients with GISTs were seen in seven patients, including an adenocarcinoma of the colon, two adenocarcinomas of the stomach, a carcinoid tumor of the small intestine, a pheochromocytoma of the retroperitoneal space, an anaplastic lymphoma and a disseminated squamous cell carcinoma. In immunohistochemical reactions (CD117, CD34, SMA, S-100, DES), attention was focused on the immunoreactivity of small GISTs, below 2 cm in size, and of multiple tumors. Immunohistochemical reactions were equally differentiated as to their presence and intensity in small tumors and in highly aggressive lesions above 5–10 cm in size. In multiple GISTs, immunohistochemical tests strongly indicated the heterogeneity of neoplastic cells, which, nevertheless, showed no consistent association with the location of the tumor, its aggressiveness, cellular structure or a tendency to form multiple foci.

Introduction

Gastrointestinal stromal tumors (GISTs), as well as tumors that develop outside the gastrointestinal tract, in the greater omentum, intestinal mesentery, gallbladder, retroperitoneal space or the urinary bladder [18, 29, 35, 44, 46, 53, 55], represent mesenchymal spindle cell and/or epithelioid cell neoplasms with a fairly specific immunohistochemical profile, characterized by a positive reaction to the CD117 antigen, frequent positive reaction to CD34, diversified reaction to smooth muscle actin (SMA), a reaction to

* The study was supported by the grant No. 3P05C05925 from the State Committee of Scientific Research (KBN).

desmin which is positive only in isolated cells, and a reaction to the S-100 protein that is either negative or expressed in no more than 10% of cells.

The histogenesis of stromal tumors is not fully elucidated, especially when one includes tumors situated outside the gastrointestinal tract. These tumors are believed to arise from the multipotential CD34+ cell, a precursor cell of the GI tract that is capable of varying degrees of differentiation into the interstitial Cajal cells (ICC) and smooth muscle cells, creating forms with an intermediate phenotype.

A positive reaction to CD117 results from the expression of a transmembrane receptor with the tyrosine kinase activity, which is encoded by the *KITC* gene on the 4q12 chromosome that – under normal conditions – binds a ligand, i.e. the stem cell factor (SCF). In the majority of GISTs (between 57 and 85%), a continuous activation of KIT is associated with a mutation in the *KITC* gene, while the remaining tumors do not manifest this mutation [21, 51]. Familial multiple GISTs result either from a point mutation in the *KITC* gene in the germ cell lines or a mutation in the platelet-derived growth factor receptor A gene (*PDGFRA*) [9, 34].

A positive reaction to CD117 is seen in various types of normal cells, including the interstitial Cajal cells of the gastrointestinal tract, submesothelial spindle cells of the greater omentum (ICC-like cells) [53, 58], bone marrow stem cells, mast cells and epidermal basal layer cells, melanocytes, as well as the epithelium of the mammary ducts and sweat glands. Pathological cells, including numerous neoplastic cells, also demonstrate a positive reaction to CD117. These are reactive myofibroblasts, as well as neoplastic cells in chronic myeloid leukemia, melanoma, clear cell sarcoma, germ cell tumors (seminoma/dysgerminoma) and angiosarcoma [61]. In addition, a focal and usually cytoplasmic reaction was observed in such tumors as synovial sarcoma, leiomyosarcoma, malignant schwannoma, liposarcoma, dermatofibrosarcoma protuberans, atypical fibroxanthoma, malignant fibrohistiocytoma, Kaposi sarcoma and adenoid cystic carcinoma [51, 52], as well as in childhood tumors: neuroblastoma, nephroblastoma, Ewing sarcoma and osteosarcoma [58].

In GISTs, the positive reaction to CD117 is observed in membrane and/or cytoplasm and – although it is usually present in the majority of tumor cells – it may be absent in some, infrequent cases, also when they show negative reactions to the remaining antibodies [32, 51, 55, 57].

Material and Methods

From the material provided by the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University, Kraków, 162 gastrointestinal mesenchymal tumors were selected, including 79 cases collected in the years 1982–1999 and identified through reclassification. The surgical specimens formalin-fixed, routinely processed and paraffin-embedded were stained with hematoxylin and eosin and immunohistochemically using a DAKO Immunostainer (DAKO, Denmark) and the following antibodies: CD117 (c-kit) (DAKO A 4502, 1:25), CD34 (DAKO M 7165, 1:25), S-100 (DAKO Z 0311, 1:200), SMA (DAKO M 0851, 1:50) and DES (DAKO M 0760, 1:50). The controls, mostly internal, were reaction results obtained in the normal tissues of the GI tract.

In addition, in an attempt to collect as many data on GISTs in the Polish population as possible, the authors received considerable assistance from other diagnostic centers in the country, such as the Department of Clinical Pathomorphology, Medical University in Poznań; Department of Pathomorphology, Pomeranian Medical University in Szczecin; Department of Clinical Pathomorphology, Medical University in Lublin; Department of Tumor Pathology, Świętokrzyski Oncology Center, as well as Division of Pathomorphology, First Chair of General Surgery, Collegium Medicum, Jagiellonian University. The provided material was collected in the years 1999–2003 and was largely preselected, representing GISTs diagnosed in the above centers or tumors suspected of being GISTs. Since the specimens were sent to Kraków for consultations (as slides stained with hematoxylin and eosin and/or paraffin-embedded specimens or non-stained preparations only), lesions other than GISTs had been eliminated. These were predominantly leiomyomas, schwannomas, melanomas and a single case of dendritic cell sarcoma, which were not included into the presented material.

