The changing landscape of poorly differentiated neuroendocrine neoplasms (NENs) and mixed tumours

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Declaration of interests

Novartis
Ipsen
Pfizer
Bayer
Sanofi
Debiopharm
Some general, « trans-organ » principles

- The main distinction in NENs is between well- and poorly-differentiated neoplasms.
- Poorly-differentiated NENs are termed neuroendocrine carcinomas (NECs).
- They always are of high grade of malignancy and could be distinguished into two subtypes according to tumor cell morphology.
- Poorly-differentiated NENs might be associated with a non-neuroendocrine component to form mixed tumors.
Overview

• The phenotypic diversity of NECs
  – The morphological basis
  – The role of immunohistochemistry
• The emerging genotypic diversity of NECs
• Consequences for diagnosis and management
• Perspectives for future classifications
The phenotypic diversity of poorly differentiated NENs
NEC morphological diversity


- oat cell carcinoma
- small cell carcinoma
- small cell neuroendocrine carcinoma
- large cell neuroendocrine carcinoma

LUNG → OTHER ORGANS

Digestive system  Head and neck
The morphological basis

Small cell

Large cell
The morphological basis

Small cell

Large cell
The morphological basis

Small cell

Not so small
Not so large

Large cell
Challenges in histological classification

• Overlapping and composite tumors

Morphometry Confirms the Presence of Considerable Nuclear Size Overlap Between “Small Cells” and “Large Cells” in High-Grade Pulmonary Neuroendocrine Neoplasms

Alberto M. Marchevsky, MD,1 Anthony A. Gal, MD,2 Swati Shah, MD,1 and Michael N. Koss, MD3

Am J Clin Pathol 2001;116:466-472

• Reproducibility

Reproducibility of Neuroendocrine Lung Tumor Classification

WILLIAM D. TRAVIS, MD, ANTHONY A. GAL, MD, THOMAS V. COLBY, MD, DAVID S. Klimstra, MD, RONI FALK, MS, AND MICHAEL N. KOSS, MD

Hum Pathol. 2010; 41: 1359–1363. DOI: 10.1016/j.humpath.2010.03.013
The role of immunohistochemistry

- Immunohistochemistry is required to demonstrate the neuroendocrine nature of a poorly differentiated carcinoma, but ...
  - Cytokeratins: weak expression
  - Synaptophysin (SYN): sensitive marker but not fully specific, resulting in several diagnostic pitfalls
  - Chromogranins (Cg):
    - Chromogranin A: specific but poorly sensitive marker
    - Chromogranin B: specific marker, available antibodies more sensitive than most available anti-CgA antibodies
  - INSM1: specific and sensitive marker
  - NCAM (CD56): not specific in most body sites and not very sensitive
  - Other markers: ASCL1, MASH-1
- Some poorly differentiated carcinomas with a suggestive morphology do not express neuroendocrine markers
  - 10% of small cell lung carcinomas are not « small cell neuroendocrine carcinomas »

### Table

<table>
<thead>
<tr>
<th>Marker</th>
<th>Antibody</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>SYN</td>
<td>DAK-SYNAP</td>
<td>94%</td>
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<tr>
<td>CgA</td>
<td>A3</td>
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<td>CgA</td>
<td>LKA2H10</td>
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<td>CgB</td>
<td>poly clonal</td>
<td>61%</td>
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<tr>
<td>INSM1</td>
<td>A8</td>
<td>93%</td>
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</table>

Poorly differentiated carcinoma suggestive of NEC
n=100, personal data
Pitfalls in immunohistochemical diagnosis

In inappropriate expression of synaptophysin in colorectal adenocarcinomas

Expression of synaptophysin in a case of NUT carcinoma
Poorly-differentiated NENs : is there a consensus definition ?

- In all body sites, the same morphological criteria are proposed to diagnose a poorly differentiated NEN and to identify the small and large cell types
  - These criteria are mainly derived from the study of lung neoplasms
- However, there is no consensus about the criteria required for the demonstration of the neuroendocrine nature of a poorly differentiated carcinoma
  - No precise criteria in most organs except for:
    - Large cell neuroendocrine carcinoma of the lung (WHO, 2015): at least 10% of tumor cells expressing synatophysin, chromogranin A and/or NCAM (CD56)
    - WHO 2019 (digestive system): «the exact extent and intensity of staining (for either SYN or CgA) have not yet been explicitly defined, but more than scattered positive cells should be present, and the morphology should also be suggestive of neuroendocrine differentiation»
  - Differences in recommendations according to the body site
    - Choice of neuroendocrine markers (SYN, CgA, NCAM, ...)
    - Number of positive markers required (1, 2, more ?)
    - Combination of positive markers required
The emerging genotypic diversity of poorly differentiated NENs
Well-differentiated NEN

TP53 wild type
RB1 wild type

Poorly-differentiated NEN

TP53 inactivation
RB1 inactivation
Small Cell and Large Cell Neuroendocrine Carcinomas of the Pancreas are Genetically Similar and Distinct From Well-differentiated Pancreatic Neuroendocrine Tumors

