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Case report

Duodenal gangliocytic paraganglioma

Report of a case and review of the literature

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Summary. A case of gangliocytic paraganglioma (GP) of the ampulla of Vater is reported and the literature reviewed, with special attention to immunohistochemical studies. The present case, which occurred in a 56-year-old woman, shows the typical histological admixture of epithelioid, ganglion and spindle cells. Immunohistochemistry reveals strong reactivity for synaptophysin, Leu-7, somatostatin, S-100 protein and vimentin. A few ganglion cells are reactive for neurofilaments. Chromogranin A, myelin basic protein, desmin and cytokeratin are absent.

Immunohistochemical data from literature regarding the cytoskeletal composition of GPs are not unequivocal: cytokeratin and neurofilament positivity is reported by some authors and denied by others. More uniformity is reported concerning the peptides produced by GPs: somatostatin and pancreatic polypeptide are the most frequently found antigens, followed by serotonin. General neuroendocrine markers like neuron specific enolase and protein gene product 9.5 are always positive, whereas chromogranins are rarely found. S-100 protein is always positive in the spindle cell component.

Our data are in keeping with those previously reported and add the diffuse positivity for the Leu-7 antigen and the positivity of ganglion cells for synaptophysin.

The nature of the tumour is still a matter of debate and it is difficult to agree with either of the proposed hypotheses – hamartoma/choristoma versus true neoplasm. However the recent reports of the occasional malignant evolution of GPs may support their true neoplastic nature.

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Introduction

Gangliocytic paragangliomas (GPs) are rare lesions of the proximal small bowel and occur almost exclusively in the second portion of the duodenum. The tumour is generally a solitary lesion, but multiple GPs have been reported involving the periampullary region of the duodenum and the peripancreatic tissue adjacent to large vessels. Rarely GPs may arise in the third and fourth parts of the duodenum and in the jejunum (Lauzon and Cadotte 1972; Lukash et al. 1966; Reed et al. 1977; Savio et al. 1974). GPs may be associated with neurofibromatosis (Kheir and Halpern 1984; Stephens et al. 1987). One of the reported cases of GP in neurofibromatosis was also associated with a somatostatin rich glandular carcinoid (Stephens et al. 1987).

GPs are generally benign lesions, that frequently come to clinical attention either as radiographic incidental findings or as the result of gastrointestinal bleeding (Perrone et al. 1985; Scheithauer et al. 1986). Only two cases of malignant GPs with lymph node metastases have been reported (Buchler et al. 1985; Korbi et al. 1987).

The histological features of GPs are an admixture of those of paragangliomas, ganglioneuromas and carcinoids. Epithelial cells, mature ganglion cells and Schwann cells are present in varying proportions. Immunohistochemical studies have demonstrated the presence of neuroendocrine markers and neuropeptides in most GPs, shedding some light on their possible histogenesis (Hamid et al.

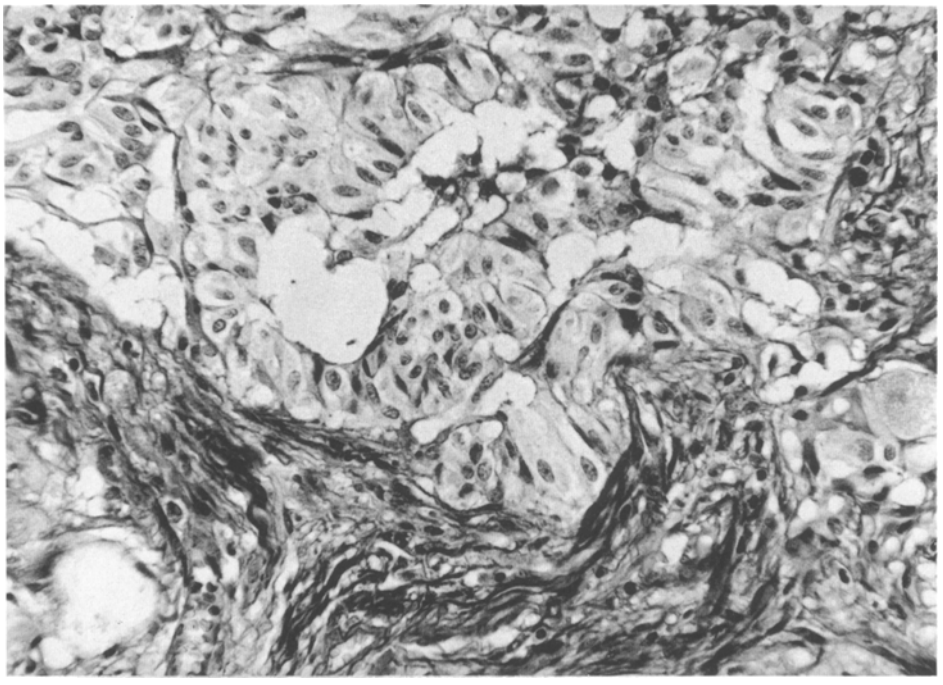


Fig. 1. Epithelioid cells with distinct pseudoglandular aspect, surrounded by spindle cells. Mallory's trichrome stain, 400×

1986; Perrone et al. 1985; Scheithauer et al. 1986). Immunohistochemical data may also be very useful in confirming the diagnosis.

We report a case of GP occurring in a 56-year-old woman along with the results of our immunocytochemical study, discussed in comparison with those in the literature.

