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Synchronous ovarian and uterine tumours: a case report of an unusual association

Alessandro Serva^{1,*}, Annalisa Tiberi¹, Patrizia Palermo², Angela D'Alfonso², Manuela Ludovisi², Giulia Del Rosario³, Nicoletta Di Stefano⁴, Donatella Serva⁵, Achille De Dominicis⁶, Maurizio Guido², Leonardo Matteo Di Stefano²

¹ Unit of Obstetrics and Gynaecology, San Salvatore Hospital, L'Aquila, Italy.

² Unit of Obstetrics and Gynaecology, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy.

³ Anatomical Pathology Unit, San Salvatore Hospital, L'Aquila, Italy.

⁴ Unit of General Medicine-Rheumatology Service, Giuseppe Mazzini Hospital, Teramo, University of L'Aquila, L'Aquila, Italy.

⁵ Unit of Gastroenterology, San Camillo De Lellis Hospital, Rieti, Italy.

⁶ Unit of Obstetrics and Gynaecology, San Camillo De Lellis Hospital, Rieti, Italy.

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*Corresponding author: Alessandro Serva, M.D. Unit of Obstetrics and Gynaecology, San Salvatore Hospital, via Lorenzo Natali 1, 67100 Coppito, L'Aquila, Italy.
Email: alessandro.serva@gmail.com.
ORCID 0000-0001-7256-9464.

ABSTRACT

Background. Add in the scientific literature another clinical case of synchronous ovarian and uterine tumours describing what has been observed and done. When these tumours occur simultaneously, the most common origin appears to be endometrial. A better understanding of synchronous genital tumours is still needed by studying as many cases as possible.

Case presentation. The beginning of our clinical case started by accidentally finding the increase in the uterine size and its endometrial thickness. In the pelvic excavation, also, a voluminous neof ormation was observed of adnexal origin. It presented as a multiloculated cystic morphology with inside a solid calcific component. There was no free intra-abdominal effusion. The patient performed the dosage of tumour markers in the blood and underwent radiological investigations. Total hysterectomy with bilateral adnexectomy and multiple peritoneal/omental biopsies were performed. The histological report described the presence of four different types of tumours: atypical endometrial hyperplasia/EIN and foci of intraepithelial endometrioid adenocarcinoma (G1), a mucinous cystadenoma, Brenner tumour and omental mesothelial hyperplasia. At 6-month follow-up, through total-body CT, the patient did not show recurrences of the disease. The patient's clinical history is compatible with the favourable prognosis generally presented by patients with synchronous uterine-ovarian tumours.

Conclusions. Contrary to the literature, our case appears anomalous in the association of the histotype. This aspect actually makes the clinical case interesting.

INTRODUCTION

In the human species there are several syndromes that involve the onset of multiple tumours, syn-

chronous and non-synchronous (Lynch syndrome, BRAC mutation 1 and 2, p 53 mutations, etc.). In gynaecological practice, although rare, it is possible to find the association of malignant

pathologies of the ovaries and uterus with a frequency of 1-6% [1, 2].

On average, synchronous utero-ovarian tumours are found in women in their fifth decade of life [3]. The symptoms reported are those attributable to each tumour also in the case of isolated onset: abnormal uterine bleeding (most frequent symptom), feeling of abdominal swelling and tenderness, palpation of pelvic growths accompanied by a Ca 125 blood rise.

When synchronous utero-ovarian tumours occur simultaneously, generally it is possible an earlier diagnosis with a 5-year life expectancy (between 84-86%) [3, 4]. The lymphatic diffusion is rare with a local prevalence of disease development.

In endometrial carcinomas, in the case of synchrony with ovarian carcinomas, the most common histological type is the endometrioid type (60.47% of cases) [3, 4] while, at the ovarian level, the most common is the endometrial histological type. This last kind of tumour association seems also to be the most favourable from a prognostic point of view [1].

The criteria drawn up by Scully in 1998 allow the distinction between metastatic tumours and synchronous tumours in the utero-ovarian area [5].

It has recently been shown that, in the vast majority of cases, synchronous endometrial ovarian tumours, classified according to Scully's criteria, are clonally related. With this we intend to assert that their development is triggered by a genetic alteration in a single cell.

To support this thesis, in total 92% of these tumours share one or more somatic mutations with high indices of clonality [6]. Compared to the metastatic spread between the ovary and uterus, these tumours show less frequent TP53 mutations, this being moreover an indicator of worse prognosis [7].

The clonal relationship between both carcinomas in concomitant cases implies that these carcinomas actually represent a unique (pseudo) metastatic disease, rather than two independently evolved carcinomas. The most common origin appears to be endometrial [6, 8-10]. The ovarian masses would be of an early metastatic secondary nature.

However, it should not be ignored that in less than 10% of cases the genetic analysis is completely different, thus demonstrating a completely independent, although synchronous, origin of the two tumours [8].

