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Hyperplasia to Neoplasia Sequence of Duodenal and Pancreatic Neuroendocrine Diseases and Pseudohyperplasia of the PP-cells in the Pancreas

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Abstract Hyperplastic changes of the neuroendocrine cell system may have the potential to evolve into neoplastic diseases. This is particularly the case in the setting of genetically determined and hereditary neuroendocrine tumor syndromes such as MEN1. The review discusses the MEN1-associated hyperplasia–neoplasia sequence in the development of gastrinomas in the duodenum and glucagon-producing tumors in the pancreas. It also presents other newly described diseases (e.g., glucagon cell adenomatosis and insulinomatosis) in which the tumors are (or most likely) also preceded by islet cell hyperplasia. Finally, the pseudohyperplasia of PP-rich islets in the pancreatic head is defined as a physiologic condition clearly differing from other hyperplastic–neoplastic neuroendocrine diseases.

Keywords Neuroendocrine cells · Hyperplasia · Neoplasia · MEN1 · Glucagon cell adenomatosis

Introduction

Several neoplasms of the neuroendocrine cell system evolve from hyperplastic lesions. Most of these diseases occur in the setting of genetically determined and hereditary tumor syndromes such as multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2). This article focuses on neuroendocrine diseases in the duodenum and the pancreas that show a hyperplasia–neoplasia sequence. It also briefly touches on the pseudohyperplasia of pancreatic polypeptide rich islets in the pancreatic head.

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Duodenum

MEN1

Among the various types of neuroendocrine tumors (NETs) in the duodenum, the gastrinomas are those which are preceded by precursor lesions if associated with the MEN1 syndrome [1]. All the other duodenal NETs, i.e., sporadic gastrinomas, somatostatin-producing tumors with and without an associated neurofibromatosis type 1 syndrome, serotonin-producing tumors, poorly differentiated neuroendocrine neoplasms and gangliocytic paragangliomas, arise from the duodenal mucosa without any preceding changes [2, 3].

MEN1-associated duodenal gastrinomas present as multicentric tumors, in contrast to sporadic gastrinomas which are solitary lesions [1]. In addition to gastrin-producing neoplasms, the duodenum of MEN1 patients may also contain single somatostatin-producing tumors. These NETs are associated with linear and nodular hyperplastic changes of the gastrin and somatostatin cells within the crypts and Brunner's glands of the duodenal mucosa (Fig. 1). The hyperplastic lesions are unevenly distributed in the duodenal mucosa and exhibit enhanced proliferative activity. They are found in all patients with MEN1 but are absent in patients with sporadic (non-MEN1-associated) duodenal gastrinomas. The fact that the hyperplastic gastrin cell changes occur throughout the duodenal mucosa explains the multicentricity of MEN1-

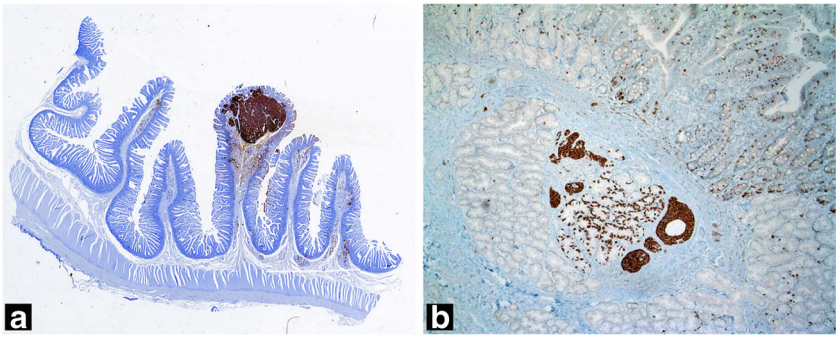

Fig. 1 One of several small duodenal gastrinomas froma MEN1-patient. **a** Duodenal mucosa segment showing a gastrin positive NET. **b** Focus of gastrin cell hyperplasia in submucosal Brunner's glands with associated small gastrin positive nodules

associated gastrinomas and the failure to cure patients with MEN1-associated Zollinger–Ellison syndrome (ZES) by simple excision of a visible duodenal NET.

