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Differential Vimentin Expression in Ovarian and Uterine Corpus Endometrioid Adenocarcinomas: Diagnostic Utility in Distinguishing Double Primaries from Metastatic Tumors

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Abstract

This study aimed to assess the diagnostic value of vimentin expression in differentiating endometrioid adenocarcinoma of primary uterine corpus and ovarian origin. Immunohistochemical analyses for the expression of vimentin in tumoral epithelial cells were performed on 149 endometrioid adenocarcinomas wherein the primary sites were not in question, including whole tissue sections of 27 carcinomas of uterine corpus origin (and no synchronous ovarian tumor), 7 carcinomas of ovarian origin (and no synchronous uterine corpus tumor) and a tissue microarray containing 91 primary uterine corpus and 24 primary ovarian carcinomas. We also assessed 15 cases that synchronously involved the uterine corpus and ovary, 15 cases of metastasis to organs/tissues other than uterine corpus or ovary as well as 7 lymph node metastases. Vimentin was negative in 97% (30/31) of primary ovarian carcinomas. In contrast, 82% (97/118) of primary uterine corpus carcinomas were vimentin-positive. Vimentin expression was discordant in 53% of synchronous tumors. The sensitivity and specificity of negative vimentin staining in predicting an ovarian primary were 97% and 82%, respectively whereas parallel values for positive vimentin staining in predicting a primary uterine tumor were 82% and 97% respectively. The pattern of vimentin expression in all cases was maintained in their respective regional lymph nodes and distant metastases. In conclusion, ovarian and uterine corpus endometrioid adenocarcinomas have different patterns of vimentin expression. If validated in larger and/or different data sets, these findings may have diagnostic value in distinguishing metastatic lesions from double primary tumors involving both sites.

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Competing interests

The author(s) declare that they have no competing interests.

Keywords

Vimentin; endometrioid adenocarcinoma; ovary; uterine corpus; double primary tumors

Introduction

When an endometrioid adenocarcinoma involves both the uterine corpus and the ovary, the challenge of distinguishing independent primary tumors from metastatic lesions from one organ to the other, are well known⁽¹⁾. This distinction, an important exercise with prognostic and management implications^(2, 3), has traditionally been based on a variety of clinicopathologic criteria that necessarily have been non-immunophenotypic in nature due to the known immunophenotypic overlap between ovarian and uterine endometrioid adenocarcinomas^(4, 5).

These clinicopathologic criteria, including those outlined by Ulbright and Roth⁽⁴⁾ as well as Scully et al⁽⁵⁾ (see Table 1) have proven to be diagnostically useful, and patients with double primary carcinomas (DPC) diagnosed based on these criteria generally have a significantly better prognosis than their counterparts with unequivocally metastatic tumors from one organ to the other^(1, 6–9). Nevertheless, these criteria are not optimally applicable in every case, which results in uncertainty regarding the necessity for adjuvant chemotherapy. At the molecular level, microsatellite instability (MSI) and X-linked clonality analyses have been reported to be helpful tools in diagnosing single or double clonal tumors in the uterine corpus and ovary, with 82% sensitivity if conventional histopathologic criteria is considered to be the gold standard^(10–12). Additionally, loss of heterozygosity (LOH)^(10, 13) and PTEN^(12, 14) mutational analysis have also been reported as useful investigative tools in differentiating primary versus metastatic endometrioid carcinoma.

Vimentin protein is a type III intermediate filament protein that is widely expressed in mesenchymal tissue. Collectively with other microtubules and actin microfilaments, vimentin plays a significant role in making up the cytoskeleton to maintain the cell shape, integrity, and stabilizing epithelial mesenchymal cellular interactions. Additionally, vimentin works as an organizer of a number of other proteins involved in attachment, migration, and cell signaling⁽¹⁵⁾. Vimentin expression by immunohistochemistry is widely applied and is a well-known marker reported to be, in combination with other markers, a helpful marker in differentiating endometrial and endocervical adenocarcinomas⁽¹⁶⁾. We assess herein the diagnostic value of vimentin expression by immunohistochemistry in distinguishing primary uterine corpus from primary ovarian endometrioid carcinomas and its value in resolving these diagnostic scenarios.

