Case Report

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DOI: 10.4103/pjog.pjog_35_21

Synchronous endometrioid endometrial and serous ovarian carcinoma: A double gynecologic jeopardy

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Abstract:

Synchronous malignant tumors are two primary tumors diagnosed at the same time during surgery. A postmenopausal, nulligravid, presented with vaginal bleeding. Ultrasound revealed an endometrial and right ovarian mass, both with nonbenign features. Cancer Antigen 125 and Human Epididymis Protein 4 were elevated. She underwent extrafascial hysterectomy with bilateral salpingo-oophorectomy with the frozen section of the endometrium and right ovary, followed by complete surgical staging. Histopathology report was endometrioid endometrial carcinoma and high-grade serous ovarian carcinoma. The endometrial and ovarian tissues tested positive for vimentin and Wilm's Tumor 1 (WT1), respectively, suggesting both are primary independent tumors. The pelvic lymph nodes and recto-sigmoid lymph nodes tested positive for vimentin and negative for WT1, suggesting endometrial tumor metastasis. The final diagnosis is synchronous endometrioid endometrial carcinoma Stage IIIC1 and high-grade serous ovarian carcinoma Stage IA, right ovary.

Keywords:

Endometrioid endometrial carcinoma, serous ovarian carcinoma, synchronous malignant tumors, vimentin, Wilm's tumor 1

Introduction

To be diagnosed with cancer is quite devastating for an individual. More so, if the individual was diagnosed to have two independent tumors at the same time! What gynecologic double jeopardy! Synchronous malignant tumors are two primary tumors diagnosed at the same time during surgery. Due to its rare occurrence and limited publications available on synchronous endometrioid endometrial and high-grade serous ovarian carcinoma, this case of a 58 year-old, nulligravid, who presented with postmenopausal vaginal bleeding, endometrial and ovarian masses with nonbenign features by ultrasound, elevated cancer antigen 125 and epididymis protein 4 and who subsequently underwent extrafascial hysterectomy with bilateral salphingo-oophorectomy with the frozen section of the endometrium and right ovary, bilateral lymph node dissection, is being presented. Immunohistochemistry staining was used to establish the primary tumor and which tumor metastasized.

Case Report

This is a case of a 58-year old, nulligravid, postmenopausal, with intermittent vaginal bleeding for 7 months, consuming one pad per day, moderately soaked, accompanied by pallor and easy fatigability. There were no other associated symptoms. She has no family history of cancer.

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Submitted: 05-May-2021
Accepted: 31-May-2021
Published: 13-Dec-2021

*Second Place, 2021 PHILIPPINE OBSTETRICAL AND GYNECOLOGICAL SOCIETY (Foundation), INC. (POGS) Residents' Interesting Case Contest, July 05, 2021, Online Platform: ZOOM Webinar

How to cite this article: Crimen AV, Martin NA, Marinas MK. Synchronous endometrioid endometrial and serous ovarian carcinoma: A double gynecologic jeopardy. Philipp J Obstet Gynecol 2021;45:204-9.

Pertinent physical examination revealed flabby, soft abdomen, with palpable mass on the right lower quadrant area, movable, nontender, measuring 6 cm × 7 cm. The internal examination result was cervix is small, almost flushed to the vault, deviated to the left. The uterus is slightly enlarged to 2 months size. There is a movable, solid mass on the right anterolateral of the uterus measuring 6 cm × 7 cm.

Transvaginal ultrasound with Doppler revealed an enlarged anteverted uterus measuring 6.84 cm × 6.5 cm × 5.67 cm with endometrial thickness of 4.41 cm, within the endometrial cavity is a heterogeneous mass measuring 6.05 cm × 5.28 cm × 4.3 cm with the moderate flow on color mapping with nonbenign features. The cervix is unremarkable. The right ovary measuring 6.18 cm × 6.55 cm × 5.02 cm converted into multilocular solid cystic structure with mixed level echoes with solid component measuring 3.69 cm × 2.96 cm exhibiting moderate flow on color mapping. Ovarian new growth, right, with nonbenign sonomorphologic features by IOTA simple rules, LR2 and IOTA ADNEX model [Table 1]. The left ovary is atrophied.

