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Triple Synchronous Primary Malignancies of Ovary, Endometrium and Cervix – A Rare Case Report

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Abstract
Synchronous primary malignancies of the female genital tract are rare. Of the reported cases, the more common synchronous cancers are those involving the ovary and endometrium. Three primary malignancies occurring simultaneously are even fewer. We found only 14 such reported cases in pub-med indexed journals till date. The single most important criterion to call these neoplasms synchronous malignancies is that they should be histologically distinct and separated from each other by normal intervening tissues, with no evidence of metastasis. The prognosis for synchronous tumors is relatively better as concurrent tumors are detected early and are associated with a low histological grade.
We are presenting a case report of a 36 year old woman who underwent surgery for complex left ovarian cyst. Intra-operative frozen section analysis of the ovarian cyst proved to be positive for malignancy. Histopathological examination of subsequent staging laparotomy specimen revealed co-existing small cell carcinoma of the ovary, well differentiated endometrioid adenocarcinoma of endometrium, and squamous cell carcinoma-in-situ of the cervix. To the best of our knowledge, simultaneous presentation of these three distinct histological patterns of gynaecological malignancies has not been reported earlier.
Keywords: *Synchronous primary malignancies, small cell carcinoma of ovary, endometrioid adenocarcinoma of endometrium, carcinoma-in-situ of cervix.*

Introduction

The female genital tract is a potential site of synchronous primary malignancies making it necessary to thoroughly examine the entire female genital tract when there is a suspicion of malignancy at any site of the FGT. Although rare, synchronous primary malignancies have been reported. Of these, the most frequently encountered are synchronous tumors involving the ovary and uterus. Synchronous tumors involving the uterus and cervix are even fewer. Triple synchronous primary malignancies involving the uterus, ovary and cervix have rarely been documented. Till date, only 14 cases of three or more synchronous primary malignancies have been reported in PubMed indexed journals[1].

When malignant lesions are detected at more than one site, it becomes important to rule out the possibility of metastasis which is more likely. Synchronous malignancies have to be

histomorphologically distinct from each other. The prognosis for synchronous tumors is relatively better as concurrent tumors are detected early and are associated with a low histological grade.

We are presenting a case report of a 36 year old woman who was diagnosed with co-existing small cell carcinoma of the ovary, well differentiated endometrioid adenocarcinoma of endometrium, and squamous cell carcinoma-in-situ of the cervix. To the best of our knowledge, simultaneous presentation of these three distinct histological patterns of gynaecological malignancies has not been reported earlier.

Case Report

A 36 year old woman was detected to have cervical carcinoma-in-situ on cervical biopsy. Ultrasound of the abdomen and pelvis revealed a large multiseptate solid cystic lesion in the midline of the pelvis with a bulky uterus having thickened endometrium and mildly bulky cervix. CT scan of the abdomen and pelvis showed a large, multiseptate, predominantly cystic lesion with a peripheral enhancing solid component in lower abdomen and pelvis, favouring complex left ovarian solid cystic lesion, likely to be neoplastic. Both anterior and posterior lips of the cervix appeared bulky in size showing heterogenous enhancement, consistent with carcinoma cervix. Endometrium appeared thickened. Laboratory investigations showed an elevated Ca125 level of 244U/ml.

Left salphingo-oophorectomy was performed and the specimen sent for intra-operative frozen section analysis. Sections from the left ovary showed features of poorly differentiated carcinoma. This was followed by a staging laparotomy procedure which consisted of radical hysterectomy, omentectomy with bilateral pelvic and para-aortic lymph node dissection. All resected specimens were subjected for routine histopathological analysis.

Histopathological examination showed well differentiated endometrioid adenocarcinoma of the endometrium involving the isthmus and less than half thickness of the myometrium. Sections from the ectocervix revealed foci of moderate to severe dysplasia amounting to squamous cell carcinoma in situ. The entire cervix was sampled and examined thoroughly; no evidence of invasive carcinoma was seen. Endocervix was uninvolved. The left ovary showed features of small cell carcinoma with focal areas of undifferentiated carcinoma.

