Case Study

Rare Case Series Of Synchronous Gynecologic Malignancies


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ABSTRACT

This is a rare case series of synchronous gynecologic malignancies. The first two typical cases of carcinoma endometrium with carcinoma ovary of endometroid type with a functioning stroma and raised inhibin-b, with high ca-125 respectively and a third rare case of synchronous ovary with cervical cancer with elevated CEA. The origin confirmed by tissue IHC for vimentin involvement, reported at AHPGIC. Synchronous gynecological malignancies are of lesser incidence, but needs extensive evaluation and use of IHC and molecular profiling to reach at diagnosis. They usually are of better prognosis if than metastatic or advanced carcinomas so, diagnosis is to be taken up seriously to confirm the same. We have made and effort to do so, which will be guidance and help to fellow gynecologist.
INTRODUCTION:
Rare Case Series Of Synchronous Gynecologic Malignancies
First two typical cases of carcinoma endometrium with carcinoma ovary of endometroid type with a functioning stroma and raised inhibin-b, with high ca-125 respectively. And a third rare case of synchronous ovary with cervical cancer with elevated CEA. The origin confirmed by tissue IHC for vimentin involvement reported at AHPGIC

CASE NO 1.
A 35 yrs female presented to the OPD with C/O -swelling abdomen and bleeding p/v for 15 days M/H- cycles regular. Presently menorrhaegic cycles O/H- unmarried, nulligravida O/E- general pallor++, febrile, no pedal oedema, noscln, chest/CVS – ned P/A- tense ascites, palpable mass of variegated consistency of 24 wks towards right flank . P/S – fleshy polypoidal mass through os

P/V &P/R- A solid cystic mass, lower pole felt ,mobile ,uterus small separate from the mass Investigations –
• hb- 8 gm/dl
• Tlc-8000/dl
• TPC-1.3LAKHS/dl
• Urea-15mg/dl
• Creatinine-.83mg/dl
• Na-135mmoles/l
• k-3.7mmoles/l
• HIV,HBsag,HCV negative
• ALP- 400IU/ml,S.G.O.T/AST- 40IU/ml,
• S.G.P.T/ALT -50 IU/ml
• ALBUMIN-2.9 gm/dl
• Serum bilirubin(direct) – 2.5mg/dl
• Serum bilirubin ( total) – 2mg/dl
• CBNAAT OF ASCITIC FLUID - NEGATIVE

Serum markers:
• Serum Alpha –fetoprotein-1.61ng/ml
• SERUM BETA Hcg - .80miU/ml
• Inhibin B - 1287.34 pg/ml
• CEA- .564 ng/ml
• Ca-125 – 500Iu/ml
• USG – Heterogenous solid lesion with internal cystic changes in pelvic cavity (b/l ovarian mass) Bulky heterogenous cervical lesion. Gross ascites and thickened endometrium. Et-30mm
• MRI - The endometrium grossly thickened 30mm with polypoidal extension filling the vagina and the fornices measuring 60x36 mm with similar intensity that of endometrium, likely so endocervical polyp. left ovary is bulky 4X6CM.Gross ascites large solid cystic mass lesion10x6.5 cm in the right adnexa s/o neoplastic etiology .
• Endometrial biopsy- adenocarcinoma grade1 with squamous metaplasia and atypical hyperplasia
**Fig-1** HPS Of Endometrial Biopsy – Adenocarcinoma Endometrium

**Fig-2** Chest – X-ray - Pleural Effusion
Fig-3 MRI Of Abdomen And Pelvis

large solid cystic mass lesion 10x6.5 cm in the right adnexa s/o neoplastic etiology. Left ovary is bulky, gross ascites

Fig-4 MRI Of Abdomen And Pelvis

The endometrium grossly thickened 30mm with polypoidal extension filling the vagina and the fornices measuring 60x36 mm with similar intensity that of endometrium, likely so endocervical
SURGERY PROCEDURE –
TAH+BSO+B/L PELVIC AND PARAORTIC LYMPHADENECTOMY
IOP- 1.moderate ascites haemoragic in nature
RT adnexa solid mass of 7x10 cm, left adnexa normal
Uterus enlarged
C/S – Infiltrative growth in the cavity of uterus, omentum, and other abdominal organs healthy

HPS -
Uterus – invasive endometroid adenocarcinoma
Architecture- GRADE -1
nuclear grade -1
myometrial invasion more than 50%
LVSI - present

Fig 6(A)
The Above HPS Shows Endometroid carcinoma Of Uterus With Myo invasion

MICROSCOPIC - Rt ovary – show endometroid adenocarcinoma

Capsule not involved
Lvsi +ve
Left ovary and bilateral tubes free of tumor

Fig-6A OVARIAN ENDOMETROID CARCINOMA OF RIGHT OVARY
Fig (7) HPS of ovarian endometroid carcinoma. The presence of stromal cell vacuolation.

fig -8 Tissue inhibin++ in stromal cells

Ref – Takatusu Yuri Et al Jun2013 Scientific Research Journal
Fig-9 Primary endometroid cancer of ovary resembling Sertoli form pattern

Cervix – chronic non specific cervicitis
Omentum – shows metastatic adenocarcinoma.