Tumor markers, cancer antigen 125, and human epididymis protein 4 are elevated at 3274.54 U/ml and at 611.7 pmol/L, respectively.

The initial plan of doing an endometrial biopsy was deferred due to a small cervix, which is almost flushed to the vault, making it difficult to do the procedure. With the high consideration of malignancy, frozen section of both endometrium and ovary is contemplated with extrafascial hysterectomy with bilateral salphingo-oophorectomy and complete surgical staging.

Intraoperatively, the uterus is slightly enlarged measuring 7 cm × 6 cm × 3.5 cm with smooth serosa on the external surface. On cut section, a soft, friable, tan to white, brain-like tissue occupying the entire endometrial cavity measuring about 3.5 cm, invading more than half of the myometrium [Figure 1]. The endometrium is thick measuring 1.4 cm. The right ovary

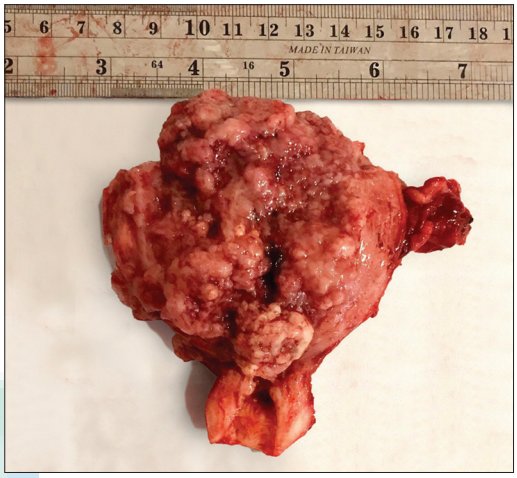

Figure 1: Cut section of the uterus, a soft, friable, tan to white, brain-like tissue occupying the entire endometrial cavity measuring about 3.5 cm, invading more than half of the myometrium

Table 1: IOTA simple rules; LR2 and ADNEX model result

IOTA Simple r			ules: Malignant		diameter
Benign features			Malignant features		
B1: Unilocular			/M1:Irregular solid tumor M2: Presence of ascites		
B2: oresence of solid components where the largest solid component has a diamtere of <7 mm			M3: ≥ papillary structures		
B3: Presence of acoustic shadows			M4: Irregular multilocular solid tumor with largest ≥100mm		
B4: Smooth multilocular tumor with largest diameter <100 mm:			M5: Very strong blood flow (Color score 4)		
B5: No blood flow (Color score 1)					
Logistic Regression 2			**ADNEX MODEL**		
Age	58		Age	58	
	yes	no			+/-
Presence of ascites		/	Referral from Oncology center		no
Presence of papillations with detectable blood flow		/	Maximal diameter of the lesion (mm)		65.5
Maximum diameter of largest solid component (mm)	65.5		Maximum diameter of largest solid component (mm)		36.9
Irregular cyst walls		/	More than 10 locules?		yes
Presence of acoustic shadows		/.	Number of papillations (papillary projections)		None
Computed LR2: 54.2%			Presence of acoustic shadows		no
Normal cut-off for benignity ≤ 10%			Ascites	no	
			Serum Ca-125 (U/ml)		
Computed chance of benign tumor				41.1%	
Computed risk of malignant tumor:				58.9%	
Computed risk of borderline tumor:				14.0%	

Table 2: Scully's Clinicopathologic Criteria

	Endometrial Primary with Ovarian Mets	Ovarian Primary with Endometrial Mets	Independent Primary Tumors
Histology	Similar	Similar	Dissimilar
Location	Deep myometrial invasion. Direct extension into the adnexa. Vascular space invasion in myometrium or combination in ovary	Ovarian tumor in parenchyma. Direct extension from ovary into outer wall uterus	No or only superficial myometrial invasion of endometrial tumor. Ovarian tumor located in parenchyma
Unilateral/Bilateral involvement	Ovarian tumor bilateral and/or multinodular	Ovarian tumor unilateral	Ovarian tumor unilateral
Metastasis	Spreads in typical pattern of Endometrial Carcinoma	Spreads in typical pattern of Ovarian Carcinoma	Absence of other evidence spread of ovarian tumor

