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Reliability of PAX8 in clinical practice to accurately determine primary site of origin in female pelvic or abdominal lesions ☆

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ABSTRACT

Female patients with gynecological malignancies can harbor peritoneal pelvic or abdominal lesions; however, other primary tumors can involve the peritoneum as well. Since sampling of the peritoneum now can be easily performed by fine needle aspiration or percutaneous biopsy, we have noticed an increase in such procedures as initial attempts to establish a diagnosis. PAX8 has been used alone or in combination with other tumor markers to accurately classify these lesions and determine primary site of origin; however, prior published studies determined expression of PAX8 within historically diagnosed cases. We reviewed the reliability of PAX8 to determine tumor type or primary site in 135 current clinical pelvic or abdominal lesions and highlight several pitfalls in its routine use, in particular, relying on the presumed expression pattern (positive or negative) within a given primary tumor and that poorly differentiated endometrial endometrioid carcinomas or undifferentiated carcinomas may have patchy PAX8 expression or even lose expression within the primary tumor or the metastasis.

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1. Introduction

Female patients with gynecological malignancies can harbor peritoneal pelvic or abdominal lesions determining advanced stage; however, other primary tumors can spread to the pelvis or abdomen as well [1]. Sampling of the peritoneum now can be easily performed by fine needle aspiration or percutaneous biopsy [2]. Occasionally, in patients with advanced stage tumors, clinicians prefer such procedures as initial attempts to establish a diagnosis. In addition, patients with a previous diagnosis of malignancy in the gynecological region can recur or develop independent primaries secondarily involving the peritoneum, highlighting the need for an accurate classification of these lesions. Not only separating benign from malignant, but tumor typing and site of origin are important. Numerous markers are currently being used to determine primary site including different subsets of cytokeratins, usually cytokeratin 7 (CK7) and cytokeratin 20 (CK20), and more specific transcription factors such as CDX2 in colon cancer or WT1 protein in ovarian malignancies to mention a few [3–6].

Recently *PAX8*, a member of the mammalian paired box genes 1 to 9 that encodes a transcription factor involved in embryogenesis has been described [7]. *PAX8* is thought to play a regulatory role in cell fate decisions during the development of the thyroid, kidney and Müllerian organs [7]. PAX8 has been reported to be expressed at a high level in ovarian cancer, and not surprisingly also in renal and thyroid cancer [7,8]. More recently, PAX8 has also been shown to be expressed in a subset of well-differentiated pancreatic neuroendocrine tumors [9]. PAX8 is expressed in pancreatic well-differentiated neuroendocrine tumors and in extrapancreatic poorly differentiated neuroendocrine carcinomas in fine-needle aspiration biopsy specimens [9]. Since it is associated with Müllerian development, it has been consistently found to be negative in non-epithelial ovarian tumors, including germ cell tumors and sex cord-stromal tumors [8]. However, most of these studies were performed retrospectively on established cases, with classic examples included.

The use of PAX8 is increasing, evidenced in the higher number of published papers on the topic. In our laboratory, we have also observed an increase in the instances the immunostain was ordered in our practice, alone or as part of a panel of immunostains. However, reliability of this immunostain in peritoneal samples to accurately classify tumor site of origin has not been well studied. We report our experience and highlight several pitfalls in the routine clinical use of PAX8, in particular, relying on the presumed expression pattern (positive or negative) within a given primary tumor.

2. Materials and methods

After institutional review board approval, a search of the pathology database to identify cases with PAX8 (rabbit polyclonal, 1/200 dilution, Protein Tech Group, Inc, Chicago, IL) ordered in female patients was performed. Cases from July 2011, when PAX8 was first available in our laboratory, until April 2013 were included. Pathology reports were reviewed as well as the histologic slides and the patients' clinical history when pertinent.

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3. Results

Immunostain for PAX8 was performed on 135 cases in a two year span; however its use increased progressively with 21 cases in 2011, 60 cases in 2012 and 54 cases in only the first three months of 2013. It was ordered 30 times in cases where renal cell carcinoma or other genitourinary lesions were exclusively in the differential diagnosis; in 18 cases where a thyroid neoplasm, primary or involving other organs was exclusively in the differential diagnosis and in 4 pancreatic neuroendocrine carcinoma cases. In the remaining 83 instances, a gynecologic malignancy was the main possible site of origin or the lesion was a high grade or undifferentiated malignancy and a gynecologic lesion was included in a broad differential diagnosis.

PAX8 was performed in multiple organ sites to rule out a metastatic carcinoma of gynecological origin or to establish a gynecologic primary; however, the most common anatomic location PAX8 was performed was the pelvic/abdominal region in 28 cases, summarized in Table 1. Of these, PAX8 was positive in 60.7% (17/28) of cases and negative in the remaining 11 cases. Based on these results, a gynecological malignancy was originally diagnosed in 13 cases; genitourinary malignancy was diagnosed in 3 cases and a thyroid-like lesion in 1 instance (peritoneal strumosis). Review of the clinical history determined that a gynecologic malignancy was ultimately the clinical diagnosis in 53.5% (15/28) cases, two more than originally determined. One of these two cases was originally interpreted as possible urothelial in origin based on focal PAX8, CK7 and CK20 positivity. However, clinical and imaging examination failed to detect a bladder, ureteral or other genitourinary lesion and the clinical diagnosis was ultimately primary peritoneal gynecological malignancy. The patient died within a 4 months of diagnosis during chemotherapy treatment.

