Endocrine Cell Hyperplasia

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21.1 Definition

The term 'endocrine cell hyperplasia' refers in fact to two separate groups of nonneoplastic disorders. The larger group encompasses several conditions in which the hyperplastic process affects the *entire endocrine cell compartment*, that is, the α-, β-, δ- and PP-cell populations. The second and much smaller group is characterized by hyperplasia of *only one specific endocrine cell type*. Thus far, endocrine cell hyperplasia of only a single cell type has been reported for the α-, β-, and PP-cell types. The group of hyperplastic disorders affecting all endocrine cell types usually represents an adaptive or secondary process, for instance in infants of diabetic mothers, or in erythoblastosis fetalis (see Chap. 13, Table 13.1). In contrast, for some of the endocrine cell hyperplasias affecting a single specific cell type, the underlying cause has been identified as a single-gene defect.

Histologically, both groups of hyperplastic processes show a similar picture that is characterized by a *diffuse* expansion of the endocrine cell compartment. The criteria for the histological diagnosis of endocrine cell hyperplasia are not well defined. An expansion of the endocrine cell mass by more than 2% in adults or 10% in infants has been proposed [1]. However, this definition is impractical in diagnostic practice. Currently, an islet size larger than 250 μm together with an increase in islet numbers is regarded by most as an acceptable definition of endocrine cell hyperplasia, provided the change is present diffusely throughout the pancreas. In addition, immunohistochemistry is required to identify the specific endocrine cell type(s) that are involved in the hyperplastic process.

Similar but *focal* hyperplastic changes affecting all endocrine cell populations are not uncommon incidental findings. In autopsy series they have been described in up to 10% of individuals, occasionally in association with endocrine microadenomas. Also to be distinguished from endocrine cell hyperplasia is the patchy, reactive enlargement and clustering of islets that is commonly seen in chronic pancreatitis. All four islet cells types are expanded, although sometimes there seems to be a preponderance of α- and PP-cells (Fig. 21.1) (see Chap. 7, Sect. 7.2.4).

A further differential diagnosis for endocrine cell hyperplasia is the endocrine microadenomatosis that occurs in patients with multiple endocrine neoplasia type 1 (MEN1) or von Hippel-Lindau syndrome. While in endocrine microadenomatosis each individual endocrine microadenoma usually has a dominant particular cell type (e.g., β-cells), the numerous tumors that are present throughout the pancreas are of varying cell types (e.g., α-, β-, δ-, PP-cells). Similarly, the diffuse hyperplasia of pancreatic endocrine cells that often accompanies endocrine microadenomatosis, also affects all endocrine cell types.

