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ORIGINAL ARTICLE

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Vesicular monoamine transporter 2 as a marker of gastric enterochromaffin-like cell tumors

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Abstract The vesicular monoamine transporter 2 (VMAT2) facilitates the ATP-dependent accumulation of biogenic amine inside the secretory granules of endocrine cells and neurons and was demonstrated in the histamine-producing enterochromaffin-like (ECL) cells of the stomach. In the present investigation, VMAT2 immunohistochemistry was tested in 85 endocrine tumors, of which 60 were well differentiated gastrointestinal and pancreatic growths, 5 poorly differentiated (neuro)endocrine carcinomas (PDEC) and 1 mixed PDEC/ECL cell carcinoma of the stomach, 12 pheochromocytomas/paragangliomas, 3 adrenocortical lesions, 2 parathyroid and 2 lung neuroendocrine tumors. Extensive and intense VMAT2 immunoreactivity was observed in 16 of 16 gastric ECL cell tumors, 6 of 6 adrenal pheochromocytomas, 2 of 2 chromaffin paragangliomas and in 3 of the 4 carotid body paragangliomas investigated. Rare VMAT2-positive cells were observed in 12 of 21 intestinal enterochromaffin (EC) cell tumors, in 9 of 11 pancreatic neuroendocrine tumors, and in the mixed PDEC/ECL cell carcinoma of the stomach (differentiated cells only). No VMAT2 immunoreactivity was observed in five gastrin, four somatostatin and three enteroglucagon/peptideYY tumors of the gastrointestinal tract, in six gastric PDECs, in three adrenocortical growths, and two parathyroid and two lung neuroendocrine tumors. These data support VMAT2 immunohistochemistry as being a useful tool for the diagnosis of gastric ECL cell tumors, separating them from all other endocrine tumors arising in the gastroduodenal area i.e., gastrin, somatostatin, EC cell and PDEC tumors, all of which proved essentially negative.

Key words VMAT2 · Stomach · ECL cell · Tumors · Immunohistochemistry

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Introduction

At present, the specific identification of human enterochromaffin-like (ECL) cells and related tumors may be achieved only using electron microscopy and histamine or histidine-decarboxylase histochemistry [5, 16, 29]. Unfortunately, electron microscopy has several disadvantages, including the need of appropriately preserved and processed tissue, the limited sampling of tumor mass, and the relatively high costs. However, histamine immunohistochemistry is severely impaired by the low histamine content of human ECL cells and its rapid dissolution in ordinary liquid fixatives. Moreover, to our knowledge no antibody for human histidine-decarboxylase histochemistry is available that works in routine formalin-fixed, paraffin sections. Thus, only a battery of light-microscopy methods, including positive chromogranin A immunostaining and Grimelius or Sevier-Munger silver, coupled with negative tests for peptide hormones such as gastrin or somatostatin, may provide data supporting a reliable diagnosis of ECL cell tumor (neuroendocrine tumor) in routine histopathologic material [3, 20, 27].

Recently, two integral membrane glycoproteins, vesicular monoamine transporters 1 and 2 (VMAT1 and 2), have been shown to facilitate the ATP-dependent accumulation of biogenic amine precursors into neuroendo-

crine secretory granules, where they may undergo decarboxylation to corresponding monoamines [13, 30]. Interestingly, the two VMAT isoforms show broad selectivity for different amines and are differently distributed in various cell types. A combination of selectivity and redundancy is probably necessary to impart selective, genetically regulated, functional properties to different monoaminergic cell types [30]. VMAT1 was found to be expressed in serotonin-producing gastrointestinal enterochromaffin (EC) tumors and the small intensely fluorescent (SIF) cells of sympathetic ganglia, whereas VMAT2 was detected in histamine-producing gastric ECL cells, in addition to central and peripheral neurons [10, 12, 13, 32]. Only chromaffin cells of the adrenal medulla expressed both VMAT1 and VMAT2. On this basis, VMAT isoforms have been tested in a case of a histamine-producing gastric endocrine tumor showing ultrastructural morphology of an ECL cell tumor. Only VMAT2 immunoreactivity was found, thus raising the possibility that this may represent a useful marker for the diagnosis of ECL cell tumors [18].