Case report

A 56-year-old woman with a history of episodes of epigastric pain, nausea and vomiting, was hospitalized for accurate clinical evaluation. Liver profile included elevated alkaline phosphatase and slightly elevated serum bilirubin. Occult blood was present in stool samples. Upper GI x-ray showed a nodular filling defect in the descending duodenum.

At operation, the duodenum was opened and a 2 cm nodular tumour of the Vater's papilla was removed. The tumour was formalin fixed and routinely processed.

Results

Microscopically the tumour was not encapsulated and showed an infiltrative pattern extending from the mucosa to the muscularis propria, dissecting the muscular layers. The mucosa shows wide superficial erosions. The tumour is composed of a mixture of epithelioid, ganglion and spindle cells. The epithelioid component consists of rounded nests or ribbons of polygonal cells with finely granular cytoplasm and vesicular nuclei. In some instances the epithelioid cells show pseudoglandular structures (Fig. 1). Ganglion cells are either indi-

Table 1. Primary antisera and antibodies and positive controls used in the present study

Antiserum/antibody	Source and code
Rabbit anti-porcine CG	Immunonuclear Corp. 63H2TP
Mouse PHE-5 antibody	Prof. A. Gown
Mouse anti Leu-7	Becton-Dickinson
Mouse anti-synaptophysin	Boehringer Biochemia SY38
Rabbit anti-somatostatin	DAKO A566
Rabbit anti-calcitonin	DAKO A576
Rabbit anti-glucagon	DAKO L1813
Rabbit anti-substance P	Immunonuclear Corp. 20064
Guinea pig anti-insulin	DAKO A564
Rabbit anti-ACTH	DAKO A571
Rabbit anti-S100	DAKO Z311
Rabbit anti-myelin basic prot.	DAKO A623
Rabbit anti-GFAP	Ortho Diagnostic Syst. 595030
Mouse anti-vimentin	DAKO M725
Mouse anti-desmin	DAKO M724
Mouse anti-cytocheratin of 52.5 kd	Ortho Diagnostic Syst. 00730
Mouse anti-cytokeratin AE1/AE3	Lipshaw K3360
Rabbit anti-human keratin	DAKO A575
Mouse anti-neurofilament	DAKO M762

The specimen contains a number of internal positive controls, i.e.: mucosal neuroendocrine cells for CG, PHE-5 antibody and somatostatin; nerve fibers for Leu-7, synaptophysin, S-100 and myelin basic protein; endothelial cells for vimentin; muscular fibers for desmin; mucosal epithelial cell layer for cytokeratin. Positive controls for somatostatin, glucagon and insulin are sections of human pancreas; for calcitonin and ACTH are sections of human thyroid and pituitary respectively; for GFAP are sections of human cerebellum and for keratin are skin sections. Negative controls are obtained by substituting primary antiserum/antibody with non immune rabbit serum or the corresponding mouse immunoglobulin