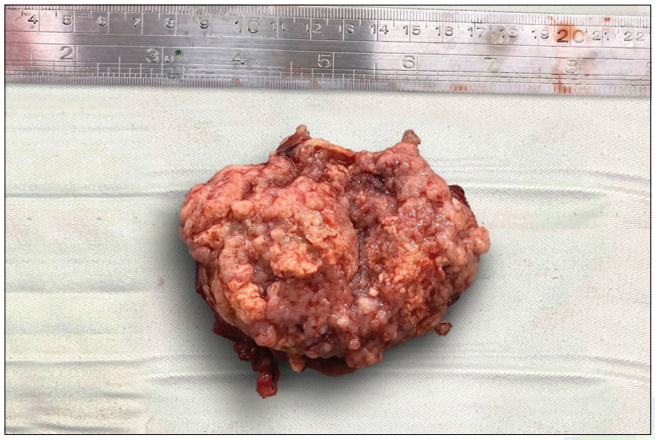

Figure 2: Cut section of the right ovary, a solid area was seen measuring 4 cm × 7 cm × 1 cm

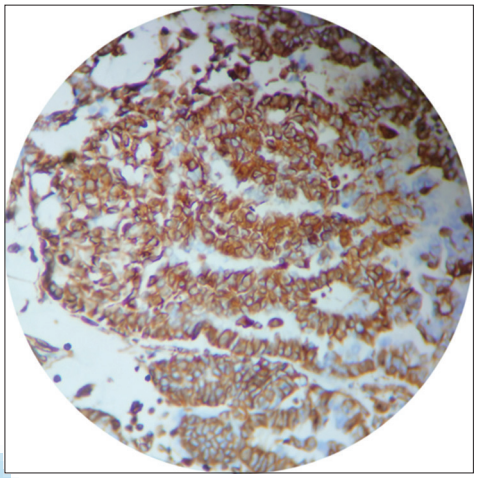

Figure 3: Immunohistochemistry staining of the endometrial tissue with vimentin revealed compatible with endometrioid carcinoma with strong cytoplasmic staining of 80%–90% tumor cells

is converted to a multilocular cystic structure measuring 5 cm × 9 cm × 3 cm with smooth external surface. On cut section, it contained serous fluid within, with solid area measuring 4 cm × 7 cm × 1 cm [Figure 2]. The cervix, bilateral fallopian tubes, and left ovary are grossly normal. There was a solid whitish round mass measuring 2 cm × 2 cm attached to the serosa of the sigmoid colon. Hence, colporrhaphy was done. Bilateral external and internal iliac and obturator lymph nodes are enlarged with sizes ranging from 0.5 to 2 cm. The estimated blood loss was 800 cc.

The postoperative course was unremarkable. She was discharged on her fourth postoperative day.

Microscopic findings of the right ovary showed ovarian tissue harboring a neoplastic tumor arranged in solid sheets and papillary pattern with individual cells exhibiting pleomorphism with hyperchromatic nuclei, coarse chromatin pattern, and prominent nucleoli. Microsections of endometrium showed endomyometrial tissue harboring a neoplastic tumor arranged in inconspicuous glandular and papillary patterns and some forming solid sheets. The cells exhibit pleomorphism with hyperchromatic nuclei, coarse chromatin pattern, and prominent nucleoli. The tumor is seen invading less than half of the myometrium. Likewise seen in the lower uterine segment, which showed lymph-vascular invasion of tumor cells. Microsections of three out of eleven pelvic lymph node tissues (right internal iliac, left internal iliac, left obturator) and one rectosigmoid lymph node showed malignant tumor invasion. Microsections of the cervix, bilateral fallopian tubes parametria, omentum has no tumor cell invasion. Histopathologic results revealed high-grade serous carcinoma, right ovary with tumor size of 8.5 cm in widest diameter, endometrioid endometrial carcinoma, grade II, involving <50% of the myometrium with tumor size of 5 cm in widest diameter and with present lympho-vascular space invasion.

