17 Poorly Differentiated Neuroendocrine Carcinoma of the Pancreas

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17.1 Definition

In the current (2010) World Health Organization (WHO) classification system, pancreatic poorly differentiated neuroendocrine carcinomas (PD-NECs) are included in the grade 3 category along with well-differentiated neuroendocrine tumors (NETs) that have more than 20 mitoses per 10 HPFs or a Ki-67 index greater than 20 % [1]. This system suggests that PD-NECs are part of a continuum with well-differentiated NETs, and therefore the two entities are closely related, and that grade should be based entirely on proliferation rate. However, evolving evidence strongly suggests that morphologic differentiation is also relevant and that PD-NECs should be regarded as a separate entity [2–5], and as such they will be discussed separately.

PD-NECs of the pancreas are clinically highly aggressive, poorly differentiated carcinomas with neuroendocrine differentiation. They are characterized and defined by high mitotic activity (by definition more than 20 mitoses per 10 HPFs, and usually 40–50 per 10 HPFs) and usually exhibit necrosis, in addition to their distinctive morphology and high-grade cytology. Morphologically, some PD-NECs are almost identical to pulmonary small cell carcinomas, but others more resemble large cell neuroendocrine carcinomas. Immunoexpression of chromogranin and synaptophysin is typical and required for the diagnosis of large cell neuroendocrine carcinoma [6–8].

17.2 Clinical Features

Primary pancreatic PD-NECs are extremely rare, accounting less than 1 % of all pancreatic carcinomas [9] and at most 2–3 % of all pancreatic neuroendocrine neoplasms [6].

Most patients are in their late 50s and there is a slight male predilection. In contrast to pancreatic well-differentiated NETs, the PD-NECs are not associated with hereditary syndromes and are usually clinically nonfunctioning [3], although individual cases with paraneoplastic syndromes such as carcinoid syndrome [10], Cushing syndrome [11], hypercalcemia [12], or hyperinsulinism [3] have been reported. The patients present with symptoms similar to those of exocrine pancreatic neoplasms such as back pain, weight lost, and jaundice, due to obstruction of the common bile duct.

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17.3 Pathologic Features

PD-NECs are more common in the head of the pancreas and present as a large (median tumor size of 4 cm), relatively circumscribed, tan-yellow, fleshy mass. Hemorrhage and necrosis are common [3].

Morphologically, these poorly differentiated carcinomas are subdivided into small and large cell variants, based on cell size. The small cell variant (small cell carcinoma) is characterized by small to intermediate cells with finely granular chromatin, high nucleus-to-cytoplasm ratio, inconspicuous nucleoli, prominent nuclear molding, and crush artifact (Fig. 17.1). These carcinomas display predominantly a diffuse, sheetlike growth pattern with confluent areas of necrosis and entrapment of pancreatic parenchyma [3, 13, 14]. Scattered tumor giant cells with hyperchromatic, bizarre nuclei or rosettes may be seen in some tumors. In a recent series of 44 histologically confirmed primary pancreatic PD-NECs, the average mitotic count and Ki-67 labeling index of small cell carcinomas were found to be 51 per 10 high power fields and 75 % (Fig. 17.2), respectively [3].

The large cell variant (large cell neuroendocrine carcinoma) is more common and characterized by large cells with prominent nucleoli and variable amounts of cytoplasm. Diffuse, nested, trabecular, gland-forming, and peripheral palisading growth patterns, often intermingled in varying proportions, are seen in most large cell neuroendocrine carcinomas (Fig. 17.3). Some tumors display pseudopapillae, composed of viable tumor cells surrounding fibrovascular cores, usually at the periphery of necrotic areas. Apoptotic cells and mitotic figures are abundant, but mitotic figures in the large cell neuroendocrine carcinomas are usually not as numerous as in the small cell carcinomas. In the aforementioned study, the average mitotic count and Ki-67 labeling index of large cell neuroendocrine carcinomas were found to be 37 per 10 high power fields and 66 %, respectively [3].

In cases with the typical cytologic features of small cell carcinoma, it is not necessary to document neuroendocrine differentiation by immunohistochemistry, provided alternative diagnoses (primitive neuroectodermal tumor, desmoplastic small round cell tumor, etc.) can be excluded. However, for large cell neuroendocrine carcinomas, positive immunohistochemical staining for chromogranin or synaptophysin should be obtained to confirm the diagnosis [1, 6, 15], although the extent and intensity of staining are usually less than in well-differentiated NETs of the pancreas.