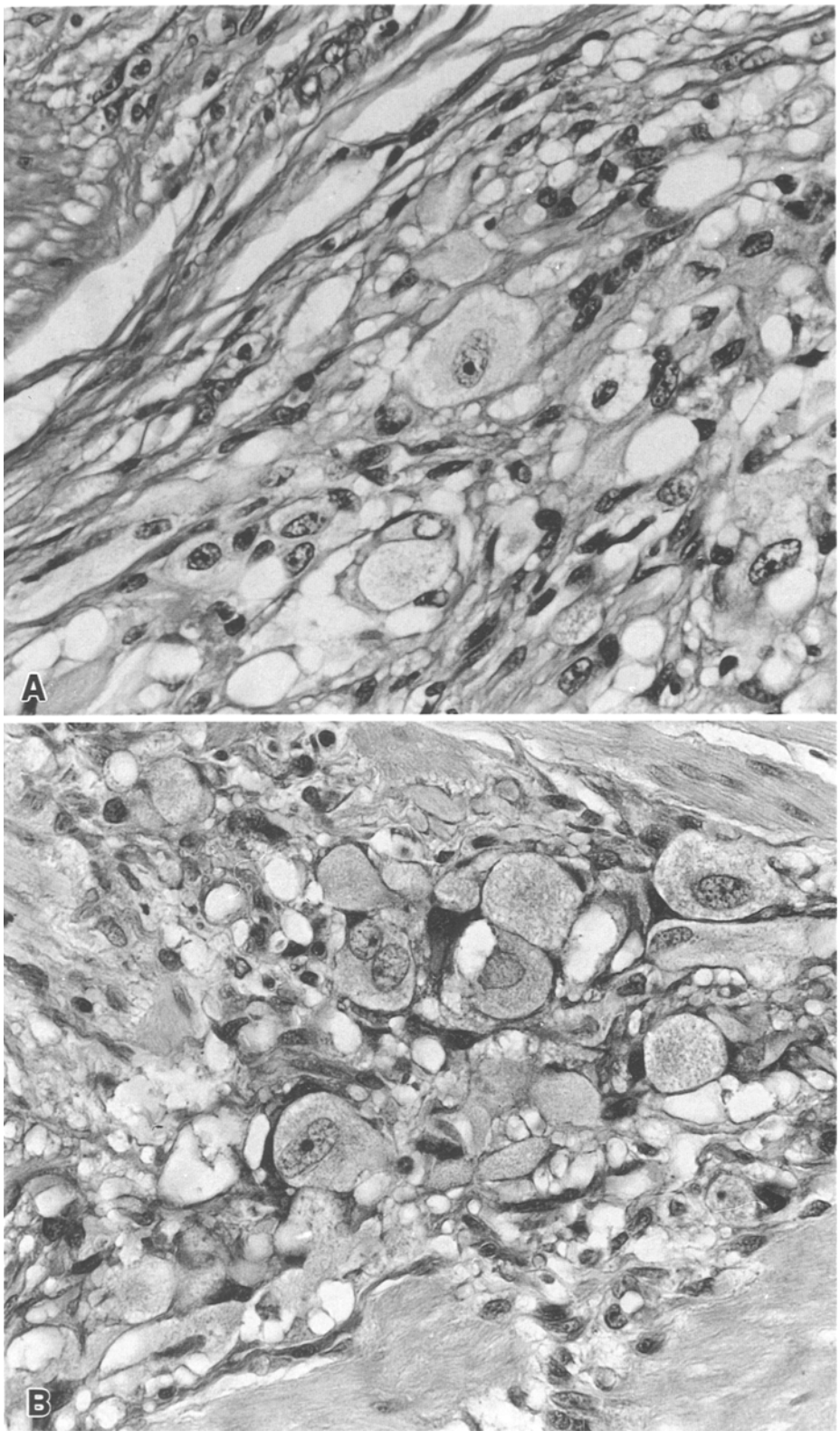
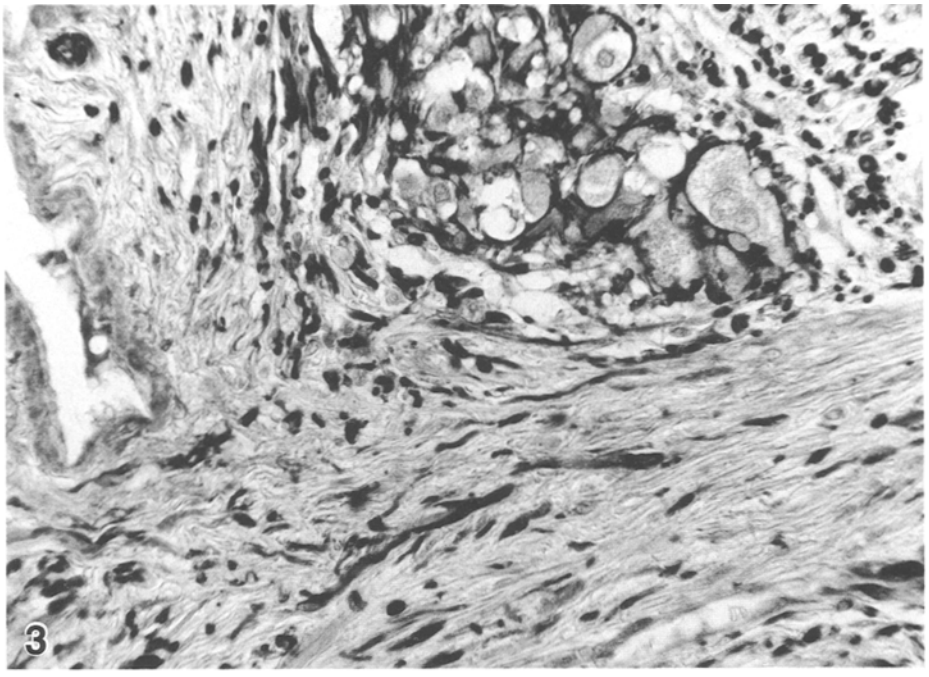


Fig. 2. Gangliocytic cells are scattered throughout the lesion, either individually (**A**) or clustered in small aggregates (**B**). Haematoxylin-eosin, 400×



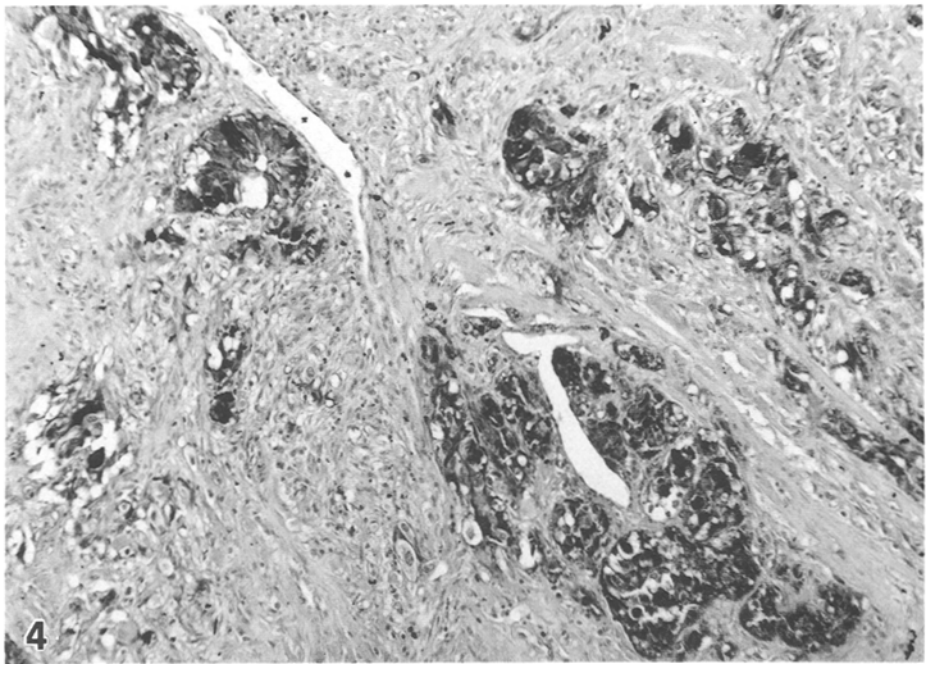


Fig. 3. The spindle cells are intensely S-100 positive and are arranged in broad fascicles or wrapped individually around ganglion cells. Immunoperoxidase for S-100, 250 ×

