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Early solitary splenic metastasis of endometrial cancer: a case report and review of literature

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INTRODUCTION

Endometrial cancer is the fifth most common cancer in women [1]. It occurs more frequently in postmenopausal women and the main risk factor is exposure to endogenous or exogenous estrogens in association with hypertension, obesity, diabetes, early menarche and late menopause, nulliparity and taking tamoxifen [2].

Most cases (75%) of endometrial cancer are diagnosed at early stage (FIGO I and II), with a 5-year survival ranging from 74 to 91% [3].

The recurrence of endometrial carcinoma mainly affects the pelvic/para-aortic lymph nodes (46%),

ABSTRACT

Spleen involvement in the patients affected by endometrial cancer is an extremely rare event. The aim of this study is to report a case of early splenic metastasis of endometrial cancer and a systematic literature review to standardize management. We describe the case of a 59-year-old patient affected by endometrial cancer FIGO stage IA G3 (N0). She developed an isolated splenic recurrence of clear cell adenocarcinoma and underwent to splenectomy and second line chemotherapy. After 55 months the patient is alive without disease.

The literature review highlights an asymptomatic onset and a 24-month recurrence presentation interval. In most cases the FIGO stage at diagnosis is the I and histotype is endometrioid. Treatment is surgery in all cases, followed by chemotherapy in 50% of cases.

upper vagina (42%), the peritoneum (28%) and the lungs (24%); the involvement of the spleen, pancreas, rectum, muscle tissue and brain is described in less than 5% of cases [4].

The aim of this study is to report a rare case of early splenic metastasis of endometrial cancer and a systematic review literature concerning splenic localization of endometrial cancer.

MATERIALS AND METHODS

Data of case report were extracted from clinical record, electronic database, instrumental imaging

and follow-up examinations. Systematic research on PubMed Central with MeSH (Medical Subject Headings): “Endometrial cancer AND splenic metastasis” was performed; information regarding age at the first diagnosis of endometrial cancer, the FIGO stage, grading and histotype, primary surgery and any adjuvant treatment, the interval of presentation of recurrence, treatment of recurrence and follow-up were obtained. The median age at the first diagnosis and the interval of presentation of splenic metastasis was calculated. The above-mentioned variables are summarized in **Table 1**.

RESULTS

The case report concerns a 59-year-old patient, multiparous, with a negative family history for cancer and a negative personal history. In May 2013, following pelvic pain and spotting, she underwent operative hysteroscopy with endometrial biopsy. The histological diagnosis was endometrioid adenocarcinoma. In August 2013 she underwent surgery by longitudinal laparotomy, with total hysterectomy, bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy. The histological diagnosis was “poorly differentiated adenocarcinoma of the endometrium with mixed aspects: serous, endometrioid and clear cell; myometrial infiltration less than 50%, free cervical canal, salpinxes, ovaries and the lymph nodes (0/15)”. In September 2013, in consideration of surgery and histological diagnosis with evidence of high-grade mixed (endometrioid, serous and clear cell) carcinoma (FIGO stage IA G3, special histotype), adjuvant treatment with platinum-based chemotherapy was recommended. Pre-treatment staging chest-abdomen CT was negative. The patient underwent chemotherapy with Carboplatin + Paclitaxel schedule every 21 days for 6 cycles until January 2014, treatment was well tolerated and without side effects. Then the patient was included in a follow-up program with visits after 2, 5 and 8 months from the end of chemotherapy and abdomen ultrasound at 5 months. The ultrasound performed in July 2014 showed a small hypoechoic splenic area of 19 mm. The PET examination revealed accumulation of tracer in a small hypodense area at the splenic hilum. In November 2014, the patient underwent surgery by longitudinal xiphoid-pubic laparotomy with splenectomy, total omentectomy and aortic lymphadenectomy. The histological examination reported splenic me-

tastasis of clear cell adenocarcinoma, free omentum and lymph nodes (0/12). In consideration of surgery, the diagnosis of isolated splenic recurrence of clear cell adenocarcinoma after first surgery and first line chemotherapy based on Carboplatin + Paclitaxel (8 months of platinum free interval), multidisciplinary team decision was second line chemotherapy. The patient underwent chemotherapy with Pegylated Liposomal Doxorubicin 40 mg/m² every 21 days for 5 cycles (6th cycle not performed due to toxicity), concluded in April 2015. After 55 months, the patient is alive, free of disease.

The details of the 19 case reports (including the case described in this paper) are summarized in **Table 1** [5-22]. Because of the unavailability of article’s full text in Polish, the remaining 18 studies were considered for the study. Median age at diagnosis was 58 years (range 43-72). Primary surgery in all of the described cases was abdominal hysterectomy with bilateral salpingo-oophorectomy (except 1 case underwent to radical hysterectomy), including 5 cases with systematic pelvic lymphadenectomy.

