Three primary synchronous malignancies of the uterus, cervix, and fallopian tube
A case report
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Abstract
Rationale: Multiple primary malignancies can occur in the same organ or in multiple organs or systems. Likewise, they can occur simultaneously or successively. Based on the timing of the diagnosis, they are classified as multiple synchronous (i.e., concurrent) or metachronous (i.e., successive) primary malignancies. The vast majority of patients have multiple metachronous malignant tumors; multiple synchronous tumors are rare.

Patient concerns: A 63-year-old woman presented with the chief complaint of vaginal fluid discharge for 3 months and abdominal pain for 1 month.

Diagnoses: The patient was diagnosed with multiple synchronous primary malignancies: 1) endometrial poorly differentiated serous adenocarcinoma, stage IV; 2) poorly differentiated squamous cell carcinoma of the cervix, stage IB1; and 3) left-sided fallopian tube carcinoma in situ.

Interventions: After total abdominal hysterectomy, bilateral salpingo-oophorectomy, and comprehensive staging and debulking, the patient was administered eight courses of adjuvant chemotherapy (taxane carboplatin/taxane cisplatin).

Outcomes: After chemotherapy completion, the patient has been undergoing regular follow-up examinations; no recurrence has been noted at 18 months.

Lessons: It is important to distinguish between multiple synchronous primary malignancies and metastasis of a primary tumor to select the appropriate treatment regimen and to adequately assess the patient’s prognosis. When a cancer patient shows clinical manifestations of another tumor, not only metastasis but also the possibility of multiple synchronous primary malignant tumors should be considered. The duration of follow-up in patients with malignant tumors should be extended as much as possible, as the timely detection and treatment of other primary malignant tumors can prolong survival and improve the quality of life.

Abbreviations: IHC = immunohistochemistry, IV = intravenous, CT = computed tomography.

Keywords: cervical cancer, endometrial carcinoma, fallopian tube cancer, multiple primary cancers, synchronous

1. Introduction
Cases of multiple primary malignancies were first reported by Billroth et al in 1889.[1] Since then, many cases of bi-primary, tri-primary, and even multiple primary malignancies have been reported. The tumors of multiple primary malignancies can affect a single or multiple organ(s).[2] According to the time of the diagnosis, multiple primary malignancies are classified as synchronous or metachronous primary tumors. The vast majority of patients have multiple metachronous malignancies as multiple malignant tumors rarely occur at the same time.[3,4] Dual primary malignancies are most common, whereas tri-primary and multiple primary malignancies account for only 0.5% and <0.1% of cases, respectively.[5]

Here, we report a rare case of uterine, cervical, and fallopian tri-primary synchronous malignancies. We obtained written consent from the patient for the publication of this case report. Institutional review board approval was not necessary as this is a case report.

2. Case report
A 63-year-old woman presented with the chief complaint of “vaginal fluid for 3 months and abdominal pain for 1 month.” She was treated for an infection at the local hospital for 10 days. However, as no significant improvement in her symptoms was seen, she visited our hospital. Pelvic examination revealed cervical papillary hyperplasia and blood on contact but no bleeding within the cervical canal. The bimanual examination showed a mass with an unclear border in the pelvis, measuring 10 cm; the mass appeared fixed and without
tenderness. The level of the tumor marker CA125 was 1611.1 U/mL (normal, <35 U/mL).

Computed tomography (CT) revealed adnexal masses (measuring 6.8 cm x 4.1 cm x 4.7 cm [left] and 8.2 cm x 6.8 cm x 9.3 cm [right]) with irregular shapes and bilateral mass fusion. An enhanced CT scan showed uneven enhancement, with a bilateral “ovarian pedicle” sign. Uterine morphology was normal; the uterine wall and bilateral adhesions accounted for the unclear boundaries. The sigmoid colon and appendix had unclear boundaries. Slight thickening of the local intestinal (but not rectal) wall and poor filling of the bladder were observed. Moreover, peritoneal nodular thickening, omental thickening, and blurring were seen. Multiple para-aortic lymph nodes at the level of the renal vessels were detected, with the largest measuring 1.9 cm x 1.3 cm. The diagnosis at admission was “pelvic mass to be diagnosed,” with a suspicion of ovarian cancer.

