Triple synchronous invasive malignancies of the female genital tract in a patient with a history of leukemia: A case report and review of the literature

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ABSTRACT

Background: Three primary synchronous cancers in the female genital tract are extremely rare. In the literature, only four studies have described three different invasive gynecologic cancers of epithelial origin identified simultaneously in the same patient.
Case presentation: This is the first case in the literature that reports on triple primary ovarian, endometrial and endocervical cancers in a 38-year-old woman with a history of previously treated malignant disease (acute lymphatic leukemia). With a preoperative diagnosis of endocervical adenocarcinoma stage Ib1 (according to International Federation of Gynecology and Obstetrics—FIGO), as well as an adnexal mass, she underwent radical hysterectomy with bilateral adnexectomy. Pathologic examination of the surgical specimen revealed a mucinous adenocarcinoma of the cervix, an endometrioid adenocarcinoma of the uterine corpus, and a mucinous adenocarcinoma of the left ovary. Eighteen months after appropriate treatment, the patient is free of disease.
Conclusion: The incidental diagnosis of more than one tumor is often a post-operative finding, usually with the detection of low-stage neoplasms. Multiple synchronous gynecologic cancers have a better prognosis than metastatic or advanced primitive disease. In a patient with multiple neoplasms, the prognosis is determined by the tumor with the worst prognosis.

1. Introduction

Synchronous primary malignancies are defined as two or more different neoplasms identified simultaneously in the same patient, where the tumors are histologically distinct and separated from each other by healthy tissue (stroma or basal lamina) [1].

In the female genital tract, two simultaneous malignancies are not usually seen, but, when it happens, are most commonly observed in ovaries and endometrium [2]; the detection of three or more tumors is extremely rare.

We present a case of a young woman with a triple simultaneous ovarian, endometrial and cervical carcinomas and a review of the literature.

2. Case presentation

In 2013, a 38-year-old Caucasian woman, PARA 1002, came to our attention for pelvic pain with vaginal bleeding that had started two weeks earlier. Her height was 165 cm, and her body-weight was 58 kg (body mass index 21.3). Her past medical history was unremarkable. At the age of 20, she had an acute lymphatic leukemia, treated with chemotherapy and autologous stem cell transplant. Since then, she had been amenorrhoeic, and she had taken contraceptive pills for eleven years, until the age of 32. She obtained a twin pregnancy at the age of 33 with an ovodonation, in vitro fertilization and embryo transfer. She did not smoke. Human immunodeficiency virus, hepatitis B, and hepatitis C tests were negative.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ASCUS, atypical squamous cells of undetermined significance; HPV, human papilloma virus; AGC-NOS, atypical glandular cells not otherwise specified; LEEP, loop electrosurgical excision procedure; CT, Computed Tomography; CEA, carcinoembryonic antigen; EIN, Endometrial Intraepithelial Neoplasia; ER, Estrogen Receptor.

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From the age of 25, the patient regularly underwent screening pap smear tests, every three years (according with the Italian National screening program), with negative results. In 2010, she had a pap test with atypical squamous cells of undetermined significance (ASCUS) with a positive high-risk human papilloma virus (HPV) DNA test and a normal colposcopic picture. One year later, Pap test revealed atypical glandular cells not otherwise specified (AGC-NOS). Colposcopy-guided biopsies and cervical curettage were performed with negative results. She did not undergo any gynecological control until December 2013, when pelvic examination revealed the presence of an irregular cervix that had increased in volume, regular uterus, and an elastic mass behind the uterus which appeared to be a large multilocular ($10.0 \times 12.0 \times 10.5$ cm in diameter) left ovarian cyst by vaginal ultrasound. Colposcopic direct biopsy and endocervical curettage showed the presence of dysplastic glandular cells (p16: positive score 3+) with associated koilocytotic HPV-related atypia. A loop electrosurgical excision procedure (LEEP) conization was performed under local anesthesia. The pathologic diagnosis of the cone (measuring $3 \times 1.2 \times 0.8$ cm) was an invasive adenocarcinoma of endocervical "usual" type, grade 1 (G1) differentiation. The neoplasm occupied the whole specimen with positive surgical margins (stage pT1b1 Nx Mx—TNM 7th edition).

Computed Tomography (CT) and laboratory tests were unremarkable. A laparotomic radical hysterectomy (type C1 sec. Querleu-Morrow), monolateral left adnexetomy, right salpingectomy, and pelvic lymphadenectomy were performed [3]. The intraoperative diagnosis of frozen sections of the ovarian cyst was negative for malignant cells. Neither ascites nor disseminated lesions were observed in the abdominal cavity; washing cytology revealed no pathological findings. There were no intraoperative or postoperative complications.