Some PD-NECs may be associated with exocrine pancreatic neoplasm component, in the form

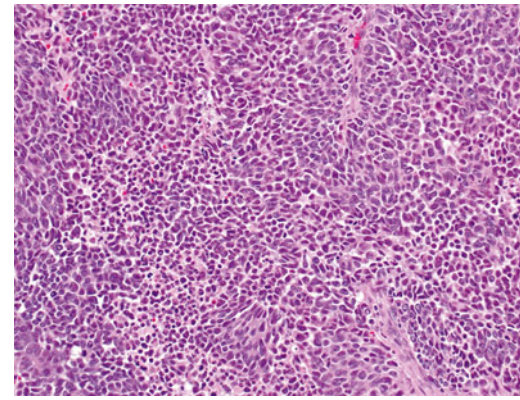

Fig. 17.1 Small cell carcinomas are characterized by loosely arranged sheets of small cells with a high N:C ratio, hyperchromatic and finely granular chromatin, inconspicuous nucleoli, and nuclear molding. High mitotic activity and necrosis are also present

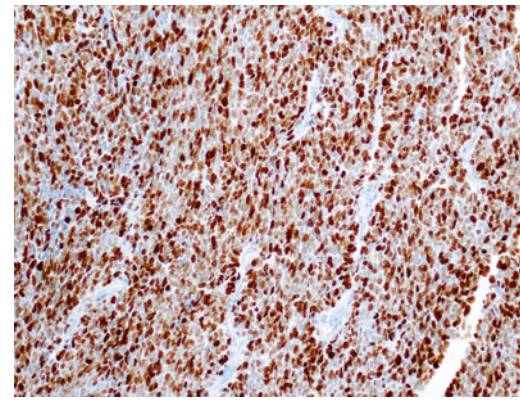

Fig. 17.2 Ki-67 labeling index of poorly differentiated neuroendocrine carcinomas is much higher than the WHO-recommended threshold (>20 %) for the grade 3 category. A small cell carcinoma with >95 % Ki-67 labeling index is depicted here

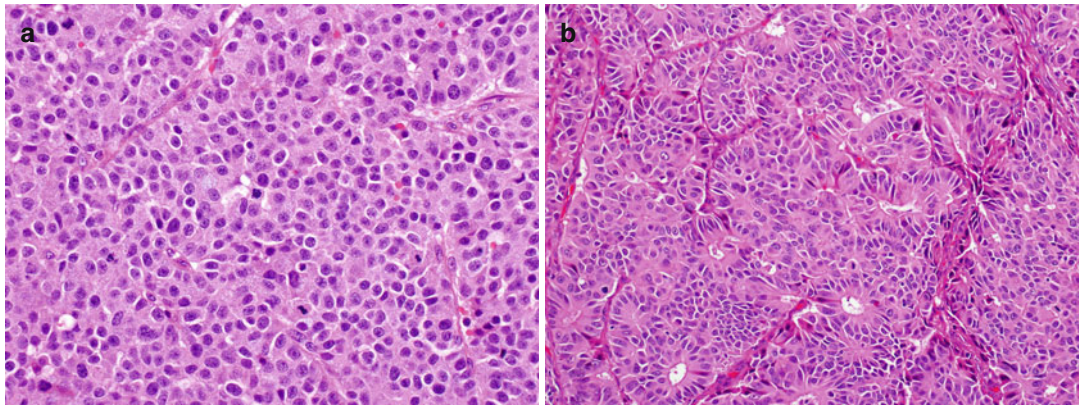

Fig. 17.3 Large cell neuroendocrine carcinoma may reveal various growth patterns (**a**, trabecular; **b**, gland-forming pattern). Compared to small cell carcinoma, their cells are larger and round to polygonal with round nuclei that have vesicular chromatin or prominent nucleoli