Immunohistochemical staining of the endometrial tissue with vimentin was compatible with endometrioid endometrial carcinoma with strong cytoplasmic staining of 80%–90% tumor cells [Figure 3]. Immunohistochemical staining of the ovarian tissue with Wilm's Tumor 1 (WT1) was compatible with serous ovarian carcinoma with moderate-to-strong nuclear staining of 50%–60% of tumor cells [Figure 4]. Immunohistochemical staining of the three pelvic lymph nodes and recto-sigmoid mass were all positive with vimentin and negative with WT1 [Table 2].

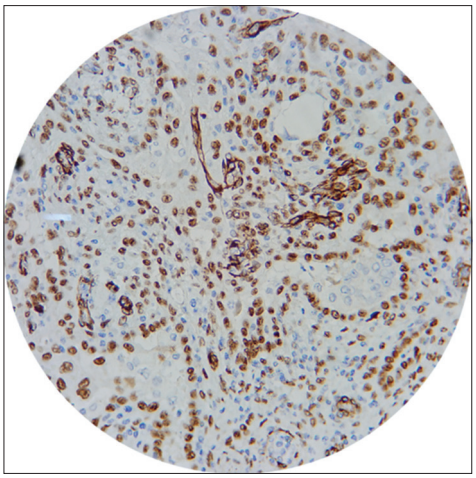

Figure 4: Immunohistochemistry staining of the ovarian tissue with WT1 revealed compatible with serous carcinoma with moderate to strong nuclear staining of 50%–60% of tumor cells

Case Discussion

Synchronous malignant tumors are two primary tumors diagnosed at the same time during surgery. Globally, the incidence rate of all gynecologic malignancies is 0.7%–1.8%.[1] In one local government hospital in the Philippines, the incidence rate of synchronous gynecologic malignancy is 0.66%. Endometrioid is the most common histologic type of synchronous carcinoma of the uterus and ovary, which accounts for 24.3% to 50.2%. Synchronous endometrial involvement is uncommon with serous high-grade carcinoma of the ovary.[2]

Differential Diagnosis

Endometrial tumors commonly present as vaginal bleeding in postmenopausal women. Ovarian tumors are hardly diagnosed early, as the symptoms can be vague or absent, but commonly presents in the late stages with abdominal pain, abdominal distension, and postmenopausal bleeding. independent primary endometrial and ovarian tumors should be differentiated from primary endometrial cancer with metastasis to the ovary and primary ovarian cancer with metastasis to the endometrium.

Scully *et al*. proposed certain clinicopathologic postoperative criteria to differentiate these three based on histology, tumor size, atypical hyperplasia, tumor location, the pattern of metastasis, unilateral or bilateral involvement, presence or absence of endometriosis, DNA indices, and karyotypic abnormalities.[2] The index case has met the following clinicopathologic postoperative criteria of Scully, *et al*. for independent primary endometrial and ovarian tumors which include histologic dissimilarity of the tumors, superficial myometrial invasion of the endometrial tumor, ovarian tumor located in the parenchyma, unilateral ovarian tumor, and absence of other evidence of spread of the ovarian tumor. To further address our question on which is the primary tumor and which tumor metastasized, immunohistochemistry staining was done.

Risk Factors Associated

The risk factors for both endometrial cancer and ovarian cancer are similar except for ovulation, which diminishes the risk for endometrial cancer whereas ovulation increases the risk for ovarian cancer. Other factors that increase the risk for Endometrial and Ovarian cancers are early onset of menarche, short or irregular menstrual cycle length, greater number of ovulatory cycles, nulliparity, late onset of menopause, use of menopausal hormones, particularly estrogen, high body mass index, polycystic ovarian syndrome, genetics, and the use of talc.[3] The risk factors presented by the index case are early menarche at the age of 10 years and nulliparity.

