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ORIGINAL ARTICLE

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Gastrointestinal pacemaker cell tumor: clinicopathological, immunohistochemical, and ultrastructural study with special reference to c-kit receptor antibody

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Abstract Recent studies indicate that a subgroup of gastrointestinal stromal tumors, including gastrointestinal autonomic nerve tumors (GANTs), originate from stem cells that differentiate toward a pacemaker-cell phenotype. These pacemaker cells form a complex network intercalated between the autonomic nerves and the muscle walls of the gastrointestinal tract and are called interstitial cells of Cajal (ICC). The c-kit receptor (CD117) is a sensitive marker for ICC. The aim of our study was to support the hypothesis that GANTs show ICC differentiation. Seven GANTs without convincing smooth muscle or neural differentiation all showed homogeneous reactivity for the c-kit receptor. CD34 was positive in three cases. On electron microscopy, the typical features of GANT were present. Six tumors contained skeinoid fibers. Most tumors were related to the small bowel. They presented as single (two cases) or multiple (five cases) tumors. The presenting symptoms were abdominal bleeding (2), abdominal mass (2), anemia (1), and small-bowel perforation (1). In two cases, liver metastases developed. Because of the close immunohistochemical and electron microscopic similarities of these tumors to the interstitial cells of Cajal, the term gastrointestinal pacemaker cell tumor seems appropriate.

Key words Gastrointestinal pacemaker cell tumor · Interstitial cells of Cajal · Gastrointestinal autonomic nerve tumor · c-kit Receptor-antibody · Electron microscopy

Introduction

Nonepithelial spindle and epithelioid cell tumors of poorly to well-developed differentiation arising in the gastrointestinal wall are described using the noncommittal term gastrointestinal stromal tumors (GISTs) [6]. Subclassification of these tumors after various studies, however, remains controversial. In 1984, Herrera et al. [12] described a subgroup of GISTs which they termed gastrointestinal autonomic nerve tumors (GANTs) or plexosarcomas.

As their light microscopic appearance is similar, GISTs require both immunohistochemical and ultrastructural studies for exact diagnosis. Since Erlandson et al. [6] found neuron-specific enolase-positive cells in one-third of their leiomyosarcoma cases, and several GANT cases in our's and previous studies [15, 18, 31] showed, at least focal, positive reaction with smooth-muscle actin (SMA), the ultrastructural demonstration of synapse-like structures, neurosecretory granules, and skeinoid fibers is inter alia essential for diagnosing GANTs.

In previous studies, GISTs were described as a group of tumors displaying a range of differentiation including smooth muscle differentiation [6, 10, 11, 26, 32, 39], neural differentiation in the form of axonal (enteric plexus, GANT) [6, 17] and in some studies also peripheral nerve sheath differentiation [5, 42], mixtures of these various features [10, 13, 22, 25] as well as cases of no differentiation (not otherwise specified). The opinion of Kindblom et al. [15] in their recent study, however, is that, although the term GIST refers to the mesenchymal nature of the lesion, it should not, in general, include tumors with true smooth muscle or schwannian differentiation. The results of their study rather support their hypothesis that GISTs originate from stem cells that differentiate toward a pacemaker-cell phenotype. These pacemaker cells form a complex network intercalated between the autonomic nerves and the muscle walls of the gastrointestinal tract [37] and are called interstitial cells of Cajal (ICCs). ICCs were found to express the kit proto-oncogene, which encodes for a transmembrane tyrosine-kinase receptor (CD 117) and has the stem cell factor as its ligand [15]. Expression of the kit gene is essential for the development of ICCs and gastrointestinal pacemaker activity [15]. Tumors previously described as

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GANT are possibly part of the neoplastic spectrum of ICCs [15].

In an immunohistochemical analysis of stromal tumors ultrastructurally sharing many features with ICCs, Kindblom et al. proved positive reaction for the kit receptor in all cases [15]. In our study, immunohistochemical analysis with the same two anti c-kit antibodies was performed in seven tumors ultrastructurally diagnosed as GANT.

Our results support the hypothesis that GANTs originate from stem cells that differentiate toward an ICC phenotype, and we agree with the proposition of Kindblom et al. that tumors with ICC differentiation should be called gastrointestinal pacemaker cell tumors (GIPACTs).

Materials and methods

Seven GANT cases diagnosed by immunohistochemistry and electron microscopy during a 7-year period were selected for this study. They were all fixed in 4% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin and periodic acid-Schiff (PAS). Small fragments of fresh glutaraldehyde-fixed tissue or formalin-fixed tumor were postfixed in osmium tetroxide, dehydrated, and embedded in epoxy resin (Epon). Ultrathin sections were stained with uranyl acetate and lead citrate and examined using a transmission electron microscope (Zeiss EM9).