Lymph node – right paraaortic node show features of metastasis, obturator +ve

Fig-10A (BPLND+BPAND Specimen)
Fig-10 B Metastatic Aortic Node

Fig-10 C Metastatic adenocarcinoma of nodes

Fig-10 D Adenocarcinomatous Deposits In Lymph Node
Fig-11 A Diffuse Strongly +++Vimentin Of The Uterine Cancer

DIAGNOSIS –
A case of synchronous carcinoma ovary, with functional stromal component and synchronous endometrial carcinoma in stage III.

Discuss- The factors in favor of a primary functional ovarian component, the stromal vacuolation, raised inhibin – B, the unilateral involvement of ovary ,the morphology histological picture of a primary ovarian tumor. The functioning stromal component is suggestive of rise in inhibin-b and perhaps the cause of hyperplasia of endometrium followed by carcinoma

FOLLOW UP- presently receiving ct rt , surviving and post surgery 6months.

CONCLUSION –
It is primary ovarian with increase inhibin which has caused endometrial cancer grade 1. The vacuolation of the stromal cell is in favor of the functional stroma of ovarian tumor. Moreover the nuclear grade one endometrial cancer rarely metastasizes the strengthening its synchronous association. The endometroid picture of the ovarian cancer is favor of of synchronicity as is also supported by literature that these synchronous tumors are of endometroid type(95% of the cases).

CASE -2
A 65 yrs female presented to the OPD with c/o of Post menopausal bleeding p/v15 days
m/h- menopause attained 10 yrs back
o/h- p3l3 lcb 35 yrs
0/e- p/a – a 22 weeks mass of variegated consistency
p/s- bleeding +
bimanual p/v p/r- a uterus bulky, a mass felt in continuity with the uterus

INVESTIGATIONS
Usg- UTERUS- antverted and bulky and measures 8.4x4.6x4.5 cm. myometrium normal echo texture. no myometrial sol. endometrium is bulky thickness measures 13.9 mm. cervix normal

OVARIES – b/l ovaries unremarkable. an ill defined hypoechoic mass noted in left adnexa with central cystic / necrotic area measuring 97x52 mm. the lesion shows central vascular with venous flow in color doppler. minimal ascites. Sol in liver.
Fig12

ENDOMETRIUM THICKENED 13MM
CA125 preop-2503.6U/ml
CA-125 -4.924 U/ML
CEA- 2.6IU/ML
Inhibin-B – 4.67 PG/ML
D/C - ↓ SA
Endometrial biopsy- endometrial carcinoma grade 1
Plan – laparotomy ↓↓ GA
IOP-ASCITES+++ 
Afungating Mass Adherent To Uterus

Adherent Uterus To Mass And Plastered.
Deposits -liver
Procedure- adhesiolysis
total abdominal hysterectomy +bso+mass resected in
total

**Histopathology**
Gross –uterus, cervix 7.0x5.05,0 cm
endometrial surface irregular

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*fig13*

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*Fig14 : Sections from the fungating mass adherent to the uterine wall was Taken*

Fungating mass adherent to uterus
Microscopic- tumor type – endometrial adenocarcinoma of endometroid type
architectural grade- g1(well, differentiated type)
nuclear grade- grade2
myometrial invasion<50%
lvsi-ve
fungating mass adherent to uterus i.e the adnexal mass- endometroid adenocarcinoma
DIAGNOSIS- Synchronous ovarian endometroid with endometrial carcinoma stage IV
The rise of ca-125 , >2000 sugestive of ovarian primary, moreso even endometrial carcinoma gade 2 with negative lvisi and <50% myo invasion unlikely metastatic to ovaries.
Treatment- adjuvant CTRT
Follow up- she is surviving post CTRT 3 YRS

CASE NO 3
45 yrs female presents with pain abdomen and PMB – 5 months, menopause attained, nulliparous
0/e- suprapubic mass of 20 wks size, firm of restricted mobility
p/s- growth from the endocervix
p/v- uterine height couldn’t be elicited, lower pole of mass felt, restricted mobility, pod full