Fig. 4. Strong somatostatin-immunoreactive epithelioid cells. Immunoperoxidase for somatostatin, 100 ×

vidual or clustered in small aggregates, and sometimes only the vesicular granular cytoplasm is evident on the section plane (Fig. 2). The third component consists of spindle cells arranged in broad fascicles or wrapped individually around ganglion cells (Fig. 3). Reticulin fibers are abundant and follow the orientation of the spindle cells. Grimelius silver impregnation for detection of argyrophilic granules is constantly negative in all cell components. Immunohistochemistry is performed using either the PAP-technique (Sternberger 1979) or the more sensitive avidin-biotin-peroxidase complex (ABC) method (Hsu et al. 1981). Antibodies, antisera and positive controls are listed in Table 1 and the results of immunostaining are summarized in Table 2 (column K). Epithelioid cells and some of the ganglion cells are immunoreactive for somatostatin (Fig. 4). Ganglion cells are stained with anti-synaptophysin antibody and a few of them are immunoreactive for calcitonin. Leu-7 antigen, a

Table 2. Immunohistochemical data on GPs (literature review). For each antigen the immunohistochemical data are subdivided for each of the cell component of the GP, i.e.: first line for epithelioid cells, second line for ganglion cells, third line for spindle cells

	References										
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*K*	Total
Antigens											
NSE	10/10	11/11	3/3	–	1/1	1/1	1/1*	1/1	1/1	–	28/28
	10/10	11/11	3/3	–	1/1	1/1	–	1/1	1/1	–	28/28
	10/10	0/11	3/3	–	1/1	1/1	–	0/1	0/1	–	16/28
SYN	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	1/1	1/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
PGP9.5	9/10	–	–	–	–	–	–	–	–	–	9/10
	9/10	–	–	–	–	–	–	–	–	–	9/10
	9/10	–	–	–	–	–	–	–	–	–	9/10
LEU-7	–	–	–	–	–	–	–	–	–	1/1	1/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	1/1	1/1
S-100	0/10	0/11	0/3	–	0/1	0/1	1/1*	0/1	0/1	0/1	0/29
	0/10	0/11	0/3	–	1/1	0/1	–	0/1	0/1	0/1	1/29
	7/10	11/11	3/3	–	1/1	1/1	–	1/1	1/1	1/1	26/29
MBP	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
CG	2/10	0/11	–	–	–	–	–	1/1	–	0/1	3/23
	0/10	0/11	–	–	–	–	–	1/1	–	0/1	1/23
	0/10	0/11	–	–	–	–	–	0/1	–	0/1	0/23
PHE-5	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
NF	0/10	0/6	3/3	–	0/1	0/1	–	–	0/1	0/1	3/23
	8/10	0/6	3/3	–	1/1	1/1	–	–	1/1	1/1	15/23
	8/10	0/6	3/3	–	1/1	1/1	–	–	0/1	0/1	13/23
VIM	–	–	–	–	–	–	0/1*	–	0/1	0/1	0/2
	–	–	–	–	–	–	–	–	0/1	0/1	0/2
	–	–	–	–	–	–	–	–	1/1	0/1	2/2
GFAP	–	–	0/3	–	–	–	1/1*	–	–	0/1	0/4
	–	–	0/3	–	–	–	–	–	–	0/1	0/4
	–	–	0/3	–	–	–	–	–	–	0/1	0/4
DESM	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
	–	–	–	–	–	–	–	–	–	0/1	0/1
CK	–	–	0/3	–	0/1	–	0/1*	0/1	1/1	0/1	1/7
	–	–	0/3	–	0/1	–	–	0/1	0/1	0/1	0/7
	–	–	0/3	–	0/1	–	–	0/1	0/1	0/1	0/7
SMTS	9/10	8/8	3/3	2/2*	–	1/1	1/1*	0/1	–	1/1	22/24
	9/10	8/8	3/3	–	–	0/1	–	0/1	–	1/1	21/24
	0/10	0/8	0/3	–	–	0/1	–	0/1	–	0/1	0/24
PP	8/10	8/8	3/3	–	–	0/1	1/1*	–	–	–	19/22
	1/10	8/8	3/3	–	–	1/1	–	–	–	–	12/22
	0/10	0/8	0/3	–	–	0/1	–	–	–	–	0/22
SEROT	–	8/8	0/3	1/2*	–	0/1	0/1*	1/1	–	–	9/13
	–	8/8	0/3	–	–	1/1	–	1/1	–	–	10/13
	–	0/8	0/3	–	–	0/1	–	0/1	–	–	0/13
VIP	0/10	0/11	2/3	1/2*	–	–	0/1*	0/1	–	–	2/25
	0/10	0/11	0/3	–	–	–	–	0/1	–	–	0/25
	0/10	0/11	0/3	–	–	–	–	0/1	–	–	0/25