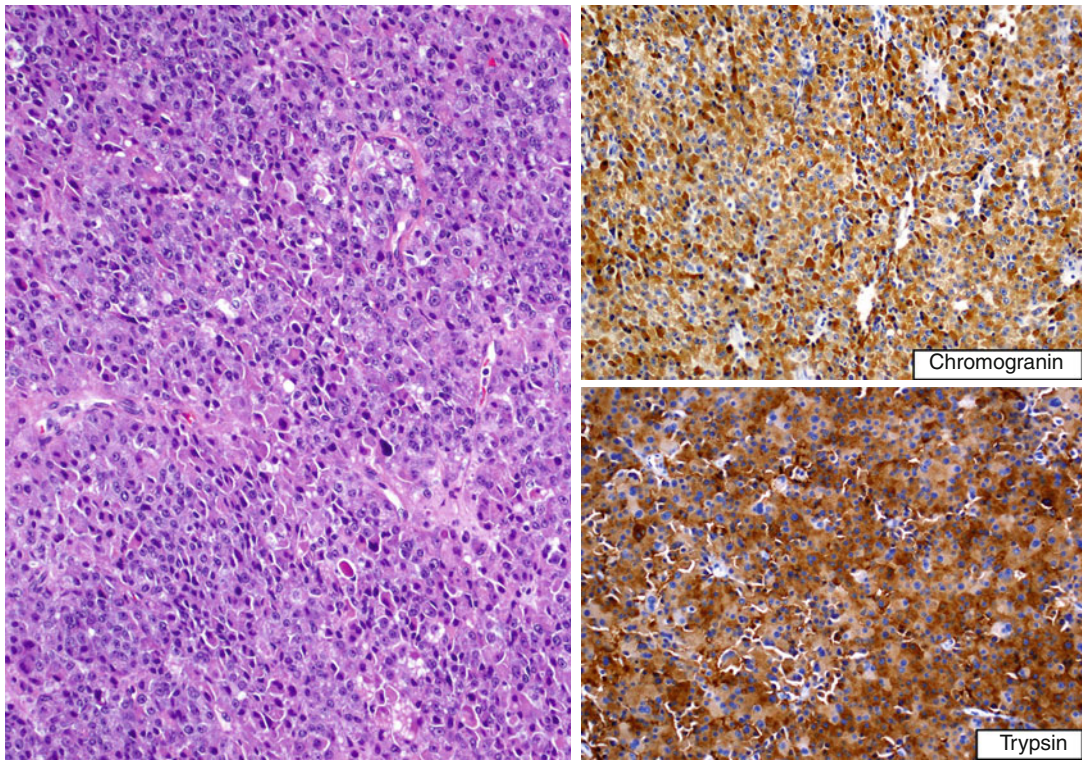

Fig. 17.4 Mixed acinar-neuroendocrine carcinomas are usually composed of morphologically homogenous population of cells, and the divergent differentiation cannot be detected without immunohistochemical labeling for both neuroendocrine and acinar differentiation markers (chromogranin and trypsin immunohistochemical stains are depicted here)

of acinar cell carcinoma (Fig. 17.4) or in the form of ductal adenocarcinoma (Fig. 17.5), intraductal papillary mucinous neoplasm, or even squamous cell carcinoma [1, 3, 6, 16–19]. The 2010 WHO classification system recommends that at least 30 % of either component be present in order to qualify a tumor as "mixed carcinoma" [1], although the figure of 25 % has also been

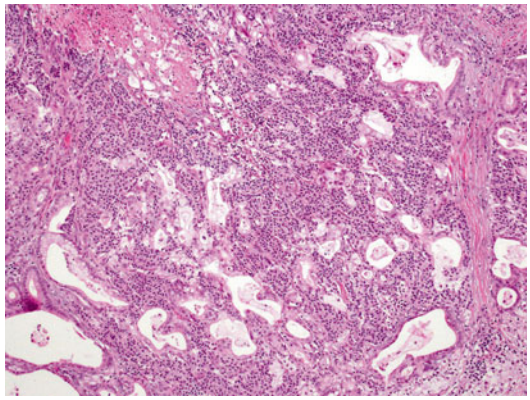

Fig. 17.5 In contrast to mixed acinar-neuroendocrine carcinomas, different components are morphologically recognizable in mixed ductal-neuroendocrine carcinomas, even if they are intimately admixed as illustrated here, as gland formations and presence of abundant intracellular mucin are striking

advocated in the AFIP fascicle on tumors of the pancreas [6].