Duodenal gastrin cell hyperplasia is pathogenetically linked to a heterozygous germline mutation of the *MEN1* gene. In MEN1 patients all somatic cells harbor a germline mutation of the *MEN1* tumor suppressor gene. A loss of heterozygosity (LOH) at the *MEN1* gene locus, often combined with LOH of centromere 11, was demonstrated in MEN1-associated duodenal NETs (some of them not larger than 300 μm in diameter [4]) but not in the accompanying gastrin cell hyperplasia [5]. This suggests that the hyperplastic cells that carry like all cells of the body, the MEN1 gerrmline mutation on one allele, had not yet assumed the neoplastic genotype characterized by the allelic loss of 11q13. We do not know what mechanisms and factors enhance the proliferation of gastrin cells and produce the hyperplastic changes in the duodenal mucosa, but this process may be related to an increased responsiveness of the gastrin cell in the setting of MEN1 to certain growth factors or some other growth enhancing mechanisms.

Non-MEN1 Lesions

Gastrin cell changes that were interpreted as hyperplasia were described in the vicinity of solitary and sporadic gastrin-producing duodenal NETs that had been endoscopically removed [6]. All these tumors were discovered incidentally and not associated with a Zollinger–Ellison syndrome or the MEN1 syndrome. As some of these tumors presented together with a *Helicobacter pylori* gastritis treated by a long-term proton pump inhibitors, a pathogenetic role of these drugs in the development of sporadic gastrin producing NETs has been discussed [6].

Pancreas

MEN1

The pancreas of patients with MEN1 typically contains multiple small (<5 mm) NETs, a finding referred to as microadenomatosis [7]. The pancreatic microadenomas in

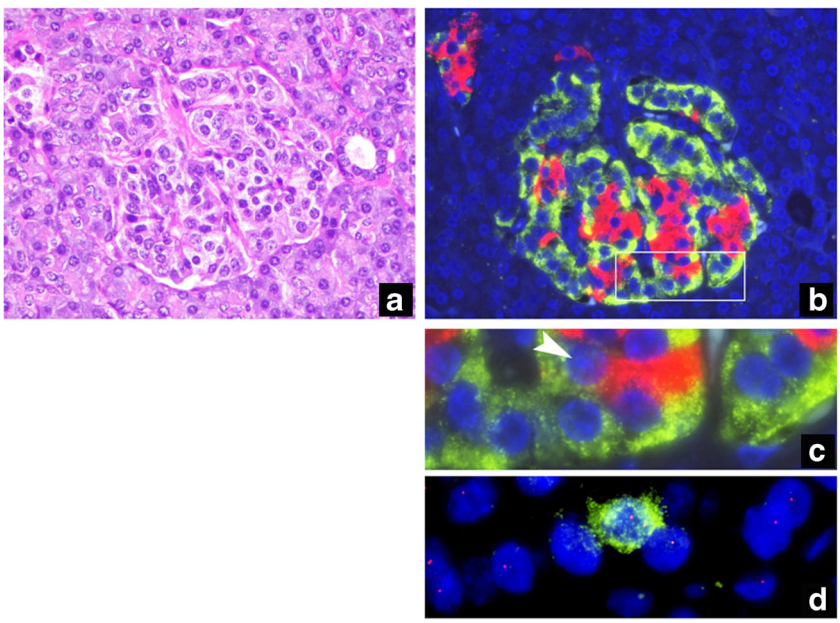

Fig. 2 Islet with glucagon cell hyperplasia turning into monoclonal cell proliferation. **a** H&E-stained islet with almost normal structure. **b** Serial section showing glucagon cell hyperplasia (immunofluorescence: glucagon in *green*, insulin in *red*). **c** Enlarged box-labeled area in **b. d** Retention of heterozygosity of 11q13 in a single insulin cell (*green and arrow head in* **b**) and LOH on 11q13 in unstained glucagon cells (from [8] with permission of publisher)

