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High-Grade Poorly Differentiated Neuroendocrine Carcinomas of the Gastroenteropancreatic System: from Morphology to Proliferation and back

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Abstract Poorly differentiated neuroendocrine carcinomas (PDNECs) of the gastroenteropancreatic system (GEP) are a heterogeneous group of aggressive malignancies with a high propensity for distant metastases and an ominous prognosis. They have traditionally been divided into small and large cell subtypes on morphological grounds. However, histological diagnosis needs to be supported by immunohistochemistry to avoid possible misdiagnoses either with the more frequent poorly differentiated adenocarcinomas and squamous cell carcinomas or with lymphomas and mesenchymal neoplasms. Although it is well known that GEP PDNECs are associated with a poor prognosis, data from some published studies seem to suggest that there is a fraction of patients with PDNECs who have better survival than expected. GEP PDNECs are currently classified according to the criteria proposed in the 2010 WHO classification. They are simply called neuroendocrine carcinomas (NECs) and are defined by mitotic count >20×10 HPF and/or Ki-67 labeling index >20 %. However, a few recent papers have indicated that some NECs, as defined by the 2010 WHO scheme, do not show a poorly differentiated morphology as expected. This category seems to show a better prognosis and, especially, does not respond to cisplatin-based chemotherapy, which represents the goal standard therapeutic approach to high-grade PDNECs. In the present review, the main morphological, immunohistochemical, and prognostic features will be discussed as well as the opportunity to introduce a new category characterized by well to moderately differentiated morphology associated with high proliferation (mitotic count >20×10 HPF and/or Ki-67 index >20 %).

Keywords Neuroendocrine carcinoma · Small cell carcinoma · Large cell neuroendocrine carcinoma · Neuroendocrine tumor · Classification

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Background

The group of gastroenteropancreatic (GEP) neuroendocrine neoplasms includes a wide spectrum of neoplastic proliferations ranging from low-proliferative well-differentiated neuroendocrine tumors (NETs) at one extremity to high-grade poorly differentiated neuroendocrine carcinomas (PDNECs) composed of atypical cells with high mitotic and Ki-67 proliferative indices at the other. Well and poorly differentiated neuroendocrine neoplasms are generally considered and grouped together because their expression of general neuroendocrine markers is similar, but they are completely different in terms of clinical presentation, prognosis, and genetic background. Interestingly, recent findings have suggested that PDNECs show a non-neuroendocrine lineage and are not as closely related to well-differentiated NETs as expected [1, 2]. Consequently, the different response to medical therapy, which leads to different therapeutic approaches between NETs and PDNECs, is not surprising. Indeed, the former should be surgically resected whenever possible in addition to the treatment with somatostatin analogs, with temozolamide or, as more recently proposed, with everolimus and sunitinib [3, 4], while the latter are generally managed with platinum-based chemotherapy [5, 6], avoiding surgery in most cases.

Distinguishing between well and poorly differentiated neuroendocrine neoplasms is generally easy on morphological grounds, while the differential diagnosis between PDNECs

and poorly differentiated non-neuroendocrine carcinomas (i.e., squamous cell carcinoma and adenocarcinoma), lymphomas, or mesenchymal neoplasms can sometimes be difficult. In about 40 % of the cases, PDNECs contain non-neuroendocrine components including adenocarcinoma, signet ring cell carcinoma and, more rarely, squamous cell carcinoma [7]. However, by definition, the diagnosis of mixed exocrine-neuroendocrine carcinomas, which were renamed with the term mixed adenoneuroendocrine carcinomas (MANECs) in the 2010 World Health Organization (WHO) classification, refers to tumors in which both neuroendocrine and non-neuroendocrine components represent at least 30 % of the tumor tissue [8, 9].

Morphological Features

PDNECs of the GEP system are high-grade malignant cancers with a high propensity for distant metastases and an ominous prognosis. They represent a heterogeneous group of very aggressive malignancies which show morphological and clinical features similar to those of the more frequent pulmonary PDNECs. Similarly to the lungs, during the last few decades, they have traditionally been divided into the small and large cell subtypes, based on the morphological features of the neoplastic cells, even though cells of an intermediate size are also frequently found [8, 9]. Small cell carcinoma was the first category described in both pulmonary and gastrointestinal tract. For this reason, most of the published literature on extra-pulmonary PDNECs is focused on small cell carcinoma. In contrast, the large cell subtype, which has only recently been accurately described in the gastrointestinal tract [10–12], has been less frequently reported. It is worth noting that, in several cases, various combinations of both small and large cells can be observed, and the term of "mixed type" has been proposed for this category [11]. Interestingly, there is no apparent difference in prognosis among these subgroups of PDNECs [11–14].