In fact, in these cases the histotypes are always of a very different nature. The future in the study of synchronous uterine-ovarian tumours is necessarily projected on the genetic research in order to better understand their etiopathogenesis and the consequent therapeutic response. Our case report appears as a further opportunity to add another clinical case to the small series of synchronous tumours.

The clinical case is brought to attention because the histological associations found are unusual. Reflecting on the clinical case, it is interesting to reflect on the reliability of the IOTA classification even in the case of ovarian neoformations synchronous with uterine tumours. Being the first finding of synchronous uterine-ovarian cancer in our hospital, the clinical case provided interesting reasons for reflection and in-depth analysis. In the past we had found multiple tumours in the same organ [11]. Finding unusual synchronous tumours, in the different genital organs of a single patient, was a first for our team.

CASE PRESENTATION

The patient is an 80-year-old woman peace maker carrier and chronically affected by hypertensive heart disease, type 2 diabetes mellitus, dyslipidaemia, chronic renal insufficiency and peripheral arterial obstructive disease. The patient had an obstetric history of 7 spontaneous deliveries and was in menopause since the age of 48.

The patient was admitted to the Cardiac Surgery Unit for critical ischemia of the left lower limb. During hospitalization a pelvic mass appeared through the execution of an ultrasound exam; the uterus was casually noted to have an increased size with endometrial thickening in relation to the age [12]. In the pelvic excavation, a voluminous neoformation of 17 × 17 × 13 cm (LL × AP × CC) was observed, probably of adnexal origin. It presented as a multiloculated cystic morphology with inside a solid calcific component of 47 mm. Moderate flow was present (colour score 3).

Two CT scans of abdomen and pelvis, with and without contrast medium, were performed instead of MRI as the patient had a pacemaker. This radiological examination confirmed the report described with ultrasound method (**Figure 1**). There was no free intra-abdominal effusion. Sub-centimetric lymph node formations were observed in

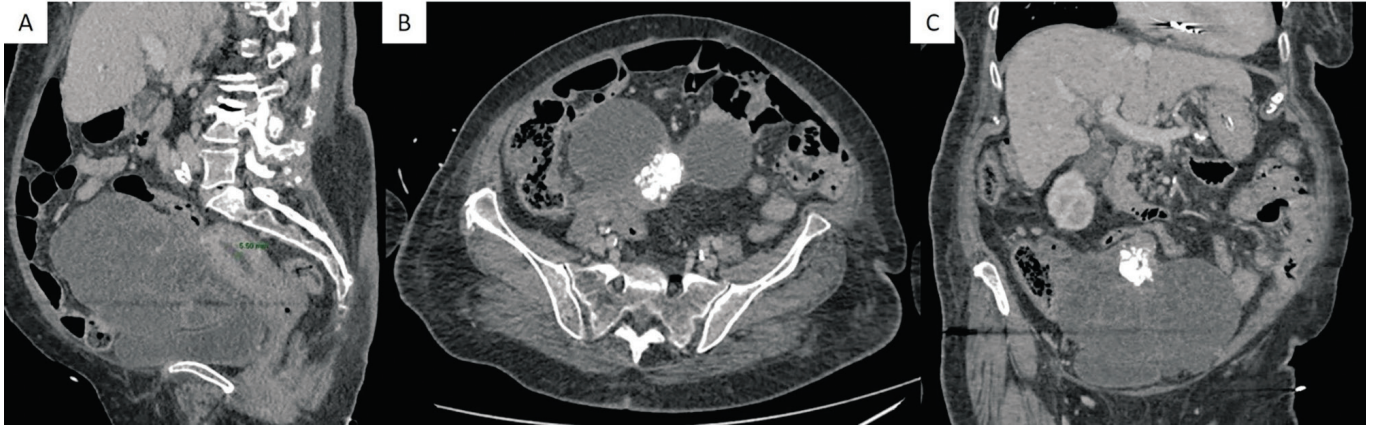


Figure 1. (A) Sagittal section of the abdomen-pelvis CT with contrast medium, portal plane. We observe the uterus increased in volume with respect to age with a longitudinal diameter of about 10 cm. It is dislocated posteriorly by the voluminous ovarian mass which also dislocates the intestinal loops antero-superiorly and inferiorly the bladder dome. Endometrial thickness increased by 5.5 mm. Absence of pelvic effusion; (B) Coronal section of the abdomen-pelvis CT with contrast medium. The ovarian mass (dimensions 17 × 17 × 13 cm LL × AP × CC) having/showing multiloculated cystic morphology with contextual solid calcific component of 47 mm is observed. A black streak is visible, artifact from a hip prosthesis; (C) Axial section of the abdomen-pelvis CT with contrast medium. The ovarian mass with cystic morphology and a hyperdense calcific solid component is observed.

the lumbo-aortic peritoneum and in the mesentery fan. No gastro-intestinal tumour pathologies were found. The dosage of tumour markers was subsequently done: the CA-125 and HE4 were above the cut-off respectively with values of 66.1 U/ml and 287.9 U/ml.