Materials and Methods

This study was approved by Vanderbilt University School of Medicine institutional review board. Immunohistochemistry (IHC) with the mouse monoclonal anti-Vimentin antibody (clone V9 from Leica Microsystems, Cat# RTU-VIM-V9), was performed on archived full face section cases of different grades and stages from endometrioid adenocarcinoma 1) of uterine corpus with no ovarian tumor (n=27), 2) of ovarian primary with no uterine corpus

tumor (n=7), 3) metastatic to sites other than uterine corpus or ovary (n=15), 4) involving uterus and ovary (n=15) and thought to be a) synchronous primaries by traditional criteria of Scully et al⁽⁵⁾ (7/15), b) metastatic from uterine corpus to ovary (7/15), c) metastatic from ovary to uterine corpus (1/15), 5) metastatic to regional lymph nodes (n=7), and 6) tissue microarray (TMA) slides containing 91 primary uterine corpus and 24 primary ovarian endometrioid carcinomas as well as normal endometrial (n=4) and ovarian (n=2) tissue (obtained from US Biomax, Inc.). Color was developed with DAB+ chromogenic substrate and hematoxylin was used as counterstain.

Vimentin expression was semiquantitatively scored as negative (no staining), weak/focal (1–10% positive), intermediate (11–50% positive) and strong (>50%) crisp and intense positive perinuclear band depending on the percentage of positive cells and intensity of staining⁽¹⁷⁾. Simple binary “negative/positive” vimentin status was used for analysis.

Results

Table 2 summarizes the clinicopathologic data of patients with endometrioid adenocarcinoma of primary uterine corpus and ovarian origin. Table 3 summarizes the results of vimentin expression in endometrioid adenocarcinoma of primary uterine corpus and ovarian origin (no synchronous uterine and ovarian tumors). Eighty-two percent (97/118) of primary uterine corpus carcinomas were vimentin-positive (Figure 1A). In contrast, vimentin expression was negative in 97% (30/31) of primary ovarian endometrioid carcinomas (Figure 1B). The breakdown of vimentin expression results for the whole tissue sections and TMA cases were as follows: 24/24 (100%) TMA ovarian endometrioid adenocarcinomas were negative for vimentin expression compared to 6/7 (86%) negative full face sections. On the other hand, 1/27 (4%) pure uterine corpus full face endometrioid adenocarcinomas were negative for vimentin expression compared to 20/91 (22%) negative TMA sections (Table 3).

The pattern of vimentin expression in the endometrioid tumors was maintained in their respective regional lymph nodes and distant metastases. Endometrioid adenocarcinomas metastatic to regional lymph nodes from primary uterine corpus origin (n=3) were positive for vimentin expression. In contrast, endometrioid adenocarcinoma metastatic to regional lymph nodes from primary ovarian origin (n=1) was negative for vimentin expression (Table 4). Endometrioid adenocarcinoma of primary uterine corpus (n=10) metastatic to organs/tissue other than ovary [omentum (1), lung (2), bone (2), soft tissue (2), spleen (1), supraclavicular LN (1), and vagina (1)] were positive for vimentin expression. In contrast, endometrioid adenocarcinoma of primary ovarian origin (n=2) metastatic to organs/tissue other than uterine corpus [omentum (1), and colon (1)] were negative for vimentin expression (Table 4).

Tables 5&6 summarize the clinicopathologic, vimentin expression and rationale for original classification data for cases with synchronous endometrioid carcinoma of uterine corpus and ovary(ies). Seven cases originally interpreted as double primary tumors by traditional criteria of Scully et al⁽⁵⁾ (Table 6) were vimentin positive in 5 and 2 uterine corpus and ovarian tumors, respectively (Figure 1C & D). Seven cases originally interpreted as

metastatic tumors from the uterine corpus to the ovary were vimentin positive in 6 and 4 uterine corpus and ovarian tumors, respectively (Figure 1E–H). One cases originally interpreted as metastatic tumors from the ovary to the uterine corpus was vimentin positive in both organs (Table 5).

No correlation was identified between vimentin staining and tumor grade or clinical stage. All endometrial glands in benign cases (n=4) strongly expressed vimentin. Normal ovarian stroma and benign inclusion cyst epithelium strongly express vimentin (n=2).

