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Do Pancreatic Well-differentiated Neuroendocrine Tumor (NET) Progress to Poorly-differentiated Neuroendocrine Carcinoma (NEC)?

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BACKGROUND

Grade 3 pancreatic neuroendocrine tumor (G3-PanNET) and neuroendocrine carcinoma (PanNEC) are both defined by Ki67>20% and/or mitoses >20 per 2mm2. PanNET and PanNEC are thought to be molecularly distinct entities and progression from PanNET to PanNEC is considered rare. *MEN1, ATRX, DAXX*, and *TSC1/2* mutations are common in PanNET, while *TP53, RB1, KRAS*, and *SMAD4* mutations are typical of PanNEC. Immunostains for *ATRX/DAXX/p53/Rb* aid in the classification of G3-NET versus NEC, and history of prior or concurrent G1/G2-NET is thought to support a G3-NET diagnosis. We have observed multiple G3 neuroendocrine neoplasms (NENs) with alterations in both NET and NEC genes, raising questions about how these cases should be classified and managed.

METHODS

Next generation sequencing was performed on 31 pancreatic G3-NENs that were classified as G3-NET during routine pathology review at UCSF. An additional 20 cases of ambiguous pancreatic G3-NEN were also sequenced. Of the ambiguous cases, 10 had alterations in NET genes and were included yielding a total of 41 cases that were either diagnosed as G3-NET or were ambiguous but harbored NET alterations. Several matched prior G1/G2-NETs (n=5) were also sequenced.

RESULTS

Of the 41 cases, 23 (56%) had history of a prior G1/G2-NET and received prior therapies, whereas the other 44% were G3 at diagnosis and treatment naive. 88% (36/41) had alterations in NET genes including in *MEN1* (63%), *DAXX/ATRX* (37%), and *TSC1/2* (31%). 27% (11/41) had alterations in both NET genes and TP53; 3 of these 11 (3/41 overall; 7.3%) had co-alteration of *TP53* and *RB1*. Of the 11 cases with alterations in *TP53* +/- *RB1*, 8 (73%) had prior G1/G2-NET (5 of which were also sequenced). All G1/G2 priors demonstrated shared identical mutations with the matched G3 NET in at least one NET gene, but none had alterations in *TP53* or *RB1*.

CONCLUSIONS

Our study demonstrates that 20% of G3-PanNET harbor alterations in *TP53* and another 7.3% harbor co-alteration of *TP53* and *RB1*. Our data suggest that *TP53* and *RB1* alterations emerge during grade progression to G3-NET, most often (73%) in the setting of previously treated G1/G2-NET. These data raise many questions: 1) Should G3-NET with *TP53* and/or *RB1* alterations be classified and treated as NEC? 2) Do specific prior therapies increase the risk of acquiring *TP53* and/or *RB1* alterations? 3) Are outcomes worse in G3-NET with or without *TP53* and/or *RB1* alterations? Further studies are needed to answer these important questions.

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