Macroscopic assessment of the left adnexa showed a cystic mass measuring ($17 \times 15 \times 10$ cm; 1030 g) with an intact surface. The cut section of the radical hysterectomy specimen received separately showed a soft, friable and hemorrhagic endometrium, whereas endocervix showed a greyish, nodular mass measuring 2×1.2 cm, apparently infiltrating the cervical wall.

Both salpinges were grossly and microscopically unremarkable.

Histopathological examination showed the presence of three different carcinomas: a moderately differentiated (G2) mucinous adenocarcinoma of endocervical "usual" type, with lymph-vascular spaces invasion (LVSI) of the cervix (horizontal extension measuring 3.5 cm, and depth of invasion measuring 1.3 cm) (Fig. 1A); an intramucosal well differentiated (G1) endometrioid endometrial adenocarcinoma, with focal mucinous and tubaric differentiation (Fig. 1B) and adjacent Endometrial Intraepithelial Neoplasia (EIN); a mucinous cystoadenoma with a focus of mucinous adenocarcinoma of the left ovary (with a maximum diameter of 0.8 cm) (Fig. 1C). A total of 27 lymph nodes were histologically examined, and all were negative.

The three malignancies detected were staged pT1b1 N0 (cervix), pT1a N0 (endometrium) and pT1a N0 (ovary), according to the pTNM criteria (2009, 7th edition) [4]. Cervical and endometrial adenocarcinoma were separated from each other by normal endometrium (1.5 cm). Immunohistochemical analysis was performed in an automated system (Benchmark-XT, Ventana, Tucson, AZ, US), and the following primary antibodies were used: p16 (monoclonal, clone G175-405, dilution 1:25; Becton-Dickinson, Franklin Lakes, NJ, US), Vimentin (monoclonal, clone V9, prediluted, Ventana, Tucson, AZ, US), Estrogen Receptor (ER) (monoclonal, clone SP1, prediluted, Ventana, Tucson, AZ, US), carcinoembryonic antigen (CEA) (polyclonal, dilution 1:350, Dako, Glostrup, Denmark). A summary of the morphologic and immunohistochemical findings of the three synchronous tumors is reported in Table 1 and in Fig. 1. Finally, the hepatic nodule demonstrated chronic hepatitis and the presence of focal cirrhosis.

Consequently, for the diagnosis of ovarian cancer, a single-agent carboplatin regimen (carboplatin AUC5) was administrated as chemotherapy for the ovarian cancer. Six treatment cycles were completed with dose reduction for grade 2 neutropenia. Eighteen months after the surgery, clinical and pelvic examination, squamous cell carcinoma antigen, Ca 125, carcinoembryonic antigen (CEA), vaginal ultrasound, abdominal and pelvic CT, Pap smear and colposcopy were negative.

3. Discussion

The causes of multiple cancer may include a single carcinogen inducing cancers in multiple organs, genetic factors, endocrine and immunologic factors, constitutional factors, and medical treatment for previous cancer [5].

This is the first case in the literature that describes a triple gynecological invasive cancer in a patient with a previous history of unrelated malignancy. The etiology of the synchronous occurrence of ovarian, cervical and endometrial carcinoma is not clear. Despite the Mullerian origin of both endometrial and ovarian epithelium, in our case, the endocervical carcinoma was HPV-related, and the endometrial histology was different from the ovarian one. Multiple oncogenic factors played a role: the patient underwent an anticancer and immunosuppressant therapy for acute lymphatic leukemia; she took hormonal drugs for infertility; her HPV test resulted positive for high-risk type.

Immunohistochemistry employing a panel of markers (ER, vimentin, p16 and CEA) could help to distinguish between a cervical and an endometrial primary tumor. Endometrial adenocarcinomas of endometrioid type typically exhibit diffuse nuclear ER and cytoplasmic vimentin positivity whereas CEA staining is usually negative. In contrast, cervical adenocarcinomas are usually, but not always, CEA-positive, vimentin (Fig. 1F) and ER-negative (Fig. 1D). Usual endocervical-type adenocarcinomas typically exhibit diffuse p16 positivity (Fig. 1E) due to the presence of high-risk HPV, while endometrial adenocarcinomas of endometrioid type are generally negative or only focally positive [6,7]. A mucinous adenocarcinoma or an endometrioid adenocarcinoma with mucinous differentiation arising in the corpus is usually vimentin-negative and CEA-positive (this immunophenotype overlaps with that of a cervical adenocarcinoma), ER-positive and p16-negative or focally immunoreactive. In our case, glands showing mucinous differentiation in endometrioid adenocarcinoma were ER and vimentin-negative (Fig. 1G and H, respectively), CEA focally positive with a membranous-apical pattern (Fig. 1I), and p16 focally positive (not shown). On the contrary, neoplastic glands with typical morphology were ER and vimentin-positive (Fig. 1G and H, respectively), CEA-negative (Fig. 1I), and p16-negative.

