



Value of Islet 1 and PAX8 in Identifying Metastatic Neuroendocrine Tumors of Pancreatic Origin

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Introduction:

Neuroendocrine tumors (NETs) can present as liver metastases before discovery of the primary tumor. The management of metastatic neuroendocrine disease hinges critically on identification of the primary tumor source. However, the primary tumor is not identified in 20-50% of gastroenteropancreatic NETs.

Immunohistochemical (IHC) staining with TTF-1 and CDX2 is currently used to identify NETs of pulmonary and gastrointestinal (GI) origin, respectively. Islet 1 and PAX8 have recently been proposed as immunohistochemical markers for NETs of pancreatic origin:

- Islet 1 is a transcription factor crucial for pancreatic and motor neuron development in mammals.
- PAX8 is a transcription factor that regulates organogenesis in various sites.

Objectives:

- (1) Compare the utility of Islet 1 and PAX8 in distinguishing pancreatic NETs from tumors of other sites
- (2) Determine the usefulness of an IHC panel including TTF-1, CDX2, Islet 1, and/or PAX8 in identifying metastatic pancreatic NETs.

Material and Methods:

A total of 183 tumors were studied. There were 110 primary NETs (33 pancreatic, 31 pulmonary, 23 ileal, 14 rectal, and 9 gastric) and 73 NETs metastatic to the liver (28 pancreatic, 5 pulmonary, 37 ileal, 1 rectal, 1 colonic, and 1 duodenal). All tumors were well-differentiated by WHO criteria.

Immunohistochemistry was performed using antibodies against Islet 1, PAX8, TTF-1 and CDX2. Tumors showing moderate to strong nuclear staining of at least 5% of cells or showing weak nuclear staining of at least 10% of cells were considered positive.

Results:

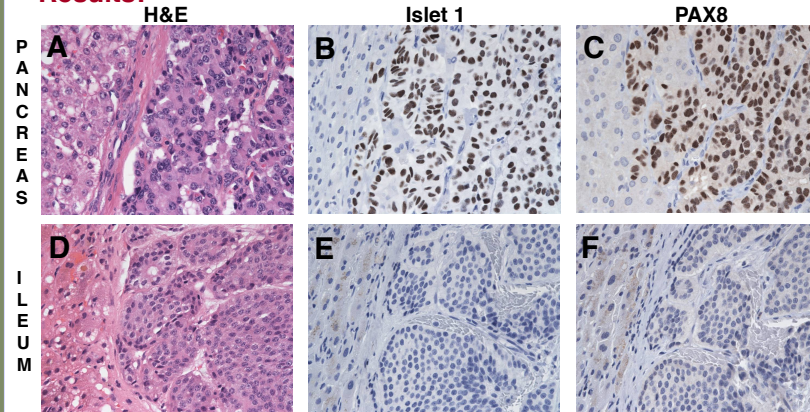


Figure 1. Islet 1 and PAX8 immunohistochemical staining in metastatic pancreatic NET and metastatic ileal NET. (A) Metastatic pancreatic NET (H&E, x 400), showing strong, 4+ staining with Islet 1 (B; x 400) and strong, 4+ staining with PAX8 (C; x 400). (D) Metastatic ileal NET (H&E, x 400), negative with Islet 1 (E; x 400) and negative with PAX8 (F; x 400).

Islet 1 and PAX8 were positive in 82% and 88% of primary pancreatic NETs, respectively, and negative in all primary ileal NETs. Among primary NETs, there was also Islet 1 positivity in 2/31 (6%) pulmonary and 12/14 (86%) rectal NETs, and PAX8 positivity in 7/31 (23%) pulmonary, 11/14 (79%) rectal, and 2/9 (22%) gastric NETs.

Immunoreactivity results for metastatic NETs are summarized in Table 1:

Metastasis from	n	Islet 1 (%)	PAX8 (%)	TTF-1 (%)	CDX2 (%)
Pancreas	28	19 (68)	15 (54)	0	1 (4)
Pulmonary	5	0	0	1 (20)	0
Ileum	37	0	0	0	33 (89)
Other GI	3	1 (33)	0	0	1 (33)

Table 1. Immunoreactivity for Islet 1, PAX8, TTF-1, and CDX2 in metastatic neuroendocrine tumors.

Overall, Islet 1 had a sensitivity of 82% (27/33) and specificity of 82% (57/77) for primary pancreatic NETs. For metastatic pancreatic NETs, Islet 1 had a sensitivity of 68% (19/28) and a specificity of 98% (44/45).

Overall, PAX8 had a sensitivity of 88% (29/33) and specificity of 74% (63/77) for primary pancreatic NETs. For metastatic pancreatic NETs, PAX8 had a sensitivity of 54% (13/28) and a specificity of 100% (45/45).

There were 6/33 primary and 10/28 metastatic pancreatic NETs which showed discordant staining between Islet 1 and PAX8, suggesting that the stains may complement each other when used together as part of an IHC panel.

Results:

A four-stain IHC panel including Islet 1, PAX8, TTF-1, and CDX2 identified 75% of metastatic pancreatic NETs, which based on ROC curve analysis was significantly better than a three-stain panel of PAX8, TTF-1, and CDX2 ($p = 0.019$) and slightly better than a three-stain panel of Islet 1, TTF-1, and CDX2 ($p = 0.072$). (Figure 2)

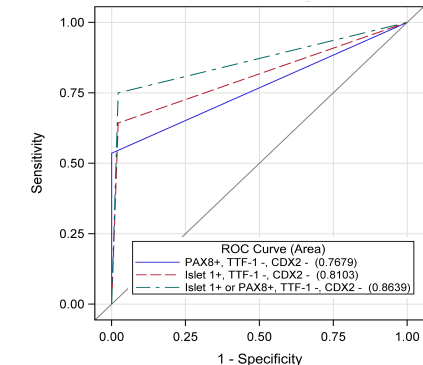


Figure 2. ROC curves comparing various immunohistochemical panels for identification of metastatic pancreatic NETs.

Conclusions:

- Islet 1 and PAX8 showed similar sensitivity and specificity for identifying NETs of pancreatic origin.
- Positive staining for either Islet 1 or PAX8 clearly differentiated between NETs of the pancreas and ileum.
- Use of a four stain IHC panel (both Islet 1 and PAX8 in conjunction with TTF-1 and CDX2) provides a benefit over other three-stain IHC panels using either Islet 1 or PAX8.
- Both Islet 1 and PAX8 are reliable IHC markers for NETs of pancreatic origin and would be useful adjuncts to other markers (TTF-1, CDX2) currently used to work up a metastatic NET of unknown primary.