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The Immunohistochemical Expression of Islet 1 and PAX8 by Rectal Neuroendocrine Tumors Should be Taken into Account in the Differential Diagnosis of Metastatic Neuroendocrine Tumors of Unknown Primary Origin

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Background: Rectal Neuroendocrine tumors (NETs) have recently been noted to exhibit positivity for Islet 1 and PAX8, which are generally considered markers of pancreatic NETs. Rectal NETs are distinct and can be subdivided by histologic pattern and secretory products into two major groups: Serotonin-producing enterochromaffin (EC)-cell NETs, which show a nested pattern histologically, and glucagon-like peptide-producing and pancreatic polypeptide/peptide YY (PP/PYY)-producing L-cell NETs, which are characterized by a predominant trabecular pattern. A majority of rectal NETs are negative for chromogranin A and CDX2. In this study, we characterized the immunohistochemical (IHC) profile of rectal NETs and sought to determine if there is any correlation between the histologic features and the IHC staining profile.

Methods: Fifty-six primary rectal NETs were histologically reviewed and stained with antibodies against Islet 1, PAX8, CDX2, chromogranin A and synaptophysin. Thirty-one of these specimens were also stained with antibodies to serotonin, pancreatic polypeptide (PP), and prostatic acid phosphatase (PAP).

Results: Tumors were classified based on the predominant growth pattern as follows: trabecular (n=31, 55%), nested (n=15, 27%), and acinar (n=2, 4%). There were 8 (14%) tumors in which both trabecular and nested patterns were present in relatively equal proportions, and these were classified as mixed type. The IHC staining results are displayed in Table 1. Islet 1 was positive in 89% and PAX8 in 79% of cases. CDX2 was negative in all cases. Serotonin was positive in 16 and PP in 97% of cases; two tumors showed positivity with both serotonin and PP and nine tumors were negative with both. Interestingly, all serotonin-positive cases were chromogranin A positive. PAP was positive in 97% of cases. There were no apparent associations between the IHC staining patterns and histologic growth pattern.

Conclusions: Like pancreatic NETs, most rectal NETs were positive for Islet 1 and /or PAX8 and negative for CDX2. In our study, staining for serotonin and PP was not mutually exclusive, and positivity for serotonin and PP did not correlate with nested or trabecular patterns, respectively. Most rectal NETs were found to be positive for PAP. Additional PAP IHC studies may be helpful in distinguishing pancreatic from rectal NETs.

Table 1. Results of immunohistochemistry in rectal neuroendocrine tumors.

Staining intensity	*Islet 1 (%)*	*PAX8 (%)*	*CDX2 (%)*	*Cg A (%)*	*Syn (%)*	*5HT (%)*	*PP (%)*	*PAP (%)*
	n=56					n=31		
Moderate to strong staining	49 (88)	39 (70)	0	17 (30)	55 (98)	4 (13)	18 (58)	10 (32)
Weak staining	1	5 (9)	0	0	1	1	1	20 (65)
Total	50 (89)	44 (79)	0	17 (30)	56 (100)	5 (16)	19 (61)	30 (97)

Cg A: chromogranin A; Syn: synaptophysin; PP: pancreatic polypeptide; PAP: prostatic acid phosphatase; 5HT: serotonin