The immunohistochemical techniques, antibodies, dilutions, and sources are summarized in Table 1. Dako en Vision was used as the detection system (Horseradishperoxidase conjugated, substrate DAB). Deparaffinized tissue sections of all neoplasms were incubated with antibodies against c-kit receptor (K963 and C-19), CD 34, vimentin, neuron-specific enolase, synaptophysin, S100 protein, chromogranin, glial fibrillary acidic protein (GFAP), SMA, muscle-specific actin (HHF35), desmin, Lu5 (pancytokeratin), and CAM5.2.

Normal ileum was incubated with the K963 and C-19 c-kit receptor-antibodies as a control.

Results

Clinical and gross findings

The clinical data are summarized and tabulated in Table 2. There were three males and four females with an age range of 53–87 years. Six tumors were diagnosed at laparatomy, and one (case no. 2) at autopsy only. The presenting symptoms were rupture of tumor with acute intra-abdominal bleeding (case no. 1 and no. 3), anemia (case no. 5), ab-

Table 1 Antibodies, dilutions, and sources. *1* Santa Cruz Biotechnology, Santa Cruz, Calif., USA; *2* Immuno-Biological Laboratories, Tokyo, Japan; *3* Bio Genex Laboratories, San Ramon, Calif., USA; *4* DAKO A/S, Glostrup, Denmark; *5* Roche Molecular Biochemicals (former Boehringer Mannheim Biochemicals), Mannheim, Germany; *6* Sigma, Saint Louis, Missouri, USA; *7* Roche, Basel, Switzerland; *8* Becton-Dickinson AG, Mississanga, Ontario, Canada

Antibody	Clone	Pretreatment	Antibody dilution	Source
c-kit (K963)	poly	None	1:50	2
c-kit (C19)	poly	None	1:200	1
CD34	QBend/10	None	1:20	3
Vimentin	V9	None	1:20	4
Neuron-specific enolase	BBS/NC/VIH14	Pressure cooker	1:100	4
Synaptophysin	SY 38	Pressure cooker	1:20	4
S100 protein	poly	None	1:2000	4
Chromogranin	LK2H10	None	1:4000	5
GFAP	GA-5	None	1:200	3
Smooth muscle actin	1A4	None	1:4000	6
Muscle specific actin	HHF35	None	1:1200	4
Desmin	DE-R11	Protease type XIV, Sigma	1:50	4
Lu5 (pancytokeratin)	mono	Protease type XIV, Sigma	1:400	7
CAM5.2	mono	Protease type XIV, Sigma	1:5	8

Table 2 Clinical data. *l* laparatomy; *a* autopsy

No.	Age (years)/ gender	Site/metastases	Size (cm)	Clinical presentation	Follow-up
1	53/male	Jejunum (subperitoneal, multicentric)	13 (l)	Rupture and intra-abdominal bleeding	Free of disease (8 months after operation)
2	87/male	Jejunum (subperitoneal)/ diffuse peritoneal tumors	11 (a)	Perforation with peritonitis and abdominal pain	Daignosed by autopsy
3	76/female	Jejunum (subperitoneal, multicentric)	10 (I)	Rupture and intra-abdominal bleeding	Relapse, death (1.5 years after operation)
4	87/female	Jejunum (subperitoneal, multicentric)	10 (I)	Cholecystitis	Free of disease (4 months after operation)
5	73/male	Diffuse peritoneal tumors	5.5 (I)	Anemia	Death after 13 months
6	69/female	Ileum (subperitoneal, multicentric)	30 (I)	Abdominal mass	Liver metastases
7	74/female	Ileum (subperitoneal)	8 (I)	Abdominal mass	Liver metastases