Therefore, immunohistochemistry has always to be interpreted in the light of the clinical, radiological, gross pathological and microscopic findings altogether.

According to the literature, the estimates of the incidence of synchronous genital tumors vary from 0.63 to 6% [8–12]. Endometrial-ovarian cancer togetherness is the most common combination in synchronous gynecologic malignancies. They occur at younger age and have a more favorable prognosis than metastatic primary gynecologic tumors [13]. In these cases, a 5-year survival rate between 68 and 73.3% has been observed [10,13].

Seven cases of triple synchronous primaries, 1 case of quadruple and 1 case of quintuple have been reported in the literature (Table 2), most of them being in situ/intraepithelial neoplasias [10,14–17].

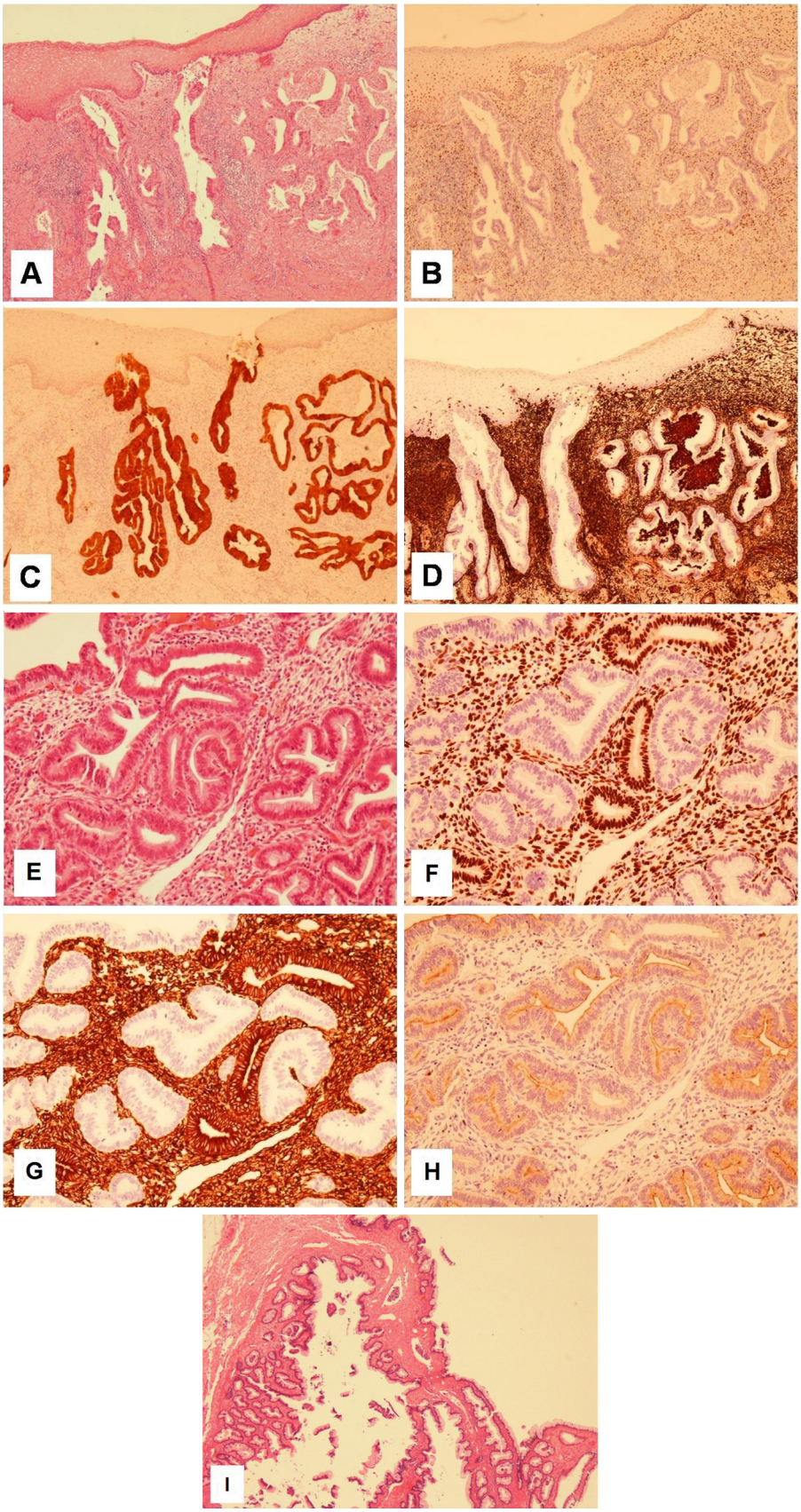

Fig. 1. *Morphologic and immunohistochemical findings in the three tumors detected.* (A) Endocervical adenocarcinoma; (B) endometrial adenocarcinoma with mucinous differentiation; (C) mucinous cystoadenoma with a focus of mucinous carcinoma of the ovary—(A–C) Hematoxylin & Eosin; (D) ERs were negative in neoplastic endocervical glands and positive in the stroma, as expected; (E) p16 was diffusely and strongly positive and (F) vimentin was completely negative in neoplastic glands and strongly positive in the surrounding stroma, as expected; (G) ERs and (H) vimentin were negative in neoplastic glands with mucinous differentiation and strongly and diffusely positive in glands showing usual morphology, as expected; (I) CEA was focally positive with a membranous-apical pattern in neoplastic glands with mucinous differentiation and negative in glands showing usual morphology (all images with original magnification 100×).

Table 1
Summary of morphologic and immunohistochemical findings of the three synchronous tumors reported.

Primary location	Staging	Grading	Morphology	ERs	Vimentin	CEA	p16
Ovary	pT1a N0	1	Mucinous	−/+			
Uterus	pT1a N0	1	Endometrioid and Mucinous/tubaric metaplasia	+ −	+ −	− +/−	− +/−
Cervix	pT1b1 N0	2	Usual type	−	−	+	+

Table 2
Cases of simultaneous primary gynecological malignancies described in the literature.

Reference	Publication year	Age	Anatomic sites	Type of tumor	Outcome follow-up
Ayhan et al. [10]	1992	Unknown	Ovary Endometrium Cervix	Mucinous adenocarcinoma Endometrioid adenocarcinoma Carcinoma in situ	DOD 28 Months
