

Case Report

Triple Synchronous Primary Neoplasms of the Cervix, Endometrium, and Ovary: A Rare Case Report and Summary of All the English PubMed-Indexed Literature

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The incidence rate of triple or more synchronous primary neoplasms of the female genital system is exceedingly uncommon. To the best of our knowledge, only 13 such cases have been reported in the PubMed-indexed English literature. Herein, we report a single case of triple synchronous primary neoplasms of the cervix, endometrium, and left ovary with three distinct histological patterns that were not reported previously. Moreover, we briefly present a summary table of all the English PubMed-indexed cases of triple or more synchronous primary neoplasms of the female genital system ($n = 13$).

1. Introduction

Synchronous primary neoplasms are defined when two or more neoplasms take place concurrently in the same patient. These neoplasms should be histologically discrete and separated from each other by means of healthy tissues, such as basal lamina or stroma [1]. Double gynecological neoplasms are occasionally observed, and the most commonly reported combination is endometrial-ovarian neoplasms [2, 3]. The incidence of triple or more synchronous primary neoplasms of the female genital system is exceedingly uncommon. To the best of our knowledge, only 13 such cases have been reported in the PubMed-indexed English literature [1, 2, 4–14]. Herein, we report a single case of triple synchronous primary neoplasms of the cervix, endometrium, and right ovary with three distinct histological patterns that were not reported previously. Moreover, we briefly present a summary table of all English PubMed-indexed existing cases of triple or more synchronous primary neoplasms of the female genital system ($n = 13$).

2. Case Report

A 55-year-old multiparous woman was referred to our hospital as a case of pelvic/abdominal mass for 2 months. The mass was associated with progressive abdominal distention, left lower abdominal pain, and occasional vaginal bleeding. Her past medical and surgical histories were unremarkable. Upon pelvic examination, a cystic, mobile, nontender pelvic mass was palpated up to the umbilicus. There were no abnormal cervical growths. Laboratory findings showed a slightly elevated CA-125 level of 36.6 U/mL (normal range: 0–35 U/mL).

Two imaging studies were conducted: ultrasound (US) and computed tomography (CT) scan. US showed a 15 cm pelvic mass at the left adnexal site. The mass was cystic and contained solid areas. CT scan showed a heterogeneous 14 × 12 cm pelvic/abdominal mass with solid components, along with multiple prominent left pelvic and para-aortic lymph nodes that were highly suspicious for metastasis. The mass was seen between uterus and rectum. The mass was most

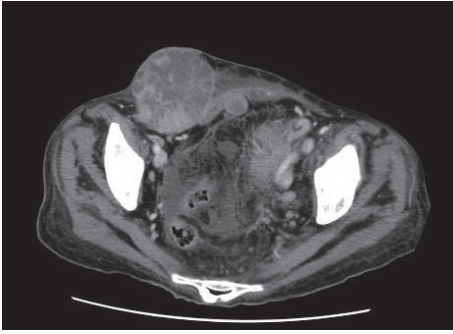


FIGURE 1: Axial CT scan showing heterogeneous 14 × 12 cm pelvic-abdominal mass between uterus and rectum, most likely originating from the left ovary and inseparable from the posterior uterus.

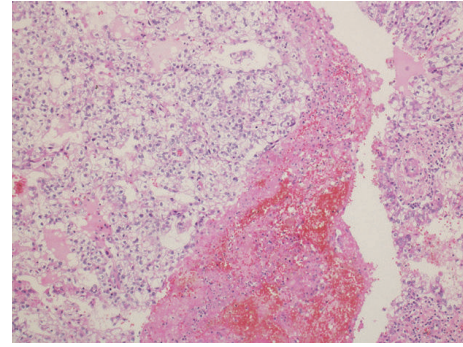


FIGURE 3: Histopathological examination showing clear-cell carcinoma of left ovary (H&E stain).