In this study, VMAT2 immunohistochemistry has been applied to gastric endocrine tumors, most of which had been diagnosed as ECL cell tumors based on previous morphological and clinico-pathological investigations [20]. For comparison, endocrine tumors from the pancreas, intestine, adrenals, parathyroids, retroperitoneum, carotid body, and lung were also tested.

Materials and methods

A total of 85 neuroendocrine tumors from the files of the Departments of Pathology of Pavia and Brescia were investigated. Of 23 gastric endocrine tumors, 21 of which were previously characterized on histopathological, histochemical, ultrastructural and clinico-pathological grounds, 16 were well differentiated gastric ECL cell tumors, 1 was a pyloric gastrinoma, 5 were poorly differentiated gastric (neuro)endocrine carcinomas (PDECs) and 1 was a mixed PDEC/ECL cell carcinoma (for diagnostic criteria see [20] and [21]). Eight of the ECL cell tumors were of type I, associated with diffuse corpus-fundus chronic atrophic gastritis (A-CAG), 4 were of type II associated with Zollinger-Ellison syndrome (ZES) and type-1 multiple endocrine neoplasia (MEN-1), and 4 were of type III, sporadic. Of 62 non gastric tumors, 32 were tumors of the gut, 11 of the pancreas, 2 adenomas and 1 carcinoma of the adrenal cortex, 6 adrenal pheochromocytomas, 2 parathyroid tumors, 2 retroperitoneal sympathetic paragangliomas, 4 carotid body tumors, and 2 bronchial neuroendocrine tumors. Of 32 gut tumors, 4 were diagnosed as duodenal gastrin-producing G-cell tumors, one of which with MEN-1; 4 as duodenal, somatostatin-producing D-cell tumors; 21 as serotonin-producing EC cell neuroendocrine tumors (1 from duodenum, 18 from the ileum and 2 from the appendix) and 3 as enteroglucagon/peptideYY (peptide

Table 1 Vesicular monoamine transporter 2 (VMAT2) immunoreactivity in 85 neuroendocrine tumors. *PDEC* poorly differentiated (neuro)endocrine carcinoma; *No.* number of investigated tumors; *n* number of positive tumors; *intensity* mean value of intensity of immunoreaction graded as +=weak; ++=moderate; +++=intense; *%* range of percentage positive cells; *ECL* enterochromaffin-like; *G* gastrin-producing cell; *D* somatostatin-producing cell; *EC* enterochromaffin cell; *L* glycentin/peptideYY-producing cell; *B* insulin-producing; *A* glucagon-producing

Site	Tumor type	Main cell type	No.	VMAT2 immunoreactivity		
				n	Intensity	%
Stomach	Argyrophil carcinoid	ECL	16	16	++	90[a]
	Gastrinoma	G	1	0	–	–
	PDEC	Protoendocrine	5	0	–	–
	PDEC/carcinoid	Protoendocrine/ECL	1	1	++	40[b]
Duodenum	Gastrin cell	G	4	0	–	–
	Somatostatin cell	D	4	0	–	–
	Argentaffin carcinoid	EC	1	0	–	–
Ileum	Argentaffin carcinoid	EC	18	12	+/++	1–10[c]
Appendix	Argentaffin carcinoid	EC	2	0	–	–
Colon–rectum	Trabecular carcinoid	L	3	0	–	–
Pancreas	Nonfunctioning	Various	3	3	++	1–20
	Functioning	B	3	2	++	1–10
		A	2	2	++	10–30
		G	3	2	++	1–10
Parathyroid	Adenoma	Chief	2	0	–	–
Lung	Argyrophil carcinoid	P	2	0	–	–
Adrenal	Cortical adenoma	Cortical	2	0	–	–
	Cortical carcinoma	Cortical	1	0	–	–
	Pheochromocytoma	Chromaffin	6	6	+++	40–80
Retroperitoneum	Paraganglioma	Chromaffin	2	2	++	15–40
Carotid body	Paraganglioma	Non-chromaffin	4	3	+++	5–80

[a] One case 30%; [b] Restricted to well-differentiated cells only; [c] One case 30%