Jobo et al. [15]	1997	35	Ovary Endometrium Cervix	Endometrioid adenocarcinoma Endometrioid adenocarcinoma Carcinoma in situ	NED 25 Months
Nakayama et al. [20]	1999	48	Ovary Endometrium Cervix	Endometrioid adenocarcinoma Endometrioid adenocarcinoma Endometrioid adenocarcinoma	NED 15 Months
Isin Dogan Ekici et al. [14]	2006	56	Ovary Endometrium Uterus	Mucinous adenocarcinoma Endometrioid adenocarcinoma Leiomyosarcoma	NED 24 Months
Phupong et al. [18]	2007	50	Ovary Ovary Endometrium Cervix	Mucinous adenocarcinoma Low malignant potential Endometrioid adenocarcinoma Endocervical adenosquamous carcinoma	DOD 3 Months
Atasever et al. [17]	2009	35	Ovary Salpinx Endometrium Cervix	Papillary serous adenocarcinoma Microinvasive carcinoma in situ Intraepithelial adenocarcinoma Endocervical in situ carcinoma	DOD 29 Months
Saglam et al. [16]	2008	63	Ovary Salpinx Endometrium Cervix	Mucinous adenocarcinoma Early papillary adenocarcinoma Endometrioid adenocarcinoma Endocervical adenocarcinoma	NED 12 Months
Hale et al. [19]	2011	49	Ovary Endometrium Cervix	Mucinous, clear cell, and endometrioid carcinoma Endometrioid adenocarcinoma Endometrioid adenocarcinoma	Unknown
Takatori et al. [5]	2014	50	Ovary Endometrium Cervix	Serous adenocarcinoma Endometrioid adenocarcinoma Mucinous adenocarcinoma	NED 18 Months
Our case	2015	38	Ovary Endometrium Cervix	Mucinous adenocarcinoma Endometrioid adenocarcinoma Mucinous adenocarcinoma	NED 13 Months

NED: no evidence of disease; DOD: died of disease.

In the literature, only 4 cases of simultaneous invasive carcinomas of the female genital tract have been described [5,18–20].

In most papers, the diagnosis of synchronous tumors was incidental, and a low grade of invasion was detected, probably because the gynecologist focuses his/her attention on the symptomatic cancer, which often is the cervical or endometrial one. Therefore, the detection of second or third cancers of the same apparatus appears to be incidental.

4. Conclusion

Synchronous gynecologic tumors seem to have a better outcome than metastatic or advanced primary carcinomas [10,13,16,18]: the prognosis of a triple neoplasm is given by the tumor with the worst prognosis at diagnosis.

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6. Disclosures

None.

7. Conflict of interest statement

None.

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