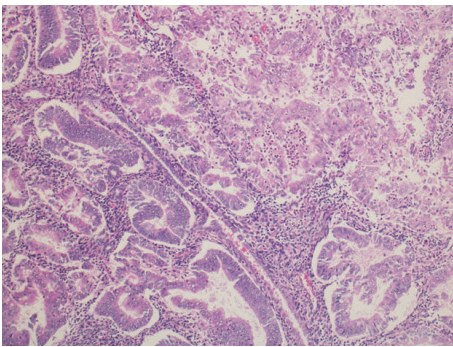


FIGURE 2: Histopathological examination showing grade-I endometrioid adenocarcinoma of the uterus (H&E stain).

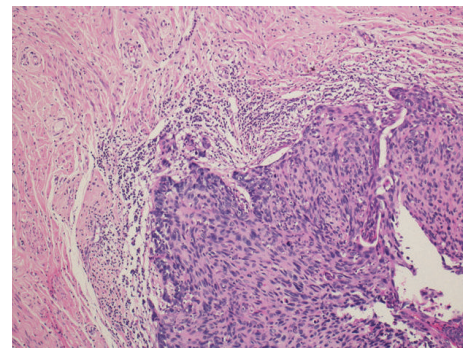


FIGURE 4: Histopathological examination showing poorly differentiated squamous cell carcinoma of the cervix (H&E stain).

likely originating from the left ovary and inseparable from the posterior uterus (Figure 1). In view of an underlying neoplastic process, a surgical staging operation was planned.

The surgical staging operation consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, sampling from the pelvic lymph nodes and para-aortic lymph nodes, and multiple biopsy specimens from various peritoneal sites. During the laparotomy, the pelvic mass was found to be most likely originating from the left ovary. The uterus was bulky and the right ovary was grossly normal. There were no ascites or other gross intra-abdominal lesions. All resected specimens were examined for histopathological analysis.

Histopathological examination showed grade-I endometrioid adenocarcinoma of the uterus with no lymphovascular invasion and less than 50% invasion into the myometrium (Figure 2). Both ovaries were examined, and the microscopic appearance of the left ovary revealed clear-cell carcinoma with no lymphovascular invasion (Figure 3). The right ovary and bilateral fallopian tubes were normal. Microscopic examination of the cervix exhibited poorly differentiated squamous cell carcinoma (Figure 4). The omentum and bilateral pelvic and para-aortic lymph nodes were negative for metastasis.

Therefore, the final histopathological diagnosis was triple synchronous primary stage 1B1 poorly differentiated squamous cell carcinoma of the cervix (pTNM: T1B1 Nx M0),

stage 1A grade-I endometrioid adenocarcinoma of the uterus (pTNM: T1A Nx M0), and stage 1A clear-cell carcinoma of the left ovary (pTNM: T1A Nx M0).

The case was discussed in the multidisciplinary tumor board meeting and the recommendation was to start adjuvant therapy. The adjuvant therapy consisted of chemotherapy and radiation therapy. The adjuvant chemotherapy was primarily intended for the high-risk ovarian cancer (clear-cell carcinoma) and included six cycles of paclitaxel 175 mg/m² plus carboplatin (area under the curve [AUC] 6). The adjuvant radiation therapy was primarily intended for the high-risk cervical cancer (poorly differentiated squamous cell carcinoma) and consisted of external beam radiation therapy (EBRT) of 51 Gy delivered in 26 fractions.

The management plan was discussed with the patient; however, she refused the adjuvant treatment. Three months later, she presented to clinic with radiological evidence of recurrence, as follows: large local recurrence in the left iliac fossa, multiple metastatic masses in the abdominal and pelvic cavities, and multiple metastatic retroperitoneal and pelvic lymph nodes.

3. Discussion

The incidence rate of double synchronous primary gynecological neoplasms is relatively uncommon and ranges from 0.6% to 5.4% [2, 3, 15–17]. The incidence rate of triple or more

TABLE 1: A summary table of all existing cases of triple or more synchronous primary neoplasms of the female genital system ($n = 13$).