Investigations –
CA 125-393IU/ML
CEA- 2.9IU/ML
Inhibin-4.5 pg/ml
Smear- metaplastic cell with nuclear atypia
Diagnostic hysteroscopy Abd endometrial biopsy and endocervical curettage done –
HPS- adenocarcinoma, with squamous metaplasia
Dh – growth filling the lower endometrial and endocervical cavity
USG- bulky uterus expanded cavity with a large necrotic mass extending down to endocervix.
CEPT- bulky uterus expanded cavity with a large necrotic mass extending down to endocervix, left side parametrical involvement seen with a globular solid necrotic deposit as left para uterine position. Adnexal region a mass of 145x83mm. Similar deposits in para colonic gutter in right iliac fossa. Tiny nodules in lung field. Minimal ascites

Plan-
Neoadjuvant ct4 cycles pacltaxel and carboplatin and staging debulking
Post chemo CECT- CX Growth 30X34XMM
Uterine Growth Of 7X6CM
Large Abdominopelvic Mass With Enhancing Deposits

Procedure ;
Type II Radical Hysterectomy+Appendicectomy+Omeectomy+RP LND
IOP-
Uterus normal size anteriorly a mass of 5x7cm
Right adnexa bearing two mass 4.5x6.5cm
Left ovary enlarged variagated
Omentum and appendix normal
No free fluid in abdomen
No deposits in left ovary and b/l tubes healthy gross –
Right Adnexa - Two Mass Of 4x5cm And 6x4cm

Fig15: Left Adnexa- enlarged
omentum, appendix, peritoneum normal
C/S

Endometrial cavity-growth in the lower uterine segment and endocervix
Endocervix – filled with growth 3x2 cm

**HISTOPATHOLOGY** -
Cervix- invasive adenocarcinoma
grade -1
>50% stromal involvement
lvs - not seen
omentum-negative

Lower uterine segment involved
both the fallopian tubes and parametrium free
right ovary- invasive adenocarcinoma of endometroid type capsule not involved.
left ovary- Extensive areas of necrosis
Uterus - no myoinvasion

*Fig 19 IHC of the growth from endocervix is vimentin positive*
Uterine nodule - leiomyoma
Appendix- chronic appendicitis
All lymphnodes – reactive hyperplasia
Adjuvant – received CTRT

**DISCUSSION-**

One of the important feature which rules out metastasis is that for endometrial cancer without myoinvasion and –lvsi to have a parauterine and ovarian involvement ,i.e in favour of synchronous cervical cancer with ovarian mass . The pap smear shows atypia is also suggestive of cervical cancer. The plasma CEA was raised to 2.9 iu/ml, favoring the endocervical growth. The endocervical growth stained negative for vimentin, confirming endocervical growth.

Diagnosis - synchronous cervical carcinoma with uterine extension and asynchronous ovary

Treatment- Adjuvant CTRT

<table>
<thead>
<tr>
<th>Serial</th>
<th>AGE</th>
<th>MORPHOLOGICAL</th>
<th>OVARIAN CANCER</th>
<th>UTERINE CANCER</th>
<th>CERVICAL CANCER</th>
<th>OVARIAN CAPSULE</th>
<th>LVSI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>DISSIMILAR</td>
<td>1</td>
<td>1</td>
<td>NIL</td>
<td>NEGATIVE</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>DISSIMILAR</td>
<td>1</td>
<td>1</td>
<td>NIL</td>
<td>POSITIVE</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>DISSIMILAR</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NEGATIVE</td>
<td>NIL</td>
</tr>
</tbody>
</table>

_**Table- 5 Description Clinicopathological Factors Of The Cases**_
<table>
<thead>
<tr>
<th>SERIAL NOS</th>
<th>ATYPICAL HYPERPLASIA</th>
<th>ASSOCIATED SQUAMOUS METAPLASIA</th>
<th>TUBAL INVOLVEMENT</th>
<th>OMENTAL INVOLVEMENT</th>
<th>NODAL INVOLVEMENT</th>
<th>LATERALITY OF OVARIAN TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PRESENT</td>
<td>POSITIVE</td>
<td>-VE</td>
<td>+VE</td>
<td>POSITIVE+VE</td>
<td>UNILATERAL</td>
</tr>
<tr>
<td>2</td>
<td>NIL</td>
<td>-VE</td>
<td>-VE</td>
<td>NIL (OMENTECTOMY NOT DONE)</td>
<td>-VE (NIL)</td>
<td>UNILATERAL</td>
</tr>
<tr>
<td>3</td>
<td>NIL</td>
<td>POSITIVE</td>
<td>-VE</td>
<td>NIL</td>
<td>_VE (NIL)</td>
<td>UNILATERAL</td>
</tr>
</tbody>
</table>