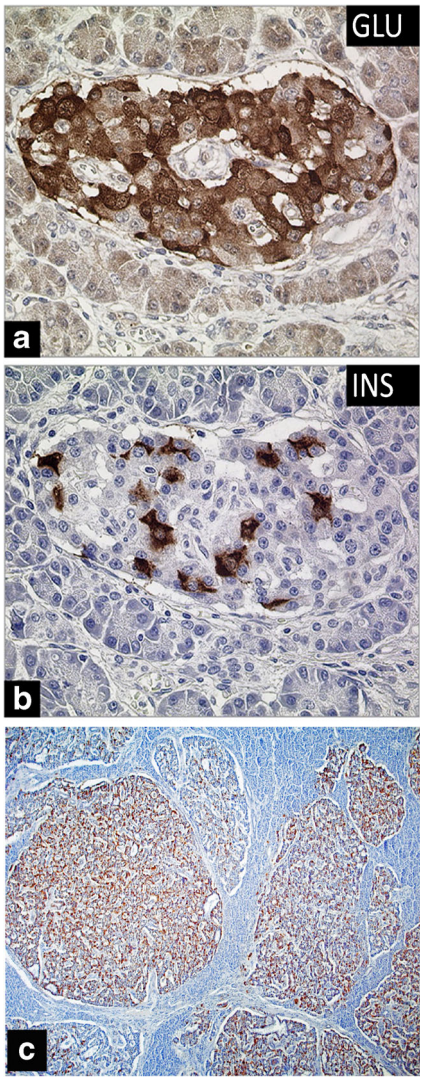

Fig. 3 Glucagon cell adenomatosis: **a**, **b** Islet with glucagon cell hyperplasia (GLU) and decreased number of insulin cells (INS). **c** Multiple small glucagon-positive NETs

MEN1 are often accompanied by one or more macrotumors (diameter >5 mm). Multihormonality is a common finding in these tumors, with one hormone usually prevailing. Most frequent are tumors that are mainly glucagon-positive, followed by PP and then insulin or somatostatin expressing tumors [7].

By combining fluorescence in situ hybridization of the *MEN1* locus at 11q13 and the centromeric region of chromosome 11q with hormone immunostaining, it was shown that microadenomas usually show LOH at 11q13 and thus lack one *MEN1* allele. Moreover, a few islets exhibited an increased number of glucagon cells which still retained both MEN1 alleles or already showed LOH [8] (Fig. 2). These results implicate, first that the allelic loss at 11q13 in an islet cell sets the stage for NET development. Second, it seems to be the glucagon cell which is the islet cell type that is most responsive to hyperplastic and finally neoplastic stimuli. The reason why glucagon cells are particularly prone to these changes is yet not known.

Glucagon Cell Adenomatosis

Recently, glucagon cell adenomatosis (GCA) has been described as a neoplastic disease of the pancreas, that is preceded by glucagon cell hyperplasia of the islets [9, 10]. The disease is characterized by multiple microadenomas and single large tumors that are usually composed of glucagon cells and only occasionally of PP-cells. In this condition, which is unrelated to MEN1 or VHL and presents with elevated serum glucagon levels but usually without a glucagonoma syndrome [9], the glucagon cell hyperplasia of the islets imperceptibly transforms into glucagon cell neoplasia. The disease was found to be associated with an inactivating glucagon receptor (GR) germline mutation [10] (Sipos B et al., unpublished results). In our series of six patients, three showed a mutated GR gene and these three patients had the most pronounced pancreatic changes (Fig. 3). The suggestion that the GR mutation plays an important role in the initiation of the disease is supported by murine models, in which the deletion of the GR gene results in glucagon cell hyperplasia and finally neoplasia [11, 12]. Why three of our patients with GCA had a wild-type GR gene, is so far not known, but this observation may indicate that GCA is a heterogeneous disease.

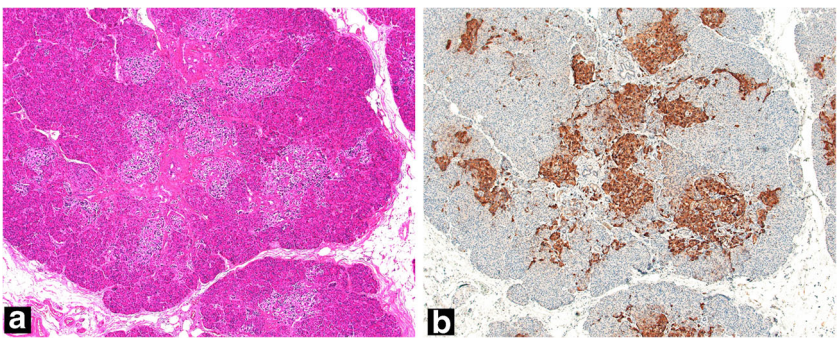

Fig. 4 Pseudohyperplasia of pancreatic polypeptide (PP) rich islets in the posterior portion of the head of the pancreas of a 75-year-old person. **a** H&E-stained section. **b** Consecutive section stained for PP

Insulinomatosis

Insulinomatosis is a neoplastic pancreatic disease in which, synchronously and metachronously, multiple small and single large insulin-producing tumors develop [13]. The affected patients present with hyperinsulinemic hypoglycemia which after removal of only the visible insulinomas typically recurs. It seems that the tumors are preceded by an insulin cell hyperplasia in the islets. So far, no genetic defect has been discovered and familiarity of the disease seems to be rare.