Results and Discussion

1. Material originating from the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University, Kraków

The re-evaluated tumors from the period of 1982–1999 had been primarily diagnosed as smooth muscle tumors (leiomyoma, leiomyoblastoma, leiomyosarcoma) or neural tumors (schwannoma, neurinoma).

I. Mesenchymal tumors other than GISTs

The diagnosis of a smooth muscle tumor (DES+, SMA+, CD117–, CD34–) was confirmed in 14 cases:

1) Esophageal tumors:
   - 5 leiomyomas (4 males aged 35-48 years and 1 female aged 55 years; tumor diameter of 3–8 cm),
   - 1 leiomyosarcoma (a 44-year old female; tumor diameter of 10 cm).

2) Gastric tumors:
   – 2 leiomyomas (a 74-year old male, tumor diameter of 1 cm, and a 76-year old female, with two adjacent tumors, 1 cm in diameter).
3) Intestinal tumors:
   – 1 leiomyoma, 14 cm in diameter (a 67-year old female),
   – 1 leiomyosarcoma, 6 cm in diameter (a 70-year old male).
4) Colonic tumors:
   – 2 leiomyomas (a 69-year old male; tumor diameter of 0.7 cm; a 67-year old male, no data available on the tumor size),
   – 2 leiomyosarcomas (a 62-year old male, tumor diameter of 22 cm, and a 65-year old female, tumor diameter of 6.5 cm).

Neural tumors (S-100+, SMA-, DES-, CD117-, CD34-):

1) Tumors of the stomach (5 patients):
   – 4 females aged 39–78 years manifested schwannoma type tumors (4.5 and 7 cm in diameter, no data available in two cases),
   – diffuse lesions in a 60-year old male – ganglioneuromatosis.
2) Tumors of the small intestine:
   – 1 tumor with the diameter of 3 cm, corresponding to malignant schwannoma (a 75-year old female).
3) Tumors involving the colon (2 patients):
   – 1 schwannoma (a 60-year old female; tumor diameter up to 6 cm),
   – 1 neurofibroma (a 70-year old male; tumor diameter of 1 cm).

Basic data are presented in the Table 1.

In addition, the investigated series included two inflammatory polyps of the stomach, one calcifying fibrous pseudotumor and two cases of tumoriform, fibromatous inflammatory granulation tissue (in the greater omentum and Meckel's diverticulum).

In two tumors previously identified as an epithelioid leiomyosarcoma and a malignant stromal tumor, the diagnosis was changed respectively to a non-Hodgkin lymphoma (the case occurred in the pre-immunohistochemistry time) and a malignant melanoma (CD117+).

One tumor of the stomach, 6 cm in diameter (an 82-year old female), originally identified as a leiomyosarcoma, ultimately escaped classification (negative reactions to the S-100 protein, SMA, DES, CD117, CD34, Leu, EMA, HMB-45); therefore, the diagnosis of a non-specified sarcoma was maintained.

In total, smooth muscle tumors accounted for 18.5% of cases in the investigated series. Six such tumors were situated in the esophagus; not a single case of GIST was found among them.

Leiomyomas are the most common mesenchymal tumors of the esophagus: they account for 8% of all tumors involving this part of the GI tract, up to 2/3 of mesenchymal tumors and more than one half of benign lesions [27, 28, 40, 62]. Only in this segment of the gastrointestinal tract do they predominate over both stromal and neural tumors.

Neural tumors are rarely seen in the gastrointestinal tract. In the investigated material, they constituted 4.9% of all cases, with five such tumors involving the stomach. The literature on the subject usually describes isolated cases, with only few larger series being reported infrequently [11, 54, 62]. Such tumors are mainly seen in adults, are more common in females and are predominantly situated in the stomach. They are encountered in the esophagus only sporadically [27, 49]. At times, they are concurrent with von Recklinghausen disease [10, 16, 60]. It should be mentioned that type 1 neurofibromatosis is also associated with multiple GISTs, especially involving the small intestine [6, 24, 36].

The remaining 79 tumors, combined with 53 cases originating from the period of 1999–2004, constitute a group of 132 gastrointestinal stromal tumors, i.e. 81% of the original series.

TABLE 1

	Leiomyoma	Leiomyosarcoma	Schwannoma	Malignant schwannoma	Neurofibroma	Ganglioneuromatosis	Total
Esophagus	5	1	–	–	–	–	6
Stomach	2	-	4		–	1	7
Small intestine	1	1	–	1	–	–	3
Colon	2	2	1	–	1	–	6
Age	35–76	44–70	39–78	75	70	60	
Gender	7M/3F	2M/2F	5F	1F	1M	1M	
Diameter	0.7–14 cm	6–22 cm	4–7 cm	3 cm	1 cm	diffuse	

2. Sixty-eight GISTs originating from the materials supplied by the above-mentioned Departments of Pathomorphology were included into the analysis.