Small cell carcinomas (Fig. 1) are composed of small- to medium-sized (2–4 times of lymphocyte size), round to oval cells with scant cytoplasm and hyperchromatic nuclei with indistinct nucleoli. Large cell subtypes (Fig. 2) are composed of large cells with vesicular nuclei showing prominent nucleoli and abundant eosinophilic cytoplasm. In both cases, tumor cells grow forming sheets or large nests (Fig. 1), although in the large cell subtype, a more structured trabecular or organoid architecture is frequently observed (Fig. 2). PDNECs show deep infiltration of the bowel wall or the peripancreatic tissue (in the pancreas) and are frequently metastatic when diagnosed. Large and, sometimes, confluent areas of necrosis, high mitotic count and perineural and vascular invasion are frequently observed. In some cases, moderate to abundant peritumoral lymphoid infiltration has been described, and this seems to be associated with better survival [12].

Immunohistochemical Profile

The histological diagnosis of PDNEC needs to be supported by immunohistochemical evidence of its neuroendocrine nature to avoid possible misdiagnoses either with the more frequent poorly differentiated adenocarcinomas and squamous cell carcinomas or with lymphomas and mesenchymal neoplasms. The first immunohistochemical approach to carcinomas with morphological features suggesting a neuroendocrine phenotype should include antibodies directed against general neuroendocrine markers, while the use of antibodies recognizing specific hormones and amines could also be considered as an additional investigation, since these specific markers are rarely expressed in PDNECs [15]. This choice depends on considering the whole clinical endocrine picture since PDNECs can develop ectopic endocrine syndromes including Cushing's syndrome due to ACTH secretion [16].

There are several commercially available antibodies directed against general neuroendocrine markers including synaptophysin, chromogranins, CD56, PGP 9.5, and neuron-specific enolase (NSE). In our routine practice, we generally use synaptophysin and chromogranin A together because they are highly specific and sensitive. Care must be taken to use chromogranin A alone because it can be only focally positive. To avoid diagnostic pitfalls, it must be employed together with synaptophysin, which is expressed intensely and diffusely in all PDNECs. We do not generally use NSE, PGP 9.5, and CD56 because, although they have good sensitivity, they are not highly specific since they are expressed in other types of non-neuroendocrine neoplasms [17, 18].

In recent years, several attempts have been made to search for site-specific markers to use in the diagnostic pathway of metastases from occult neuroendocrine neoplasms. A significant number of relatively new indicators have been identified, and they are mainly represented by transcription factors involved in the development of neuroendocrine cells during fetal life. CDX2 is a good marker of midgut origin [19, 20], TTF1 is expressed in a subset of lung carcinoids [21], PDX1 seems to be a good marker of pancreatic origin [22] as well as ISL1 [23], although the latter has also been identified in NETs of rectal origin [24]. This group of recently investigated transcription factors works relatively well in the identification of the primary site of well-differentiated NETs. However, they must be used with extreme caution in the search for the primary site of an occult PDNEC, since TTF1 expression can be frequently detected in extra-pulmonary PDNECs [21], while CDX2 immunoreactivity can also be found in lung PDNECs, especially in the large cell subtype [20]. ISL1, commonly considered as a marker of pancreatic origin, has recently been found in several extra-pancreatic PDNECs [25]. The expression of the transcription achaete-scute homolog 1 (ASH1) has also recently been investigated in a large series of lung and extra-pulmonary PDNECs with the aim of using it as a