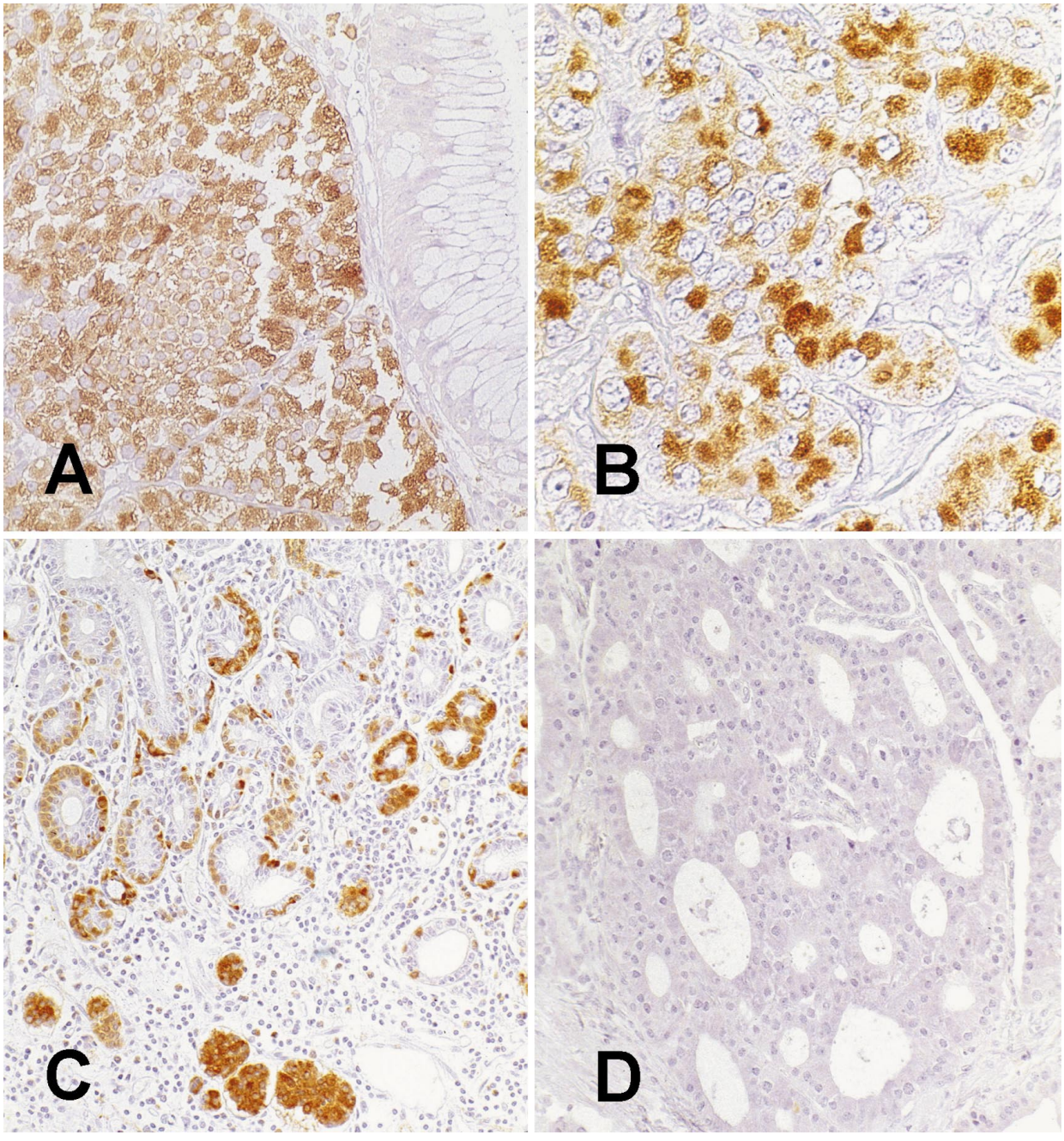