II. GISTs – location within the gastrointestinal tract

1. Material supplied by the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University, Kraków

In 83 patients (63.3%), GISTs were located in the stomach. The group included 33 males (mean age – 62 years) and 51 females (mean age – 63 years). The tumors predominantly involved the gastric body and the cardia. Their size ranged from 0.5 to 22 cm; including 62 cases with tumors of 3 and more centimeters in diameter. Six patients presented with multiple tumors. Macroscopically isolated lesions of more than 1 cm in size had a dome-like form and were covered with slightly smoothened mucosa, at times showing ulceration at the top. In the majority of cases, a round tumor would extend intramurally, more rarely it was hour-glass shaped and formed a bulge under the serosa, was well delineated, its section showed a zonular and lobular (polycyclic) structure and its color in fragments situated beyond the foci of hemorrhage and necrosis in larger lesions was cream-pink. Small tumors with the diameter of 0.5–0.7 cm, if they developed within the muscularis propria, were usually accidentally found on autopsy or in stomach specimens resected for other reasons. More superficially situated lesions were shaped as round polyps with a broad base.

Macroscopically, intestinal tumors were similar. Ulcerations were seen in large lesions, but no typical central crater was noted. Thirty-six stromal tumors (27.4%) were situated in the small intestine, including 20 in male patients (at the mean age of 62 years – in two cases no data were available) and 16 in females (mean age, 60.3 years). Twenty-one tumors were 3 cm or more in diameter (no data were available in six cases). In four patients, multiple lesions were detected; of this number, it was a local dissemination in two cases.

In six individuals (4.5%), the tumor was situated in the colon; this group included four males (mean age, 54 years) and two females (mean age, 79.5 years). The size of these tumors ranged from 1 to12 cm, with five being 3 cm or more in diameter.

In the remaining six patients, the tumors were situated in the peritoneum (two cases, including one most likely representing a disseminated disease originating from an unidentified primary site), retroperitoneal space (two cases), while in the other two patients, the clinical information on the location of the tumor was limited to a statement „in the abdominal cavity".

2. Material originating from the Departments of Pathomorphology, Medical University in Poznań, Pomeranian Medical University in Szczecin, Medical University in Lublin, Department of Tumor Pathology, Świętokrzyski Oncology Center, and Division of Pathomorphology, First Chair of General Surgery, Collegium Medicum, Jagiellonian University

Out of 68 stromal tumors, 35 were situated in the stomach (51%), including 19 in males (mean age, 64 years) and 16 in females (mean age, 64.4 years). Twenty-three GISTs were detected in the small intestine (33.8%) – eight in men (mean age, 58.1 years) and 15 in women (mean age, 48.5 years). Three GISTs developed in the colon: two in males with the mean age of 57.5 years and one in a 56-year old female. The remaining seven tumors were situated in the retroperitoneal space and within "the abdominal cavity" (10% of the series); the tumors were seen in six females (mean age, 59.9 years) and in a 66-year old male.

GISTs constitute the majority of the investigated gastrointestinal mesenchymal tumors and – with the exception of the esophagus – are predominant in particular segments of the GI tract. They are the most commonly seen in the stomach, accounting for 48 to 84% of gastric mesenchymal tumors (up to 2/3 of the total number, on the average) [17, 20, 64, 66]. The second most often involved organ is the small intestine, followed by the anorectum, colon and esophagus [17, 30, 36, 66].

In this respect, the present results (51–63% of GISTs situated in the stomach and 27–33% in the small intestine) are well within the mean reported percentage.

III. GISTs – age and gender of the patients

1. Material originating from the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University

The entire group of patients showed a slight predominance of females: 70 (i.e. 53.4%) women aged 14–97 years and 61 men (46.5%) at the age range of 26–93 years.

The mean age of both male and female patients with GISTs situated in the stomach and small intestine was similar – slightly above 60 years of age, but 16 out of 132 individuals (12.1%) were below 45 years of life. The group of younger patients included 11 women (ten cases involving the stomach and one – the small intestine) and five men (four tumors of the stomach and one involving the small intestine), as well as five of eight cases of multiple tumors (four involving the stomach and one – the small intestine).

2. Material provided by the Departments of Pathomorphology, Medical University in Poznań, Pomeranian Medical University in Szczecin, Medical University in Lublin, Department of Tumor Pathology, Świętokrzyski Oncology Center, and Division of Pathomorphology, First Chair of General Surgery, Collegium Medicum, Jagiellonian University

The patients included 38 women (56%) aged 37–90 years (mean age, 57.1 years) and 30 men (44%) in the age

range of 28 to 82 years (mean age, 61.4 years). Six individuals – four males and two females – were below 45 years of life (8.8%); this group included three patients with tumors of the stomach, two – with GISTs situated in the small intestine and one – in the retroperitoneal space. Two patients had multiple lesions; in both cases the lesions involved the small intestine and the patients were above 45 years of life.

On diagnosis, the majority of GIST patients are in their 6th or 7th decade of life [7, 20, 31, 55, 59, 66]. Nevertheless, not a single age group is risk-free: GISTs are diagnosed in children and a case of a congenital GIST was described [32, 65]. In general, males fall to the disease more frequently [20, 41, 59, 66]. And thus, although the mean age of patients from our series does not differ from the anticipated value, yet 12% of them were below 45 years of life. In this subgroup, as well as among the entire series of patients, women predominated.