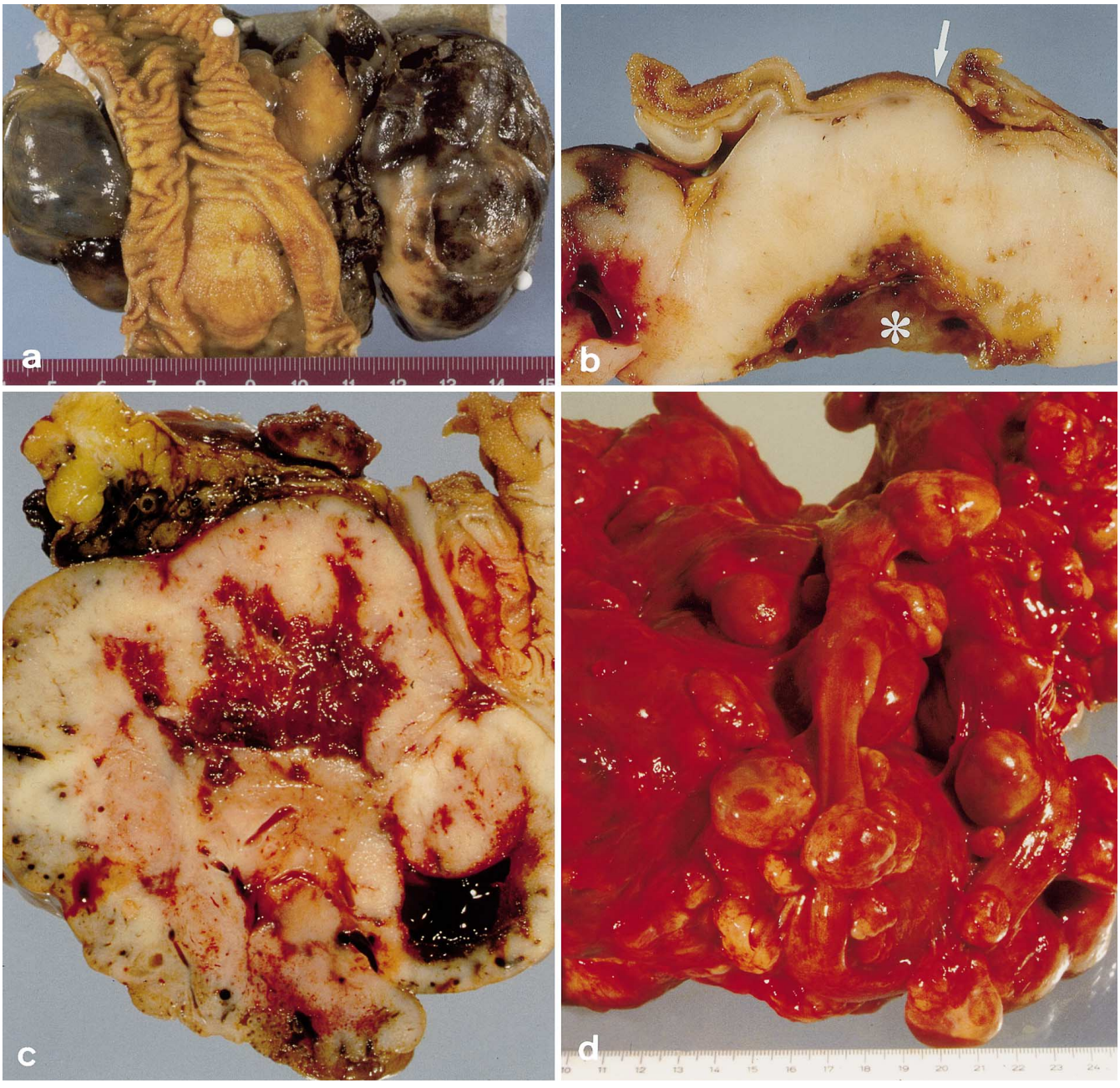

Fig. 1a –d Gross findings. **a** Multiple subserosal tumor nodes with focal hemorrhage (case no. 1). A loop of small intestine was attached to the tumor, showing a flattening out of the mucosal relief and a small ulcer in the center. **b** Cut surface of one of the tumor nodes of **a** with basal infiltration of the mucosa (*arrow*) and cystic change in the center (*asterisk*). **c** The cut surface of this tumor (case no. 3) revealed white-tan, "brain-like" tissue of friable consistency with cystic and hemorrhagic areas. The tumor was connected to the serosal membrane without proven infiltration of the bowel wall. **d** Diffuse peritoneal tumors (autopsy of case no. 5)

dominal mass (case no. 6 and no. 7), small-bowel perforation with fibrinous purulent peritonitis and abdominal pain (case no. 2), and subacute ulcerous cholecystitis in one patient (case no. 4) with a tumor localized in the retroperitoneum (bulbus duodeni/head of the pancreas).

Five of the tumors (case nos. 1, 2, 3, 6, and 7) were associated with the small bowel, all of them predominantly subperitoneal (Fig. 1a); three were multicentric (case nos. 1, 3, and 6); and one of them (case no. 2) showed diffuse peritoneal nodules. One (case no. 5) of the seven tumors consisted of multiple peritoneal tumors (Fig. 1d). The tumor of case no. 4 was located in the retroperitoneum (bulbus duodeni/head of the pancreas).

Tumor size ranged from 5.5 cm to 30 cm in the longest axis. They revealed cystic areas (5 of 7), hemorrhagic areas (5 of 7), focal necrosis (3 of 7), had a "brain-like" appearance (6 of 7) and were remarkably friable (Fig. 1b, c).

Two patients (case no. 1 and no. 4) are free of disease after follow-up periods of 8 months and 4 years, respectively. Case no. 6 and no. 7 show a progression with liver