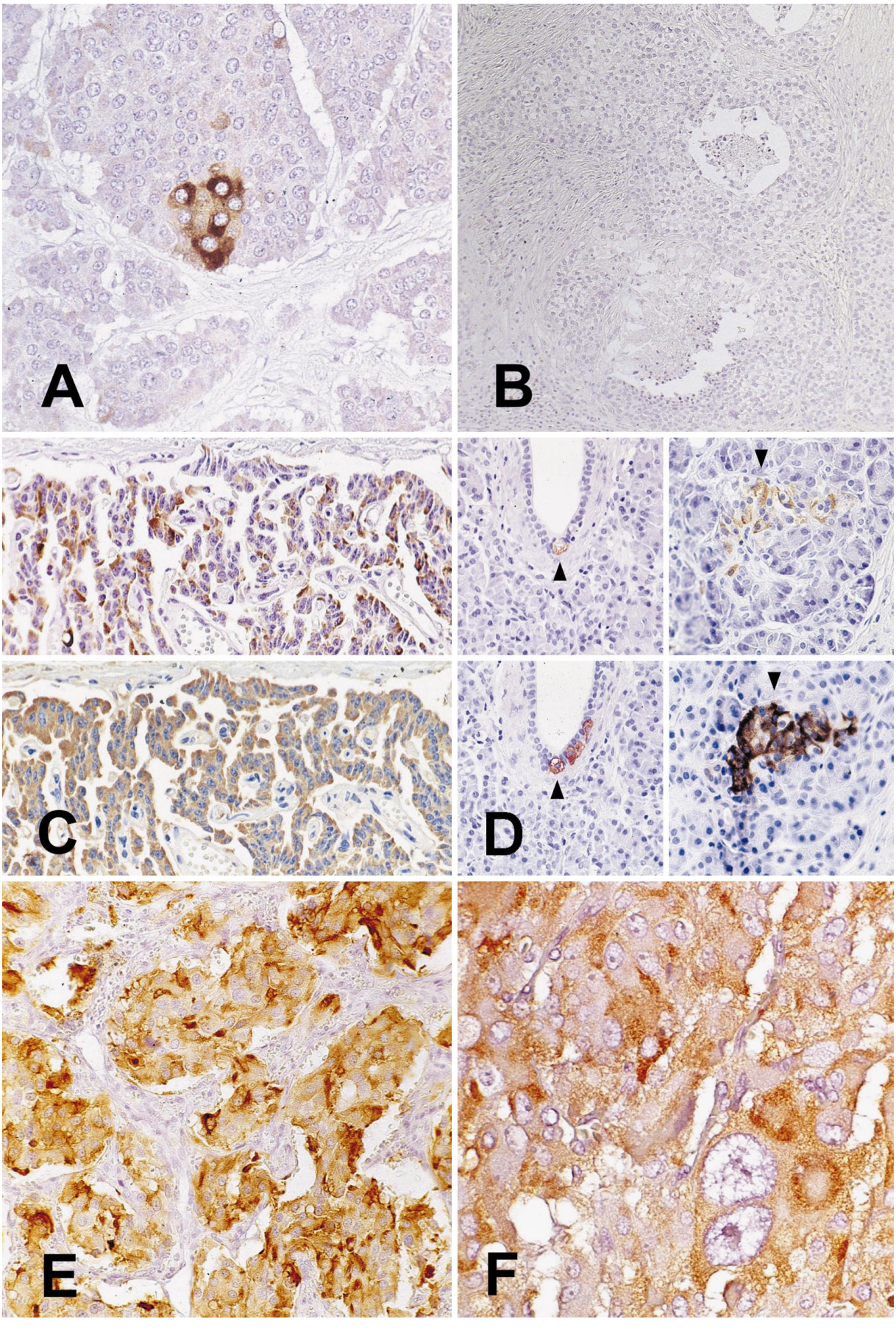


