Gastroenteropancreatic G3 neuroendocrine neoplasms (G3 NENs) with deceptively well-differentiated histologic features have a poor outcome
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Introduction:
• The 2010 WHO classification stratifies NENs into 3 tiers based on cellular proliferation. The G3 NENs (mitotic count >20/10 HPF and/or Ki-67 index >20%) are classified as neuroendocrine carcinomas (NECs). G3 NENs and poorly-differentiated NECs (PDNECs) are categorized the same.
• PDNECs exhibit small cell (SC) or large cell (LC) morphology with severe nuclear atypia, necrosis and high mitotic activity. G3 NENs may show features similar to well-differentiated NENs, except for high Ki-67 index. This study evaluates the clinicopathological features of G3 NENs with well-differentiated histology (G3-WD).

Results:
9 cases of G3-WD (6 pancreatic, 3 gastrointestinal) were identified. The tumor cells were uniform and largely arranged in an organoid pattern. None could be classified as neuroendocrine carcinoma of small cell or large cell type. 3 and had an oncocytoid appearance; 4 had focal higher grade cytologic features; 4 had prior diagnosis or current foci of low or intermediate grade NEN. All the pancreatic tumors were negative for acinar cell carcinoma markers. 5 PDNECs (all gastrointestinal with small cell morphology) were used as controls.

Design:
• Gastroenteropancreatic G3 NENs with well-differentiated histology and poorly differentiated neuroendocrine carcinomas were retrieved from the anatomic data base from 2000 to 2011.
• H&E slides and immunostains (synaptophysin, chromogranin, chromotrypsin, trypsin and Ki-67) were reviewed. Outcome data were obtained from the tumor registry.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Mean age</th>
<th>M:F</th>
<th>Mean (range) of mitoses/10 HPF</th>
<th>Mean (range) of Ki-67 (%)</th>
<th>Distant metastases (%)</th>
<th>Mean follow-up (months)*</th>
<th>AWD/AWOD/DOD **</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3 NEN (n=9)</td>
<td>51</td>
<td>2:7</td>
<td>7 (1-20)</td>
<td>34 (24-46)</td>
<td>100</td>
<td>19</td>
<td>2/1/6</td>
</tr>
<tr>
<td>PDNEC (n=5)</td>
<td>65</td>
<td>3:2</td>
<td>&gt; 50</td>
<td>85 (80-90)</td>
<td>100</td>
<td>11</td>
<td>0/1/4</td>
</tr>
</tbody>
</table>

* Mean follow-up in both groups from time of high grade tumor diagnosis ** AWD=alive with disease; AWOD=alive without disease; DOD= died of disease

Conclusions:
• G3 NENs with well-differentiated histology have a poor clinical outcome although fare slightly better compared to poorly differentiated neuroendocrine carcinomas.
• G3 NENs with well-differentiated histology may represent transformation from prior low or intermediate grade NENs. When such transformation occurs, aggressive treatment may be warranted.

Control case
Case 2
Case 4
Case 1
Case 6

Case 2
Case 4
Case 1
Case 6

Case 1
Case 6
Case 2
Case 4

Case 6
Case 2
Case 4
Case 1

Case 1
Case 6
Case 2
Case 4

Case 6
Case 2
Case 4
Case 1

Case 1
Case 6
Case 2
Case 4

Case 6
Case 2
Case 4
Case 1

Case 1
Case 6
Case 2
Case 4