Table 7 Clinicopathological Factors

<table>
<thead>
<tr>
<th>STAGE/ SERIAL NOS</th>
<th>VIMENTIN CX GROWTH</th>
<th>VIMENTIN OF OVARIAN TISSUE</th>
<th>VIMENTIN OF UTERINE GROWTH</th>
<th>CA-125 IU/ML</th>
<th>CEA IU/ML</th>
<th>INHIBIN PG/ML</th>
<th>ENDOMETRIOSTIS/FIBROID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE NOS 1 STAGE III</td>
<td>NIL</td>
<td>-VE</td>
<td>++++VE</td>
<td>500</td>
<td>.564</td>
<td>1287 (INHIBIN-8)</td>
<td>NIL</td>
</tr>
<tr>
<td>CASE NOS 2 STAGE II</td>
<td>NIL</td>
<td>NIL</td>
<td>++++VE</td>
<td>2000</td>
<td>2.6</td>
<td>4.67</td>
<td>+VE (ENDOMETRIOSIS)</td>
</tr>
<tr>
<td>CASE NOS 3 (PARAMETRIUM -VE) STAGE I</td>
<td>NEGATIVE (-VE) IN IHC OF THE ENDOCERVICAL GROWTH</td>
<td>NIL</td>
<td>393</td>
<td>2.9</td>
<td>4.5</td>
<td>FIBROID -VE</td>
<td></td>
</tr>
</tbody>
</table>

3013
TABLE 8 Analysis Of Imaging (USG) Characteristics Of The Above synchronous Malignancies

<table>
<thead>
<tr>
<th>Serial Nos</th>
<th>Abdomino/Pelvic mass</th>
<th>Uterine enlargement</th>
<th>Endometrial thickening</th>
<th>Sol in uterus/cervix (heterogenous/homogenous)</th>
<th>Laterality of ovarian/adnexal mas</th>
<th>ascites</th>
<th>Solid/cystic</th>
<th>Heterogenous/papillary/septa</th>
<th>RI/PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+/+) present (abdomino pelvic)</td>
<td>Present</td>
<td>30mm</td>
<td>Polypoidal lesion in cervix</td>
<td>b/l enlarged ovaries right adnexa (10x6.5 cm) left bulky 94x5 cm</td>
<td>+ve</td>
<td>(+/+)(+/(+) of right side</td>
<td>heterogenous</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Present -DO-</td>
<td>-DO-</td>
<td>13.9 MM</td>
<td>NO SOL</td>
<td>(Left adnexal Mass)</td>
<td>Ascites +VE</td>
<td>Left</td>
<td>-DO-hypoechoic</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Present -DO-</td>
<td>DO</td>
<td>5 MM</td>
<td>Endocervical Growth</td>
<td>Left adnexal Mass</td>
<td>-DO</td>
<td>Left</td>
<td>-DO-</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION-

The study of the clinic pathological features above three cases reveal that. They present with abnormal uterine bleeding. The imaging in all the cases revealed a unilateral ovarian/adnexal mass. The masses are morphologically dissimilar. The ovarian carcinoma are of endometroid type so also the uterine cancer. The histological grade of the synchronous tumor are grade 1, in ovary, uterus and cervix. All the ovarian cancer are unilateral. Both the tubes were healthy in all the three cases. There are associated squamous hyperplasia of endometrium.

The case no three had a abnormal pap smear and final histology of adenocarcinoma with vimentin –ve rules out uterine cancer and a rise in CEA is favor of endocervical carcinoma of cervix. Fibroid and endometriosis was present in two cases. The rise of inhibit-b and ca125 in case no 1, is another factor, in favor of primary ovary. The inhibit was done in these case of AUB with adnexal mass but was raised in one of the cases, whereas ca-125 was elevated in all the cases. The vimentin was strongly positive in endometrial cancer in both the cases and negative in ovarian cancer specimen. Thus we conclude that the first two case are synchronous ovarian with uterine and the last is a synchronous cervix with ovarian cancer. The field effect (3) was evident by the presence of fibroid and endometriosis in two cases. The cases are surviving post surgery and treatment for one and half years and on follow up.

