ESMO ADVANCED COURSE ON NENS

Clinical Features of GEP-NENs

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DISCLOSURES

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endocrine glands
pituitary, parathyroids, NE adrenal

endocrine islets
within another glands or pancreas

endocrine cells
between exocrine cells (carcinoid tumors)
Many Challenges in NENs

- Heterogeneous
- Increasing incidence
- Sporadic/ Hereditary (MEN/VHL/NF1/TSC)
- Majority Well Differentiated ENETS G1 & G2
- Frequently (65%) metastatic at diagnosis
- Variety of therapeutic options (dedicated NET-MDT)

Dasari A. et al., JAMA Oncol, April 2017
NENs: Synthesis of amines & peptides

- A special feature of NE cells
- Usually, more than 20 single „hormonal markers“ described
- Rarely, multiple & secondary hormone secretion (ACTH, PTH-RP, Calcitonin, GHRH etc.)

<table>
<thead>
<tr>
<th>Cell</th>
<th>Amino/Peptide hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Glucagon</td>
</tr>
<tr>
<td>β</td>
<td>Insulin</td>
</tr>
<tr>
<td>CC</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>K</td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>Somatostatin (SS)</td>
</tr>
<tr>
<td>EC</td>
<td>Serotonin, Substance P</td>
</tr>
<tr>
<td>ECL</td>
<td>Histamine</td>
</tr>
<tr>
<td>G</td>
<td>Gastrin</td>
</tr>
<tr>
<td>GIP</td>
<td>Gastric inhibitory peptide</td>
</tr>
<tr>
<td>L</td>
<td>Glucagon like Peptide (GLP)</td>
</tr>
<tr>
<td>PP</td>
<td>Pancreatic Polypeptide</td>
</tr>
<tr>
<td>S</td>
<td>Secretin, etc.</td>
</tr>
</tbody>
</table>

Vinik A et al., De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. 2018
NENs, a Clinical Challenge

NENs

NF-NENs (~75%)

Incidental/Tumor-mass related symptoms

Pain, jaundice, nausea, vomiting, weight loss, etc.

Insulin (Insulinoma)
Gastrin (Gastrinoma)
Glucagon (Glucagonoma)
VIP (VIPoma)
Calcitonin, multi-hormones, etc.

Hormone-hypersecretion related symptoms

F-NENs (~25%)

Serotonin, etc. (Carcinoid Sdr.)
ACTH/CRH (Cushing Sdr.)
PTH-RP (Hypercalcemia)
GHRH/GH (Acromegaly)

Jensen RT. et al, ENETS Guidelines, Neuroendocrinology, 2012
Gastric NENs (Gastric Carcinoids) - Clinical picture

- Relatively rare: ~7% of all NETs (~2% of all stomach neoplasms).
- 3 main subtypes, each one with a distinct pathophysiologic mechanism, resulting in diverse clinical outcomes and demanding different management.

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>70%-80%</td>
<td>5%-10%</td>
<td>10%-15%</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Pernicious anemia; H. Pylori; CAG; APAC+; pH high (&gt;4)</td>
<td>ZES/MEN1 pH low (&lt;2)</td>
<td>None - sporadic pH normal</td>
</tr>
<tr>
<td>Gastrin level</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Tumor characteristics</td>
<td>Multicentric, &lt; 2 cm</td>
<td>Multicentric, &lt; 2 cm</td>
<td>Solitary, &gt; 2 cm</td>
</tr>
<tr>
<td>Metastatic potential</td>
<td>5%-18%</td>
<td>10%-30%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Endoscopic resection &amp; surveillance; SSA ± SSA</td>
<td>Endoscopic resection &amp; surveillance; PPI ± SSA gastrinoma resection</td>
<td>Formal surgical resection</td>
</tr>
</tbody>
</table>

Grozinsky-Glasberg S et al, Endocrinol Metab Clin North Am. 2018
SI NENs - Clinical picture

- ~30% of all GINENs
- Equal frequency in males and females
- Age peak in the 6th - 7th decades of life
- Multicentricity ~ 30%
- ~ 30%: associated with other non-NET malignancies
- Non-specific symptoms
  - intermittent abdominal discomfort, misinterpreted as IBS for years (79%)
  - weight loss (36%)
  - small bowel obstruction d/t peritumoral fibrosis and adhesions of intestinal loops or luminal stricture (18%)
  - GI-bleeding (10%)
  - night sweats (8%)
  - jaundice (4%)
  - non-secretory diarrhea d/t bacterial overgrowth

Pape et al., Endocr Rel Cancer, 2008
SI NENs - Clinical picture, cont.