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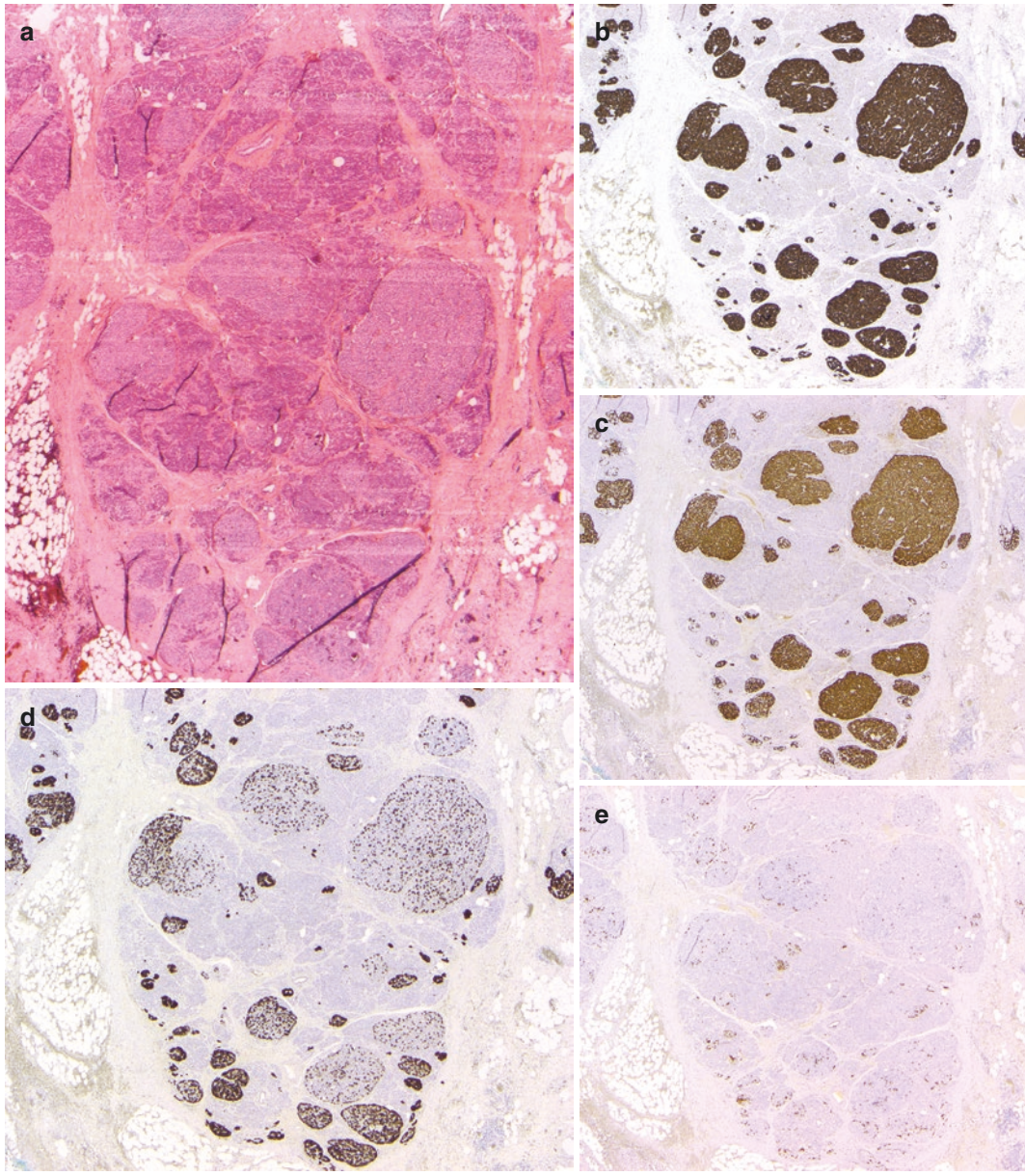

Fig. 21.1 Reactive islet enlargement with expansion of α-cells: enlarged islets, usually in the context of acinar atrophy, may be seen in various settings, including chronic pancreatitis (**a**: HE-staining, **b**: immunostaining for synaptophysin). Immunostaining shows a dominance of glucagon-producing α-cells (**c**) over insulin-producing β-cells (**d**) and somatostatin-producing δ-cells (**e**). Compare with the dominance of β-cells over α-cells in normal islets as shown in Fig. 1.19

Described below in more detail are three forms of endocrine cell hyperplasia of the pancreas in the strict sense, that is, the nonneoplastic processes characterized by hyperplasia of a single specific endocrine cell type. While these conditions are rare, the incidence differs depending on which specific endocrine cell type is affected: β-cell hyperplasia is significantly more frequent than hyperplasia of the α- or PP-cell population, of which only a few cases have been reported so

far. Equally different are the clinical signs and symptoms, the morphological features, and possible genetic aberrations of these three disorders. In none of the conditions is there evidence for an association with MEN1, MEN4, von Hippel-Lindau syndrome, neurofibromatosis type 1, or the tuberous sclerosis complex [2].

21.2 Beta-Cell Hyperplasia

Beta-cell hyperplasia is the morphological change seen in infants and neonates with persistent hyperinsulinemic hypoglycemia (PHIH) and in the rare condition found in adults with non-insulinoma-pancreatogeneous hypoglycemia (NIPH). The majority of PHIH patients show diffuse changes in size and shape of the islets, which still contain all endocrine cell types in a preserved spatial distribution but with an overall increase in the number of β-cells. In approximately a third of patients with PHIH, β-cell hyperplasia is focal and characterized by huge islet-like structures, which contain all types of endocrine cells, but lead to an overall increase in the proportion of β-cells (raised from the normal 50% to 70–90%). Distinction of both forms of PHIH is clinically important, because partial pancreatectomy is sufficient for patients with the focal form, whereas (sub-)total pancreatectomy is required for those with the diffuse form. Recent advances in genetics have linked congenital PHIH to mutations in 14 different genes that play a key role in regulating insulin secretion [3].