REVIEW LITERATURE

HPS Features Primary Endometrial And The Primary Ovary Carcinoma

- No surface implants, ovarian parenchyma involvement
- Morphologically different
- Lack of tumor multiple lesion
- No evidence of tubal spread
- Atypical hyperplasia, sometimes squamous metaplasia
- Endometriosis in ovary favors a primary carcinoma
- Pattern of ovarian involvement
IHC

Profile For Metastatic /Double Primary Uterine Endometroid And Ovarian Endometroid (1)

- Vimentin as a potential marker helpful in differentiating primary uterine endometroid and ovarian endometroid carcinoma. It is strongly positive in uterine cancer.
- The marker is negative in a primary ovarian cancer but is positive some case of endometroid cancer.
- It is expressed in 82% of primary uterine corpus
- 97%-100% of ovarian endometroid associated with corpus cancer were negative for vimentin.

*Fig- 20 A,B IHC stratification of primary and metastatic role of vimentin.*
• Synchronous account for .7-.8% gynecological malignancies
• Synchronous ovarian with endometroid are predominant 40-50%.
• Etiopathogenesis – “field effect” (2)

The most common features of such tumor are abnormal uterine bleeding
• Such hyper-functioning of stroma of ovarian is associated with hyperestrornism
• Synchronous ovarian tumors can be endometroid mucinous, clear cell serous mixed ,mucinous.(3)
• 90 % of synchronous are endometroid variety.
• The presence of co-existent ovarian an endometrial carcinoma has been identified in 3-30% 0f endometrial malignancies and 3-10% of ovarian malignancies and 31% with coexisting endometriosis
• etiopathogy enesis- “ field effect “association endometriosis, and fibroid is one of hypothesis. (3) . This suggest that the hormonal field effect may account for development of endometroid cancer, supporting the theory of estrogen receptors etfel. Etal.(4)
• studies on for another hypothesis to explain the synchronicity of gynecological malignancies that an ‘extended’ or secondary Mullerian system exist so that similarity of female upper genital tract undergoing common metaplastic diseases as could be explained i.e. the presence of squamous metaplasia in endometrium, in such cases.

Molecular Markers Synchronous malignancy (4)
• MSI ,PTEN AND CTNNB1 proposed makers for synchronous malignancy
• DNA flow cytometry, loss of heterozygosity
• x- chromosome inactivation

Fig20 IHC staining of the molecular markers in lynch syndrome loss of MSH 2,MSH6.(1)
Role of inhibin in synchronous ovarian and endometrial cancer. (5)

- Inhibin is elevated in granulosa cell tumor and mucinous tumors
- It is normally low in endometroid cancers
- But rise in inhibin is associated with a functioning stroma in endometroid carcinoma and well differentiated tumor in comparison to poorly differentiated
- In premenopausal group benign ovarian lesion usually have very low inhibin.
- It has high sensitivity with ca 125 and 95% specificity as diagnostic test.

PROGNOSIS (6)

- Studies showed low grade synchronous ovarian endometroid and early stage have a better survival
- 80% -90% with advanced have a poorer prognosis
- recent multicenter international study show that they have the same prognosis as primary
- pre-treatment ca125 and tumor stage are two independent variables.
- Inhibin B Considerably Influences The 5 Yr Survival
- Inhibin is elevated in granulosa cell tumor and mucinous tumors
- It is normally low in endometroid cancers
- But rise in inhibin is associated with a functioning stroma in endometroid carcinoma and well differentiated tumor in comparison to poorly differentiated
- In premenopausal group benign ovarian lesion usually have very low inhibin.
- It has high sensitivity with ca 125 and 95% specificity as diagnostic test.

Recent studies clinicopathological features of synchronous ovary and endometroid cancer suggest nulliparity and (zaino etal), (8) younger age and a median age of 50 yrs. There was no statistically significant in BMI in endometroid type. However other histological types did have a statistical significance with BMI.(Soliman etal)(7)

Eifel etal (9) reported than bleeding p/v was

Major complain of endometroid type and pelvic mass was the presenting symptom of non endometoid type. The majority presented in stage 1 grade 1 and endometroid type.

A study by jiraprapa etal (8) showed that there was no difference in size of tumor in endometroid and other types.Most of them presented in grade1 with endometroid type. The lvisi was in 14 cases of 43 cases , there was no statistical difference in endometroid and other histology types

Overall survival of women with synchronous tumors of uterus and ovary are excellent. Zaino et al reported 5 yrs and 10 yrs survival of 86% and 80%

In addition Soliman etal(8) showed the women endometroid type had significant survival better than othr type(median survival119 mos /48mos p==.02)

The recent studies do show a rise in CEA in adenocarcinoma of cervix. (10)(11) CEA is found to raised more in cases of adenocarcinoma cervix than squamous cell carcinoma. A study done by kentucky etal revealed a CEA more than 2.5 ng/ml

REFERENCES


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11) J.r van nagel et al NIH 1978

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Conflict of Interest: None declared

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