Rare Case Series of Synchronous Gynecologic Malignancies


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I. INTRODUCTION

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 no1.

P/V & P/R - A solid cystic mass, lower pole felt, mobile, uterus small separate from the mass.

Investigations –
- hb - 8 gm/ml
- Tlc - 8000/ml
- TPC - 1.3LAKHS/ml
- Urea - 15mg/ml
- Creatinine - .83mg/ml
- Na - 135mmoles/l
- k - 3.7 mmoles/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/ml
- 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

Hcinbin 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 XRAY - PLEURAL EFFUSION
FIG-3 MRI OF ABDOMEN AND PELVIS
FIG-4 MRI OF ABDOMEN AND PELVIS

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

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 polyn.large solid cystic mass lesion10x6.5 cm in the right adnexa s/o neoplastic etiology, left ovary is bulky gross ascites

large solid cystic mass lesion10x6.5 cm in the right adnexa s/o neoplastic etiology, left ovary is bulky gross ascites
FIG – 5 GROSS PICTURE OF THE SPECIMEN OF SOLID TUMOR OF RIGHT ADNEXA, LEFT TUBE AND OVARY, C/S OF UTERUS OMENTUM, B/L PELVIC AND PARAORTIC NODES

**HPS** -

**Uterus** – invasive endometroid adenocarcinoma
- Architecture - GRADE - 1
- nuclear grade - 1
- myometrial invasion more than 50%
- LVSI - present
FIG 6(A)

FIG 6(B)

THE ABOVE HPS SHOWS ENDOMETROID CARCINOMA OF UTERUS WITH MYOINVASION MICROSCOPIC - Rt ovary – show endometroid adenocarcinoma
Capsule not involved
Lvsi+ve
Left ovary and bilateral tubes free of tumor

FIG 6(C)

STROMAL CELL WITH CYTOPLASMIC CLEARING (LIPID CONTENT)
FIG (6D)

FIG (7) Hps of ovarian endometroid carcinoma. The presence of stromal cell vacuolation.
Fig-8 Tissue inhibin++ in stromal cells

Fig-9 Primary endometroid cancer of ovary resembling sertoliform pattern
Cervix – chronic non specific cervicitis
Omentum – shows metastatic adenocarcinom.
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 favour 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 receiveing 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 favour of the functional stroma of ovarian tumor. Moreover the nuclear grade one endometrial cancer rarely metastasises the strengthening its synchronous association. The endometroid picture of the ovarian cancer is favour 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- p.3l3 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.
CA125 preop-2503.6U/ml
CA-125 -4.924 U/ML
CEA- 2.61U/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 -dive
PROCEDURE- ADHESIOLYSIS
TOTAL ABDOMINAL HYSTERECTOMY +BSO+MASS RESECTED IN TOTO
HISTOPATHOGY
GROSS –UTERUS,CERVIX 7.0X5.0,0 CM
Microscopic: Tumor type – Endometrial adenocarcinoma of endometroid type
Architectural grade - G1 (well-differentiated type)
Nuclear grade - Grade 2
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 suggestive of ovarian primary, moreover endometrial carcinoma grade 2 with negative LVSI and <50% myo invasion unlikely metastatic to ovaries.

Treatment: Adjuvant CRT
Follow up: She is surviving post CRT 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 could'nt be elicited, lowerpole 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 CURRETAGE DONE –
HP5- ADENOCARCINOMA, WITH SQUAMOUS
METAPLASIA
DH – GROWTH FILLING THE LOWER
ENDOMETRIAL AND ENDOCEVIRICAL CAVITY
USG- bulky uterus expanded cavity with a large necrotic
mass extending down to endocervix.ET-5mm. An adnexal
mass on left side.
CECT- bulky uterus expanded cavity with a large necrotic
mass extending down to endocervix, leftside parametrical
involvement seen with a globular solid necroticdepositas left
para uterine position. Adnexal region a mass of 145x83mm.
Similare depositsin para colonic gutter in right iliac fossa
.Tiny nodules in lung feild. 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+OMECTECTOMY
+RPLND
IOP-
UTERUS NORMAL SIZE ANTERIORY A MASS OF
5X7CM
RIGHT ADNEXA BEARING TWO MASS 4.5X6X6.5CM
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
omentum, appendix, peritoneum normal
C/S

FIG15
LEFT ADNEXA- enlarged

ENDOMETRIAL CAVITY-GROWTH IN THE LOWER
UTERINE SEGMENT ANDENDOCERVIX
ENDOCERVIX – FILLED WITH GROWTH 3X2 CM
HISTOPATHOLOGY -
CERVIX- INVASIVE ADENOCARCINOMA
GRADE -1
>50% STROMAL INVOLVEMENT
LVSI – NOT SEEN
OMENTUM-NEGATIVE