Pathogenesis

Endometrial and ovarian carcinomas from members of a family frequently display a mutator phenotype as manifest by high levels of microsatellite instability (MSI). MSI occurs in 17%–32% of sporadic endometrial carcinomas, more common among endometrial carcinomas with endometrioid histology and 3%–17% of sporadic ovarian carcinomas display MSI. It is hypothesized that there might be a higher rate of MSI in tumors from women with synchronous primary carcinomas of the ovary and endometrium. Microsatellites are repeat sequences of one to several DNA bases. Repeat errors during DNA replication are likely to occur in these regions and are usually repaired by DNA mismatch repair (MMR) genes. Germ-line defects in DNA MMR genes result in a tumor replication error repair phenotype that is detectable as generalized instability of short, tandemly repeated DNA sequences. MSI is characterized by the accelerated accumulation of single nucleotide mutations and alterations in the length of microsatellite sequences leading to the development of neoplastic lesions.[4]

Diagnostic Modalities

Endometrial biopsy is the diagnostic choice for women suspected of endometrial cancer with a sensitivity of 90%.[5] However, this procedure was deferred due to a small cervix, almost flushed to the vault making it difficult to do the procedure.

Transvaginal ultrasound can measure deep myometrial invasion in uterine malignancy with a sensitivity of 83%

and specificity of 72%. Transvaginal ultrasound has 92% sensitivity and 59% specificity for diagnosing ovarian cancer. Additional Doppler studies can be helpful in the preoperative evaluation by providing better vascular characteristics of the ovarian masses.[5]

Tumor markers, Cancer Antigen 125 (CA125) and human epididymis protein 4 are elevated at 3,274.54 U/ml (normal value in postmenopausal is <35 U/ml) and at 611.7 pmol/L, (normal value in postmenopausal is <140 pmol/L), respectively. CA125 and HE4 are both elevated in ovarian and endometrial carcinomas.[5]

Immunohistochemistry staining is an important application of monoclonal or polyclonal antibodies to determine the tissue distribution of a certain antigen, particularly important for the diagnosis of cancers. The application of immunohistochemistry staining, in this case, has two objectives:

- To determine which tumor is of primary origin and independent
- To determine which tumor metastasized.

Selection of Stain to Determine Primary Tumor

The tumor antigen receptors expressed in Serous Ovarian Cancer are CK7, WT1 and CA 125, ER/PR (up to 50% of cases), and p53 in 30%–50% of cases. ER and PR expression is weak in poorly differentiated endometrioid carcinomas, serous and clear-cell carcinomas.[6] A recent study by Acs *et al*. found no WT1 expression in serous carcinomas of the endometrium, suggesting that WT1 could be useful in identifying the primary site of serous ovarian carcinomas.[7] The sensitivity for the staining of serous carcinoma is high, and nuclear staining is seen in more than 90% of cases reported in some studies. For metastatic serous carcinoma of endometrial origin, p53 and WT1 are both negative.[8]

In a study by Desouki *et al*., vimentin was negative in 97% of primary ovarian carcinomas. In contrast, 82% of primary uterine corpus carcinomas were vimentin positive. The sensitivity and specificity of negative vimentin staining in predicting an ovarian primary tumor were 97% and 82%, respectively, whereas parallel values for positive vimentin staining in predicting a primary uterine tumor were 82% and 97%, respectively.[9]

Hence, WT1 for the ovarian tissue and vimentin for the endometrial tissue were selected for immunohistochemistry staining to determine which tumor is of primary origin and independent. The results revealed that both endometrial and ovarian tumors were positive for vimentin and WT1, respectively, suggesting that both tumors are primary and independent of origin. This is further supported by their dissimilarity of histologies, endometrioid for endometrial carcinoma, and serous high grade for ovarian carcinoma.

To determine which of the two tumors metastasized, both vimentin and WT1 were used to stain all the three pelvic lymph nodes and the recto-sigmoid lymph node, which were histologically positive for metastasis. Immunohistochemistry staining results revealed all three pelvic lymph nodes and recto-sigmoid lymph nodes were positive for vimentin and negative for WT1, suggestive of endometrial cancer metastasis.