Ref	Author	Year	Age (yr)	Presentation	Site	Tumor histology	Tx	FU (mon)	Outcome
[14]	Matlock et al.	1982	77	Anorexia Abdominal pain Weight loss	Ovary Ovary Uterus	Papillary serous cystadenocarcinoma Mucinous cystadenocarcinoma papillary adenocarcinoma with psammoma bodies	CT	4	DOD
[2]	Ayhan et al.	1992	NM	NM	Ovary Uterus Cervix	Mucinous adenocarcinoma Endometrioid adenocarcinoma Carcinoma in situ	NM	28	DOD
[7]	Jobo et al.	1997	35	Vaginal bleeding	Ovary Uterus Cervix	Endometrioid adenocarcinoma Endometrioid adenocarcinoma Carcinoma in situ	CT	25	NED
[1]	Ree et al.	2003	46	Vaginal bleeding	Ovary Ovary Uterus	Clear-cell carcinoma Borderline mucinous cystadenoma Endometrioid adenocarcinoma	CT	17	NED
[9]	Isin Dogan Ekici et al.	2006	56	Pelvic pain Vaginal bleeding	Ovary Uterus Uterus	Mucinous adenocarcinoma Endometrioid adenocarcinoma Leiomyosarcoma	CT	24	NED
[11]	Phupong et al.	2007	50	Menorrhagia	Ovary Ovary Uterus Cervix	Mucinous adenocarcinoma Low malignant potential Endometrioid adenocarcinoma Endocervical adenosquamous carcinoma	RT	3	DOD
[13]	Pekin et al.	2007	62	Spotting Vaginal bleeding	Ovary Ovary Cervix	Brenner tumor Granulosa tumor Squamous cell carcinoma	NM	NM	NM
[8]	Saglam et al.	2008	63	Postmenopausal bleeding Abdominal distention	Ovary FT Uterus Cervix	Mucinous adenocarcinoma Early papillary adenocarcinoma Endometrioid adenocarcinoma Endocervical adenocarcinoma	CT	12	NED

TABLE I: Continued.

Ref	Author	Year	Age (yr)	Presentation	Site	Tumor histology	Tx	FU (mon)	Outcome
[10]	Atasever et al.	2009	50	Pelvic pain Lower abdominal distention	Ovary FT FT Uterus Cervix	Papillary serous adenocarcinoma Microinvasive carcinoma in situ Microinvasive carcinoma in situ Intraepithelial adenocarcinoma Endocervical in situ carcinoma	CT	29	DOD
[6]	Hale et al.	2011	49	Fatigue Ankle edema Abdominal distention	Ovary Uterus Cervix	Mucinous, clear cell, and endometrioid carcinoma Endometrioid adenocarcinoma Endometrioid adenocarcinoma	NM	NM	NM
[12]	Zhang and Lerwill	2011	79	Abdominal distention Abdominal pain Dyspnea	Ovary Uterus Uterus	Leydig cell Myxoid leiomyosarcoma Mucinous adenocarcinoma	None	10	NED
[4]	Takatori et al.	2014	50	Metrorrhagia	Ovary Uterus Cervix	Serous adenocarcinoma Endometrioid adenocarcinoma Endometrioid adenocarcinoma	CT	18	NED
[5]	Chiofalo et al.	2016	38	Pelvic pain Vaginal bleeding	Ovary Uterus Cervix	Mucinous adenocarcinoma Endometrioid adenocarcinoma Mucinous adenocarcinoma	CT	18	NED
	Our case	2017	55	Abdominal distention Abdominal pain Vaginal bleeding	Ovary Uterus Cervix	Clear-cell carcinoma Endometrioid adenocarcinoma Poorly differentiated squamous cell carcinoma	None	3	DP