IV. Assessment of tumor malignant potential

To date, no uniform criteria have been established that would describe the risk of an unfavorable course of GIST, apart from such obvious clinical properties as local recurrent disease, infiltration of adjacent organs or metastases. Nevertheless, among prognostic factors, the size of a tumor and the number of mitoses generally occupy the leading position. While assessing the possible development of the tumors, the authors used the scale proposed by Fletcher [14], according to which the boundary values separating low and medium degrees of aggressiveness are as follows: tumor diameter of 5 cm and the number of mitotic figures up to 5/50 HPF.

Table 2 presents the number of tumors with the predicted degree of aggressiveness situated in particular segments of the GI tract (the numbers are given as aggregates for both series).

Thus, when 25 cases with the assessment hindered by lack of clinical information had been excluded, the investigated GISTs were found to show a preponderance of moderately and highly aggressive tumors, accounting for 53% of the total group. Moderately aggressive GISTs with metastatic potential are as a matter of fact unpredictable tumors. In a patient of ours with a tumor 6 cm in diameter metastasizing into the liver, the number of mitoses in the primary lesion was 1/50 HPF. Such a situation has been commonly observed. The very histological assessment of tumor aggressiveness in multiple lesions also poses a problem, exemplified by the histology of familial GISTs described by Maeyama as spindle cell tumors, showing no mitotic activity, and yet of a fatal course [34].

Patients with tumors showing high histological aggressiveness constituted up to 1/3 of all individuals in the investigated series; the result is comparable to or lower than values reported by other authors [26, 64]. Wang [64] divided 76 GISTs originating from Chinese patients into 38 benign and 35 malignant tumors [46%]. Wang based his classification on unquestionable criteria: recurrent disease, metastases or infiltration, and thus the number of cases with a clinically malignant course might have been higher. The likelihood of an unfavorable course of GIST is higher when the tumor is situated in the small intestine, where GISTs account for more than 13% of malignancies [7, 13, 14]. In our series, moderately and highly aggressive tumors accounted for more than 55% of the small intestine lesions and less than 50% of the gastric tumors. GIST metastases are found in approximately 47% of cases, being predominantly seen in the liver and peritoneum, more rarely in the lungs and bones and only infrequently in the lymph nodes [7, 12, 38, 59]. One should also bear in mind atypical location of metastases, such as the breast, skin or cavernous sinus [2, 23, 56]. Five-year survival rate in GISTs is approximately 54% [12].

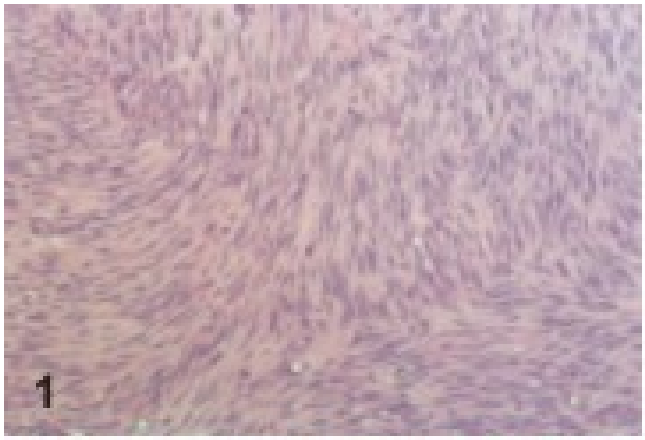
V. Epithelioid cell and spindle cell tumors

In both series (excluding multiple lesions), 24 epithelioid GISTs (12%) were noted. This group indeed included more aggressive tumors (a total of 12 cases), but the authors also found six lesions belonging to the low and very low aggressiveness category and originating from the stomach and the small intestine. Thirteen epithelioid cell GISTs

TABLE 2

Degree of aggressiveness	Stomach (119)	Small intestine (59)	Colon (9)	Other (13)	Total (200)
Very low	17	3	1	–	21
Low	36	11	–	1	48
Moderate	30	11	1	3	45
High	24	22	7	8	61
Difficult to assess *	12	12	–	1	25