FIGO stage at first diagnosis was: I in 10 (55%) cases; II in 3 (16%) cases; III in 2 (11%) cases; IV in 1 (5%) cases; unknown in 2 (11%) cases. All the described cases (excluding our case) had an endometrioid histotype. Grading was G2 in 6 patients, G3 in 5 cases, unknown in the remaining 7. The adjuvant treatment for surgery was: external beam radiotherapy in 8 cases, 2 of which with brachytherapy; chemotherapy in 2 cases; follow-up in 4 cases; chemo-radiotherapy in 2 cases; hormone therapy in 1 case; 1 unknown case. In all cases the diagnosis of splenic metastasis was metachronous to endometrial adenocarcinoma, except for 1 case in which the splenic localization was synchronous with the primary tumor. The median time interval of splenic metastasis was 24 months (range 0-120). Recurrence occurred asymptotically in 8 (44%) patients, with left hypochondrial pain in 6 (33%), 2 (11%) cases of vaginal bleeding (1 for synchronous vaginal recurrence with splenic recurrence, 1 case for synchronous splenic localization to endometrial cancer), 1 (5%) case with palpable splenomegaly. The imaging method used to diagnose splenic metastasis was the abdomen ultrasound in 6 patients (33%), alone or in association with CT (3 cases) and PET (1 case); CT (6, 33%) was used alone or in association with PET (1 case) and MRI (1 case); the remaining cases were diagnosed with PET-CT (1 case) and MRI in association with PET (1 case); 4 case reports did not report the imaging method used.

Table 1. Published case report of splenic metastasis by endometrial adenocarcinoma.

Author, year	Age at first diagnosis (years)	FIGO stage, histotype	Treatment primary tumor	Symptoms	Imaging	Time of recurrence (months)	Treatment of relapse	Follow-up
Pecorino, 2021 (this case)	59	IA G3, serous-endometrioid-clear cell	TAH+BSO+PL CHT (Carboplatin+Paclitaxel)	Asymptomatic	US, PET	8	SPLENECTOMY CHT (Doxorubicin)	55 months NED
Pissarra, 2019 (synchronous)	70	IA G3, endometrioid	TAH+BSO CHT (Carboplatin+Paclitaxel)	Vaginal bleeding (synchronous)	MR, PET	0	SPLENECTOMY CHT (Carboplatin+Paclitaxel)	14 months NED
Gallotta, 2017	53	IB G2, endometrioid	TAH+BSO+PL FOLLOW-UP	Asymptomatic	PET-TC	37	ROBOTIC SPLENECTOMY CHT (Carboplatin + Doxorubicin)	2 months NED
Arif, 2013	50	IA G2, endometrioid	TAH+BSO FOLLOW-UP	Left hypochondrial pain	US, TC	50	SPLENECTOMY CHT (not specified)	Not available
Andrei, 2011 (full text not available)	Unknown	Unknown	Unknown	Unknown	Unknown	20	SPLENECTOMY CHT (not specified)	Unknown
Kara, 2011	56	IIIA, endometrioid	TAH+BSO+PL	Asymptomatic	TC, PET	26	Unknown	Unknown
Wei, 2009	54	IVA G3, unknown	TAH+BSO CH-RT (CYS+PTX)	Asymptomatic	US, TC	22	SPLENECTOMY CHT (not specified)	Unknown
Piura, 2009	58	IIB, endometrioid	TAH+BSO+PL EBRT+BRT	Asymptomatic	CT, PET	18	SPLENECTOMY CHT (Paclitaxel)	6 months NED
Gogas, 2004	52	IB G2, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	Unknown	30	SPLENECTOMY CHT (unknown)	46 months NED
Hadjileontis, 2004	53	endometrioid	TAH+BSO HT	Splenomegaly	Unknown	120	SPLENECTOMY HT	NED (time not recorded)
Takahashi, 2003	60	II, endometrioid	TAH+BSO EBRT	Asymptomatic	CT, MR	18	LAPAROSCOPIC SPLENECTOMY	18 months, NED
Aga-Mohammadi, 2001	62	IIB G2, unknown	RAH+PL FOLLOW-UP	Left hypochondrial pain	CT	82	SPLENECTOMY	Unknown
Giuliani, 1999	58	I G2, endometrioid	TAH+BSO+PL FOLLOW-UP	Vaginal bleeding (synchronous vaginal recurrence)	CT	28	SPLENECTOMY CHT	12 months, NED
Hamy, 1995	47	III, endometrioid	TH+BSO CHT (Adriamycin+Endoxan+Cisplatin) EBRT (30 Gy)	Asymptomatic	US, CT	82	SPLENECTOMY	36 months NED
Arend, 1992	62	IB, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	Unknown	12	SPLENECTOMY EBRT HT (Oral Progestin)	6 months AWD
Blake Gilks, 1989	72	IB G3, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	CT	33	SPLENECTOMY	6 months DOD
Nannestad Jorgensen, 1988	59	IA G3, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	US	7	SPLENECTOMY HT (Oral progestin)	10 months DOD
Klein, 1987	66	IA G2, endometrioid	TAH+BSO EBRT+BRT	Asymptomatic	US	20	SPLENECTOMY EBRT	27 months DOD
Kopacz, 1970 (full text not available)								