The sensitivity, specificity, positive predictive value and negative predictive value calculated from cases with no synchronous tumors (uterine corpus=118 and ovarian=31) of positive vimentin staining in predicting a primary uterine corpus tumor were 82%, 97%, 99% and 59%, respectively. The sensitivity, specificity; positive predictive value and negative predictive value for negative vimentin staining in predicting a primary ovarian tumor were 97%, 82%, 59% and 99%, respectively.

Discussion

The diagnosis of synchronous endometrioid adenocarcinomas of uterine corpus and ovary as double primary or metastatic tumors requires a wholistic consideration of gross, microscopic, immunohistochemical and molecular factors^(12, 18, 19), with any resultant conclusions having important implications for appropriate diagnosis, prognosis, staging and treatment. Conventional pathological features (Table 1) will permit the distinction in most cases^(4, 5, 18). However, a subset of cases will exhibit overlapping criteria and followup may be the single most conclusive factor⁽¹⁸⁾. In addition to conventional histomorphologic criteria, ancillary techniques would be required to solve these problems.

One of the ancillary techniques to differentiate double primary from metastatic carcinoma is using molecular methods as microsatellite instability (MSI)^(20–22), mutations in PTEN⁽²³⁾ and the beta-catenin genes (CTNNB1)^(18, 24, 25). Endometrioid carcinomas of primary ovarian origin have been reported to exhibit similar frequency of beta - catenin abnormalities and lower incidence of MSI and PTEN mutations compared to uterine corpus counterparts⁽²¹⁾. Of particular note, beta-catenin/CTNNB1 has been reported to provide important diagnostic and prognostic information in the distinction of double primary versus metastatic tumors⁽¹⁸⁾. MSI has been reported in 50% and 33% of double primary uterine corpus and ovarian carcinoma, respectively⁽¹⁸⁾.

Double primary tumors mostly show similar immunohistochemical profiles^(26, 27), and as such IHC has generally been considered to be of limited utility in this distinction. However, it has been reported that metastatic tumors from one organ to the other may show distinct profiles for bcl-2, ER, and PR in a subset of cases⁽²⁷⁾. Although vimentin is well known to be strongly positive in endometrioid adenocarcinoma of primary uterine corpus origin, and is useful in the distinction of the latter from endocervical adenocarcinomas, its expression in primary ovarian endometrioid carcinoma has not been analyzed in detail previously^(28–32).

In the current study, we investigated the usefulness of vimentin as a single marker in the distinction of endometrioid carcinomas of primary uterine corpus origin from those of

ovarian origin. We found that vimentin was expressed in 82% of uterine corpus cases not associated with synchronous ovarian tumors, which is broadly consistent with previously reported findings^(28, 30). We also found that 97% of ovarian endometrioid adenocarcinoma cases (not associated with synchronous uterine corpus counterpart) were negative for vimentin. The latter is in contrast to single published report showing a relatively high expression rate of vimentin in ovarian endometrioid carcinoma (31%)⁽³⁰⁾. One possible cause for this discrepancy could be related to methodological differences, given the use of TMA in the present study compared to full face sections in Dabbs et al study⁽³⁰⁾. In the current study 24/24 (100%) pure ovarian endometrioid adenocarcinomas were negative for vimentin expression compared to 6/7 (86%) negative full face sections (Table 3).

The sensitivity, specificity, positive predictive value and negative predictive value for positive vimentin staining in predicting a uterine corpus tumor were 82%, 97%, 99% and 59%, respectively and that for negative vimentin staining in predicting a primary ovarian tumor were 97%, 82%, 59% and 99%, respectively. Although we considered alternative diagnoses of serous carcinoma and metastatic colonic cancer to potentially explain lack of vimentin expression in our cases, these were excluded based on morphological features and/or clinical findings.

Fifteen cases of synchronous uterine corpus and ovarian endometrioid adenocarcinomas have been included in the current study: None of the cases were known to have a history of primary endocervical adenocarcinoma. Vimentin expression was discordant in 10/30 tumors (33%) with negative expression in cases considered by conventional criteria to be uterine corpus (6/21; 29%) and was positive in cases considered to be ovarian (4/9; 44%). The frequency of discordant cases exceeded the sensitivity and specificity of vimentin expression in cases without synchronous tumors especially in predicting ovarian origin of the tumor (Tables 5 & 6). However, Vimentin expression should be considered along with histomorphologic and clinical data for classification of synchronous tumors as double primaries or metastatic from one organ to the other. Follow up data of clinical outcome may benefit in this setting especially for those cases with discordant results being metastatic from one organ to the other rather than double primaries. However, due to the nature of the study, follow up data were not available.