Microadenomatoses in Von Hippel–Lindau Disease

In Von Hippel–Lindau (VHL) disease, the pancreas may show multiple serous cystic neoplasms and/or neuroendocrine tumors, commonly positive for somatostatin. These tumors also appear to arise on a background of microadenomatosis [14]. It is not known so far whether the microadenomas evolve from a hyperplasia of islet cells.

Pseudohyperplasia of PP-Rich Islets

The dorsal portion of the head of the pancreas is densely populated by pancreatic polypeptide-cell rich islets (PPRI). This physiologic finding has often given rise to the false diagnosis of PP cell hyperplasia, although the "PP-lobe" in the pancreas has already been described in 1979 [15]. It was found that PP cells are not equally distributed in the human pancreas. They are abundant in the posterior part of the pancreatic head, where they account for 70–80 % of the islet cells ("PP-rich islets", PPRI) but scarce in the remaining gland. This distinct distribution of the PP cells in the pancreas is explained by the gland's complex ontogeny. The posterior portion of the pancreatic head that harbors the PPRI stems from the ventral pancreatic anlage, which accounts for approximately 10 % of the total pancreas parenchyma [16], while the remainder of the gland that contains the insulin-rich islets derives from the dorsal anlage. In subjects older than 50 years, the PPRI appear to be larger and more numerous because of a reduction of the surrounding acinar cells. The reason for this change is unclear, but it leads to pseudohyperplasia of the PPRI that may be misinterpreted as true hyperplasia or even neoplasia. Thus, the hyperplasia-like changes of the PP-lobe represent a normal condition in elderly people. In the literature, eight cases of "PP-cell hyperplasia" have been reported (for review see [17]). In retrospect, it seems that all these reports describe pseudohyperplastic PPRI aggregates in the pancreatic head. Why some of the cases were associated with a Zollinger–Ellison syndrome (ZES), or the syndrome of watery diarrhea, is not known. However, what is clear from the reports is that the pseudohyperplastic islet aggregates in the pancreatic head neither produced gastrin nor VIP and could therefore not have caused the syndrome, which in case of a ZES was most likely be due to a small gastrinoma in the duodenum [1].

Regarding the question why in elderly people PPRI cluster in pseudohyperplastic aggregates, it is of interest that insulin exerts a trophic effect on acinar cells (Fig. 4). This is known from the pancreas of type 1 diabetics with long lasting disease, which shows atrophic acinar cells surrounding the islets without insulin cells [18]. The islets of the PP-lobe still contain their insulin cells in elderly people, but as the insulin cells account only for 30 % of the islet cell population, this insulin cell number might not provide a sufficient lifelong trophic effect on all the surrounding acinar cells. The result might be a cellular and numeric atrophy of the acinar cells in the PP lobe resulting in a clustering of PPRI in elderly subjects. Since PP-cells and all other islet cells in the PPRI clusters strongly express somatostatin receptors, a signal may be recognized in somatostatin receptor scintigraphy that mimics the uptake associated with a tumor and may therefore lead to the false diagnosis of a pancreatic NET (Albers MB et al., Pancreatic polypeptide rich islets in the posterior portion of the pancreatic head—a tumor mimic in somatostatin receptor scintigraphy. Accepted for publication in The Pancreas 2013) [19].

Conclusions

There are distinct neuroendocrine diseases in the duodenum of the pancreas that show a hyperplasia–neoplasia sequence. Most of these diseases arise in the setting of genetic and hereditary syndromes such as MEN1, and the recently discovered glucagon cell adenomatosis associated with a mutation in the glucagon receptor gene. Diseases that may also follow a hyperplasia–neoplasia sequence are insulinomatosis and microadenomatosis in the pancreas of VHL patients. The clustering of islets rich in PP-cells in the dorsal portion of the pancreatic head is a physiological age-dependent change that shows no evolution into a hyperplasia–neoplasia sequence.

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