*No data available on the tumor size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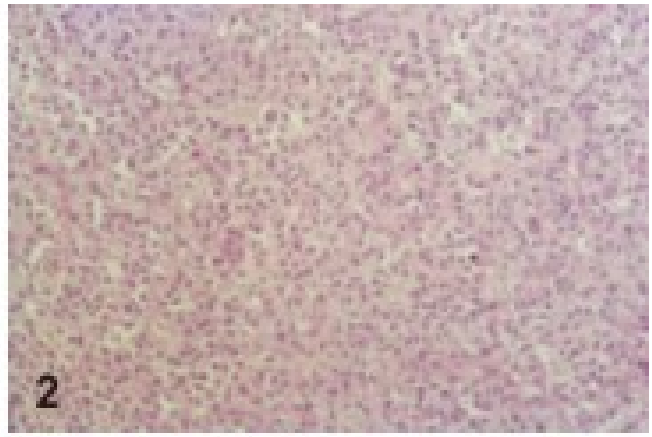
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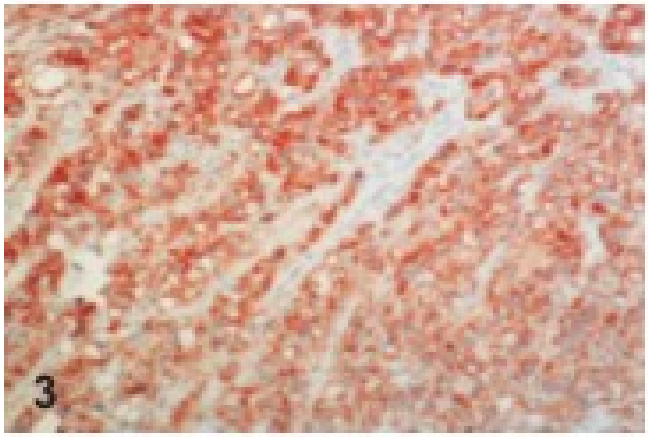
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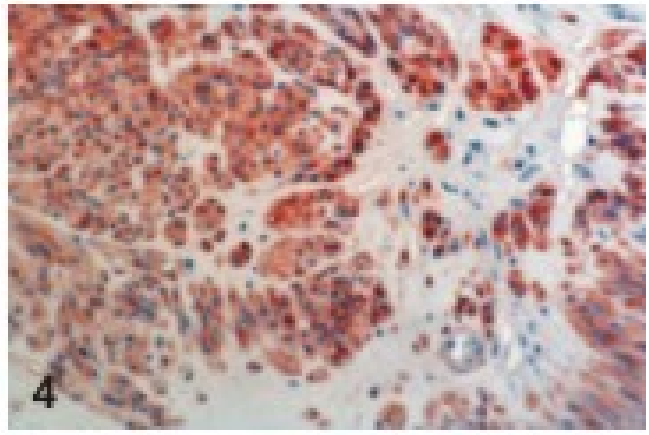
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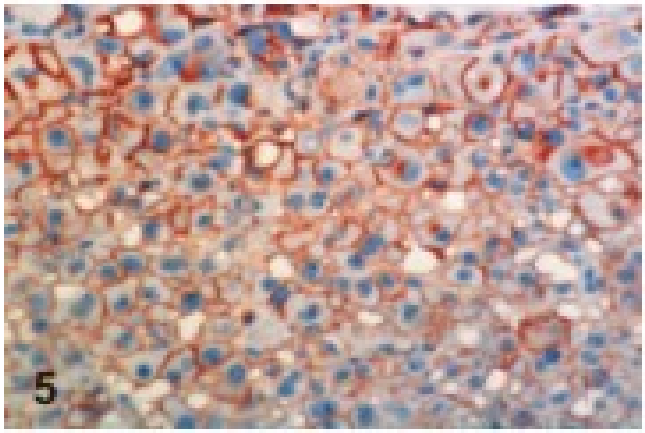
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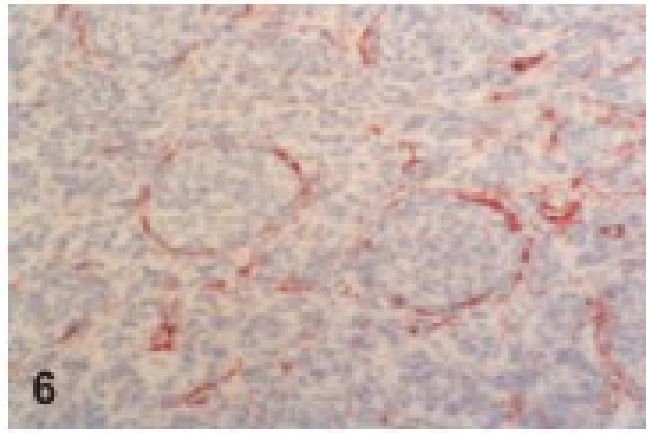
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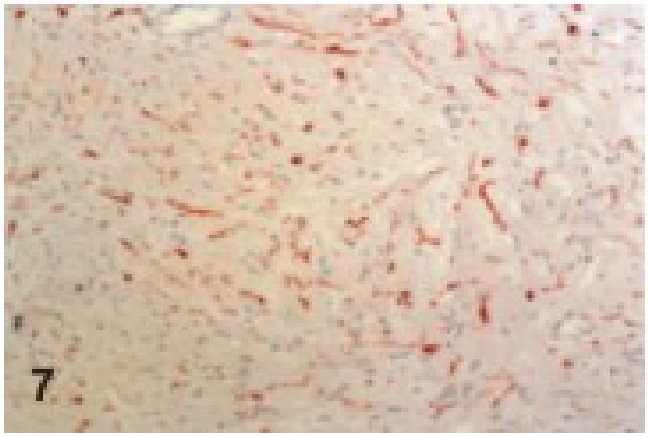
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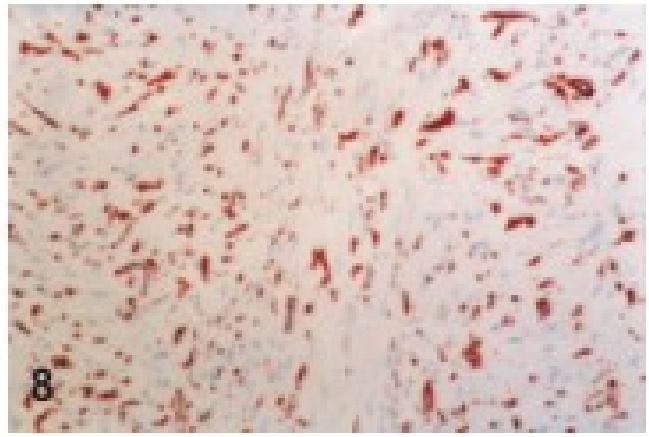
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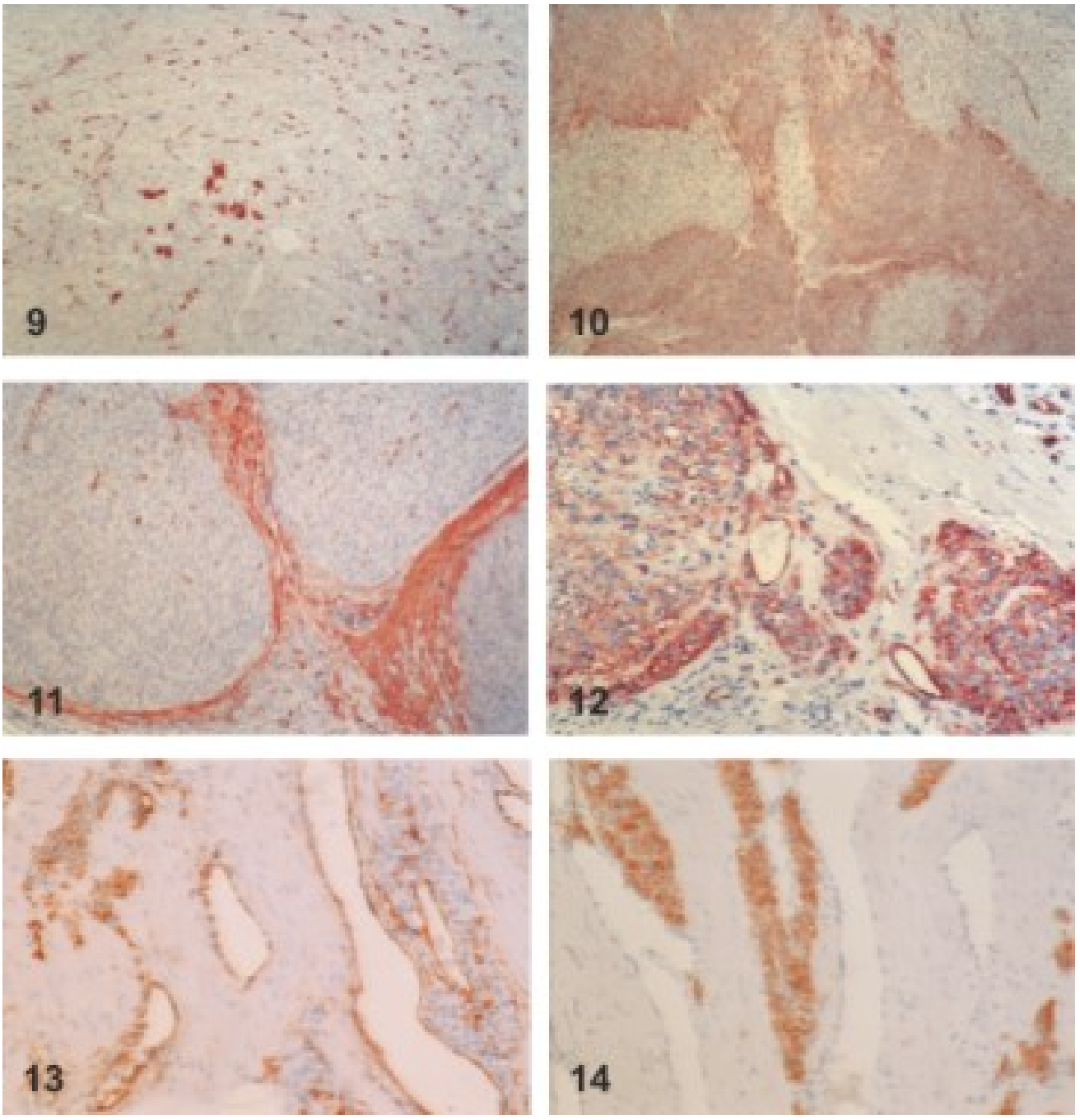

