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).

Design:

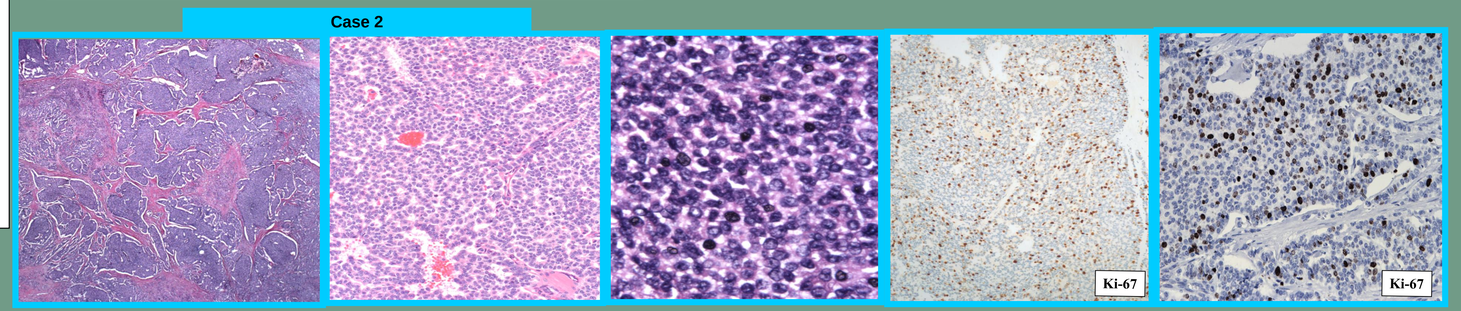
- Gastroenteropancreatic G3 NENs with well-differentiated histology and poorly differentiated neuroendocrine carcinomas were retrieved from the anatomic data base from 2000 to 2011.
- H&E slides and immunostains (synaptophysin, chromogranin, chymotrypsin, trypsin and Ki-67) were reviewed. Outcome data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

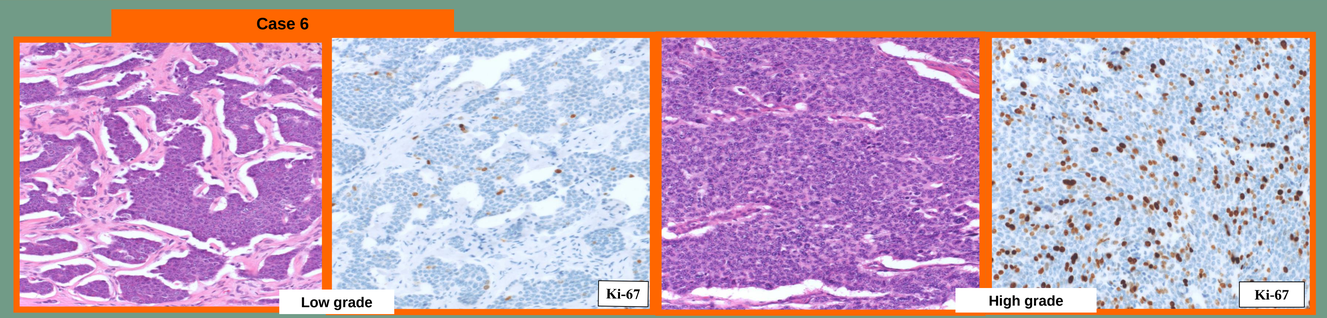
Results:

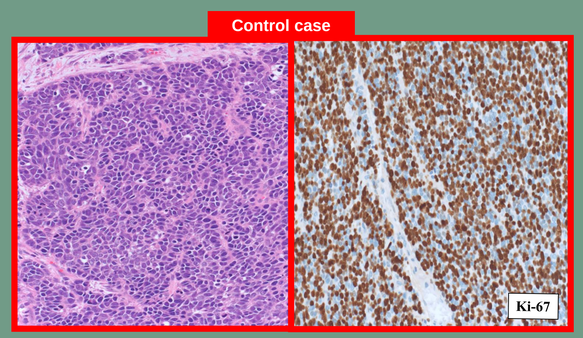
9 cases of G3-WD (6 pancreatic, 3 gastrointestinal) were identified. The tumor cells were uniform and largely arranged in an organoid pattern. None could be classified as neuroendocrine carcinoma of small cell or large cell type. 3 and had an oncocytoid appearance; 5 had focal higher grade cytologic 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.

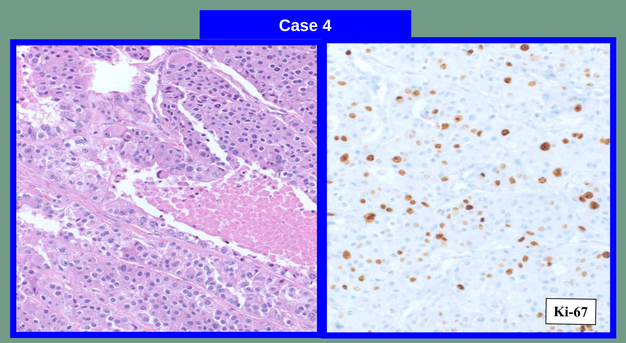
Categories	Mean age	M:F	Mean (range) of mitoses/10 HPF	Mean (range) of Ki-67 (%)	Distant metastases (%)	Mean follow-up (months)*	AWD/AWOD/DOD **
G3 NEN (n=9)	51	2:7	7 (1-20)	34 (24-46)	100	19	2/1/6
PDNEC (n=5)	65	3:2	> 50	85 (80-90)	100	11	1/0/4

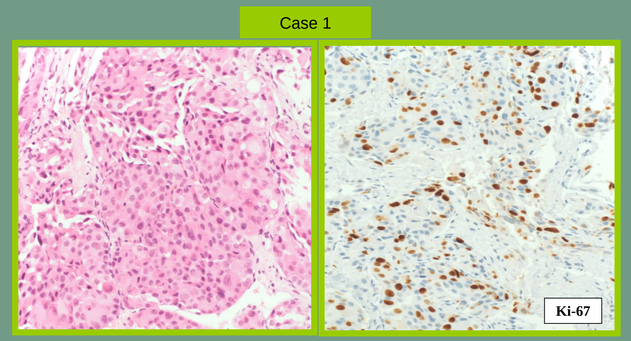
* Mean follow-up in both groups from time of high grade tumor diagnosis ** AWD=alive with disease; AWOD=alive without disease; DOD= died of disease











Case	Specimen (Imaging)	Mitosis (per 10 hpfs)	Ki-67 proliferative index	Outcome	Follow-up (mths)	Age/Sex
1	Liver core biopsy (Pancreas mass)	2	30%	DOD	18	35/M
2	Distal pancreatectomy	5	30%	DOD	18	44/F
3	Liver biopsy (Pancreas mass)	3	45%	DOD	13	69/F
4	Liver wedge (prior distal pancreatectomy 2 yrs back)	5	34%	DOD	22	46/F
5	Liver core biopsy (Pancreas mass)	8	24%	AWD	11	54/F
6	Small bowel resection and liver metastasis	20	34% (2% in other areas	DOD	17	67/M
7	Liver wedge (prior G2 distal pancreatic tumor 8 yrs back)	1	20-30%	AWOD	11	39/F
8	Appendix with peritoneal metastasis	1	30% (5% in other areas)	AWD	56	53/F
9	Small bowel resection and liver metastasis	17	30% (2% in other areas)	DOD	13	63/F

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.