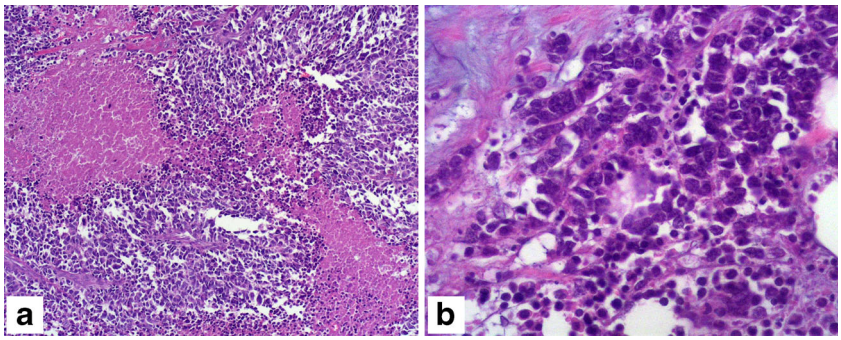

Fig. 1 Small cell neuroendocrine carcinoma of the colon characterized by sheets of neoplastic cells in which abundant necrosis is well evident (**a**). Tumor cells are round to oval, small- to medium-sized (2–4 times of lymphocyte size) with scant cytoplasm and hyperchromatic nuclei with indistinct nucleoli (**b**)

marker of lung origin since ASH1 is involved in the development of fetal lung neuroendocrine cells [26]. However, as it has been observed for other transcription factors, ASH1 expression was found in both lung and extra-pulmonary PDNECs. Interestingly, in this study, ASH1 expression was almost exclusively restricted to PDNECs while it was lacking in NETs, with the only exception of rare lung carcinoids showing a focal and faint immunoreactivity. For this reason, ASH1 has been proposed as a marker of poor differentiation rather than a marker of lung origin [26]. ASH1 immunohistochemistry may be a useful tool in the diagnostic pathway of small bioptic specimens when morphology alone is not sufficient to make a diagnosis of PDNEC. Similarly, the immunoreactivity of other markers can help in the correct diagnosis of difficult cases, especially in bioptic specimens with small amount of available diagnostic material. The expression of TTF1 in gastric or intestinal bioptic specimens may suggest the diagnosis of PDNEC, because TTF1 immunoreactivity in gastrointestinal or pancreatic NETs is practically absent. The expression of p53 can also help, because it can be frequently observed in GEP PDNECs while it is rather rare in NETs [2, 12, 27].

Prognostic Markers

Although it is well known that GEP PDNECs are high-grade cancers associated with a poor prognosis [6], data from a few published studies [11, 12, 28] and from anecdotal experience seem to suggest that there is a fraction of patients with PDNECs who have a better survival rate than expected. However, it is difficult to identify this small group of patients. Recently, markers that may help in identifying these cases have been proposed for colonic PDNECs. The immunohistochemical expression of CD117 was found to be associated with a much worse outcome in both univariate and multivariate analyses [12], and this finding has recently been confirmed by our group in a large series of GEP PDNECs including more than 100 cases of different sites (unpublished results). Interestingly, c-kit gene mutation in CD117 immunoreactive colorectal PDNECs has never been demonstrated [29, 30], suggesting that, in this cancer subset, CD117 overexpression is not mediated via activating mutations and that imatinib mesylate (Glivec) therapy is not useful in these patients [31]. On the contrary, our group has recently demonstrated that the simultaneous presence of microsatellite instability (MSI) and widespread gene methylation is a predictor of better outcome in patients with colorectal PDNECs, suggesting that the identification of this molecular subset may help in the prognostic stratification of patients [12]. Interestingly, this specific molecular category of PDNECs showed peculiar morphological and immunohistochemical features, including large cell subtype, abundant peritumoral lymphoid infiltrate, and lack of both histologically documented vascular invasion and CD117 expression. Among these parameters, peritumoral lymphoid infiltration seems particularly interesting because it indicates that a host lymphoid response to a tumor may play a pivotal role in the biology of such cancers as has already been demonstrated in patients with colorectal adenocarcinomas [32]. There is a good correlation of MSI with the immunohistochemical loss of MLH1 protein, suggesting that immunohistochemistry for the mismatch repair proteins (MLH1, MSH2,

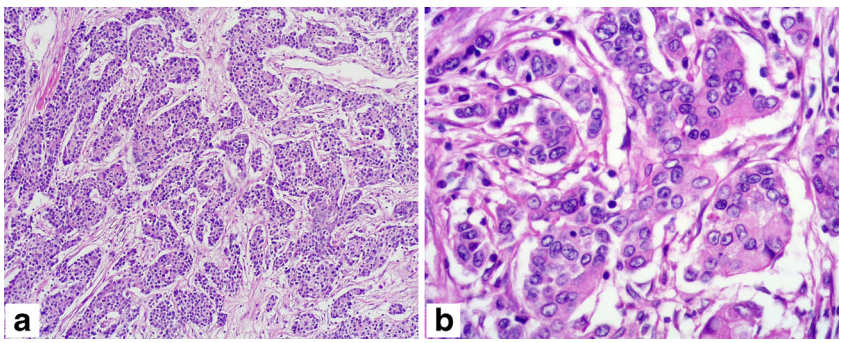

Fig. 2 This large cell neuroendocrine carcinoma showing trabecular architecture (**a**) is composed of large cells with vesicular nuclei showing prominent nucleoli and abundant eosinophilic cytoplasm (**b**)

MSH6, and PMS2) should be included in the diagnostic panel to identify unstable carcinomas potentially correlated with a better prognosis.