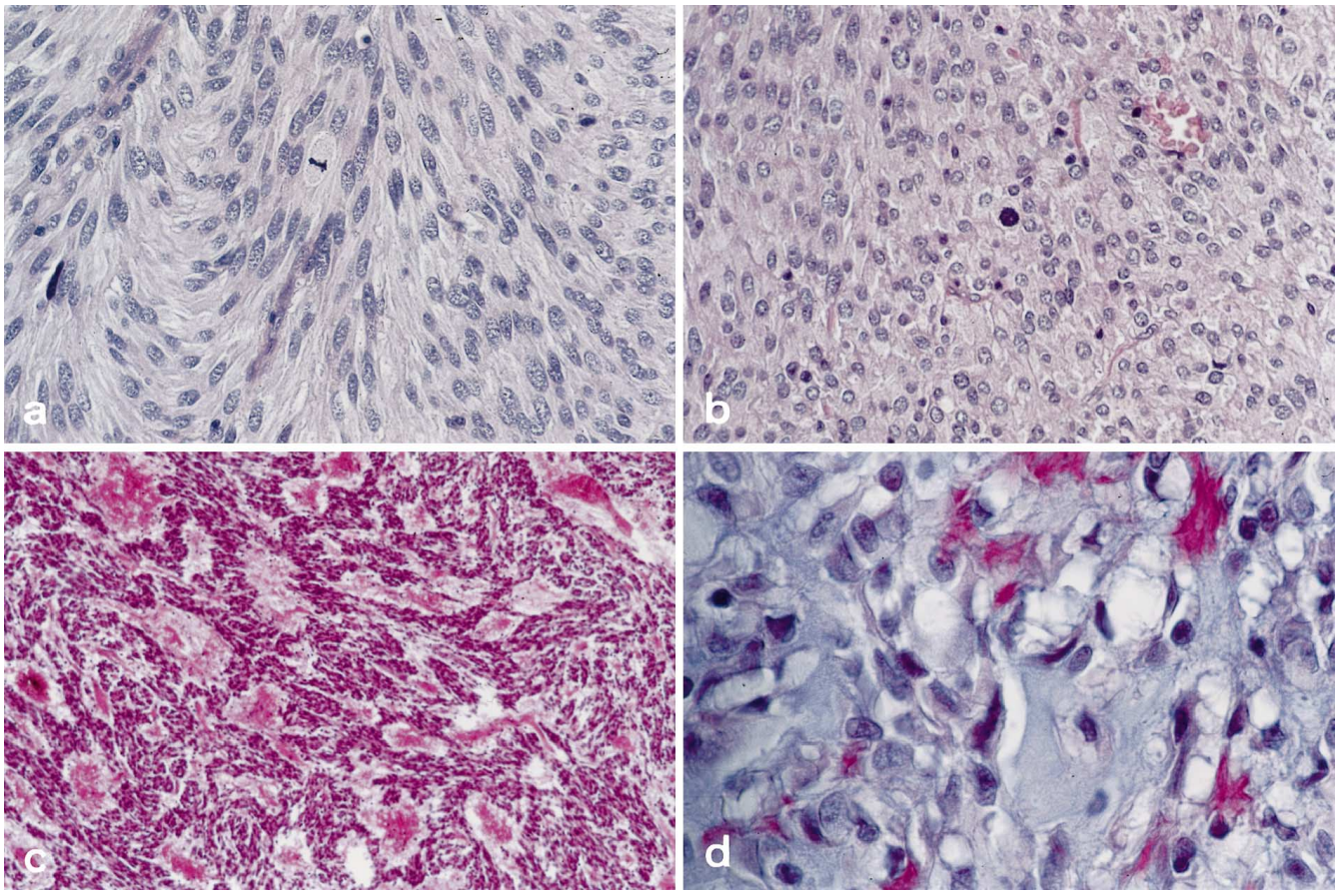

Fig. 2a–d Light microscopic findings. **a** The tumors consist mainly of spindle cells with a fascicular arrangement (case no. 3). A mitosis is seen in the center. Hematoxylin and eosin (HE) ×100. **b** The same tumor as in **a** showing areas of epithelioid cells. HE ×100. **c** Tumor (case no. 2) revealing a pattern similar to hemangiopericytoma. HE ×25. **d** Periodic acid-Schiff (PAS)-positive interstitial fibers presumably correspond to skeinoid fibers. PAS ×250

metastases. Patients no. 3 and no. 5 died of disease after 1.5 years and 13 months, respectively. In case no. 2, the neoplasm was diagnosed only at autopsy.

Light microscopic features

The majority of the tumors consist of spindle cells, but half the tumors show an admixture of spindle and epithelioid cells (Fig. 2a, b). Tumor cells are arranged in a diffuse fashion or in interlacing fascicles. One neoplasm (case no. 5) shows severe, three neoplasms (case nos. 1, 4, and 6) moderate, and the other three slight nuclear pleomorphism. In case no. 6, an additional plexiform pattern is striking. Most lesions are richly vascularized and necrosis is also evident in three cases (Fig. 2c). PAS-positive interstitial material (presumably skeinoid fibers, Fig. 2d) are present in six cases (nos. 1, 2, 3, 4, 6, and 7). Case no. 2 shows no mitosis, case no. 4 exhibits one mitosis per 10 high-power fields (HPF), and case nos. 1, 3, 6, and 7 display two to eight mitoses per 10 HPF. Case no. 5 shows 31 mitoses per 10 HPF and a pronounced nuclear pleomorphism. Infiltration of the mucosa is evident in three cases (nos. 1, 6, and 7).

Immunohistochemistry

The results of immunohistochemical studies are summarized in Table 3. All tumors show strong immunoreactivity with the C-19 kit receptor antibody as well as with the K963 kit antibody (Fig. 3a, b). The adjoining lamina muscularis propria, submucosa, and mucosa are negative (Fig. 3a).