In conclusion, ovary and uterine corpus endometrioid adenocarcinomas have different patterns of vimentin expression, with vimentin negativity having a high sensitivity and specificity for primary ovarian tumors and vimentin positivity having the same for primary endometrial tumors. As such, vimentin expression, in addition to conventional clinicopathologic criteria, may be an excellent diagnostic adjunct in differentiating endometrioid adenocarcinomas of primary uterine corpus from primary ovarian origin, for diagnosing double primary tumors of both sites and metastatic lesions from one site to the other, a distinction of immense clinical significance. If these preliminary findings are validated in larger and/or different datasets, vimentin immunohistochemistry may be useful in the resolution of diagnostic problems in this challenging area.

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Image 1.

Vimentin expression in endometrioid adenocarcinoma of uterine corpus and ovarian origin. Pure uterine (A) and ovarian (B) tumors with positive and negative vimentin expression, respectively. Synchronous primary tumors of the uterine corpus (C) and the ovary (D) with positive and negative vimentin expression, respectively. Primary (E) and metastatic uterine corpus carcinoma to the ovary (F) with positive vimentin expression in both organs. Discordant uterine corpus (G) and ovarian (H) tumors originally classified as synchronous double primaries with positive vimentin expression in both organs.

Table 1

Histopathologic criteria of independent primary endometrioid tumors of the uterine corpus and ovary⁽⁵⁾

1. Morphologically dissimilar tumors
2. No (or superficial) myometrial invasion
3. No lymphovascular invasion in the uterine corpus or ovaries
4. Absence of spread to other organs or tissue
5. Presence of atypical endometrial hyperplasia
6. Unilateral involvement of ovaries (~90%)
7. Ovarian parenchyma involvement (no ovarian surface implants)
8. Endometriosis of the ovaries
9. Different DNA ploidy
10. Divergent molecular genetic or karyotypic abnormalities

(5) see corresponding reference

Table 2

Clinicopathological data of uterine corpus and ovarian endometrioid adenocarcinoma

Variable	Primary uterine corpus origin (n=118)	Primary ovarian origin (n=31)
Age (years)		
Mean	58	57
Range	31–78	34–80
Tumor grade ⁽³³⁾		
Grade 1	36	7
Grade 2	58	9
Grade 3	24	15
FIGO* stage ^(34, 35)		
Stage I	85	17
Stage II	3	5
Stage III	3	2
Stage IV		1

* FIGO= International Federation of Gynaecological Oncologists

(33, 34 and 35): see corresponding references

Table 3
Differential vimentin expression in uterine corpus and ovarian endometrioid adenocarcinoma

Vimentin (IHC)*	Primary uterine corpus		Primary ovarian		
	TMA [†]	Full face sections	Total	TMA [†]	Full face sections
Negative	20 (22%)	1 (4%)	21 (18%)	24 (100%)	6 (86%)
Weak/focal	24 (26%)	0 (0%)	24 (20%)	0	0
Intermediate	15 (16%)	2 (7%)	17 (14%)	0	0
Strong	32 (35%)	24 (89%)	56 (47%)	0	1 (3%)
Total	91	27	118	24	7
					31

[†]TMA=Tissue microarray

* Vimentin expression was semiquantitatively scored as negative (no staining), weak/focal (1–10% positive), intermediate (11–50% positive) and strong (>50%) crisp and intense positive perinuclear band depending on the percentage of positive cells and intensity of staining.

Table 4

Differential vimentin expression in lymph nodes and distant metastasis from uterine corpus and ovarian endometrioid adenocarcinomas

Vimentin (IHC)	Primary uterine corpus origin		Primary ovarian origin	
	Lymph node met [*]	Distant met [*]	Lymph node met ^{**}	Distant met ^{**}
Negative	0	0	1	2
Weak/focal	0	1	0	0
Intermediate	1	1	0	0
Strong	2	8	0	0
Total	3	10	1	2

* The corresponding primary tumors were positive for vimentin with equivalent IHC score

** The corresponding primary tumors were negative for vimentin.

Table 5

Clinicopathologic and differential vimentin expression in synchronous uterine corpus and ovarian endometrioid adenocarcinomas.

