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Clinical and Immunohistochemical Features of High Grade Neuroendocrine Neoplasia of the Gastrointestinal Tract

Allison Zemek[1]; Michael A. DiMaio[1]; Shirley S. Kwok[1]; Pamela L. Kunz[2]; Teri A. Longacre[1]

[1]Department of Pathology, Stanford University Medical Center, Stanford, CA
[2]Department of Medicine, Stanford University Medical Center, Stanford, CA

Background: Neuroendocrine neoplasms of the gastrointestinal tract and pancreas are classified in the WHO 2010 system into three grades, using mitotic figure counts and Ki-67 indices. There is increasing evidence that neuroendocrine carcinomas, WHO grade 3, have a broad range of clinical behavior. Morphology and immunohistochemistry may aid in predicting outcome and distinguishing between poorly-differentiated neuroendocrine tumors and poorly-differentiated neuroendocrine carcinoma.

Methods: A retrospective search of the surgical pathology database of a large academic medical center identified 19 cases diagnosed as neuroendocrine carcinoma of gastrointestinal tract or pancreas over the past 12 years. H&E sections were examined and classified as well-differentiated neuroendocrine tumor (WDNET), poorly-differentiated neuroendocrine tumor (PDNET), or poorly-differentiated neuroendocrine carcinoma (PDNEC) based on morphologic features (cytology, trabecular/nested versus sheet-like growth, mitotic activity). Immunohistochemistry for Ki-67, p53, and p16 was performed on each tumor. Survival data were also analyzed.

Results: Of 19 tumors initially diagnosed as neuroendocrine carcinoma, 5 were reclassified as WDNET, 7 as PDNET, and 7 PDNEC based on morphologic features. WDNETs had low-grade cytology and mitotic figures less than 20 per 10 high power fields, PDNECs demonstrated high grade cytology, sheet-like growth, and higher mitotic activity. PDNETs had intermediate features. Ki-67, p53, and p16 expression data are shown in Table 1. P53 expression in less than 30% of the tumor was considered negative.

Conclusion: Tumors with features of well-differentiated neuroendocrine tumors do not express p53 and rarely express p16. Poorly-differentiated neuroendocrine tumors exhibit Ki-67 indices between 15-40%, with intermediate expression of p53 and p16. Poorly-differentiated neuroendocrine carcinoma with Ki-67 expression greater than 40% had the highest levels of p53 and p16 expression and the worst survival from the time of diagnosis. These data suggest that patients with neuroendocrine neoplasms of the gastrointestinal tract currently classified as WHO grade 3 have variable survival, and expression of p53 and p16 correlate with increasing grade and worse survival.

Table 1

Tumor (n)	Average Ki-67 (range)	p53 expression (%)	p16 expression (%)	Average Survival (patients with survival data)
WDNET (5)	4.7% (0.6-11.3%)	0/5 (0%)	1/5 (20%)	36 months (n=2)
PDNET (7)	25.3% (16.1-38.5%)	3/7 (42.9%)	2/7 (28.6%)	15.2 months (n=5)
PDNEC (7)	58.2% (45.6%-82.0%)	6/7 (85.7%)	4/7 (57.1%)	5.8 months (n=4)