The 2010 WHO Classification

The 2010 WHO classification of digestive neoplasms redefined the terminology to classify neuroendocrine neoplasms of the gastrointestinal tract and pancreas [9]. In such a classification, which is derived from the European Neuroendorcrine Tumor Society (ENETS) scheme published in 2006 [33], the proliferative activity represents the most important tool for classifying neuroendocrine neoplasms in three distinct clinicopathologic categories, while morphological features reduced their diagnostic impact with respect to the previous WHO classifications [8, 34]. Following this new scheme, neuroendocrine neoplasms have been divided into three groups (Table 1): G1 NET, G2 NET, and neuroendocrine carcinoma (NEC) that, by definition, are grade 3 (G3) neoplasms. This last category should correspond to the previously defined PDNEC category. In general, both G1 and G2 NETs correspond to the previous well-differentiated NET (both benign and uncertain behavior categories) and well-differentiated neuroendocrine carcinoma categories. It is worth noting that there is no strict relationship between G1 and G2 NETs and the categories of the previous classification. Indeed, G1 NETs do not necessary correspond to well-differentiated NETs of the previous classification just as G2 NETs do not strictly correspond to well-differentiated neuroendocrine carcinomas. In other words, G1 NETs can correspond to both well-differentiated NETs and well-differentiated neuroendocrine carcinomas of the 2000 and 2004 WHO classifications like G2 NETs. This has recently been demonstrated for NETs of the stomach [35] and appendix [36].

Open Questions and Future Perspectives

Although the 2010 WHO classification has the great advantage of being easier to use than the previous one, especially for the diagnosis of low and intermediate malignant tumor types, it seems to present some difficulties in adequately recognizing the so-called NEC category. This is mainly due to the fact that NECs are neoplasms that, by definition, show a wide range of proliferation with a Ki-67 index ranging from 20 to 100 % and a mitotic index >20 mitoses×10 HPF, independently of the morphological picture. The observation that some tumors showing a well to moderately morphological differentiation together with a Ki-67 index higher than 20 % has appeared since the beginning of the application of the 2010 WHO classification in routine practice, and a few papers have described and reported this possible discrepancy. In the stomach, these tumors were defined as histologically moderately differentiated with high proliferation [35], while, in the pancreas, they were defined as neuroendocrine neoplasms G3 and separated from neuroendocrine carcinomas [25]. These studies only described the dichotomy between morphology and proliferation without studying, in detail, the clinical and therapeutic features of this intermediate category.

This topic has recently been investigated by at least three research teams, and three interesting studies (two papers and one abstract) have been reported in the English literature. Basturk et al. [37] demonstrated that pancreatic neuroendocrine neoplasms showing a G2 mitotic count (2–20 mitoses× 10 HPF) but a G3 Ki-67 proliferative index (>20 %) were associated with a statistically (p=0.017) better behavior than G3 tumors characterized by both >20 mitoses×10 HPF and >20 % Ki-67 index. Similar results were found by Vélayoudom-Céphise et al. [38] who investigated a series of 28 cases of neuroendocrine neoplasms with a Ki-67 proliferative index >20 % in which 12 showed a well-differentiated morphology and 16 a poorly differentiated morphology resembling large cell neuroendocrine carcinomas. These authors first classified tumors morphologically following the criteria proposed for lung [39] and GEP neuroendocrine neoplasms [8]. They did not find a significant difference in the overall survival between the two categories (p=0.34). However, they more rarely observed a short survival (<2 years) in G3 well-differentiated NETs (25 % of the cases) than in G3 large cell neuroendocrine carcinomas (62.5 % of the cases, p=0.049). An important finding of this study was represented by the fact that patients with G3 well-differentiated NETs did not show a response to cisplatin-based chemotherapy in contrast to high-grade large cell neuroendocrine carcinomas [38]. The different response to cisplatin-based chemotherapy was also found by Sorbye et al. who observed a statistical difference in survival and response to therapy when NECs were divided into two categories using a cutoff of 55 % for the Ki-67 index [40]. In particular, patients bearing gastrointestinal neuroendocrine neoplasms with less than 55 % had a significant longer survival (p<0.05), even if it was only 4 months, than patients with highly proliferative neoplasms (Ki-67>55 %). More interestingly, these patients were also less responsive to chemotherapy resembling the patients with G3 well-differentiated NETs described by Vélayoudom-Céphise et al. [38].