Fig. 1. A typical spindle cell GIST. Broad, interwinding bands of cells characterized by low degree of polymorphism, with quite abundant, eosinophilic cytoplasm resembling a leiomyoma. HE.
Fig. 2. An epithelioid cell GIST. The empty spaces in the cytoplasm, constitute a fairly common artifact and may at times suggest a carcinoma. HE.
Fig. 3. Positive cytoplasmic and membranous immunohistochemical reaction to CD117 in numerous GIST cells.
Fig. 4. Positive cytoplasmic CD117 dot-like staining in GIST cells (so-called Golgi-zone pattern).
Fig. 5. Positive immunohistochemical reaction to CD34 in an epithelioid tumor visible as a relatively rare membranous staining pattern.
Fig. 6. A whorl-like pattern in a spindle cell tumor, emphasized by peripherally arranged SMA-positive cells, most likely originating from small vessel walls.
Fig. 7. Positive cytoplasmic reaction to CD117 in scattered, spindle and highly elongated GIST cells.
Fig. 8. Positive immunohistochemical reaction to CD34 seen solely in numerous, small vessels within the tumor. This GIST is CD34-negative.
Fig. 9. Positive immunohistochemical reaction to S-100 protein in a small number of GIST cells, including several pleomorphic cells.
Fig. 10. Contrasted, strongly CD34-positive and CD34-negative GIST regions.
Fig. 11. A multifocal GIST – one of several tumors was a conglomerate, the structure of which was emphasized by bands of smooth muscles (SMA+).
Fig. 12. A multinodular GIST. Within the satellite tumor – a small neoplastic focus separated from the main tumor mass – the immunohistochemical reaction to CD34 is more intensive (see the right side of the photograph).
Figs. 13 and 14. The same groups of GIST cells in perivascular spaces on the periphery of multiple tumors – CD34-negative (Fig. 13) and CD117-positive (Fig. 14).