Fig. 1A, B Vesicular monoamine transporter 2 (VMAT2) immunoreactivity in gastric well-differentiated enterochromaffin-like (ECL) cell tumors either associated with chronic atrophic gastritis and hypergastrinemia (type I) (**A**) or sporadic (type III) (**B**). Note that the diffuse and intense immunoreactivity is distributed in the cytoplasm (**A**) and in the Golgi area of tumor cells (**B** only). **C** Positive VMAT2 immunoreactivity in hyperplastic ECL cells in non-tumor gastric mucosa of a patient with type-I multiple ECL cell carcinoids. **D** Absence of VMAT2 immunoreactivity in a duodenal D-cell tumor not associated with hyperfunctional syndrome – note the typical glandular structure. **A–D** immunoperoxidase, ABC method

with C-terminus and N-terminus tyrosine)-producing L-cell tumors of the rectum. The 11 pancreatic tumors were all well differentiated with variable tumor cell populations at immunohistochemical analysis. According to the pertinent clinical settings, three were diagnosed as nonfunctioning and eight as functioning tumors (three insulinomas, three gastrinomas, and two glucagonomas). For non-ECL cell tumors, the diagnosis was based on conventional histopathological criteria, positive silver stain and immunoreactivity for the general neuroendocrine markers chromogranin-A or synaptophysin, coupled with immunoreactivity for the cell-specific endocrine peptides or amines and electron microscopy [4, 6, 7, 14, 28]. Samples of non-tumor gastrointestinal mucosa, pancreas and adrenals from tumor-bearing and tumor-free cases were also investigated.

Formalin- or Bouin-fixed, 4-µm paraffin sections were brought to water and immunostained with anti-human VMAT2 affinity-purified serum (see below for details) after microwave antigen retrieval [9], and with antibodies specific for the gastrointestinal hor-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mones serotonin, gastrin, somatostatin, glycentin, and peptideYY using the avidin–biotin–peroxidase technique [17], as detailed elsewhere [5, 7, 14, 20]. For double localization studies, serial or reverse face 2-µm paraffin sections were used. Controls consisted of omission of the first layer and use of tissue with or without the pertinent antigen.

The anti VMAT2 serum was generated by immunization of rabbits with a fragment encoding the amino acids 42–133 of bovine VMAT2, corresponding to the large intravesicular loop [22]. Subsequently the serum was first filtered through glutathione-*S*-transferase (GST) immobilized on glutathione-sepharose, to eliminate antiGST antibodies, and then the anti VMAT2 antibodies were purified by adsorbing the flowthrough on the VMAT fusion protein immobilized on glutathione-sepharose.

Results

The results are summarized in Table 1. Specific VMAT2 immunoreactivity was found in 49 of the 85 endocrine tumors investigated, including all the 16 ECL cell tumors (irrespective of clinicopathological subtypes), 1 mixed PDEC/ECL cell tumor, 12 of 21 EC cell tumors, 9 of 11 pancreatic tumors, the 6 adrenal pheochromocytomas, the 2 extra-adrenal sympathetic paraganglioma, and 3 of 4 carotid body paragangliomas (Fig. 1 and Fig. 2). Of digestive tract tumors, VMAT2 immunoreactivity was restricted to gastric ECL cell, intestinal EC cell, and pancreatic growths. VMAT-2 immunoreactivity was cytoplasmic and granular, and varied in intensity in different tumor cell types. Of 16 well-differentiated gastric ECL cell tumors, 15 were intensely positive in the large majority of tumor cells (Fig. 1A, B). One type-III ECL cell tumor showed only about 30% of tumor cells positive for VMAT2. This tumor previously proved to be moderately differentiated (G2) on histological and histochemical grounds [21]. VMAT2-positive EC cells ranged from 1% to 10% in tumors (Fig. 2A), one case displaying up to 30% of positive cells. In pancreatic tumors, VMAT2-positive cells ranged from 1% to 30% and appeared to be mainly concentrated in areas rich in pancreatic polypeptide-producing (PP) or glucagon-producing (A) cells in consecutive sections, although usually corresponding to a fraction only of the latter cells (Fig. 2C and Table 1). Weak immunostaining of some cells in insulinomas was also observed. Adrenal and extra-adrenal paragangliomas showed intense VMAT2 immunoreactivity accounting for 40–80% of tumor cells (Fig. 2E, F). No VMAT2 immunoreactivity was detected in gastrin-, somatostatin- (Fig. 1D) or enteroglucagon/peptideYY-producing gut endocrine tumors, in non-argentaffin bronchial neuroendocrine tumors, in gastric PDECs (Fig. 2B), in parathyroid and adrenocortical tumors.