Ref: reference; yr: years; Tx: therapy; mon: months; CT: chemotherapy; RT: radiotherapy; NM: not mentioned; DOD: died of disease; NED: no evidence of disease; DP: disease progression.

synchronous primary neoplasms of the female genital system is exceedingly uncommon. To the best of our knowledge, only 13 such cases have been reported in the PubMed-indexed English literature [1, 2, 4–14] (Table 1). There was only one case of quintuple synchronous neoplasms [10] and two cases of quadruple synchronous neoplasms [8, 11]. On the other hand, there were only 10 cases of triple synchronous neoplasms. In our study, the distinctive combination of poorly differentiated squamous cell carcinoma of the cervix, grade-I endometrioid adenocarcinoma of the uterus and clear-cell carcinoma of the left ovary has never been previously reported.

The etiology of synchronous primary neoplasms of the female genital system remains poorly defined. It has been assumed that in genetically predisposed individuals, the Mullerian tissues with similar embryological origin may respond as a single structural entity when simultaneously exposed to carcinogenic, hormonal, therapeutic, or other triggering factors [2]. In our study, there were three different histological subtypes identified in the surgical specimens (squamous, endometrioid, and clear-cell). This unusual presentation raises thoughts about potential underlying epigenetic/bimolecular explanations, and this is an interesting arena for future research.

Several clinicopathological criteria have been suggested to assist clinicians and pathologists in distinguishing synchronous primary gynecological neoplasms from related metastatic foci. These criteria include either one major criterion or all the four minor criteria. The one major criterion is the existence of distinct histological types of the neoplasms. 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 of distant metastasis [18, 19]. In our case, all the above-mentioned major and minor criteria were met, hence confirming the diagnosis of triple synchronous primary neoplasms of the female genital system.

It is critically crucial to differentiate between synchronous primary gynecological neoplasms and related metastatic diseases. This is because both management and prognosis vary substantially. Regarding prognosis, synchronous primary gynecological neoplasms are associated with better survival rates than metastatic or advanced primary ones [2, 3, 17]. This observation may be attributable to the younger age of presentation, earlier disease stage, and lower disease grade at the time of clinical diagnosis [17]. The prognosis of a triple neoplasm is largely determined by the neoplasm with the poorest prognosis [5].

There are no specific guidelines regarding the management of synchronous primary gynecological neoplasms. Proper management should be largely individualized taking into consideration several parameters, such as age of patient, disease type, disease stage, disease grade, and extent of the neoplastic invasion [10]. Management modalities include surgical debulking and/or adjuvant radiotherapy and/or adjuvant chemotherapy, as seen clinically appropriate. Patients with advanced stage, higher grade, and poor histological synchronous primary neoplasms should be treated with more aggressive management modalities.

Clear-cell carcinoma (CCC) of the ovary is regarded as a grade III and high-risk neoplasm, irrespective of the disease stage. Also, CCC of the ovary is recognized to be less sensitive to first-line platinum-based chemotherapy [20]. Previous evidence advocated that irinotecan was more effective against primary [21] and recurrent [22] ovarian CCC when compared to other cytotoxic regimens. However, a recent randomized phase III trial of paclitaxel plus carboplatin (PC) versus irinotecan plus cisplatin (CPT-P) in patients with ovarian CCC showed no superiority of CPT-P over the gold standard PC regimen [23].

Poorly differentiated squamous cell carcinoma of the cervix is regarded as a high-risk factor influencing the likelihood of recurrence. Hence, an adjuvant therapy may be recommended. The administration of concurrent cisplatin-based chemotherapy and radiation therapy (in the form of EBRT or brachytherapy) has been shown to substantially improve progression-free and overall survival for high-risk, early-stage patients with cervical cancer [24].

4. Conclusion

Although exceedingly uncommon, the likelihood of triple synchronous primary neoplasms should be considered when evaluating neoplasms of the female genital system. Careful pathological examination of the surgical specimens can substantially aid in recognizing such synchronous neoplasms.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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