In February 2016, a laparotomy was performed under general anesthesia. A small amount of bloody ascites was seen during surgery. Bilateral adhesions and cystic masses with diameters of about 10 cm were observed. The ovaries and fallopian tubes had an abnormal appearance, and the cystic masses, uterus, and bladder adhered closely. After separating the adhesions, the uterus was visualized in the posterior position; its size was comparable to 40+ days of pregnancy. Widely scattered miliary nodules were detected on the pelvic peritoneal surface. The omentum was pie-shaped, with miliary nodular lesions of grayish color. Moreover, a mass measuring 4 cm x 3 cm was seen in the ileocecal area. The appendix was invaded by the tumor. The appendiceal opening was blocked, and the appendiceal effusion was expanding. Enlargement and stiffening of the bilateral obturator, iliac, and para-aortic lymph nodes were observed, with dense adhesions to the surrounding vessels without obvious boundaries.

The intraoperative frozen section diagnosis of the right adnexal mass was poorly differentiated serous adenocarcinoma. The intraoperative diagnosis of 2 para-aortic lymph nodes was metastatic adenocarcinoma. Therefore, the following procedures were performed: total abdominal hysterectomy + bilateral salpingo-oophorectomy + comprehensive staging and debulking + omental resection + intestinal resection (ileocecal resection, including the appendix) + intestinal anastomosis. No residual disease was seen after the surgery.

The postoperative pathology of the uterine tumor was endometrial poorly differentiated serous adenocarcinoma of the uterus (Fig. 1) with diffuse and deep infiltration of the cervical interstitium (Fig. 2). The tumor penetrated the uterine serosa and metastasized to the adnexa (Fig. 3), rectum, peri-intestinal lymph nodes, appendix, and its surrounding tissues.

Immunohistochemistry (IHC) revealed the following: P53++, P16++, CA125+, progesterone receptor-, estrogen receptor-, CK5/6-, WT-1+, and a Ki67 positive rate of about 70%.

The postoperative pathology of the cervical tumor was poorly differentiated squamous cell carcinoma (Fig. 4). IHC indicated squamous cell carcinoma: WT-1+, P53++, P16++, and a Ki67 positive rate of about 90%.

The postoperative pathology of the left fallopian tube was epithelial multifocal atypical papillary hyperplasia with focal in situ carcinogenesis.

In summary, the postoperative diagnosis was: endometrial poorly differentiated serous adenocarcinoma, stage IV; poorly differentiated squamous cell carcinoma of the cervix, stage IB1; and left-sided fallopian tube carcinoma in situ.
Two weeks after the surgery, the patient was administered 8 courses of adjuvant chemotherapy (regimen: intravenous [IV] taxane/carboplatin or taxane [IV]/cisplatin, intraperitoneal). Additional radiotherapy was recommended, but the patient did not undergo radiotherapy for personal reasons. Eighteen months after the completion of the chemotherapy, her CA125 levels were in the normal range in follow-up tests. A pelvic examination and CT showed no signs of cancer recurrence.

3. Discussion and literature review

Multiple primary malignancies can occur in the same organ or in multiple organs or systems. Likewise, they can occur simultaneously or successively. Multiple synchronous primary malignancies are defined as ≥2 primary tumors that are each diagnosed at an interval of not more than 6 months; in contrast, multiple metachronous primary malignancies are defined as ≥2 primary tumors that are each diagnosed at an interval of >6 months. However, the definition of multiple primary malignancies is unclear. The definition proposed by Worten and Gates is generally accepted as the diagnostic criterion for multiple primary malignancies; it includes the following conditions: every tumor must be malignant; the pathological type of each tumor must be different; and metastases from the primary tumor must be excluded. In our case, the patient’s malignancy occurred in the uterus, cervix, and left fallopian tube. The pathological types of uterine and cervical tumors are significantly different from that of fallopian tube carcinoma in situ; all 3 tumors were diagnosed at the same time, consistent with the diagnostic criteria for multiple primary malignant tumors.