were situated in the stomach, six – in the small intestine, two – in the abdominal cavity, and another two – in the retroperitoneal space.

VI. GISTs and synchronous tumors

Material provided by the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University

In seven patients, other cancers developed concurrently with GISTs; in some cases the former dominated over the clinical picture:

- in a 74-old male, a GIST situated in the stomach, measuring 17 cm in diameter and disseminated within the abdominal cavity occurred concomitantly with a colonic adenocarcinoma (B2);
- a 57-year old male patient with a gastric GIST, 18 cm in diameter, presented with a disseminated squamous cell carcinoma;
- a 53-year old male was diagnosed with a colonic GIST, 12 cm in diameter, and a concomitant carcinoid tumor situated in the small intestine,
- a 38-year old male with multiple tumors of the small intestine, up to 2.5 cm in size, also showed a pheochromocytoma in the retroperitoneal space,
- two patients with small stromal tumors (M/61, two GISTs, 0.5 cm each, and another M/69, one GIST, 2 cm in diameter), also had adenocarcinomas of the stomach – in one of them, it was an early carcinoma,
- in a 55-year old female patient deceased due to anaplastic lymphoma, the gastric GIST measured 0.5 cm.

It appears that the group of GIST patients that were additionally (or predominantly) burdened with another tumor was fortunately small. Apart from individuals with von Recklinghausen disease, only a single case of a synchronous mesenchymal tumor situated at the same site was reported; this was a lipoma of the stomach [3]. In addition, patients with GISTs were also diagnosed with concomitant Burkitt's lymphoma, osteosarcoma, melanoma, neuroblastoma, primary kidney tumor, Carney's triad, MEN I syndrome, colonic adenocarcinomas and gastric adenocarcinomas, including a one case of collision tumors [4, 5, 8, 15, 25, 33, 43, 45, 48, 63].

VII. Multiple GISTs

Material originating from the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University

Eight patients presented with two or more concurrent tumors situated intramurally within the same organ. The group included four males and four females in the age range of 14–66 years (five patients were below 45 years of life). The size of the lesions oscillated between 0.5 and 4.5 cm, and the number of tumors ranged from two to almost twenty. The stomach was involved in six cases, and the small intestine – in two. In addition, two patients were diagnosed with synchronous tumors: an early stage cancer of the gastric body and cardia in a 61-year old man (two GISTs, 0.5 cm in diameter, in the stomach) and a pheochromocytoma of the adrenal gland in a male patient aged 38 years of life (two GISTs, 2.5 cm in diameter, situated in the small intestine).

Some lesions that macroscopically seemed to be a unity were in fact conglomerates of smaller and larger tumors separated by bands of normal smooth muscles (Fig. 11). This type of multifocal proliferation was clearly seen in two patients (a 14-year old and a 20-year old females) with an extensive involvement of the stomach, but it was also present in the case of two other, partially hyalinized tumors of the small intestine, where separate small, microscopic foci were seen in the immediate vicinity (Fig. 12).

With respect to their cellular structure, particular tumors observed in a single patient were usually similar, although one of the spindle cell conglomerates also contained a single epithelioid tumor. Mitotic activity in bifocal lesions was comparable, while in multifocal lesions it ranged from 0–1 mitotic figure/50 HPF in small tumors to 11 mitoses/50 HPF in larger ones. Thus, this group of lesions included GISTs with a predicted course ranging from benign to malignant (histological assessment).