Case #	Age (years)	Vim UC	Vim OV	Vim LN	Vim distant	Original interpretation	Concordance ^I
1	46	3	0			DPT	Yes
2	66	3	0			DPT	Yes
3	51	1	0		0*	DPT	Yes
4	43	0	0			DPT	Met from ov
5	43	0	0			DPT	Met from ov
6	55	3	3			DPT	Met from UC
7	37	3	3			DPT	Met from UC
8	44	3	3			Met from UC	Yes
9	66	3	3			Met from UC	Yes
10	65	3	3	0		Met from UC	Yes
11	75	3	3	3		Met from UC	Yes
12	82	0	0	0	0**	Met from UC	Met from ov
13	63	3	0			Met from UC	DPT
14	62	3	0		3***	Met from UC	DPT
15	41	3	3			Met from ov	Met from UC
	mean 56						

* Metastasis to pericolic fat;

** metastasis to Perirectal fa,

*** metastasis to soft tissue of abdominal wall

^I Concordance with original interpretation, vimentin positive tumor is hypothetically considered of uterine corpus origin and negative one is considered to be of ovarian origin.

Distant=Metastasis to sites other than UC or ovary; DPT=Double primary tumors; LN=Metastasis to lymph nodes; Met=Metastasis; OV=Ovarian tumor; UC= Uterine corpus tumor; Vim= Vimentin expression by IHC;.

Table 6

Rationale for original classification of synchronous uterine corpus and ovarian endometrioid adenocarcinomas (criteria listed in table 1 above).

Case #	UC tumor grade/size (cm)	OV tumor grade/size (cm)	Morphologic similarity	Myometrial invasion	Lympho-vascular invasion	Distant met	Atypical endometrial hyperplasia	Laterality of ovarian involvement	Ovarian surface implants	Endometriosis of the ovary(ies)
1	1/0.8	1/0.5	Similar	5%	Absent	No	Present	Unilateral	Absent	Present
2	2/6	1/U	Dissimilar	63%	Absent	No		Unilateral	Present	Present
3	1/2.6	1/11.5(L) 3/6.5 (R)	Dissimilar	5%	Absent	Pericolic fat	Absent	Bilateral	Absent	Absent
4	1/U	1/3.5	Similar	12%	Absent	No	Present	Unilateral	Absent	Absent
5	2/2	2/21(L) 2/19 (R)	Similar	24%	Absent	omentum		Bilateral		Absent
6	1/3	1/27	Similar	22%	Present	No	Present	Unilateral	Absent	Absent
7	2/1.5	2/3.5	Dissimilar	0%	Absent	No	Present	Unilateral	Absent	Present
8	1/3	1/0.5	Similar	0%	Absent	No	Absent	Unilateral	Present	
9	1/10	1/7.2	Similar	66%	Absent	FT, cx	Absent	Unilateral	Absent	
10	2/6	2/0.1	Similar	67%	Absent	pelvic LNs	Absent	Unilateral	Absent	Present
11	3/5.9	3/0.1 (L) 3/0.4 (R)	Similar	38%	Absent	cx	Absent	Bilateral	Absent	Absent
12	2/2	2/U	Similar	56%	Present	Perirectal fat, multiple LNs, pelvic soft tissue	Absent	Unilateral	Absent	Absent
13	2/7	2/27	Similar	58%	Absent	cx, pelvic soft tissue, LNs	Absent	Unilateral	Present	Absent
14	1/3.2	1/6.5	Similar	0%	Absent	Abdominal soft tissue	Hyperplasia without atypia	Unilateral	Absent	Absent
15	1/3.5	1/5 (L) 1/12 (R)	Dissimilar	60%	Absent	no	Absent	Bilateral	Absent	Present

Cx=uterine cervix; Distant=metastasis to sites other than UC or ovary; FT=fallopian tube; L=left; LN=metastasis to lymph nodes; Met=Metastasis; OV=Ovarian tumor; R=right; U=unknown; UC= uterine corpus tumor