- Hormones hypersecretion syndromes (functionality)
  - 30% initially, 40% during disease time
  - Carcinoid syndrome
    - in 95% of patients with liver mets
    - in 5% tachykinin-serotonin production from retroperitoneal metastases can bypass the liver and enter the systemic circulation
      - Flushing 83-90%
      - Diarrhea 73%
      - Bronchospasm 6%
  - CHD 19% - 40%
  - Carcinoid crisis: flushing, hypo- or hypertension, diarrhea, severe bronchospasm and arrhythmias

Pape et al., Endocr Rel Cancer, 2008
Clinical Case 1 (H. D.)

- 58y old woman, asymptomatic
- On routine colonoscopy an incidental TI polyp
- On biopsy: NET with Ki-67=2%
- Laparoscopic excision
- Path report:
  - TI NET
  - 4 mitoses/10HPF; Ki-67=10%
  - invading the whole wall
- Normal 5-HIAA and CGA (pre- and post-op.)

**Diagnosis: WD NET G2 of the Terminal Ileum**
Clinical Case 2 (N. M.)

- 58y old woman; diarrhea, anasarca
- Echocardiography: CHD
- Abdominal CT:
  - mesenterial lesion + “desmoid reaction”
  - multiple hypoechoic liver lesions up to 15 cm
- 5-HIAA = 134 mg/24h (normal, 2-8)
- CGA = 1105 ng/ml (normal, 24-98)
- Liver biopsy: NET, Ki-67 = 10%

**Diagnosis:** WD NET G2 of the Terminal ileum, Metastatic to the Liver & LN, CS & CHD
Colonic NENs - Clinical picture

- 7.5% of all NETs with a mean age of diagnosis ~ 55-65 y
- 30 - 40% of these tumors will have metastases at the time of diagnosis
  - liver, lymph nodes, mesentery, or peritoneum
- due to the high capacitance of the right colon, the tumor reaches a large size (>2 cm), inducing
  - pain, bleeding, altered bowel habits, weight loss and anorexia
  - bowel obstruction, anemia or a palpable liver
- 5-year survival rate of about 43–50%
- adenoCa of the colon is common in patients with NET, especially over the age of 40 years
Appendiceal NENs - Clinical picture

- 2-3/1.000.000/year
- 3-9/1000 appendicectomies
- age: 38 - 51y
- reported in pediatric patients: 4.5 - 19.5y
- ~ 70% located at the tip of the appendix.
- Size is important:
  - < 2 cm, with no other risk factors, poses no further risk of recurrence after appendicectomy.
  - ≥ 2 cm or any size ± at least 2 risk factors, confer a relevant risk of recurrence and right hemicolecotomy is warranted.
    - risk factors: MAI, LVI, PNI, base localization, margins involved, ≥G2

ENETS Consensus Guidelines, Neuroendocrinology 2016
Rectal NETs - Clinical picture

- Increasing incidence:
  - 18% of all NETs, 27% of all GI NETs (SEER)
- Mean age of 56.2 y
- Small, polypoid lesions, between 4 - 20 cm above the dentate line on the anterior or lateral rectal wall.
- Discovered incidentally on routine sigmoidoscopy.
- Symptoms (if present): rectal bleeding, constipation, pain/tenesmus.
- CS is unusual (the tumors do not contain serotonin)
- Metastases observed in:
  - 2% of patients of rectal NETs <1.0 cm
  - 10%–15% of rectal NETs 1.0–2.0 cm
  - 60%–80% in rectal NETs >2.0 cm
Pancreatic NENs - Clinical picture

- ~3-5% of all pancreatic neoplasms
- Increase in the annual incidence to 1.2 per 100,000
- Survival related to disease spread & grade
- Most are sporadic
- Familial syndromes
  - MEN-1
  - Tuberous sclerosis
  - Neurofibromatosis (ampulla of Vater)
  - Von Hippel-Lindau
- Clinically
  - Incidental, asymptomatic
  - Non-secreting: tumor-mass related symptoms
  - Hypersecreting (insulin, gastrin, glucagon, VIP, serotonin, ACTH, etc): hormonal ± tumor mass related symptoms
The Diagnostic Pathway in NENs

Clinical Symptoms/Incidental Finding

Suspicions of NEN

Lab tests

Strong suspicion of NEN/Evidence of functionality

Imaging, anatomic

Proof of tumor & staging

Histopathology

Ki67 index

Molecular staging

Imaging functional

Proof of NEN & Grading

Surgery Systemic, etc.

Therapeutic Decision:

Prognostic staging
WHAT THE CLINICIAN SHOULD KNOW WHEN THE DIAGNOSIS IS NEN?

1. What is the grade of the tumor? (cell morphology & Ki67/MI)
2. Is it functional/hypersecreting?
3. Sporadic/Familial?
4. What is the molecular imaging profile (SRI, FDG-PET, F-DOPA, etc.)? (for staging & theranostics purpose)
5. Aim of therapy? (curable or palliative)