The other case involved a female patient with a Bloom-Richardson grade II invasive ductal carcinoma of the left breast, pT1pN1 diagnosed in 1997. The carcinoma was estrogen receptor (ER) and progesterone receptor (PgR) positive and *HER2neu not* amplified (percentage or intensity of receptors not available). She was treated with breast conserving surgery followed by adjuvant chemoradiation and 5 years of tamoxifen. She had mastectomy completion in 2009 for a multifocal pT1a left breast recurrence. The recurrence had a similar histomorphology and was ER positive (95% with strong staining intensity), PgR negative and *HER2neu* amplified with a HER2/CHR 17

Table 1
Summary of peritoneal lesions

Case	Age	Biopsy site	Diagnosis	Positive immunostains	Negative immunostains	Final origin
1	64	Retroperitoneal/abdominal LN	Metastatic renal carcinoma	PAX8	CK7, CK20	Renal cell carcinoma
2	74	Retroperitoneal mass and omental LN	Poorly differentiated carcinoma GYN origin	PAX8, WT1, CK7, patchy CK20	CDX2, calretinin	Ovarian primary clinically
3	66	Omental mass	Carcinoma with clear cells, favor urothelial origin	PAX8, CK7, CK20	p16, PAX2	Primary peritoneal
4	75	Retroperitoneal mass	High-grade carcinoma, renal origin unlikely	CK7, patchy CK20	PAX8	Renal carcinoma (pax8 positive in nephrectomy)
5	61	Retroperitoneal mass	Mullerian carcinosarcoma	PAX8, WT1, p53		Ovarian carcinoma in 2009 (outside hospital)
6	40	Retroperitoneal mass	Adrenocortical neoplasm	Melan-A, inhibin, calretinin	PAX8	Adrenal primary
7	68	Peritoneum	Peritoneal strumosis	PAX8, TTF1		No thyroid carcinoma
8	88	Omentum	High-grade serous carcinoma	PAX8, WT1, CK7		Ovarian carcinoma
9	64	Omentum	High-grade serous carcinoma	PAX8, WT1, p16	p53	Primary peritoneal, not involving ovary tubes
10	53	Parametrial tissue	Metastatic colon carcinoma	CDX2, CK20	PAX8, CK7	Colon carcinoma
11	69	Omentum	High-grade serous carcinoma	PAX8, WT1, CK7, p16, p53	CK20	Primary peritoneal, involving ovarian surface and tubes
12	75	Peritoneal nodule	High-grade serous carcinoma	PAX8, WT1, CK7, p16, p53, patchy CK20	CDX2, calretinin	Treated, no residual disease in ovaries or tubes
13	57	Retroperitoneal mass	Poorly differentiated carcinoma of GI origin	CK7, CK20, CDX2	PAX8	Unknown primary
14	80	Omentum	Metastatic carcinoma, favor pancreatobilliary	CK7, CK20	PAX8, CDX2, WT1	Unknown primary, favored pancreatobilliary
15	60	Splenic hilum soft tissue	High-grade carcinoma, ovarian primary	PAX8, WT1		Ovarian carcinoma
16	65	Peritoneal mass	Neuroendocrine carcinoma, favor pulmonary	TTF1, CK7, chromogranin, equivocal PAX8	WT1	Lung carcinoma
17	72	Abdominal mass	High-grade carcinoma, ovarian primary	PAX8 WT1, CK7	CDX2, TTF1	Ovarian carcinoma
18	59	Omental mass	Leyomyoma with benign mullerian glands	PAX8	WT1, calretinin, D240	No malignancy
19	51	Peritoneal nodule	Mucinous carcinoma, favor GI origin	CK20	PAX8, CK7, WT1	Unknown primary
20	60	Peritoneal mass	High-grade carcinoma, ovarian primary	PAX8, WT1		Ovarian carcinoma
21	32	Retroperitoneal mass	Epitheloid carcinoma, favor renal origin	Patchy PAX8, AE1/AE3		Renal cell carcinoma
22	54	Mesenteric mass	High-grade carcinoma, endometrial or ovarian primary	PAX8, ER, patchy CK7, CK20	CDX2	Endometrial carcinoma
23	88	Retroperitoneal mass	High grade B-cell lymphoma	CD20	PAX8	Lymphoma
24	49	Retroperitoneal LN	Poorly differentiated adenocarcinoma, favor GI origin	CK7, CK20	PAX8, WT1	Unknown primary, favored pancreatobilliary
25	54	Retroperitoneal mass	Adrenal cortical lesion	Inhibin, calretinin	PAX8, CAM5.2	Benign adrenal neoplasm
26	70	Omentum	High-grade serous carcinoma	PAX8, WT1, CK7	CDX2, CK20	Primary peritoneal, involving ovarian surface
27	61	Omentum	High-grade serous carcinoma	PAX8, p16, p53		Primary peritoneal, involving ovarian surface
28	77	Peritoneal nodule	Metastatic mammary carcinoma		PAX8, p16, p53, ER, PR	Endometrial carcinoma

LN, lymph node; GYN, gynecologic; GI, gastrointestinal; CK, cytokeratin; ER, estrogen receptors; PR, progesterone receptors.

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