In every case, tumor cells are positive for vimentin and neuron-specific enolase (Fig. 3e), whereas S100 protein is positive in four cases, CD 34 (Fig. 3d) and synaptophysin in three cases, SMA (Fig. 3f) in two cases and muscle-specific actin focally in one case. Desmin, chromogranin, GFAP, Lu5 (pancytokeratin) and CAM5.2 are consistently negative. Immunoreactivity with neurofilament was only examined in two cases (no. 3 and no. 4). It is negative in both cases.

Normal ileum shows a network of slender spindle cells between the circular and longitudinal muscle layers that is positive for both c-kit antibodies. The same cells can be observed to surround Auerbach's ganglia and to spread out into the muscle wall (Fig. 3c).

All results are identical with both kit-receptor antibodies (C-19 and K963).

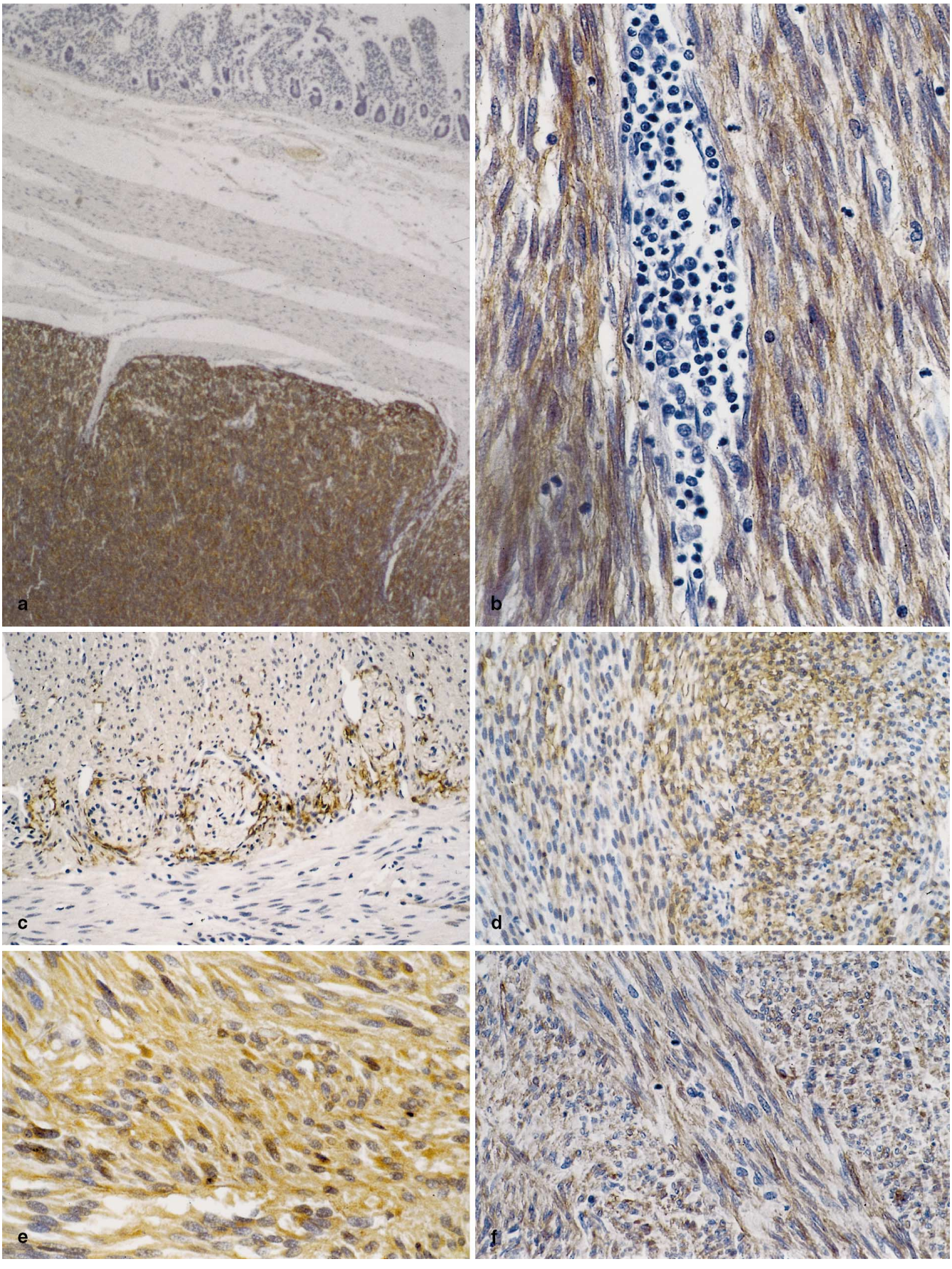
a
b
c
d
e
f

Table 3 Immunohistochemical findings

	Case no.						
	1	2	3	4	5	6	7
c-kit (K963)	+	+	+	+	+	+	+
c-kit (C-19)	+	+	+	+	+	+	+
CD34	–	–	+	+	–	+	–
Vimentin	+	+	+	+	+	+	+
Neuron-specific enolase	+	(+)*	+	+	(+)	+	+
Synaptophysin	(+)	(+)	+	–	–	–	–
S100 protein	+	–	+	–	+	–	+*
Chromogranin	–	–	–	–	–	–	–
Glial fibrillary acidic protein	–	–	–	–	–	–	–
Smooth-muscle actin	–	–	–	–	–	+	+*
Muscle–specific actin	–	–	–	–	–	–	(+)*
Desmin	–	–	–	–	–	–	–
Lu5 (Pancytokeratin)	–	–	–	–	–	–	–
CAM5.2	–	–	–	–	–	–	–

* Focal staining () weak positivity

Ultrastructural findings

All tumor cells show interdigitating cytoplasmic processes, connected with primitive desmosomes in some areas. There are dense core granules as well as empty vesicles in the cytoplasm, especially within the processes or associated with the Golgi zones (Fig. 4a). Some of the tumor cells display an abundance of mitochondria and smooth endoplasmic reticula. Microtubules and intermediate filaments are seen in most of the neoplastic cells. The tumor cells are surrounded