Shinichiro Yachida, MD, PhD,* Efrevis Vokiani, MD, PhD;† Catherine M. White, BS;§
Yi Zhong, MD, PhD,* Tyler Saunders, HS, Richard Morgan, MS; Roelands F. de Wilde, MD,*
Anirban Maitra, MBBS, Jessica Hicks, BS, Angelo M. DeMuro, MD, PhD;‡
Chunjuan Shi, MD, PhD§ Rajini Sharma, PhD; Daniel Laheru, MD;‡ Barish H. Eidel, MD,‡
Christopher I. Wolfgang, MD, PhD; Richard D. Schulick, MD; Ralph H. Hruban, MD;‡
Laura H. Tang, MD, PhD;§ David S. Klimstra, MD;† and
Christine A. Iacobuzio-Donahue, MD, PhD;*‡


**TABLE 2. Immunohistochemical Features of Pancreatic Neuroendocrine Neoplasms**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Ki67 (%)</th>
<th>Mitotic Rate</th>
<th>Proliferation</th>
<th>Markers of PanNET*</th>
<th>Markers of Neuroendocrine Differentiation</th>
<th>Markers of Cell Cycle Regulation</th>
<th>PDAC Marker</th>
<th>Therapeutic Target</th>
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<td>Well-differentiated NET (G1, low grade)</td>
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</tbody>
</table>

*P = 0.02, mean Ki67 labeling index of small cell NEC versus large cell NEC.
†Areas of both positive and negative immunolabeling present in the same section (heterogeneity).
NA indicates not analyzed or technical failure; NET, neuroendocrine tumor.
NEC, small cell type

TP53 and RB1 inactivation >90% of cases

NEC, large cell type

TP53 and RB1 inactivation 30-70% of cases
Lung large cell NECs (LCNECs)

Three molecular signatures:
- « small-cell » like
- « adenocarcinoma » like
- « NET » like
Colorectal NECs and mixed tumors
Pancreatic neuroendocrine carcinomas reveal a closer relationship to ductal adenocarcinomas than to neuroendocrine tumors G3

Björn Konukiewitz MD a,1, Moritz Jesinghaus MD a,1, Katja Steiger VMD b, Anna Melissa Schlitter MD a,2, Atsuko Kasajima MD a, Bence Sipos MD b, Giuseppe Zamboni MD c, Wilko Weichert MD a,2, Nicole Pfarr MSc a,3, Günter Klöppel MD a,3
Head and neck LCNECs

Another example of HPV-associated LCNEC
Large cell NEC: a diverse entity

- A heterogeneous group
- A certain degree of morphological heterogeneity (including the frequent combination with carcinomatous components in mixed or combined tumors)
- A high degree of genomic heterogeneity
  - « small cell NEC » molecular signature: double inactivation of $TP53$ and $RB1$
  - « (adeno)carcinoma » molecular signatures: molecular alterations comparable to those observed in the (adeno)carcinomas of the same location
  - « NET » signatures: molecular alterations comparable to those observed in NETs of the same location
Consequences for diagnosis and management
Lessons for diagnosis and management

- Importance of the differential diagnosis between the small cell and the large cell types
  - Prognosis
  - Response to treatment
- Importance of the molecular characterization of large cell neuroendocrine carcinoma
  - Prognosis
  - Predictive markers
  - Actionable targets
Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets

Natascha Rokitan1, Maria C. Akdas1, Matthew D. Hellmann1, Jarushka Naidoo7, Arashi Aneza1, Helen Won6, Darrenh F. Hellepenny1, Hangjun Wang1, Shaohou K. Tian1, Anya M. Lwhen1, Paul K. Pak1, Alexander E. Drkopol2, Nicholas Socol1, John T. Perner5, Rongli Shen1, Michael P. Berger4, André L. Moreira1, William D. Travis1, Charley M. Rudn2, and Marc Ladanyi1

Pulmonary large cell neuroendocrine carcinoma with adenocarcinoma-like features: napsin A expression and genomic alterations

Natascha Rokitan1, Catherine M. Pietanza2, Joshua Suhre2, Joseph Montesalvo1, Hangjun Wang1, Omar Hafez1,2, Kyutchi Kodolu1,2, Prasad Adusumilli3, Charley M. Rudn2, Marc Ladanyi1, William D. Travis1 and Philipp Lewin1,2

Table 3: Key genomic alterations in napsin A-positive large cell neuroendocrine carcinomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Alteration type of NS12/3</th>
<th>Alteration type of STK33</th>
<th>Mutated/lost</th>
<th>Molecular method</th>
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<td>Case 1</td>
<td>Negative</td>
<td>NA*</td>
<td>Sequence genotyping/Fragalysis</td>
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<td>NSG-IMP/ACT</td>
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<td>Case 3</td>
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<td>Case 4</td>
<td>KRAS G12V</td>
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<td>Case 5</td>
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Distinct clinicopathologic features, genomic characteristics and survival of central and peripheral pulmonary large cell neuroendocrine carcinoma: From different origin cells?