Taken together, all these new findings suggest that high-proliferative activity, as defined by G3 grading according to the ENETS and 2010 WHO proposals, should not be

Table 1 2010 WHO classification [9]

	Mitoses	Ki-67 (%)
NET G1	<2	≤2
NET G2	2–20	3–20
NEC	>20	>20

NET neuroendocrine tumor, *NEC* neuroendocrine carcinoma

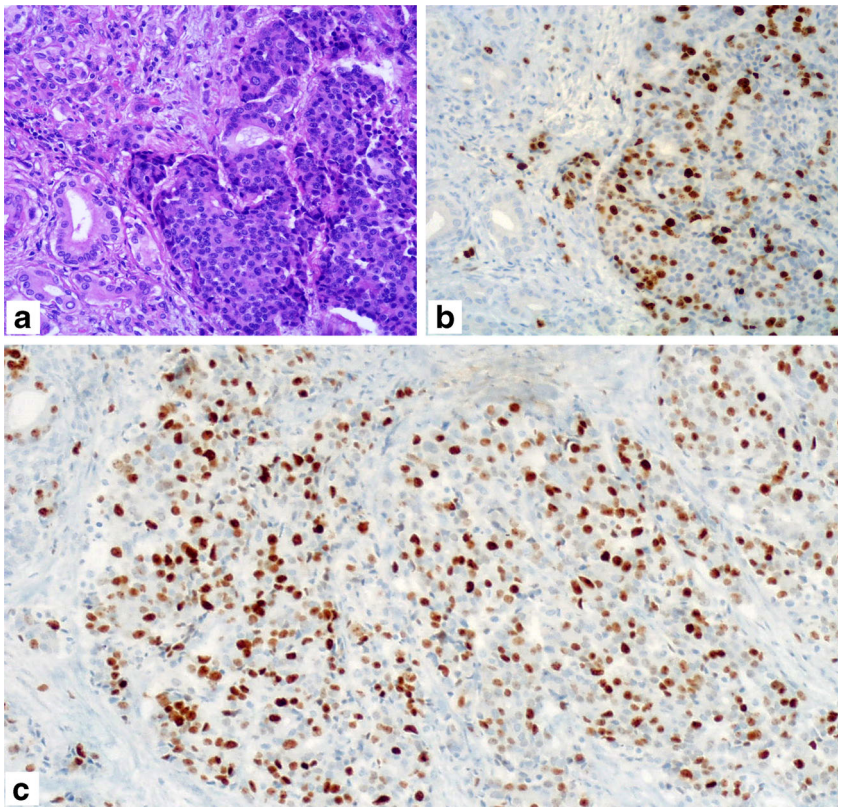

Fig. 3 Pancreatic neuroendocrine tumor showing a well-differentiated morphology (**a**) associated with a Ki-67 index higher than 20 % (**b**). In panel **c**, a lower power view is shown to better demonstrate the high Ki-67 labeling index

considered per se as synonymous of poorly differentiated NEC. This implies that proliferation alone is not sufficient for the classification of high-grade neuroendocrine neoplasms and we need to go back to morphology and add it to proliferative indices to correctly classify these neoplasms. A new category of high-grade NENs defined by the combination of G3 proliferation grade and well to moderately differentiated morphological features (Fig. 3) should be created and separated from neoplasms showing the typical morphological features of either small or large cell neuroendocrine carcinomas. Although the prognostic meaning of this distinction needs to be validated in large tumor series, data so far reported seem to suggest that this difference is mainly important for the choice of chemotherapy treatment. The evaluation of the immunohistochemical pattern of chromogranin A reactivity has recently been proposed as an additional useful tool to help in the differential diagnosis between high-grade PDNECs and NETs with high proliferation [14]. Indeed, chromogranin A is generally focal with a dot-like paranuclear expression in PDNECs, while it is diffusely and strongly positive in the cytoplasm of most cells in NETs with high proliferation.