Multiple GISTs are mostly described as a familial autosomal dominant disease with mutations involving the c-kit or *PDGFRA* genes [9, 34, 50]. In some of these patients, c-kit is also activated in the mast cells and skin melanocytes (what is clinically manifested as urticaria pigmentosa and hyperpigmentation); these individuals also present with dysphagia, not associated with typical achalasia [22]. Multiple GISTs more often develop in the small intestine than in the stomach, also when the patient has concomitant von Recklinghausen disease [6, 19, 24, 34, 36, 47]. According to clinical data, the above mentioned eight patients showed no skin lesions; no information was either provided that would indicate familial disease. In one patient with a synchronous pheochromocytoma, tests aiming at a possible diagnosis of Carney's triad had been suggested. Our data are incomplete and at times, Carney's triad becomes apparent after many years, yet one may suspect that multiple GISTs may also appear sporadically. Any predictions as to the course of the disease become problematic when we deal with small and theoretically benign tumors that have been surgically removed in a salvaging procedure, providing we assume that the entire organ (gastrointestinal tract?) is susceptible to GIST development. In addition, as it can be exemplified by one small GIST of the small intestine from our series, a tendency towards forming multiple lesions may escape detection. Only after numerous sections had been pre-

pared – the fact being related to technical rather than diagnostic issues – did the second, microscopic in size, but clearly delineated tumor become visible.

VIII. Immunoreactivity, including multiple GISTs and small GISTs

Material provided by the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University

For a long time now, diversified expression of CD34, SMA and KIT (CD117) with respect to reaction intensity and the number of positive cells, also within a single tumor, has been emphasized. In the group of highly aggressive GISTs one expects to find tumors markedly diversified in the above respects. Positive reactions to CD34 were noted in 58% to 80% of all GISTs, while in the case of CD117, only a few tumors tested negative. There were also cases when – within a single section – CD34-negative and CD117-positive zones were observed (Figs. 13 and 14). The descriptions also included tumors - although they were singular only – classified as CD117-positive GISTs, which showed a positive reaction to desmin. CD34 was more frequently seen in GISTs of the colon and the esophagus, while SMA positivity was more common in small intestine tumors [1, 31, 37, 42, 57, 66].

In our series, among 124 single GISTs, three tumors were CD117-negative, including one that tested negatively in all the employed reactions, while two lesions were CD34-positive. Positive reactions to CD34 were present in 97 (78%) cases, while concomitant positivity to CD34 and CD117 was seen in 94 lesions. Seventeen tumors were only CD117-positive. A strong reaction to SMA in more than 80% of tumor cells was observed in 19 lesions situated in the stomach and 11 involving the small intestine. The present series did not include any GISTs of the esophagus and only a small number of tumors located in the small intestine. One of the below described tumors was desmin-positive.

In several highly aggressive GISTs, a weak reaction to CD117 and CD34 was noted only in single fields within the lesion. We assumed that single, small and benign tumors would be uniform in character; this, however, was not the case.

In the investigated series, 23 tumors were identified, which were characterized by a diameter below 2 cm (between 0.5 and 2 cm) and constituted singular, spindle cell lesions almost identical in HE, without mitotic activity. However, immunohistochemistry demonstrated their high versatility, from a 0.7-cm in diameter GIST that was CD34-positive only in 10% of the cells, to a 2-cm GIST with a positive reaction to CD117, CD34 and SMA in 100% of the cells; both the tumors were situated in the stomach. In another small lesion, zones highly CD34-positive were strongly contrasted with negative zones (Fig. 10), while the differences associated with CD117 were slightly less pronounced.

Further investigations of this versatility can be best done in multiple tumors, and especially in tumor conglomerates.

Multifocal lesions showed marked differences in their immunoreactivity, which resulted from the heterogeneous character of neoplastic cells:

– in a 42-year old male, one tumor of the stomach showed a positive reaction to CD117 in all the cells, while the second – only in 10%, while both lesions were CD34-positive in 50% of their cells;
– in a 14-year old and a 20-year old female patients, the intensity of CD117 reaction was similar in all the lesions, but positive CD34 reaction ranged from 0 to 100% of the cells;
– in another patient (a 57-year old male), two tumors differed with respect to four reactions: CD117 – 50% positive/5% positive; CD34 – 90% positive/negative; SMA – negative/5% positive; S-100 – 10% positive/negative, while DES – 50% positive/50% positive.

In all the above four patients, the lesions were classified as moderately to highly aggressive.

Clearly stronger reactions to CD34 and CD117 were seen in tumor cell bands that infiltrated the surrounding tissues and in small tumor foci developing in the vicinity of the primary mass.

Based on the above data and the results reported in the literature, one may say that in diagnostic management of tumors in particular patients, the sole significance of immunohistochemical reaction versatility lies in the fact that it may hinder a firm diagnosis, especially in endoscopic sections and thick-needle biopsies. However, it shows no stable association with tumor location, aggressiveness, cellular structure or tendency to form multifocal lesions. Doubtlessly, such important issues as the recruitment of patients for Glivec therapy, assessment of tumor resistance to treatment, detection of familial cases and concurrent neoplastic syndromes, all require genetic studies. This only emphasizes the significance of an early and accurate GIST detection in routine diagnostic management.

Conclusions

1. Investigations of GIST cell immunoreactivity are necessary in differential diagnostics of these lesions. This postulate has been confirmed by the present results.
2. Co-expression of SMA and CD117, demonstrated in our material – in some cases in more than 80% of cells, confirms the fact of GIST developing from precursor cells differentiating to Cajal cells.

3. The introduction of a multicenter register has facilitated differential diagnosis of GISTs and allowed for an improved assessment of difficult and rare cases. This can expand to a nation-wide register.

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