Studies on multiple primary malignant tumors have elucidated their mechanism of development. The occurrence of multiple primary malignancies is affected by a combination of environmental and genetic factors and is believed to be closely linked to factors such as genetic predisposition, immunological status, and overexposure to carcinogenic factors. It was reported that many genetic backgrounds are associated with multiple primary malignancies. For example, Li-Fraumeni syndrome, a rare condition, is associated with an increased incidence of various malignancies (breast cancer [most common], bone and soft tissue sarcoma, brain tumors, leukemia, and adrenal cortex cancer). Li-Fraumeni syndrome is associated with mutations in the CHEK2 and TP53 genes; more than 50% of families with Li-Fraumeni syndrome have inherited TP53 gene mutations. Chemotherapy and radiotherapy are also carcinogenic. Chemotherapy drugs, particularly alkylating agents, can damage dividing cells in normal tissues, such as the bone marrow and gastrointestinal mucosal cells, by affecting DNA synthesis and function. The current literature indicates that receiving multiple rounds of chemotherapy promotes the occurrence of other tumors.

Among female cancer patients, multiple primary female reproductive tract malignancies account for 1% to 2% of gynecologic malignancies; of these, 50% to 70% simultaneously occur in the endometrium and ovaries. Approximately 10% of patients with ovarian cancer also have endometrial cancer, and about 5% of patients with endometrial cancer also have ovarian cancer. In patients with endometrial cancer aged <50 years, multiple malignant tumors are more likely to occur synchronously.

Since the prognosis of patients with multiple primary malignancies is significantly better than that of patients with metastatic tumors, it is important to examine whether patients have multiple synchronous primary malignancies to select the appropriate treatment regimen and adequately assess their prognosis. At present, the diagnosis of multiple primary malignancies mainly depends on clinical findings and histopathology. However, due to uncertain histology, further molecular tests (e.g., microsatellite instability, lack of chromosomal heterozygosity, and inactivation of cloned X chromosomes; or screening for mutations in female genital tract tumor genes such as PTEN, TP53, KRAS, and CTNBN1) and cytogenetic analyses (e.g., IHC of β-catenin) are often required. However, due to the uniqueness of each tumor and the inherent inhomogeneity, these analyses often fail to reach a definitive conclusion. Therefore, diagnosing multiple primary malignant tumors is very difficult. It has been reported that mitochondrial DNA screening is helpful for the diagnosis of synchronous endometrial and ovarian cancers as it can identify primary and metastatic tumors of the female genital tract. However, further confirmation of the efficacy, accuracy, and usefulness of this approach is needed.

According to the current literature, a second primary tumor should be resected as early as possible, and its treatment should be similar to that of a single tumor. In the treatment of patients with multiple synchronous primary malignancies, the tumor stage, its biological behavior, the age and life expectancy of the patient, and comorbidities should be considered as these factors affect the choice of treatment strategy and prognosis.

Kourtspoulos et al. reviewed the literature on ≥3 primary malignancies and found that, although rare, it is not particularly rare. The exposure to oncogenic factors (e.g., smoking or alcohol abuse), genetic risk (e.g., Li-Fraumeni or Beckwith–Wiedemann syndrome), and the adverse effects of previous chemotherapy and/or radiotherapy may lead to an increased risk of developing a second tumor in patients with a history of cancer. With improvements in chemotherapy and radiotherapy as well as novel therapeutic approaches, the survival of cancer patients and accordingly, the risk of developing a second tumor, have been increasing. Thus, extending the duration of follow-up of cancer patients after treatment is necessary. Moreover, clinicians should not automatically assume that a second tumor implies metastasis when cancer patients show tumor-associated symptoms and manifestations. Instead, the possibility of a second and locally treatable tumor should be considered and evaluated. Tumor marker assessments and positron emission tomography-CT are beneficial for the follow-up of such patients.
In conclusion, when clinical manifestations of another tumor appear in a cancer patient, not only tumor metastasis but also the possibility of synchronous multiple primary malignant tumors should be considered. Moreover, the duration of follow-up in patients with malignant tumors should be extended as the timely detection and treatment of additional primary malignant tumors may prolong the patients’ survival and improve their quality of life.

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