LOWER UTERINE SEGMENT INVOLVED
BOTH THE FALOPIAN 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 

Uterine nodule - leiomyoma
Appendix- chronic appendicitis

All lymph nodes – reactive hyperplasia
Adjuvant – received CTRT

DISCUSSION - One of the important feature which rules out metastasis is that for endometrial cancer without myoinvasion and –lvis to have a parauterine and ovarian involvement, i.e in favour of synchronous cervical cancer with ovarian mass. The papsmear shows atypia is also suggestive of cervical cancer. The plasma CEA was raised to 2.9 iu/ml, favouring 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 1: Description of Clinico-pathological Factors of the Cases

<table>
<thead>
<tr>
<th>Serial NOS</th>
<th>Age</th>
<th>Morphological Dissimilarity</th>
<th>Ovarian Cancer Grade</th>
<th>Uterine Cancer Grade</th>
<th>Cervical Cancer Grade</th>
<th>Ovarian Capsule Involvement</th>
<th>Myo-Invasion</th>
<th>LVI</th>
</tr>
</thead>
<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>
<td>POSITIVE</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>
<td>NEGATIVE</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>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>

### Table 5: Description Clinico-pathological 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</th>
<th>Ofovarian Tumor</th>
<th>Omentectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Present</td>
<td>Positive</td>
<td>-VE</td>
<td>+VE</td>
<td>POSITIVE</td>
<td>UNILATERAL</td>
<td>UNILATERAL</td>
<td>Nil</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>
<td>UNILATERAL</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>
<td>UNILATERAL</td>
<td>UNILATERAL</td>
</tr>
</tbody>
</table>
### TABLE 7 CLINICOPATHOLOGICAL FACTORS

<table>
<thead>
<tr>
<th>STAGE/ SERIAL NOS</th>
<th>VIMENTIN OF CX GROWTH</th>
<th>VIMENTIN OF OVARIAN TISSUE</th>
<th>CA 125 IU/ML</th>
<th>CEA IU/ML</th>
<th>INHIBIN PG/ML</th>
<th>ENDOMETRIOSIS/FIBROID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE NOS 1 STAGE III</td>
<td>NIL -VE</td>
<td>++++VE</td>
<td>500</td>
<td>.564</td>
<td>1287 (INHIBIN-B)</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>
</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>
</tr>
</tbody>
</table>

### 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 Ous/homogenous)</th>
<th>Laterality of ovarian/adnexal mass</th>
<th>ascites</th>
<th>Solid/cystic</th>
<th>Heterogenous/papillary/septate</th>
<th>RI/PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+/-) present (abdominopelvic)</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 94x5cm</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>13.9MM</td>
<td>NO SOL</td>
<td>(LEFT ADNE XAL MASS</td>
<td>ASCITES +VE</td>
<td>LEFT</td>
<td>-DO HYPOECHOIC</td>
<td></td>
</tr>
</tbody>
</table>
II. CONCLUSION-

The study of the clinicopathological 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 an abnormal pap smear and final histology of adenocarcinoma with vimentin –ve rules out uterine cancer and a rise in CEA is in favour of endocervical carcinoma of cervix. Fibroid and endometriosis was present in two cases. The rise of inhibin-b and ca125 in case no1, is another factor, in favour of primary ovary. The inhibin was done in these case of aub with adnexal mass but was raised in one of the cases, where as 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.

III. 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 favours a primary carcinoma
- pattern of ovarian involvement

![METASTATIC OVARIAN CARCINOMA](image-url)
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 and 97%-100% of ovarian endometroid associated with corpus cancer were negative for vimentin.

![IHC D/D PRIMARY/METS TATIC OVARIAN CARCINOMA FIG-9](image)

**FIG- 20 A,B IHC STRATIFICATION OF PRIMARY AND METASTATIC ROLE OF VIMENTIN.**

- Synchronous account for 7.8% gynaecological 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 hyperestronism
  - 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 enometrial carcinoma has been identified in 3-30% of endometrial malignancies and 3-10% of ovarian malignancies and 31% with coexting endometriosis
  - etiopathogenesis- “field effect”association endometrtosis, and fibroid is one of hypothesis. (3). This suggest that the hormonal field feild effect may account for development of endometroid cancer, supporting the the theory of estrogen receptors eifel. Etal.(4)
- studies on for another hypothesis to explain the synchronicity of gynaecological malignancies that an “extended” or secondary muellerian system exist so that similarity of female upper genetal tract undergoing common metaplastic diseasesa 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 heterozygosty
- x- chromosome inactivation
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 a 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 multicentre international study showed that they have the same prognosis as primary
- Pre-treatment ca125 and tumor stage are two independent variable.
- 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 et al),(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 et al)(7)

Eifel et al(9) reported than bleeding p/v was major complaint of endometroid type and pelvic mass was the presenting symptom of non endometroid type. The majority presented in stage 1 grade 1 and endometroid type.

A study by jiraprapa et al (8) showed that there was no difference in size of tumor in endometroid and other types. Most of them presented in grade 1 with endometroid type. The lvi was in 14 cases of 43 cases. There was no statistically significant 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 et al(8) showed the women endometroid type had significant survival better than other type (median survival119 mos/48 mos 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 et al revealed a cca more than 2.5 ng/ml

REFERENCES


[10] Chandana etal journal scientific cancer prevention and research 2017 j.r van nagel etal NIH 1978

Authors