In mixed ductal- or squamous-neuroendocrine carcinomas, different components, sharply segregated or intimately admixed, are usually morphologically recognizable (Fig. 17.4). Of note, PD-NECs, especially large cell neuroendocrine carcinomas, with gland formations should not be mistaken for mixed ductal-neuroendocrine carcinomas. Absence of detectable mucin and careful attention to the cytologic appearance aid in proper diagnosis in the former (see Chap. 18 for detailed discussion). In contrast, mixed acinar-neuroendocrine carcinomas display less segregation of the two cell types (Fig. 17.4). In fact, in most cases, it is not possible to recognize with certainty that two lines of differentiation are present without immunohistochemical staining for both neuroendocrine and acinar differentiation markers [3, 6, 19]. If only neuroendocrine staining is performed, these cases can be misinterpreted as neuroendocrine carcinomas. Therefore, it is not surprising that many cases that are diagnosed as PD-NECs prove to be mixed acinar-neuroendocrine carcinoma once studied more carefully [3, 19].

On cytology, small cell carcinoma is characterized by often crushed, small- to intermediate-sized tumor cells with irregular nuclear borders, high nucleus-to-cytoplasm ratio, and nuclear molding. In addition to brisk mitotic activity, there is extensive single-cell and background necrosis. For large cell neuroendocrine carcinoma, tumor cells are usually larger with variable cytoplasm as well as prominent central nucleoli. However, these tumors may resemble a poorly differentiated adenocarcinoma and may not show the classical coarsely clumped chromatin of well-differentiated NETs or the nuclear molding of their small cell counterpart. If a neuroendocrine carcinoma is not suspected at the time of evaluation, the diagnosis may be easily missed [20].

17.4 Differential Diagnosis

Primary pancreatic PD-NECs are extremely rare and must be distinguished from metastatic PD-NECs from another organ or direct invasion from a contiguous site, particularly the ampulla of Vater [21] or stomach. When there is a single mass in the pancreas and, after critical evaluation, no convincing clinical, radiographic, or pathologic evidence of a lung primary (or another site), then pancreatic origin is reasonable. It should be kept in mind that TTF1 immunohistochemical staining is not helpful, as small cell carcinomas from both pulmonary and a variety of extrapulmonary sites are TTF1 positive. Clinical information and a history of a previous carcinoma are especially important in the accurate diagnosis of such cases.

Pancreatic well-differentiated NETs can show significant nuclear pleomorphism or small cell change (high nuclear/cytoplasmic ratio resembling small cell carcinoma) [22], and features such as a markedly infiltrative growth pattern and necrosis can also be identified [6]. On casual examination, these findings falsely suggest a PD-NEC. If thorough mitotic counting as well as immunolabeling for Ki-67 are not performed, misclassification can occur, which can have therapeutic consequences [2, 23]. A recent landmark study has shown that not all patients with a grade 3 NEC defined based on WHO 2010 criteria benefit from the platinum-based chemotherapy typically used for PD-NECs. In this study, grade 3

tumors with a Ki-67 index <55 % were less responsive than grade 3 NECs with a Ki-67 index ≥55 %, although the latter group experienced early recurrence of shorter ultimate survival than the group with a Ki-67 in the 20–55 % range [2], supporting the concept that the 2010 WHO grade 3 category is heterogeneous, and the tumors at the lower end of the grade 3 range are in fact well-differentiated NETs with an elevated proliferation rate. These well-differentiated NETs typically have a Ki-67 index around 40 %, whereas PD-NECs' Ki-67 index is about 70 % [3, 4]. Also, a recent study has shown that most pancreatic PD-NECs abnormally immunolabel for p53 (nuclear expression) and Rb (loss of expression) in 95 % and 74 % of cases, respectively. In that study, the abnormal expression of these proteins correlated with intragenic mutations in the *TP53* and *retinoblastoma* genes coding for these proteins. By contrast, immunohistochemical studies only detect rare p53 abnormalities and Rb immunolabeling is intact in pancreatic well-differentiated NETs [5, 24]. In addition, approximately 45 % of sporadic pancreatic well-differentiated NETs show mutually exclusive loss of expression of DAXX (death-domain-associated protein) or ATRX (α-thalassemia/mental retardation syndrome X-linked) immunohistochemical stains, which correlates with mutations in the *DAXX* and *ATRX* genes [5, 25] (see Molecular Pathology section for more details).