For these reasons, the 2010 WHO classification may be modified to introduce a new category between G2 NET and NEC that could be defined as G3 NET. In this new possible classification, the term NEC should be restricted to those neoplasms showing the typical morphological features of either small or large cell neuroendocrine carcinomas as defined in the 2000 WHO classification which also show more than 55 % of Ki-67 index.

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References

1. Furlan D, Bernasconi B, Uccella S, Cerutti R, Carnevali I, Capella C (2005) Allelotypes and fluorescence in situ hybridization profiles of poorly differentiated endocrine carcinomas of different sites. Clin Cancer Res 11:1765-1775
2. Yachida S, Vakiani E, White CM, et al (2012) Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. Am J Surg Pathol 36:173-184
3. Yao JC, Shah MH, Ito T, et al (2011) Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514-523
4. Fazio N, Scarpa A, Falconi M (2014) Molecular targeted therapy in enteropancreatic neuroendocrine tumors: from biology to clinical practice. Curr Med Chem 21:1017-1025
5. Moertel C, Kvols L, O'Connel M, Rubin J (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 68:227-232
6. Smith J, Reidy-Lagunes D (2013) The management of extrapulmonary poorly differentiated (high grade) neuroendocrine carcinomas. Semin Oncol 40:100-108
7. La Rosa S, Marando A, Sessa F, Capella C (2012) Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: an update. Cancers 4:11-30