by an incomplete external lamina in two cases (no. 5 and no. 7); there is no evidence of a basal lamina in the other five cases. Intercellular aggregates of skeinoid fibers are seen in the same six cases that show interstitial PAS-positive material in light microscopy (Fig. 4b). These irregular curving fibers show a thickness of 36 nm and a transverse banding with a periodicity of 41 nm. Evidence of skeinoid fibers in the remaining tumor (case no. 5) is uncertain.

In the two cases (no. 6 and no. 7) which show positivity for SMA (one of them is also focally positive for muscle-specific actin), no smooth-muscle differentiation is evident by electron microscopy.

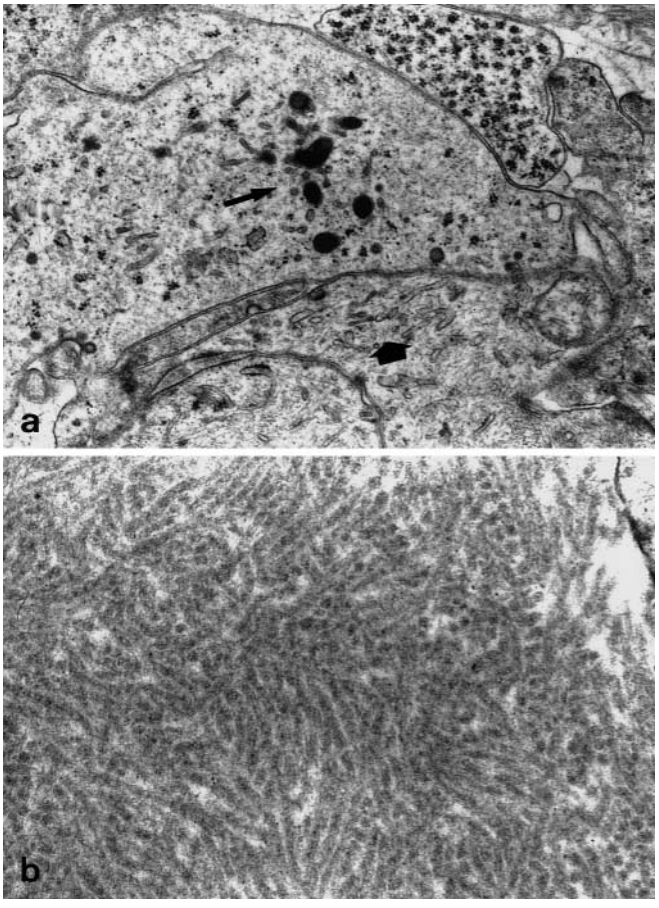

Fig. 4a,b Ultrastructural findings. **a** Interdigitating cytoplasmic processes (case no. 1) containing dense core granules (*arrow*) and microtubules (*arrowheads*). ×12,000. **b** Skeinoid fibers in the intercellular space (case no. 1), with a periodicity of approximately 40 nm. ×30,000

◀ **Fig. 3a–f.** Immunohistochemical findings. **a** All tumors reveal strong immunoreactivity with the c-kit receptor antibody (case no. 5, incubation with K963). Adjoining lamina muscularis propria, submucosa, and mucosa are negative. ×12.5. **b** The tumor cells show positive reaction for the c-kit receptor (case no. 6, incubation with C19), whereas vascular structures are negative. ×100. **c** Normal ileum shows a network of c-kit-positive cells between the circular and longitudinal muscle layers, surrounding Auerbach's ganglia and spreading out into the muscle wall. ×50. **d** Three of seven tumors are CD34 positive (case no. 3). ×50. **e** Tumor cells are positive for neuron-specific enolase in every case (case no. 3). ×100. **f** Two of the tumors (case no. 6 and no. 7) co-express CD117 and smooth muscle actin (SMA). This figures shows SMA positive tumors cells. ×100