Staging

Endometrial Cancer with metastasis to the pelvic lymph nodes and recto-sigmoid lymph node, is classified as FIGO Stage IIIC1 while the High-Grade Serous Ovarian Cancer with tumor limited to one ovary with intact capsule, is classified as FIGO Stage IA.[5] The Endometrial Carcinoma Stage IIIC1 is further supported by the Vimentin-positive pelvic and recto-sigmoid lymph nodes. A WT1-negative pelvic and recto-sigmoid lymph nodes further support the high-grade serous ovarian carcinoma Stage IA. A negative WT1 also provides evidence of the absence of spread of the ovarian tumor and supports Scully's clinic-pathologic postoperative criteria for independent primary tumors. The final staging is synchronous endometrioid endometrial carcinoma Stage IIIC1 and high-grade serous ovarian carcinoma Stage IA, right ovary.

Management

Chemotherapy

Chemotherapy for synchronous endometrioid endometrial Stage IIIC1 and high-grade serous ovarian carcinoma Stage IA will follow the treatment protocol for the tumor in the more advanced stage. Chemotherapy for endometrial carcinoma Stage IIIC1 will include carboplatin area under the curve 5 + paclitaxel 175 mg/m2/3 h every 4 weeks for six cycles followed by pelvic external beam radiotherapy with vaginal brachytherapy.[5]

Metastatic work-up

A positron emission tomography/computed tomography (PET/CT) scan or magnetic resonance imaging (MRI) should be carried out to rule out extrauterine metastasis, especially in the advanced stages. A repeat CA 125 postsurveillance is suggested since it corresponds to the residual tumor volume. It can be used to monitor for tumor progression or recurrence. A ≥75% decline of CA-125 may reflect the decrease of tumor burden and better outcomes before starting chemotherapy.[10]

Postsurgical surveillance monitoring

The recommended follow-up schedule is every 3 months in the first 0–2 years postsurgery, every 6 months in the next 2–5 years postsurgery, and yearly thereafter, if more than 5 years postsurgery with a repeat CA 125 and CT/PET when recurrence is suspected.[5]

Prognosis

Late-stage endometrial cancer has a poor prognosis with a 17% 5-year survival rate.[5] The patient was lost to follow-up for a year. She returned with a progressive disease and unfortunately succumbed to death.

Summary

A case report of a rare synchronous endometrioid endometrial and serous ovarian carcinoma in a 58-year old, nulligravid, postmenopausal woman with vaginal bleeding has been presented. Synchronous endometrioid endometrial involvement is uncommon with serous high-grade carcinoma of the ovary. Independent Primary Tumors should be differentiated from Primary Tumor of the Endometrium or the Ovary with metastasis. Early menarche and nulliparity are associated with increased risk for endometrial and ovarian cancers. The pathogenesis of synchronous tumors may be explained by the high levels of MSI, which is caused by a failure of the DNA MMR system to repair errors that occur during replication of DNA. Endometrial biopsy, ultrasound with Doppler studies, tumor markers particularly, CA 125 and Human Epididymis Protein 4 are routine diagnostic work-ups for gynecologic malignancy. Immunohistochemistry of the endometrial and ovarian tissues, using Vimentin and WT1, respectively, have been helpful in establishing that both tumors are primary and independent. Immunohistochemistry staining has also helped identify which tumor metastasized as evidenced by a Vimentin positive staining of the lymph nodes suggesting endometrial cancer that has metastasized, thereby, providing an accurate diagnosis and staging of the tumors, a requisite for subsequent intervention. Chemotherapy will follow the protocol of the tumor in the more advanced stage. Metastatic work-ups will include a PET/CT scan or MRI and a repeat CA 125. Postsurgical surveillance monitoring will include a recommended follow-up schedule with a CA 125 at each visit and a CT/PET Scan if recurrence is suspected. The final diagnosis is synchronous endometrioid endometrial carcinoma Stage IIIC1 and high-grade serous ovarian carcinoma Stage IA, right ovary, with a poor prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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