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The Role of Microbiome in Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs)

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BACKGROUND: Gut microbiome balance has a key role in human health and is linked to a variety of diseases, including cancer. In this study, we analyzed the role of gut microbiome (both fungal and bacterial species) alterations in patients with metastatic gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs).

METHODS: Fecal samples were collected and matched with healthy control samples using linear regression models. Differences in microbiome profiles between GEP-NENs and control samples were performed. Next, the association of microbiome profiles with different behavioral and dietary habits, clinicopathological features (differentiation, grade, primary tumor site) and therapeutic responses was examined. All tests are two-sided and P-values ≤ 0.05 were considered statistically significant.

RESULTS: Gut samples of 36 patients (14 males, 22 females, median age 65 years) with metastatic GEP-NENs (24 small bowel, 10 pancreatic, 1 gall bladder, and 1 unknown primary) were analyzed. 31 patients were diagnosed with well differentiated GEP-neuroendocrine tumors (GEP-NETs), (G1= 20, G2=13, G3=3) versus 5 patients with GEP-poorly differentiated neuroendocrine carcinomas (GEP-NECs). Our data showed that GEP-NENs had significant decrease in relative abundance of bacterial species and an increase in relative abundance of fungi (notably *Candida* species) compared to controls (Figure 1). GEP-

NECs had significantly enriched bacteria and fungi (such as *Enterobacter hormaechei*, *Bacteroides fragilis* and *Trichosporon asahii*) compared to those with GEP-NETs ($p=0.048$, 0.0022 & 0.034 respectively), (Figure 2A). In addition, higher grade GEP-NETs were associated with significant higher *Bacteroides fragilis* ($p=0.022$), *Eubacterium dolichum* ($p=0.049$), and *Eggerthella lenta* ($p=0.00018$) species compared to lower grade tumors (Figure 2B). There were substantial differences associated with dietary habits and therapeutic responses (Table.1).

CONCLUSION: This is the first study to analyze the role of the microbiome environment in patients with GEP-NENs. There were significant differences between GEP-NETs and GEP-NECs, supporting the role of the gut microbiome in the pathogenesis of these two distinct entities.

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