Immunohistochemistry was performed on sections of ovary; tumor cells were immunoreactive for CD 56, chromogranin, and synaptophysin, confirming the diagnosis of small cell carcinoma. Mib index was more than 90%. The patient was screened for microsatellite instability, expression of all four MMR proteins (MLH1, MSH2, MSH6, PMS2) was found to be intact.

The right ovary and bilateral fallopian tubes were unremarkable. Adventitial surface and bilateral parametria were free of tumor. Vaginal cuff cut margin showed mild dysplasia. The omentum, bilateral pelvic and para-aortic lymph nodes were negative for metastatic deposits.

Table 1: list of cases of triple synchronous primary malignancies of female genital tract.

Author	Ovary	Uterus	Cervix	Fallopian tube
Ahmed abu-zaid et al	Clear cell carcinoma	Endometrioid adenocarcinoma	Poorly differentiated SCC	-
Chiofalo et al	Mucinous adenocarcinoma	Endometrioid adenocarcinoma	Mucinous adenocarcinoma	-
Takatori et al	Serous adenocarcinoma	Endometrioid adenocarcinoma	Endometrioid adenocarcinoma	-
Zhang and lerwill et al	Leydig cell tumor	Myxoid leiomyosarcoma	Mucinous adenocarcinoma	-
Hale et al	Mucinous, clear cell and endometrioid adenocarcinoma	Endometrioid adenocarcinoma	Endometrioid adenocarcinoma	-
Atasever et al	Papillary serous	Intraepithelial	Endocervical in situ	Bilateral

	adenocarcinoma	adenocarcinoma	carcinoma	microinvasive carcinoma in situ
Saglam et al	Mucinous adenocarcinoma	Endometrioid adenocarcinoma	Endocervical adenocarcinoma	Early papillary adenocarcinoma
Pekin et al	Brenner tumor, Granulosa cell tumor	-	Squamous cell carcinoma	-
Phupong et al	Mucinous adenocarcinoma Low malignant potential	Endometrioid adenocarcinoma	Endocervical adenosquamous carcinoma	-
Author	Ovary	Uterus	Cervix	Fallopian tube
Isin dogan ekici et al	Mucinous adenocarcinoma	Endometrioid adenocarcinoma, Leiomyosarcoma	-	-
Ree et al	Clear cell carcinoma, Borderline mucinous cystadenoma	Endometrioid adenocarcinoma	-	-
Jobo et al	Endometrioid adenocarcinoma	Endometrioid adenocarcinoma	Carcinoma in situ	-
Ayhan et al	Mucinous adenocarcinoma	Endometrioid adenocarcinoma	Carcinoma in situ	-
Matlock et al	Papillary serous cystadenocarcinoma, Mucinous cystadenocarcinoma	Papillary adenocarcinoma with psammoma bodies.	-	-

Figure 1: Frozen section (A) and routine FFPE sections (B) from the ovary – a poorly differentiated carcinoma with small cell morphology and high mitotic activity.