In adults, NIPH is characterized mainly by postprandial hypoglycemia (rather than the fasting hypoglycemia of patients with insulinoma). Islets have a preserved structure with normal distribution of all endocrine cell types, but the β-cells are more numerous, and the islets are increased in size and number. Unlike the β-cell hyperplasia found in infants and neonates, NIPH in adults is not associated with mutations of the ATP-sensitive potassium channel. Nesidioblastosis, which in the current strict morphological sense describes budding of endocrine cells (of any type, not only β-cells) from duct epithelium, is seen in both PHIH and NIPH. Neither NIPH nor PHIH has ever been observed in association with the development of pancreatic endocrine tumors, nor have these conditions been described in patients with MEN1 or von Hippel-Lindau syndrome.

Beta-cell hyperplasia must be distinguished from insulinomatosis, a disease characterized by the synchronous and metachronous occurrence of insulinomas, β-cell endocrine microadenomas, and small β-cell clusters in patients with insulinomatosis (see Chap. 20, Sect. 20.14).

21.3 Alpha-Cell Hyperplasia

Alpha-cell hyperplasia is part of the inherited autosomal recessive disorder glucagon cell hyperplasia and neoplasia, which is described in Chap. 20, Sect. 20.13 (see Fig. 20.32).

21.4 PP-Cell Hyperplasia

The morphological findings in PP-cell hyperplasia are similar to those described for α-cell hyperplasia, except that the hyperplastic cell population is of a PP-cell type (Fig. 21.2) [4, 5]. PP-cell hyperplasia is a diffuse process that affects the entire pancreas, and is therefore readily distinguished from the diffuse islets, which also contain an increased number of PP-cells but are confined to the posteroinferior part of the pancreatic head (see Chap. 1, Sect. 1.4.4). In most patients, PP-cell hyperplasia is an incidental finding in pancreatic specimens resected for other reasons. As serum PP levels have not been measured in most reported cases, it is currently not clear if PP-cell hyperplasia causes elevated PP levels. Some of the reported patients presented with diarrhea, but it is uncertain whether this is related to PP-cell hyperplasia. The etiology of this condition remains elusive so far.

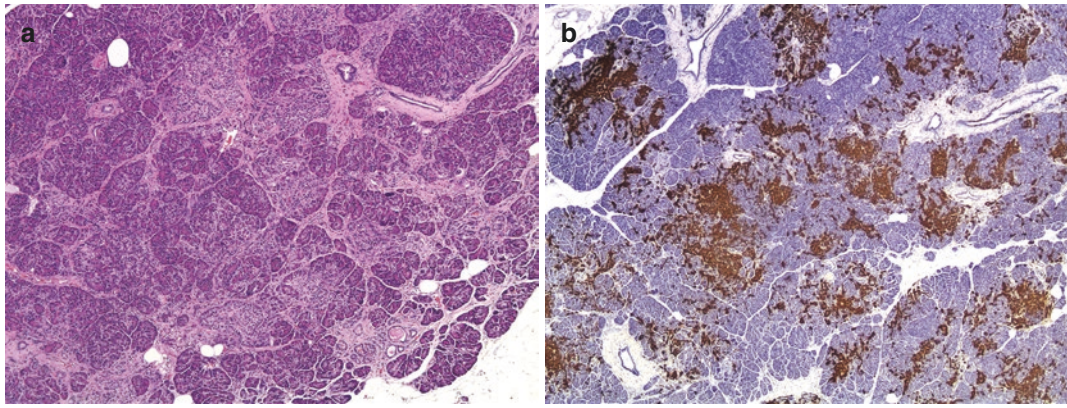

Fig. 21.2 PP-cell hyperplasia: numerous ill-defined and enlarged islets are present throughout the pancreatic tissue (**a**). Immunostaining illustrates the dominance of PP-cells within the expanded endocrine compartment (**b**)

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