Scattered VMAT2-immunoreactive cells resembling ECL cells in morphology and distribution were found in the acidopeptic, non-tumor mucosa of several gastric samples. Intense VMAT2 reactivity was also observed in the hyperplastic and/or precarcinoid (dysplastic) ECL cell changes associated with ECL cell tumors in samples from hypergastrinemic patients with diffuse A-CAG or ZES-MEN-1 syndrome (Fig. 1C). No VMAT2-positive cells were found in the pyloric or intestinal mucosa, apart from rare, weakly reactive cells observed in occasional specimens of the small intestine (not shown). In serial sections of non-tumor pancreas, VMAT2 immunoreactivity was colocalized in PP cells, either in islets, especially of the posterior part of the head (PP-rich islets), or scattered in the exocrine parenchyma (Fig. 2D), in glucagon cells (not shown), and in a subpopulation of insulin-producing (B) cells (Fig. 2D). No significant colocalization was appreciated in somatostatin-producing D cells.

VMAT2-immunoreactive neurons and/or nerves were observed in the gut wall and in the adrenal capsule. Some VMAT2-reactive mononuclear cells scattered in tumor and non-tumor connective tissue were interpreted as mast cells. VMAT2 immunoreactivity was considerably influenced by histology procedures. In general, Bouin-fixed tissues gave more intense and reproducible reactions than formalin-fixed ones. Microwave treatment was necessary in most cases, especially with Bouin or prolonged formalin fixation; however, poor staining was observed in samples after short formalin fixation.

◀ **Fig. 2** **A** Isolated vesicular monoamine transporter 2 (VMAT2) immunoreactive tumor cells in an argentaffin enterochromaffin (EC) cells tumor of the small intestine. **B** Absence of VMAT2 immunoreactivity in a poorly differentiated (neuro)endocrine carcinoma of the stomach. Note the structure made by solid aggregates with central necrosis. **C** VMAT2 (*top*) and glucagon (*below*) immunoreactivities in consecutive sections of a nonfunctioning tumor of the pancreas rich in glucagon-producing A and PP cells. Note the diffuse and even distribution of glucagon immunoreactivity – only a fraction of glucagon-positive cells appear to colocalize VMAT2. **D** One single, VMAT2-immunoreactive pancreatic duct cell (*arrowhead, top left*) colocalizes PP-immunoreactivity (*arrowhead, below left*) in consecutive sections. Note that some PP-immunoreactive cells are negative for VMAT2; VMAT2 positive cells (*top, right*) colocalizing insulin-immunoreactivity (*below, right*) in consecutive sections: the *arrowheads* indicate one area rich in cells colocalizing both antigens. **E, F** Strong VMAT2 immunoreactivity in non-chromaffin cells (*non-CC*) of a carotid body paraganglioma (**E**) and in chromaffin cells (*CC*) of a pheochromocytoma (**F**). **A–D** Immunoperoxidase, ABC method

Discussion

The above findings outline the specificity of the histamine transporter VMAT2 as a marker of gastric ECL cell tumors and related hyperplastic or dysplastic lesions. Extensive and intense VMAT2 immunoreactivity was detected in all clinicopathological subtypes of well-differentiated ECL cell tumors. These include sporadic type-III cases, usually not associated with hypergastrinemia and sometimes showing clinical evidence of histamine production [1, 18], as well as those associated with hypergastrinemia, either due to diffuse chronic atrophic gastritis of the corpus-fundus mucosa (type-I cases) or to combined MEN/ZES (type-II cases), usually lacking signs of histamine hypersecretion and the histamine syndrome [2, 3, 8, 20, 27]. In addition, most cells forming

the hyperplastic-dysplastic growths associated with type-I and type-II ECL cell tumors were intensely VMAT2 positive.