Fei Zhao1, Lijun He1,2, Ting Ding1,2, Quanming Song1, Xiaoxia Chen1, Chunhui Su1, Wei Li1, Guanghui Gao1, Shengzhong Ren1, Fengying Wu1, Jianguo Sun1, Chunxiao Wu1, Jie Zhang1, and Calcun Zhou1,2

D

D

mOS: 1.51 vs. 4.04 y, p<0.001

100%

Overall Survival (%)

0

Time (years)

0

3

4

5

0

10

20

30

40

50

60

70

80

90

100

Molecular alterations (%)
Rb status: a predictive marker of response to cisplatin therapy in NEC?
Rb status: a predictive marker of response to cisplatin therapy in NEC?
MSI status: a prognostic and predictive marker in NECs and MiNENs?

**Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity**

Nora Sahnane, Daniela Furlan, Matilde Monti, Chiara Romualdi, Alessandro Vanoli, Emanuela Vicari, Enrico Sicilia, Carlo Capella, Fausto Sessa and Stefano La Rosa

Endocrine-related Cancer, 2015;22:35-45

**Diagnosis**

**Prognosis**

**Treatment**

**Immunotherapy**

*Figure 1*

Unstable neuroendocrine carcinoma showing abundant intraepithelial lymphocytes. Although they can be recognized in the H&E-stained section (A), they become much more evident in the CD3 immunostained section (B) (original magnification 250×).
Actionable targets in NEC

Lung large cell NEC: a case report
A precision oncology approach to the pharmacological targeting of mechanistic dependencies in neuroendocrine tumors

Mariano J. Alvarez1,2,40, Prem S. Subramaniam1,40, Laura H. Tang3, Adina Grunn1, Mahalaxmi Aburi1, Gabrielle Rieckhof4, Elena V. Komissarovad, Elizabeth A. Hagan5, Lisa Bodel3,6, Paul A. Clemons7, Filemon S. Dela Cruz8, Deepti Dhall9, Daniel Diolaiti8, Douglas A. Fraker10, Afshin Ghavamib, Daniel Kaemmerer12, Charles Karon13, Mark Kidd14, Kyoung M. Kim15, Hee C. Kim15, Lakshmi P. Kunju16,17,18, Ullo Langel19,20, Zhong Li21, Jeeyun Lee2,21, Hai Li13, Virginia LiVolsw, Roswitha Pfragnerr, Allison R. Rainey8, Ronald B. Realubit13, Helen Remott23, Jakob Regberg19, Robert Roses10, Anil Rustg10, Antonia R. Sepulveda23, Stefano Serra24, Chanjuan Shl25, Xiaopu Yuan9, Massimo Barberis6, Roberto Bergamaschi26, Arul M. Chinnalayand, Tony Detre21, Shereen Ezzat24, Andrea Frilling29, Merten Hommann12, Dirk Jaeger20, Michelle K. Kim31, Beatrice S. Knudson9, Andrew L. Kung8, Emer Leahy11, David C. Metz10, Jeffrey W. Milsom22, Young S. Park15, Diane Reidy-Lagunes2, Stuart Schreiber7,23, Kay Washington25, Bertram Wiedenmann34, Irvin Modlin25* and Andrea Califano1,26,37,38,39*
Perspectives for future classifications
Must we reevaluate the «NEC» category?

- Genomic data suggest the existence of several pathways able to converge into a similar phenotype
  - «Primary» NECs with site-independent characteristics
  - «Secondary» NECs, due to the acquisition of a neuroendocrine phenotype, with site-dependent characteristics, by aggressive non-neuroendocrine carcinomas
    - Either spontaneous or therapy-induced
    - When «incomplete» (limited to some tumor clones), the basis of most mixed (or composite) tumors
  - «Progressive» NECs, emerging from well-differentiated NETs
Must we reevaluate the «NEC» category?

- Clinical and pathological evidence confirms that both «large and small cell NEC» phenotypes might emerge from previous conventional adenocarcinoma either upon treatment or spontaneously:
  - well known in the prostate and the bladder
  - probably valid elsewhere
Tumors are not only made of genes ...
Perspectives: must we reevaluate the whole «NEC» category?

- Would it be necessary to differentiate «primary» and «secondary» neuroendocrine carcinomas, or their various molecular groups, in the future classifications?
  - Integrative approach
  - Diagnostic tools and screening tests
  - Impact on prognosis and treatment
Conclusion

• Accumulating phenotypic and genotypic evidence reveals an unexpected degree of diversity in poorly differentiated neuroendocrine neoplasms

• These data might change our practice, raise new issues and open new perspectives for future classifications as well as for the understanding of neuroendocrine tumor biology

• Future work should focus on:
  – Robust morphological and immunohistochemical criteria for diagnosis
  – Integrative strategies combining data from phenotype to genotype and back, in the light of clinical annotations