Discussion

GISTs were first interpreted to be smooth muscle in origin [2, 3, 4, 7, 24]. Subsequent studies described them as a complex group including smooth-muscle differentia-

tion (leiomyomas/leiomyosarcomas; spindle cell, epithelioid, or a mixture), neural differentiation in the form of axonal (referred to as GANTs, myenteric plexus tumors) [1] and peripheral nerve sheath differentiation [5, 42], dual smooth-muscle and neuronal differentiation, or no differentiation (GIST NOS, not otherwise specified) [6, 22, 35]. The classification of GISTs remains confusing. In other studies, the term has been controversially defined as lacking obvious smooth muscle, schwannian, or other differentiating features [19]. Kindblom et al. in their recent study [15] suggested that GISTs originate from stem cells that differentiate toward a pacemaker-cell phenotype, for which they introduced the term GIPACT.

GISTs, regardless of whether they are smooth muscle, neural, or mixed in origin, show a similar histological pattern, and methods other than light microscopy are necessary to prove the origin of the different tumor cells. As immunohistochemical studies give insufficient information in most cases, electron microscopy is required for exact diagnosis. Recent convincing studies [15, 31] indicate that CD 117 (kit receptor) might be very helpful as a sensitive marker. This antibody is, however, also expressed in subsets of hematopoietic stem cells, mast cells, and melanocytes [31]. In an extensive immunohistochemical study, Sarlomo-Rikala et al. [31] found occasional CD117 reactivity of dermatofibrosarcoma protuberans, hemangiopericytoma, clear cell sarcoma, metastatic melanoma, and malignant fibrous histiocytoma. Almost all GISTs were positive, whereas leiomyomas and schwannomas were consistently negative for CD117. They conclude that CD117 is a sensitive marker for GISTs (GIPACTs), in tumors that occur in the GI tract and adjacent regions.

Sircar et al. [36], in a recent study of 43GIMTs (gastrointestinal mesenchymal tumors), had similar results, and they emphasized that ICCs appear to be the only c-kit-, CD 34-, and vimentin-positive cells in the gut [36]. Sircar et al., however, suggest the term ICC tumor (ICCT).

Since Erlandson et al. [6] found neuron-specific enolase-positive cells in one-third of their leiomyosarcoma cases, this antibody does not help to exclude smooth-muscle differentiation. Two of our seven GANT cases revealed a positive reaction with SMA (one of them only focal, but in combination with a weak focal positivity for muscle-specific actin). Ultrastructurally, no myogenic elements such as microfilaments and dense bodies were observed. Neurogenic structures, for example long cytoplasmic processes, dense core granules, intermediate filaments and skeinoid fibers were, however, present. We believe that SMA positivity is not indicative of smooth-muscle differentiation without other supporting evidence. Previous studies showed SMA-positive GANT/-GIPACT as well [15, 18, 31], electron microscopy revealing both neurogenic elements and myogenic elements. The incomplete myoid differentiation seen in stromal tumors may reflect the myoid features of ICC, which may be derived from smooth-muscle progenitor cells [15, 37, 38].

CD34 antigen was originally described as a hematopoietic stem-cell marker [14]. Immunoreactivity for CD34 has, however, been observed in a wide range of normal tissues and tumors, including endothelium and various vascular tumors, peripheral nerve sheath tumors, localized fibrous tumors of various sites, dermatofibrosarcoma protuberans, and epithelioid sarcoma among others [14]. Previous studies [19, 20, 21] describe a CD34 positivity in the majority of GIST/GIPACT and it is important to distinguish between these tumors and gastrointestinal leiomyomas and schwannomas, which are CD34 negative [40]. Miettinen et al. [19] emphasized the value of this marker in combination with S100 protein, as leiomyomas were negative for CD34 and S100 protein, and schwannomas were positive for S100 protein and negative for CD34. Kindblom et al. [15] found in their recent study that 56 of 78 GISTs/GIPACTs were strongly CD34 positive, whereas all 78 tumors were consistently S100 negative.

Our results, however, were different. We observed a CD34 positivity in only three of seven tumors, but four cases showed a positive reaction with S100 protein (one of them focal). Peripheral neurogenic tumors were proven to have a trend toward an inverse correlation between their CD34 expression level and malignancy degree [41]. Sircar et al. showed loss of either CD34 or c-kit positivity in their malignant GIST [36]. Three of our four CD34-negative GANT cases, in fact, had high mitosis rates (5, 6, and 31 mitosis per 10 HPF). Another hypothesis is that CD34-negative and -positive GANTs/-GIPACTs display a different ICC phenotype [15, 37]. Kindblom et al. suggest that only a subpopulation of ICC is CD34 positive.