Table 2 (continued)

	References										
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*K*	Total
GLUC	–	–	1/3	0/2*	–	0/1	1/1*	–	–	0/1	1/5
	–	–	1/3	–	–	0/1	–	–	–	0/1	1/5
	–	–	0/3	–	–	0/1	–	–	–	0/1	0/5
INSUL	–	–	1/3	0/2*	–	0/1	0/1*	–	–	0/1	1/5
	–	–	0/3	–	–	0/1	–	–	–	0/1	0/5
	–	–	0/3	–	–	0/1	–	–	–	0/1	0/5
NT	–	0/11	0/3	–	–	–	–	–	–	–	0/14
	–	0/11	0/3	–	–	–	–	–	–	–	0/14
	–	0/11	0/3	–	–	–	–	–	–	–	0/14
LENK	–	–	2/3	1/2*	–	–	–	–	–	–	2/3
	–	–	3/3	–	–	–	–	–	–	–	3/3
	–	–	0/3	–	–	–	–	–	–	–	0/3
MENK	–	0/11	0/3	1/2*	–	–	0/1*	–	–	–	0/14
	–	0/11	0/3	–	–	–	–	–	–	–	0/14
	–	0/11	0/3	–	–	–	–	–	–	–	0/14
CALC	0/10	–	0/3	2/2*	–	0/1	0/1*	–	–	0/1	0/15
	0/10	–	0/3	–	–	0/1	–	–	–	1/1	1/15
	0/10	–	0/3	–	–	0/1	–	–	–	0/1	0/15
CCK	0/10	–	0/3	2/2*	–	–	0/1*	–	–	–	0/13
	0/10	–	0/3	–	–	–	–	–	–	–	0/13
	0/10	–	0/3	–	–	–	–	–	–	–	0/13
GASTR	0/10	0/11	0/3	1/2*	–	0/1	1/1*	0/1	–	–	0/26
	0/10	0/11	0/3	–	–	0/1	–	0/1	–	–	0/26
	0/10	0/11	0/3	–	–	0/1	–	0/1	–	–	0/26
SUBST P	–	–	0/3	1/2*	–	–	1/1*	–	–	0/1	0/4
	–	–	0/3	–	–	–	–	–	–	0/1	0/4
	–	–	0/3	–	–	–	–	–	–	0/1	0/4
ACTH	–	–	0/3	0/2*	–	–	0/1*	–	–	–	0/3
	–	–	0/3	–	–	–	–	–	–	–	0/3
	–	–	0/3	–	–	–	–	–	–	–	0/3
BOMB	–	0/11	0/3	0/2*	–	–	0/1*	0/1	–	–	0/15
	–	0/11	0/3	–	–	–	–	0/1	–	–	0/15
	–	0/11	0/3	–	–	–	–	0/1	–	–	0/15
MCP	–	–	2/3	–	–	–	–	–	–	–	2/3
	–	–	0/3	–	–	–	–	–	–	–	0/3
	–	–	0/3	–	–	–	–	–	–	–	0/3
GIP	–	0/11	–	–	–	–	–	–	–	–	0/11
	–	0/11	–	–	–	–	–	–	–	–	0/11
	–	0/11	–	–	–	–	–	–	–	–	0/11
NPY	0/10	–	–	–	–	–	–	–	–	–	0/10
	0/10	–	–	–	–	–	–	–	–	–	0/10
	0/10	–	–	–	–	–	–	–	–	–	0/10
PYY	0/10	–	–	–	–	–	–	–	–	–	0/10
	0/10	–	–	–	–	–	–	–	–	–	0/10
	0/10	–	–	–	–	–	–	–	–	–	0/10

References. A: Hamid et al. 1986; *B:* Scheithauer et al. 1986; *C:* Perrone et al. 1985; *D:* Guarda et al. 1983; *E:* Dante et al. 1987; *F:* Stephens et al. 1987; *G:* Anders et al. 1987; *H:* Korbi et al. 1987; *I:* Grouls et al. 1987; *K:* present case

Antigens. NSE, neuron specific enolase; Syn, synaptophysin; PGP 9.5, protein gene product 9.5; S-100, S-100 protein; MBP, myelin basic protein; CG, chromogranin; PHE-5, anti-chromogranin A (Riddell et al. 1987; Gown 1989; Mosca et al. 1988; Wittaker and Sandusky 1988; Lloyd et al. 1988). NF, neurofilaments; VIM, vimentin; GFAP, glial fibrillary acidic protein; DESM, desmin; CK, cytokeratin; SMTS, somatostatin; PP, pancretic polypeptide; SEROT, serotonin; VIP, vasoactive intestinal peptide; GLUC, glucagon; INSUL, insulin; LENK, leu-enkephalin; NT, neurotensin; MENK, met-enkephalin; CALC, calcitonin; CCK, colecystokinin; GASTR, gastrin; SUBST P, substance P; ACTH, adrenocorticothropin; BOMB, bombesin; MCP, molluskan cardioexcitatory peptide; GIP, gastric inhibitory polypeptide; NPY, neuropeptide Y; PYY, peptide YY

* Different reactivity in the three cell components not specified by the authors. These cases are not included in the total count (last column of the table)

newly recognized neuroendocrine marker (Martin and Maung 1987; Michels et al. 1987; Tsutsumi 1984; Tischler et al. 1986) is weakly positive in some epithelioid cells and strongly positive in the spindle cells. The spindle cells are immunoreactive for S-100 protein (S-100), Leu-7 and vimentin and negative for myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP). No reactivity could be detected with the PHE-5 monoclonal antibody and with antisera against native porcine chromogranin, glucagon and insulin. Desmin immunostaining decorates the very abundant smooth muscle cells. Cytokeratins (CK) are present in the duodenal mucosa epithelium, but not in the tumour cells. Neurofilament (NF) immunoreactivity is restricted to very few ganglion cells and to occasional and isolated nerve fibers.

