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Original contribution

CDX2 may be a useful marker to distinguish primary ovarian carcinoid from gastrointestinal metastatic carcinoids to the ovary☆

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Summary Primary ovarian carcinoids and metastatic tumors share similar morphologic features. Metastatic carcinoids must be excluded from primary ones for prognostic and therapeutic reasons. Gastrointestinal neuroendocrine (carcinoid) tumors are much more common with the majority arising from small intestine and appendix. The aim of this study is to evaluate the role of immunohistochemistry for CDX2 in differentiating primary ovarian from metastatic carcinoids of primary gastrointestinal origin. Thirty primary pure ovarian carcinoids, 16 primary ovarian carcinoids arising in association with benign teratomas, 10 ovarian carcinoids metastatic from primary gastrointestinal tract and 70 gastrointestinal neuroendocrine tumors were studied for the expression of CDX2 by immunohistochemistry. CDX2 expression revealed that 40 (57.1%) of 70 cases of gastrointestinal carcinoids and 9 (90%) of 10 ovarian metastatic carcinoids showed positive nuclear staining (diffuse or focal). On the other hand, 3 (18.8%) of 16 primary carcinoids with teratomatous elements showed weak positivity. Among the 70 gastrointestinal carcinoids, CDX2 was positive in 38 (90.5%) of 42 cases in the duodenum, small intestine, appendix, and only in 2 (11.8%) of 17 cases of colorectal carcinoids and none of the 11 cases in the stomach. It is concluded that CDX2 may be a useful marker to distinguish primary ovarian carcinoid from metastasis from small intestinal and appendiceal neuroendocrine tumors.

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1. Introduction

Primary ovarian carcinoids are the second most frequent monodermal teratomas. They may occur in pure form (15%) or combined with other teratomatous components (85%), such as a mature teratoma or a struma ovarii [1,2]. In spite of the fact that primary ovarian carcinoids are rare tumors, they are still more common than ovarian metastatic carcinoids, which are usually of primary gastrointestinal (GI) origin [1,2]. While most primary ovarian carcinoids behave in a benign fashion, metastatic tumors tend to be aggressive and associated with poor outcome. Therefore, the distinction between ovarian primary and metastatic carcinoids is crucial and is of clinical and prognostic implications [2,3].

Clinical and radiological findings may help to delineate the primary site of carcinoid tumors. However, there are no histomorphologic criteria or immunophynotype to distinguish primary ovarian carcinoids from metastatic ones [4]. Morphologically, both primary and metastatic carcinoids look alike with no distinguishing features. Some features that are considered to be suggestive of primary ovarian carcinoid are the association with ovarian teratoma and unilaterality [5,6]. On the other hand, bilaterality, nodular growth pattern, and the presence of lymphovascular space invasion favor metastatic carcinoid [3,7].

Immunohistochemical staining has also been recently used to distinguish primary tumors from metastasis in different organs. Studies of GI carcinoids, for example, have demonstrated CDX2 as a useful marker to differentiate between primary midgut, foregut and hindgut carcinoid tumors and their metastases to the liver. Midgut carcinoids and their metastatic tumors to the liver express high levels of CDX2 compared to foregut and hindgut carcinoids [8–10]. Additionally, other immunohistochemical markers such as transcription termination factor 1 (TTF-1) [11,12], CK7, and CK20 [13,14] have also been used to characterize GI and metastatic neuroendocrine carcinomas [10].

CDX2 is a transcription factor related to the development and differentiation of the bowel [15–18], and it is a relatively specific marker for intestinal epithelium. To the best of our knowledge, CDX2 expression has not been assessed in primary ovarian carcinoids in a comprehensive study. The aim of this study is to evaluate CDX2, by immunohistochemistry (IHC), in differentiating primary ovarian carcinoids from metastatic carcinoid tumors to the ovary from primary GI origin.

2. Material and methods

2.1. Case selection

Pure primary ovarian carcinoids (n = 30; 23 insular and 7 trabecular types) and primary ovarian carcinoids arising in association with benign ovarian teratomas (n = 16; 12 insular and 4 trabecular types), ovarian neuroendocrine (carcinoid) metastatic from GI (n = 10; 8 from small intestine, 1 from colon and 1 from stomach) were selected from the files of the Armed Forces Institute of Pathology from 1970 to 2004 [19,20] and from the Department of Pathology, Peking University Cancer Hospital. Primary GI carcinoids (n = 70) were selected from the pathology department at the University of Pittsburgh Medical Center. All cases were reviewed by at least two authors. Institutional review board approvals were obtained.

2.2. Immunohistochemistry

IHC for CDX2 was performed in the immunohistochemical laboratory, department of Pathology at Magee Womens Hospital. A polyclonal antibody recognizing human CDX2 was obtained from Biogenix and used at a 1:100 dilution in TBS-plus (Biocare Medical, Concord, CA) with 0.1% Tween 20 (DakoCytomation, Carpinteria, CA). Assays were performed as described previously [21]. Antigen retrieval was performed using Reveal solution (Biocare Medical) in a pressure cooker for 3 minutes at 20 psi with heat. After 30-minute incubation in pre-warmed Reveal solution, endogenous peroxidases and other endogenous oxidizers were quenched in 6% H_2O_2 in methanol for 30 minutes.

The anti-CDX2 antibody was manually applied to the sections for 1 hour at room temperature, and the detection method used was the Elite ABC system (Vector Laboratories, Burlingame, CA) with biotinylated horse antimouse/rabbit IgGs and the avidin-biotin complex reagent for 45 minutes each with intervening rinses of TBS-plus with 0.1% Tween 20. Signal was generated by incubation for 2 minutes in 0.08% diaminobenzidine tetrahydrochloride with 0.024% H_2O_2 added. Sections were counterstained with hematoxylin.

2.3. Interpretation and scoring of immunohistochemical preparations

Nuclear staining of CDX2 was considered positive. For overall positivity, immunostaining in >5% of cells was considered positive, and ≤5% positive cells was considered negative. Additionally, both extent (based on the percentage of positive cells) and intensity of immunostaining were evaluated by a semiquantitative system. Extent was scored as 0, ≤5%; 1+ (1 point), 6%-25%; 2+ (2 points), 26%-50%; 3+ (3 points), 51%-75%; and 4+ (4 points), 76%-100%. Intensity was arbitrarily scored as weak (1 point), moderate (2 points), or strong (3 points). Intensity was designated as weak when immunostaining was present but only barely detectable.

In positive cases, these values were converted into composite IHC scores by multiplying the individual scores of extent times the intensity with a possible range of values from 1 to 12 [20]. For example, a case with 3+ extent (3 points) and moderate intensity of immunostaining (2 points) would have an immunohistochemical composite score of 3 × 2 = 6.