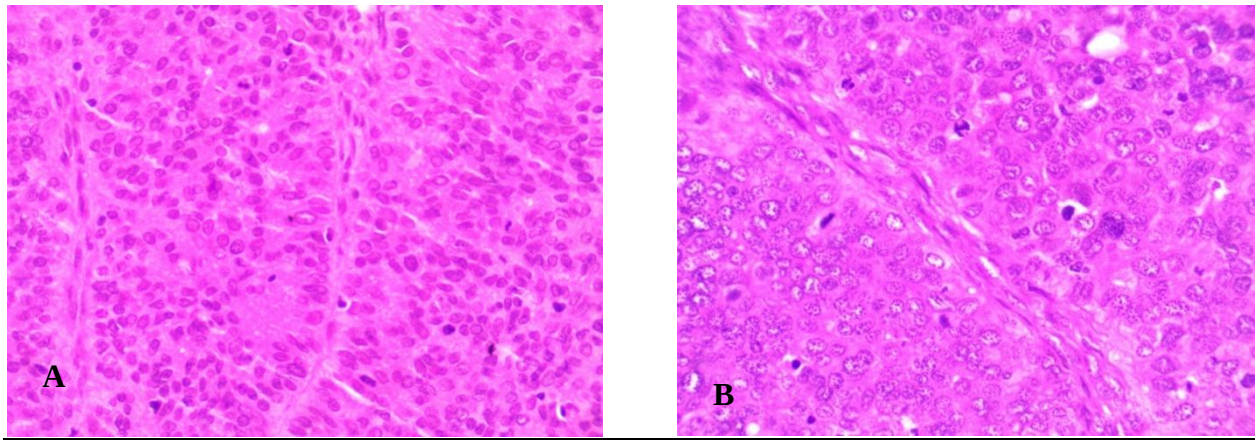


Figure 2:

(C) Section of endometrium showing features of well differentiated endometrioid adenocarcinoma.

(D) Section of cervix showing squamous cell carcinoma-in-situ.