Discussion

To date we are aware of 69 reported cases of GP (Anders et al. 1987; Buchler et al. 1985; Cremer and Addicks 1985; Dante et al. 1987; Grouls et al. 1987; Guarda and Ordonez 1987; Hamid et al. 1986; Kawaguchi et al. 1985; Korbi et al. 1987; Mayol Belda et al. 1988; Perrone 1986; Sando et al. 1986; Scheithauer et al. 1986; Stephens et al. 1987). The tumours arise almost exclusively in the second part of the duodenum and are either sessile or pedunculated. The age of the patients ranges from 15 to 80 years with a mean value of approximately 52 years. Male to female ratio is 1:0.63. The most frequent symptoms are upper gastrointestinal bleeding and only one case presented with biliary obstruction (Scheithauer et al. 1986).

Clinical data in our case correlate well with the reported values of age and location: the patient was a 56-year-old woman and the tumour arose in the periampullary region of the duodenum. Moreover histology and immunohistochemistry fit with the reported patterns for GPs.

Immunohistochemical data from literature are listed in Table 2. Most Authors report immunoreactivity for general neuroendocrine markers like neuron specific enolase (NSE) (Hamid et al. 1986; Perrone et al. 1985; Scheithauer et al. 1986; Seshi et al. 1988) and protein gene product 9.5 (PGP 9.5) (Hamid et al. 1986) in both epithelioid and ganglion cells. Our case shows distinct NSE immunoreactivity and, in most ganglion cells, synaptophysin positivity. Chromogranin (CG) immunoreactivity has been rarely reported and the few positive stainings are restricted to epithelioid cells (Grouls et al. 1987; Hamid et al. 1986; Korbi et al. 1987). Most cases, including the present one, are devoid of CG immunoreactivity (21 of the 23 tested cases, 91.4%).

General agreement exists regarding the S-100 positivity of the spindle cells. Moreover we demonstrated a distinct positivity of these cells for vimentin and Leu-7 antigen and a clear negative reaction for myelin basic protein (MBP). The Leu-7 positivity confirms their neuroendocrine nature (Martin and Maung 1987; Michels et al. 1987; Tsutsumi 1984; Tischler et al. 1986), whereas the absence of MBP immunoreactivity helps to define better the functional attitude of these cells. The spindle cells could therefore be of Schwannian origin, as indicated by S-100 positivity, but without any myelinosynthetic activity, as suggested by the absence of MBP immunoreactivity.

Epithelial and ganglion cells are reported to be immunoreactive for a variety of neurohormonal peptides. The most frequently detected peptides in epithelial cells are somatostatin (25 out 28 tested cases, including the present one – 89.2%), pancreatic polypeptide (21 out of 23 tested cases – 91.3%), and serotonin (10 out of 14 tested cases – 71.4%). Ganglion cells show analogous immunoreactivities, with a lower incidence of pancreatic polypeptide positivity (13 out of 23 tested cases – 56.5%).

These immunohistochemical data led some authors to hypothesize that GPs might be related to pancreatic islet-cell tumours (Guarda et al. 1983; Hamid et al. 1986). Perrone et al. (1985) compared the immunohistochemical profile of GPs with that of duodenal carcinoids, conventional paragangliomas, pheochromocytomas and ganglioneuromas, stating: "there is evidence to support an endodermal, and specifically a pancreatic origin for its epithelial cells". The histogenesis of the GP should be related to "defective primordial ventral pancreatic rests that have recruited nerves, ganglion cells, and smooth muscle of the bowel to participate in a complex that strongly resembles the endodermal-neuroectodermal complexes of the pancreas, appendix, small and large intestines, and liver" (Perrone et al. 1985; Perrone 1986). In this view GPs could be regarded as hyperplasias or hamartomas/choristomas, similar to the argentaffin neuromas of the appendix. These latter lesions, described by Masson (1930), are regarded as precursors of appendiceal carcinoids. If the two lesions are similar, GPs may be a precursor of duodenal carcinoids as well. In fact a synchronous association of GPs and duodenal carcinoid has been recently reported (Stephens et al. 1987).

Perrone's hypothesis (1986) however is questioned by Scheithauer et al. (1986) who compare

duodenal GPs with paragangliomas of the cauda equina, as they show similar histological patterns and are immunoreactive for serotonin and somatostatin as well (Ironside et al. 1985; Sonneland et al. 1986).

The cytoskeleton of GPs has been studied by various authors, but the results are quite contradictory. NF immunoreactivity is reported by Perrone et al. (1985); Hamid et al. (1986); Dante et al. (1987) and Grouls et al. (1987), whereas it is denied by Scheithauer et al. (1986). Grouls et al. (1987) find CK immunoreactivity, whereas Dante et al. (1987) and Perrone et al. (1985) do not. GFAP immunoreactivity is described by Anders et al. (1987), but is denied by Perrone et al. (1985). Our present case is devoid of CK, desmin and GFAP reactivity and NF positivity is restricted to a limited number of ganglion cells. These conflicting data may be due to fixation artifacts or to different specificities of the various antibody/antisera employed.