TAH: Total Abdominal Hysterectomy; RAH: Radical Abdominal Hysterectomy; PL: pelvic lymphadenectomy; US: ultrasound; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance; CHT: Chemotherapy; CH-RT: Chemo-radiation therapy; EBRT: External beam radiotherapy; BRT: Brachytherapy; HT: Hormone therapy; NED: No evidence disease; AWD: Alive with disease; DOD: Dead of disease.

Splenic recurrence was isolated in 16 (88%) patients, while in 2 cases (12%) it occurred synchronously with recurrence of the vaginal cuff (1 case) and lung localization (1 case). The treatment of splenic metastasis was splenectomy in all cases, one of which laparoscopic and one robotic; after surgery 9 patients (50%) underwent chemotherapy; 2 cases (11%) radiation therapy; 2 patients (11%) oral progestogen therapy; 3 cases (16%) sent for follow-up; 1 case (5%) unknown.

DISCUSSION

The spleen is a rare target of endometrial cancer and it is a rare event for all malignant neoplasms. About half of the cases of splenic metastasis originate from female genital tract tumors, more frequently the ovary and less frequently endometrium, cervix and tuba [23].

Some authors argue that the incidence of splenic metastases is underestimated because this event is asymptomatic often [24] and detectable only by imaging methods such as CT and MRI. In the present case, the splenic lesion was asymptomatic and diagnosed only by abdominal ultrasound and PET. The analysis of published cases showed that 44% of splenic metastasis of endometrial cancer was completely asymptomatic.

In consideration of the cases published before 2000, abdominal ultrasound alone is enough to diagnose recurrence. A particularity of the case described concerns the PET examination. The first and only work in the literature in this regard [12] highlights the validity of PET to identify early recurrences in the first follow-up year.

The median time of recurrence for all localizations is 13 months after the first surgery, with 65% of recurrences diagnosed within the second year [7]. ESMO Guidelines [6] for follow-up in patients affected by endometrial cancer suggests examinations every 3-4 months for the first two years and the execution of imaging methods in case of suspicious relapse. PET seems to be more sensitive and specific in these patients than CT and ultrasound. Spleen involvement can be the consequence of hematogenous or lymphatic metastases, intraperitoneal dissemination or it can develop due to contiguity from adjacent organs [25]. Almost invariably splenic involvement is characterized by a single parenchymal metastasis and is an indicator of poor prognosis [10]. Splenic metastasis exhibits 3 macroscopic patterns of

localization: macronodular, micronodular and diffuse [26]; the lesions infiltrate the upper or lower pole and the hilus, the capsule less frequently [27].

When the splenic lesion is solitary and circumscribed, it does not cause any functional alteration of the organ and does not give any symptoms, as occurred in our case and in the literature. When present, the symptoms and signs are asthenia, weight loss, abdominal pain, anemia and thrombocytopenia [10]. Even more rare is the possibility that the diagnosis of metastasis is made after emergency surgery for atraumatic splenic rupture.

The first endometrial carcinoma was FIGO IA stage, poorly differentiated. To date, the literature has not yet established any association between the time of presentation of the splenic metastasis and the starting stage of the endometrial tumor. Adnan's review of 2013 analyzed 13 cases with an average time of recurrence of about 35 months (range 11-120 months) [10], similar to the one reported in this review (24 months, range 0-120).

CONCLUSIONS

There is unanimous consensus (100% of cases) about the treatment of the splenic localization of endometrial carcinoma, which is based on splenectomy. In most cases the treatment was chemotherapy (9 cases out of 18) but the data concerning the protocols were reported only in a small number of patients. There is unanimous consensus regarding the most suitable treatment for this type of recurrence, consisting of splenectomy, possibly laparoscopic, followed by chemotherapy or less according to PFI (platinum free interval). In the present case, in consideration of the early relapse, a second line chemotherapy treatment based on pegylated liposomal doxorubicin was chosen. In conclusion, the splenic metastasis of endometrial cancer represents a rare event, the diagnosis is often instrumental, and the treatment of choice is based on splenectomy followed by chemotherapy.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

B.P.: Writing – original draft. G.S., M.F.: Writing – review & editing. A.D.S. Writing – original draft. P.S.: Conceptualization and supervision.

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N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

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