8. Solcia E, Klöppel G, Sobin LH, et al (2000) Histological typing of endocrine tumours. WHO International Histological Classification of Tumours, 2nd Edition. Springer, Berlin
9. Rindi G, Arnold R, Bosman FT, et al (2010) Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). WHO classification of tumours of the digestive system. IARC Press, Lyon, pp 13-14
10. Jiang SX, Mikami T, Umezawa A, Saegusa M, Kameya T, Okayasu I (2006) Gastric large cell neuroendocrine carcinomas: a distinct clinicopathologic entity. Am J Surg Pathol 30:945-953
11. Shia J, Tang LH, Weiser MR, et al (2008) Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol 32:719-731
12. La Rosa S, Marando A, Furlan D, Sahnane N, Capella C (2012) Colorectal poorly differentiated neuroendocrine carcinomas and mixed adenoneuroendocrine carcinomas: insights into the diagnostic immunophenotype, assessment of methylation profile, and search for prognostic markers. Am J Surg Pathol 36:601-611
13. Basturk O, Hruban RH, Adsay NV, et al (2014) Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. Am J Surg Pathol 38:437-447
14. Volante M, Birocco N, Gatti G, Duregon E, Lorizzo K, Fazio N, Scagliotti GV, Papotti M (2014) Extrapulmonary neuroendocrine small and large cell carcinomas: a review of controversial diagnostic and therapeutic issues. Hum Pathol 45:665-673
15. Rindi G, Bordi C, La Rosa S, Solcia E, Delle Fave G (2011) Gastroenteropancreatic (neuro)endocrine neoplasms: the histology report. Dig Liver Dis 43(Suppl 4):S356-S360
16. Corrin B, Gilby ED, Jones NF, Patrick J (1973) Oat cell carcinoma of the pancreas with ectopic ACTH secretion. Cancer 31:1523-1527
17. Wick MR (2000) Immunohistology of neuroendocrine and neuroectodermal tumors. Semin Diagn Pathol 17:194-203
18. DeLellis RA, Shin SJ, Treaba DO (2010) Immunohistology of endocrine tumors. In: Dabbs DJ (ed). Diagnostic Immunohistochemistry: Theranostic and genomic applications. Saunders Elsevier, Philadelphia, pp 291-339
19. Barbareschi M, Roldo C, Zamboni G, Capelli P, Cavazza A, Macri E, Cangi MG, Chilosi M, Doglioni C (2004) CDX-2 homeobox gene product expression in neuroendocrine tumors: its role as a marker of intestinal neuroendocrine tumors. Am J Surg Pathol 28:1169-1176
20. La Rosa S, Rigoli E, Uccella S, Chiaravalli AM, Capella C (2004) CDX2 as a marker of intestinal EC-cells and related well-differentiated endocrine tumors. Virchows Arch 445:248-254
21. La Rosa S, Chiaravalli AM, Placidi C, Papanikolaou N, Cerati M, Capella C (2010) TTF1 expression in normal lung neuroendocrine cells and related tumors: Immunohistochemical study comparing two different monoclonal antibodies. Virchows Arch 457:497-507
22. Hermann G, Konukiewitz B, Schmitt A, Perren A, Klöppel G (2011) Hormonally defined pancreatic and duodenal neuroendocrine tumors differ in their transcription factor signatures: expression of ISL1, PDX1, NGN3, and CDX2. Virchows Arch 459:147-154
23. Schmitt AM, Riniker F, Anlauf M, Schmid S, Soltermann A, Moch H, Heitz PU, Klöppel G, Komminoth P, Perren A (2008) Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. Am J Surg Pathol 32:420-425
24. Koo J, Zhou X, Moschiano E, De Peralta-Venturina M, Mertens RB, Dhall D (2013) The immunohistochemical expression of Islet 1 and PAX8 by rectal neuroendocrine tumors should be taken into account in the differential diagnosis of metastatic neuroendocrine tumors of unknown primary origin. Endocr Pathol 24:184-190
25. Agaimy A, Erlenbach-Wünsch K, Konukiewitz B, Schmitt AM, Rieker RJ, Vieth M, Kiesewetter F, Hartmann A, Zamboni G, Perren A, Klöppel G (2013) ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. Mod Pathol 26:995-1003
26. La Rosa S, Marando A, Gatti G, Rapa I, Volante M, Papotti M, Sessa F, Capella C (2013) Achaete-scute homolog 1 as a marker of poorly differentiated neuroendocrine carcinomas of different sites: a validation study using immunohistochemistry and quantitative real-time polymerase chain reaction on 335 cases. Hum Pathol 44:1391-1399
27. La Rosa S, Sessa F, Capella C, Riva C, Leone BE, Klersy C, Rindi G, Solcia E (1996) Prognostic criteria in nonfunctioning pancreatic endocrine tumors. Virchows Arch 429:323-333
28. Power DG, Asmis TR, Tang LH, Brown K, Kemeny NE (2011). High-grade neuroendocrine carcinoma of the colon, long-term survival in advanced disease. Med Oncol Suppl1:S169-S174
29. Akintola-Ogunremi O, Pfeifer JD, Tan BR, et al (2003) Analysis of protein expression and gene mutation of c-kit in colorectal neuroendocrine carcinomas. Am J Surg Pathol 27:1551-1558
30. Ishikubo T, Akagi K, Kurosumi M, Yamaguchi K, Fujimoto T, Sakamoto H, Tanaka Y, Ochiai A (2006) Immunohistochemical and mutational analysis of c-kit in gastrointestinal neuroendocrine cell carcinoma. Jpn J Clin Oncol 36:494-498
31. Gross DJ, Munter G, Bitan M, et al (2006) The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R. Endocr Relat Cancer 13:535-540
32. Pages F, Galon J, Dieu-Nosjean MC Tartour E, Sautès-Fridman C, Fridman WH (2010) Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene 29:1093-1102
33. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virschows Arch 2006; 449:395-401
34. DeLellis RA, Lloyd RV, Heitz PU, Eng C (2004) Pathology and genetics of tumours of endocrine organs. World Health Organization Classification of Tumours. IARC Press, Lyon
35. La Rosa S, Inzani F, Vanoli A, Klersy C, Dainese L, Rindi G, Capella C, Bordi C, Solcia E (2011) Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol 42:1373-1384
36. Volante M, Daniele L, Asioli S et al (2013) Tumor staging but not grading is associated with adverse clinical outcome in neuroendocrine tumors of the appendix: a retrospective clinical pathologic analysis of 138 cases. Am J Surg Pathol 37:606-612
37. Basturk O, Yang Z, Tang LH, et al (2013) Increased (>20 %) Ki67 proliferation index in morphologically well differentiated pancreatic neuroendocrine tumors (PanNETs) correlates with decreased overall survival. Mod Pathol 26(Suppl 2):423A
38. Vélayoudom-Céphise FL, Duvillard P, Foucan L, et al (2013) Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 20:649-657
39. Travis WD (2010) Advances in neuroendocrine lung tumors. Ann Oncol Suppl 7:vii65-71
40. Sorbye H, Welin S, Langer SW, et al (2013) Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol 24:152-160