We feel that there is a need for more studies on this subject, with special regard to CK and NF expression. In fact the frequently reported negativity for CK should prompt a more extensive study regarding the nature of the so called "epithelial cells".

From the diagnostic point of view it is our opinion that immunohistochemistry may be very useful to confirm the histological diagnosis of GPs. Hallmarks for the diagnosis should be S-100, neurohormonal peptides, like somatostatin or pancreatic polypeptide, and general neuroendocrine markers, like synaptophysin, NSE, Leu-7 or PGP 9,5. Moreover, absence of CK and CG expression distinguishes GPs from nerve sheath tumours with epithelial component which are positive for both antigens as well as for somatostatin, pancreatic polypeptide and other neuropeptides (Christensen et al. 1988). From the immunohistochemical point of view GPs are distinguishable from paragangliomas, due to their different CG immunoreactivity (Johnson et al. 1988).

In conclusion, from the analysis of the literature concerning GPs and of our personal case, it is difficult to agree either with the hyperplastic - choristomatous nature of GPs or with the neoplastic theory. Perhaps, recent data on the occasional malignant evolution of GPs (Buchler et al. 1985; Korbi et al. 1987), may favour the hypothesis that GP is a true neoplasm with a multiple element composition like other neuroendocrine tumours with a S-100 positive cell component. In fact S-100 positive cells have been detected in paragangliomas and pheochromocytomas (El-Salhy et al. 1986; Schroder and Johannsen 1986) appendiceal and bronchial carcinoids (Barbareschi et al. 1987; Barbareschi et al. 1988; Wilander et al. 1985) and ganglioneuroblastomas (Adam and Hochholzer 1981).

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References

Adam A, Hochholzer L (1981) Ganglioneuroblastoma of the posterior mediastinum: A clinicopathologic review of 80 cases. Cancer 47:373–381

Anders KH, Glasgow BJ, Lewin KJ (1987) Gangliocytic paraganglioma associated with duodenal adenocarcinoma. Case report with immunohistochemical evaluation. Arch Pathol Lab Med 111:49–52

Barbareschi M, Floresta AM, Mariani C, Allegranza A, Mosca L (1984) The nature of perineuronal cells in human gastrointestinal tract. Acta Neurol 6:326–327

Barbareschi M, Mauri MF, Muscara' M, Mauri FA, Lo Re V (1987) S-100 protein in human lung neuroendocrine neoplasms. Immunohistochemical study of 14 cases and review of the literature. Histol Histopathol 2:185–192

Barbareschi M, Frigo B, Ferrero S, Mariscotti C, Mosca L (1988) Bronchial carcinoid with S-100 positive sustentacular cells. Tumori 74:699–705

Buchler M, Malfertheiner P, Baczako K, Krautzberger W, Beger HG (1985) A metastatic endocrine-neurogenic tumor of the ampulla of Vater with multiple endocrine immunoreaction: malignant paraganglioma? Digestion 31:54–59

Cremer H, Addicks K (1985) Polypoid gangliocytic paraganglioma of the duodenum. Pathologe 6:211–216

Christensen WN, Strong EW, Bains MS, Woodruff JM (1988) Neuroendocrine differentiation in the glandular peripheral nerve sheath tumor. Am J Surg Pathol 12:417–426

Dante S, Viale G, Dalla Palma P (1987) Gangliocytic paraganglioma of the duodenum: case report. Tumori 73:425–429

El-Salhy M, Lundqvist M, Wilander E (1986) Bronchial carcinoids and phaeochromocytomas. A comparative study with special emphasis on S-100 protein, serotonin and neuron-specific enolase (NSE) immunoreactivity. Acta Path Microbiol Immunol Scand Sect A 94:229–235

Grouls V, Pickartz H, Reis HE (1987) Peduncolated polypoid gangliocytic paraganglioma of the afferent jejunal loop of a Billroth II stomach. Leber Magen Darm 17:327–333

Guarda LA, Ordonez NG, Del Junco GW, Luna MA (1983) Gangliocytic paraganglioma of the duodenum: An immunocytochemical study. Am J Gastroenterol 78:794–798

Guarda LA, Ordonez NG (1987) Gangliocytic paraganglioma of the duodenum: report of cytologic, histologic, immunohistochemical and ultrastructural features of a case. Diagn Cytopathol 3:314–319

Hamid QA, Bishop AE, Rode J, Dhillon AP, Rosemberg BF, Reed RJ, Sibley RK, Polak JM (1986) Duodenal gangliocytic paragangliomas: A study of 10 cases with immunocytochemical neuroendocrine markers. Hum Pathol 17:1151–1157