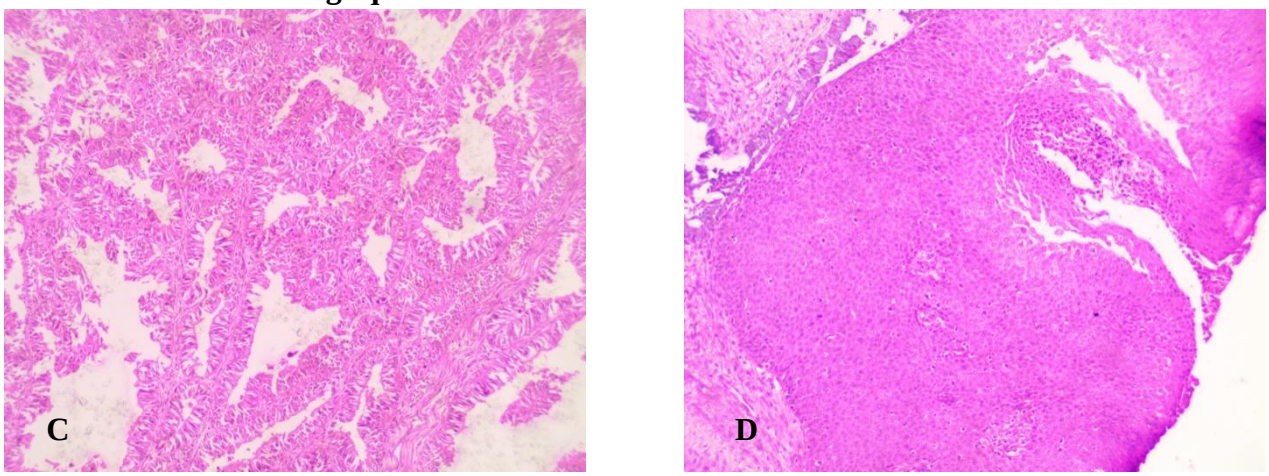
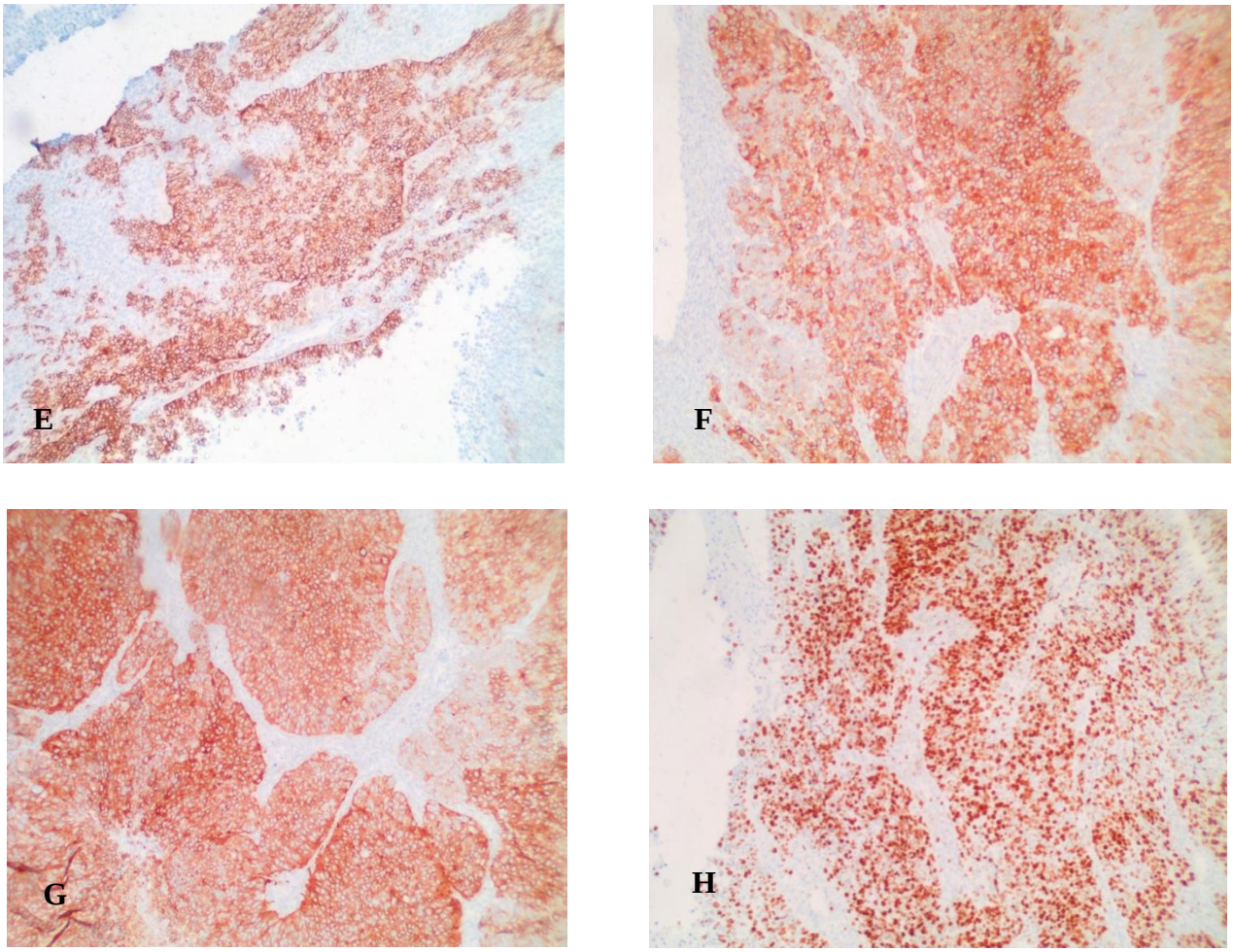


Figure 3: Immunostaining of sections of ovary showing positivity for CD 56 (E), Synaptophysin (F), Chromogranin A (G) and high Mib 1 index (H).



Discussion

Synchronous primary malignancies of the female genital tract are rare. Their incidence is only 1–6% of all genital neoplasms[11]. Most of the synchronous primary malignancies reported so far have been dual malignancies, of which the most frequently reported involve the ovaries and the uterus (0.3%), followed by those of the uterus and cervix (0.025%)[5].

The incidence of triple primary malignancies occurring simultaneously in the same patient is extremely low. Only 14 such cases have been reported in PubMed indexed journals so far[1]. Atasever et al reported a case of five synchronous primary neoplasms involving the uterus, cervix, ovary and bilateral Fallopian tube. Two cases of four synchronous neoplasms, one reported by Phupong et al involving uterus, cervix and bilateral ovaries, another reported by Saglam et al involving uterus, cervix, and unilateral adnexa have been reported. The rest are of triple synchronous malignancies involving uterus, cervix and ovaries in varying combinations. [1, 6-8]. A comparative list of the reported cases has been listed in Table 1.