A variable, usually minor population of moderately VMAT2-reactive cells was observed in 12 of 20 serotonin-producing, EC cell tumors of the distal small intestine and no reactivity in the single duodenal EC cell tumor investigated (Fig. 2A). This finding may be related to the property of occasional catecholamine production reported for EC cell tumors [15], in addition to their regular and extensive serotonin production, and may contribute to the relative heterogeneity of EC tumor cells previously appreciated on histochemical grounds [31]. The vast majority of EC tumor cells were, however, VMAT2 negative, in keeping with the lack of VMAT2 in normal human EC cells, known to express VMAT1 only [13]. In addition, no VMAT2 was observed in intestinal, well-differentiated, peptide hormone-producing tumors such as gastroduodenal gastrin and somatostatin cell tumors or colorectal enteroglucagon/peptideYY cell tumors. The extensive and intense VMAT2 expression observed in well-differentiated gastric ECL cell tumors relative to the substantial lack of VMAT2 in other endocrine gut tumors supports the specificity of VMAT2 expression for ECL cell tumors. Considering that the endocrine cell population of the human stomach is composed by a variety of cell types, including, besides ECL cells, G, D, EC, X (A-like) and P cells [23, 26], all of which may also occur in tumors [20, 25], our results support the usefulness of VMAT2 as a tool for the differential diagnosis of gastric endocrine tumors. Indeed, none of the above cell types, apart from ECL cells, and none of the tumors arising in the gastroduodenal area, except for ECL cell tumors, have been found to react with VMAT2 antibodies.

A limited proportion of VMAT2 positive cells were observed in the pancreatic endocrine tumors investigated, mainly concentrated in areas rich in PP or A cells in consecutive sections (Fig. 2C), although only a fraction of these cells were involved. Weak VMAT2 immunoreactivity was also observed in limited subpopulations of insulinomas (Table 1). In addition, VMAT2 expression was localized in PP, A, and B islet cells of non-tumor pancreatic samples. These findings are in accordance with the previously reported presence of uncharacterized reactive cells in normal human pancreas [13] and indicate that some A, B, and PP islet cells may indeed actively transport amines, as repeatedly shown in islet cells of mammals injected with amine precursors [24]. Whether such cells in man do normally store monoamines as they do in other species and what the physiological significance of such a feature is remain to be elucidated.

In keeping with VMAT2 demonstration in all chromaffin cells of human adrenal medulla and the extraction of VMAT2 mRNA from human pheochromocytomas [13], we detected widespread VMAT2 immunoreactivity in all cases of the adrenal pheochromocytomas investigated. In addition, we immunolocalized VMAT2 in extra-adrenal paragangliomas, either of the retroperitoneal chromaffin type or of the carotid body non-chromaffin type. Both kinds of tumors are known to produce catecholamines [11, 19]. Despite the widespread pattern of VMAT2 reactivity, these tumors should not interfere with the histopathological characterization of ECL cell tumors unless at metastatic sites.

No VMAT2 immunoreactivity was observed in the pure gastric PDECs investigated. At the ultrastructural level, gastric PDEC cells show evident small synaptic-like vesicles with rare, immature or abortive endocrine granules, and retain, at light microscopy, neuroendocrine antigens of the cytosol (e.g., NSE and PGP9.5) or synaptic-like vesicles (synaptophysin), while lacking almost completely markers of the secretory granule, such as chromogranin-A and hormones [20, 21]. Therefore, the lack of VMAT2 immunoreactivity in PDECs reflects the poorly differentiated status and the poor secretory granule content of their cells.

In conclusion, the data here presented support the usefulness of VMAT2 to separate gastric ECL cell tumors from other types of gastrointestinal endocrine tumors on routine histology specimens. In particular, VMAT2 immunohistochemistry adds a specific positive marker to the general endocrine markers such as chromogranin A, synaptophysin, or silver stains and to the specific but negative peptide hormone tests so far utilized. Although, as shown in previous studies, minor populations of gastrin-, somatostatin-, or pancreatic polypeptide-producing cells may be found in tumors mostly composed of ECL cells [3, 20], our study confirms that the large majority of gastric endocrine tumors is made by ECL cells. The detection of an overwhelming population of VMAT2-positive cells allows us to easily ascertain the ECL cell nature of such tumors – even in the absence of electron microscopy – and to separate them from other gastrointestinal tumors such as the VMAT2-negative, gastrin, somatostatin, and enteroglucagon cell tumors or the poorly differentiated, highly malignant (neuro)endocrine carcinomas. Previous investigations show absence of VMAT2 immunoreactivity in the rare gastric EC cell tumors [18]. Separation of gastric ECL cell tumors from EC cell tumors of the distal intestine and pancreatic endocrine tumors is facilitated, besides by their different topography and specific hormone contents, by the focal pattern of VMAT2 immunoreactivity of the latter tumors relative to the widespread pattern of ECL cell tumors.

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