Hsu SM, Raine L, Fanger H (1981) Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase technique. A

comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:577–580
Ironside JW, Royds JA, Taylor CB, Timperley WR (1985) Paraganglioma of the cauda equina: A histological ultrastructural and immunocytochemical study of two cases with a review of the literature. J Pathol 145:195–201
Johnson TL, Zarbo RJ, Lloyd RV, Crissman JD (1988) Paragangliomas of the head and neck: Immunohistochemical neuroendocrine and intermediate filament typing. Modern Pathol 1:216–223
Kawaguchi K, Takizawa T, Koike M, Tabata I, Goseki N (1985) Multiple paraganglioneuromas. Virchows Arch [A] 406:373–380
Kheir SM, Halpern NB (1984) Paraganglioma of the duodenum in association with congenital neurofibromatosis. Cancer 53:2491–2496
Korbi S, Kapanci Y, Widgren S (1987) Le paragangliome malin du duodénum. Etude immunohistochimique et ultrastructurale d'un cas. Ann Pathol 7:47–55
Lauzon A, Cadotte M (1972) Paragangliome gangliocytaire du duodénum. Union Med Can 101:1584–1586
Lloyd RV, Cano M, Rosa P, Hille A, Huttner WB (1988) Distribution of chromogranin A and secretogranin I (chromogranin B) in neuroendocrine cells and tumors. Am J Pathol 130:296–304
Lukash WM, Hyams VJ, Nielsen OF (1966) Neurogenic neoplasms of the small bowel: Benign nonchromaffin paraganglioma of the duodenum: report of a case. Am J Dig Dis 11:575–579
Martin JME, Maung RT (1987) Differential immunohistochemical reactions of carcinoid tumors. Hum Pathol 18:941–945
Masson P (1930) The significance of the muscolar "stroma" of argentaffin tumors (carcinoids). Am J Pathol 6:499–514
Mayol Belda MJ, Sanchez Ramos MA, Van der Hofstad Alberola C, Vasquez Echarri J (1988) Duodenal gangliocytic paraganglioma. Rev Esp Enferm Apar Dig 73:214–216
Michels S, Swanson PE, Robb JA, Wick MR (1987) Leu-7 in small cell neoplasms. An immunohistochemical study with ultrastructural correlations. Cancer 60:2958–2964
Mosca L, Barbareschi M, Mauri MF, Munguia-Barrera J, Frigo B, Muscarà M, Valentini L, Mariscotti C (1988) Neuroendocrine lung structures and tumours: immunohistochemical study by specific markers. Histol Histopathol 3:367–376
Ortiz-Rivas LA, Longo J, Juanco C, Silvan M, Guerra I (1986) Gangliocytic paraganglioma of the duodenum. Presentation of a case and review of the literature. Rev Esp Enferm Apar Dig 69:363–365
Perrone T, Sibley RK, Rosai J (1985) Duodenal gangliocytic paraganglioma. An immunohistochemical and ultrastructural study and a hypothesis concerning its origin. Am J Surg Pathol 9:31–41
Perrone T (1986) Duodenal gangliocytic paraganglioma and carcinoid. Am J Surg Pathol 10:147–150
Reed RJ, Daroca PJ, Harkin JC (1977) Gangliocytic paraganglioma. Am J Surg Pathol 1:207–216
Riddell K, Tippens BS, Gown AM (1987) PHE-5 a new monoclonal antibody to a unique neuroendocrine granule protein. Lab Invest 56:64A
Sando WC, Mills SE, Rodgers BM (1986) Duodenal gangliocytic paraganglioma occurring in adolescence. J Pediatr Gastroenterol Nutr 5:659–664
Savio OS, Ganzales BN, Cortés FG, Barry HG, Rodriguez MMA, Rodriguez NA (1974) Paraganglioma no cromafinico del yeyuno. Rev Cubana Cir 13:497–505
Scheithauer BW, Nora FE, LeChago J, Wick MR, Crawford BG, Weiland LH, Carney JA (1986) Duodenal gangliocytic paraganglioma. Clinicopathologic and immunohistochemical Study of 11 cases. Am J Clin Pathol 86:559–565
Schroder HD, Johannsen L (1986) Demonstration of S-100 protein in sustentacular cells of phaechromocytomas and paragangliomas. Histopathology 10:1023–1033
Seshi B, True L, Carter D, Rosai J (1988) Immunohistochemical characterization of a set of monoclonal antibodies to human neuron-specific enolase. Am J Pathol 131:258–269
Sonneland PR, Scheithauer BW, LeChago J, Crawford BG, Onofrio BM (1986) Paraganglioma of the cauda equina region. Clinicopathologic study of 31 cases with special reference to immunocytology and ultrastructure. Cancer 58:1720–1735
Stephens M, Williams GT, Jasani B, Williams ED (1987) Synchronous duodenal neuroendocrine tumours in von Recklinghausen's disease-a case report of co-existing gangliocytic paraganglioma and somatostatin-rich glandular carcinoid. Histopathology 11:1331–1340
Sternberger LA (1979) Immunocytochemistry, 2nd ed. John Wiley & Sons, New York
Tsutsumi Y (1984) Leu7 immunoreactivity as histochemical marker for paraffin-embedded neuroendocrine tumors. Acta Histochem Cytochem 17:15–21
Tischler AS, Mobtaker H, Mann K, Nunnemacher G, Jason WJ, Dayal Y, De Lellis RA, Adelman L, Wolfe HJ (1986) Anti-lymphocyte monoclonal antibody HNK-1 (Leu7) recognizes a constituent of neuroendocrine granule matrix. Lab Invest 54:64A
Wilander E, Lundqvist M, Movin T (1985) S-100 protein in carcinoid tumors of appendix. Acta Neuropathol 66:306–310
Wittaker MH, Sandusky GE (1988) Synaptophysin, Chromogranin A, PHE-5 and Chromogranin (LK2H10). Immunoreactivity in abdominal carcinoids. Modern Pathol 1:102A

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