To designate tumors as synchronous primaries, each tumor should have distinct histological features and the possibility of metastasis must be ruled out after a thorough objective gross and microscopic evaluation. Warrens and Gates established the following criteria for the diagnosis of multiple primary tumors: (1) each of the tumors must present a definite picture of malignancy; (2) each must be clinicopathologically distinct; (3) the probability of one being a metastasis or recurrence must be excluded[9].

Several other clinicopathological criteria have been detailed for accurate differentiation of

synchronous tumors from metastatic deposits. One of these guidelines entails either one major criterion or four minor criteria. The most important and major criterion to designate them as synchronous primary malignancies is the presence of distinct histomorphology. The four minor criteria include (a) neoplasms which are limited to primary locations, (b) absence of direct extension between neoplasms, (c) absence of lymphovascular neoplastic invasion, and (d) absence metastasis [1, 12, 13].

Our case meets all the above criteria. A unique combination of small cell carcinoma of the ovary, well differentiated endometrioid adenocarcinoma of the uterus and carcinoma-in-situ of the cervix proves that one malignancy could not be a metastasis from another. To the best of our knowledge, such a distinct histomorphological combination has not been reported in previously published literature. A brief review of previously reported cases of synchronous malignancies from Pub Med indexed articles has been summarised in Table 1.

Numerous attempts have been made to explain the pathogenesis of multiple synchronous primary malignancies. Tissues that share a common embryonic origin show an increased propensity to develop concurrent tumors when they are repeatedly and simultaneously exposed to carcinogens, hormones and other triggers [5,6]. The concept of field cancerization, as explained by Slaughter et al, in 1953 for tumors of the head and neck region has also been proposed as a plausible explanation to multiple primaries of the female genital tract.

Microsatellite instability was first described in colorectal cancers occurring in cases of HNPCC/Lynch Syndrome. Families with Lynch syndrome are at an increased lifetime risk of developing colorectal cancer (80%), endometrial cancers (40% - of distant 60%) and ovarian cancer (10%-12%). Endometrial carcinoma develops before colorectal cancer in more than 50% of patients with HNPCC. MSI is also seen in 17% - 32% of sporadic endometrial carcinomas and 3% - 17% of sporadic ovarian carcinomas [14,16]. It has been found to be more common in endometrioid type of endometrial adenocarcinomas and MSI-H is often found in younger patients [15]. The Society of Gynecology Oncology recommends systematic screening of all women diagnosed with endometrial carcinoma for Lynch syndrome. Molecular testing on all cancers diagnosed at age less than 60 years is recommended regardless of personal/family history.

Testing for defective DNA mismatch repair proteins (MSH 2, MSH 6, MLH 1 and PMS 2) by immunohistochemistry is a cost effective method. Lynch syndrome related endometrial carcinoma is always associated with MSH 2 and MSH 6 mutations[17].

Conclusion

It is important to distinguish multiple primary tumors form metastatic deposits as the treatment and prognosis of both differ considerably. Synchronous malignancies have relatively better survival rates as compared with metastatic disease as they are detected at a relatively early age and are often associated with lower histological grade and disease stage. This is especially true when malignancies of uterus or uterine cervix are involved because their symptoms occur earlier as compared to those of ovarian neoplasms. The prognosis of synchronous primary malignancies depends on the histological grade and prognosis of the poorest primary[1,5].

Management of these cases depends on not only the detection of synchronous malignancies but also their histological grade and clinical stage. Also, management modalities are different for different cases and therapy must be individualized. The various treatment options available are surgery with adjuvant chemotherapy, radiotherapy and brachytherapy, as clinically relevant. Timely diagnosis and appropriate treatment have been shown to improve progression-free survival and disease free survival of these patients[1].

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