As discussed above, the distinction of acinar cell carcinoma and mixed acinar-neuroendocrine carcinomas from PD-NECs is also problematic [3]. Both entities usually have a high proliferation rate; acinar cell carcinomas can have a diffuse growth pattern and, along with large cell neuroendocrine carcinomas, can have prominent nucleoli. The correct diagnosis may not be established without immunohistochemical evaluation using acinar and neuroendocrine differentiation markers. Given the rarity of primary pancreatic PD-NECs, relative to acinar neoplasms, it is thus recommended that a diagnosis of PD-NEC should not be rendered unless acinar differentiation has been excluded immunohistochemically.

The crushed and molded tumor cells of small cell carcinoma may resemble a high-grade lymphoma. Morphologic distinction is often impossible and immunohistochemistry is required for diagnosis. Other small, round, blue cell tumors, such as primitive neuroectodermal tumor (PNET) and desmoplastic small round cell tumor, may also involve the pancreas primarily or secondarily and need to be distinguished from small cell carcinoma, especially in younger patients [14]. PNETs generally have small, round, monotonous nuclei with inconspicuous nucleoli and scant cytoplasm, although pancreatic examples can be more epithelioid and can express keratin strongly [14]. The proliferation rate is variable but can overlap with that of PD-NEC. Immunolabeling for CD99 can be helpful, since most PNETs show strong, diffuse membranous staining. CD99 does label a subset of well-differentiated NETs of the pancreas, however. In questionable cases, molecular studies can be performed to search for the diagnostic [t(11;22)] translocation of PNETs [14, 26].

17.5 Molecular Pathology

Recently, pancreatic small cell carcinomas and large cell neuroendocrine carcinomas were shown to be genetically related but distinct from pancreatic well-differentiated NETs. The genetic changes frequently seen in these poorly differentiated carcinomas, such as inactivation of the TP53 and the retinoblastoma/p16 pathways [5], are rarely observed in well-differentiated NETs, with only 4 % of well-differentiated NETs revealing a mutation in the *TP53* gene and none in the *retinoblastoma* gene [25]. In addition, immunohistochemical studies only detect rare p53 abnormalities in well-differentiated NETs [5, 24]. Of note, dysregulation of the TP53 pathway – through aberrant activation of its negative regulators (MDM2, MDM4, and WIP1) – may still be involved in pancreatic well-differentiated NETs as gene amplification and protein overexpression of these negative regulators are detected in some pancreatic well-differentiated NETs [24]. Conversely, approximately 45 % of sporadic pancreatic well-differentiated NETs harbor mutually exclusive mutations in either *DAXX* (death-domain-associated protein) or

ATRX (α-thalassemia/mental retardation syndrome X-linked) genes [25]. *DAXX* and *ATRX* encode nuclear proteins, which form a chromatin remolding complex and are involved in chromatin remolding at telomeric and pericentromeric regions. Mutations of these genes are associated with loss of DAXX/ATRX protein expression.

Of note, BCL2 protein, which is overexpressed in small cell carcinoma of the lung, is also overexpressed in PD-NECs (100 % of small cell carcinoma and 50 % of large cell neuroendocrine carcinomas) but is variably expressed in well-differentiated NETs [5].

17.6 Prognosis

The clinical course of pancreatic PD-NECs is worse than that of morphologically well-differentiated NETs that would be classified as 2010 WHO grade 3 on the basis of proliferation rate [4]. Most cases are rapidly fatal with widespread metastases involving regional and distant lymph node as well as intra- and extra-abdominal organs such as the liver and lung [2, 3]. Cisplatin- and etoposide-based regimens have shown some promise in controlling their growth; however, their overall prognosis remains grim [2, 27–30] with a median survival of 11 months [3]. Of note, there is no difference in survival among the morphologic subtypes of PD-NEC (small cell carcinoma vs. large cell neuroendocrine carcinoma) [2, 3]. The recent demonstration of BCL2 overexpression by PD-NECs [5] suggests that BCL2 antagonists may prove useful in their treatment in a manner similar to their current use in small cell carcinoma of the lung, which also expresses BCL2.

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