S100 protein positivity in GANTs, in contrast to the results of Kindblom et al. [15], does not seem to be a rare feature. Matsumoto et al. observed positive reaction with S100 protein in 11 of 12 GANTs and Segal et al. in 6 of 10 cases [18, 33]. It is possible that some GANTs show a Schwann-like component [23] as ultrastructural examination of examples with focal S100 protein expression confirmed a dual population [9, 42].

Despite various studies, the criteria to predict the biological behavior of GISTs remain vague and do not even enable a confident discrimination between benign and malignant lesions. A score based on several significant indicators might improve the accuracy of prognostic models [27]. Rudolph et al. therefore performed a multivariate analysis to determine which parameters could be considered as independent prognosticators and to establish their hierarchy [27]. Concerning overall survival, these parameters were the Ki-67 labeling index, tumor grade, mitotic count (≥5 per 10 HPF), necrosis, presence of atypical mitoses, tumor size (>5 cm ∅), cellular density, DNA ploidy and gender. As to metastasis risk, tumor location replaced the ploidy status and mitotic atypia. Mucosal infiltration, however, was not described. They found inter alia that tumors of the small intestine metastasized more frequently (overall survival was comparable with that of gastric tumors), that male gender

was associated with a markedly poorer survival prognosis and an increased occurrence of metastases, and that the patient's age did not have any influence. They concluded that the Ki-67 labeling index (cut off 10%) emerged as the most relevant predictor of overall survival, followed by the presence of atypical mitoses. Seidal et al., in a recent study, also showed that the expression of Ki-67 in the nuclei of GIST cells was the most important prognostic factor [34].

As no official grading system has been described in the present literature, we did not use any grading system for tumor classification. In our cases, there was no difference between males and females concerning prognosis. Tumor size was more than 5 cm in diameter in all of the seven cases. Of the five patients with tumors revealing five or more mitoses per 10 HPF, two died of disease, two are suffering progression with liver metastases and one patient is free of disease 8 months after tumor removal. In three of these five patients, mucosal infiltration was proven (including the patient who is free of disease at the moment). We believe that these five tumors should be considered as malignant, whereas dignity in the other two cases is uncertain.

Lasota et al., in a recent study, evaluated 43 GISTs and 14 smooth-muscle tumors for mutations in the exon 11 of c-kit using a polymerase chain reaction assay [16]. They found that these mutations occur preferentially in malignant rather than benign GISTs and do not occur in leiomyomas or leiomyosarcomas. The mutation status did not correlate with immunohistochemically detectable expression of the CD117, as virtually all GISTs with or without such mutations showed CD117 immunoreactivity [16]. As the c-kit mutations occur mainly in malignant GISTs, they might be a clinically useful adjunct marker [16].

With the c-kit antibody, a separation of GIPACT from gastrointestinal leiomyomas/leiomyosarcomas and schwannomas seems to be possible. Kindblom et al. observed that gastrointestinal stromal tumors show striking morphological and immunophenotypic similarities with ICCs [15]. All 78 GISTs/GIPACTs that they immunophenotyped revealed strong reactivity for the c-kit receptor. Thirty control tumors, including gastrointestinal leiomyoma, leiomyosarcoma, schwannoma, carcinoid, malignant fibrous histiocytoma, inflammatory fibrosarcoma, angiosarcoma, and metastatic melanoma, were all negative for the c-kit receptor. Our histological, immunohistochemical, and ultrastructural examinations support their results. The seven GANTs all showed positive reaction for the c-kit receptor. As in the cases of Kindblom et al. [15], the distribution and intensity of the immunoreaction for the c-kit receptor were not related to histological pattern, gastrointestinal location, or malignant potential of the tumor. The ultrastructurally observed interdigitating cytoplasmic processes, close apposition of cells connected with primitive desmosomes, synapse-like contacts, dense core granules, intermediate filaments, microtubules, abundance of smooth endoplasmic reticula, and incomplete external lamina are typical features of ICCs [8, 14, 28, 29, 30, 37, 38]. GANTs are defined as originating from the myenteric plexus. The ultrastructural features described as being diagnostic of GANT are, however, the same as for gastrointestinal pacemaker cells [15]. Kindblom et al. [15] postulate that tumors previously described as GANTs are part of a neoplastic spectrum, with GANTs displaying a higher degree of ICC differentiation than is seen in most stromal tumors. However, the clinical, histological, and immunophenotypic features of their "GANTs" did not differ from the other stromal tumors in their series. We believe that there is no ultrastructural difference either, and that GANTs are, in fact, the same as GIPACTs.

We conclude that benign and malignant tumors with definite smooth muscle or neuronal differentiation should be called by their proper name (leiomyoma, schwannoma, neurofibroma, ganglioneuroma, paraganglioma, and their malignant counterparts). Gastrointestinal spindle cell tumors without convincing, incomplete or completely lacking smooth muscle or neuronal differentiation, but showing c-kit receptor positivity, should be called GIPACTs, based on the close immunohistochemical and electron microscopic similarities of these tumors with the system of ICCs. The term GIST should remain for stromal tumors without any clear differentiation and without c-kit expression, as well as for stromal tumors without any further examination except light microscopy.

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