As a consequence, there was indication for the laparotomic execution of a total hysterectomy with bilateral adnexectomy. A left paramedian pubo-umbilical laparotomy was performed. When the abdominal cavity was opened, a large neoformation about 20 cm in size twisted on its peduncle (3 turns) was evident, occupying the entire small pelvic cavity and part of the abdominal cavity (Figure 2).

This adnexal neoformation resulted adherent to some loops of the jejunum and ileum. Below it there was the uterus, increased in volume and attached to the posterior inferior wall of the bladder. A peritoneal washing was performed for cytological examination. The intraoperative staging highlighted small repeats, the size of 2-3 mm (non-invasive implants), at the level of the ascending and descending colon easily removable digitally. The peritoneal surface subjected to biopsies (prevesical region - right and left parietocolic groove and subdiaphragmatic region) did not show particular evidences indicating a repetition. The omentum had no macroscopic signs. The aforementioned neoformation was removed without breaking the cystic capsule. An extemporaneous

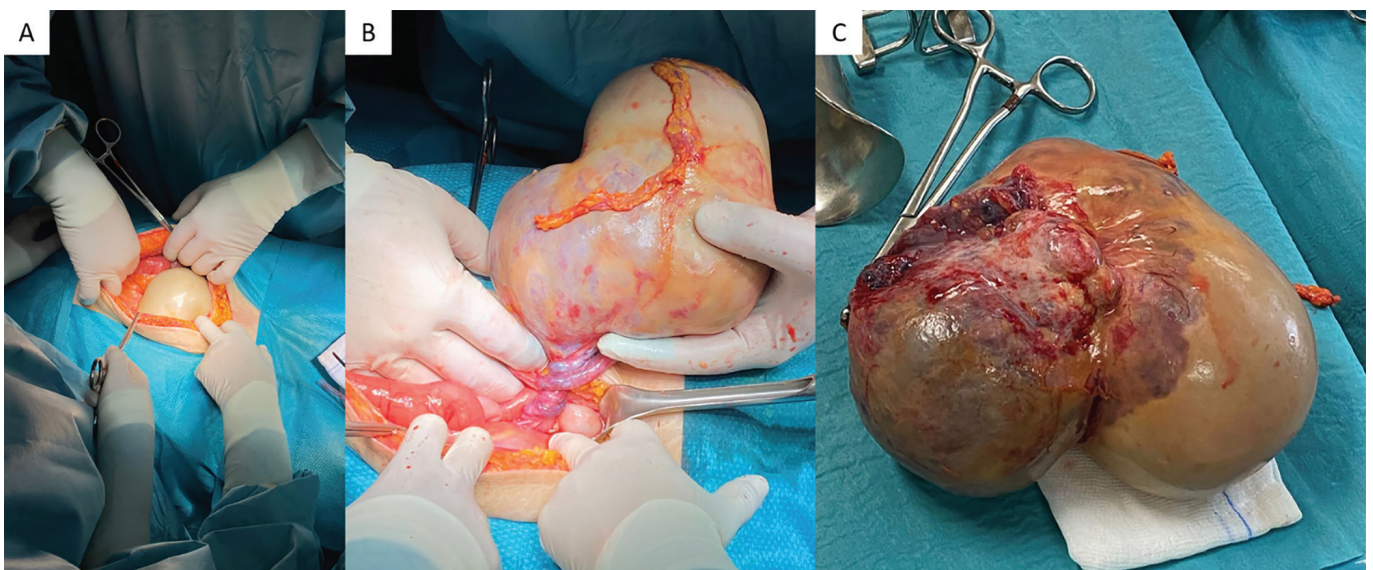


Figure 2. (A) Presentation of the adnexal neoformation at the opening of the abdominal wall; (B) Presentation of the adnexal neoformation twisted three times around its vascular pedicle; (C) Adnexal neoformation removed.

histological examination was requested which described: necrotic material with impossibility of extemporaneous diagnosis. A total hysterectomy was carried out by means of forcipressure, sectioning and ligation of the main ligamentous and vascular structures, including haemostatic border of the vagina after application of gauze soaked in betadine (removed at the end of the operation). Surgical absence of the appendix was noticed, as per previous surgery. After examining the hepatic surface, which appeared steatotic, an infracolic omentectomy was performed. Two drainages were applied at the level of the right and left parietocolic grooves.

The assessment of the patient's frailty indicated a high risk of post-operative complications [13]. Post-operatively, the patient's only complication was a cardiologically based congestive pulmonary oedema. The definitive histological report described the presence of 4 different types of tumours (images 3 and 4). In the uterine cavity, a glandular endometrial polyp of the uterus fundus was found with areas of atypical endometrial hyperplasia/EIN and foci of intraepithelial endometrioid adenocarcinoma (G1) with immunophenotype: p16±, ER+, PR+ (Figure 3).

The status associated with this neoplasm, according to FIGO classification, was stage IA, PT1 according to TNM (VIII edition). The remaining endometrium was hypotrophic with inactive cystic glands and stroma. As satellite findings, submucosal and intramural adenomyosis and glandular cystic cervicopathy were found.

The left ovary had an inclusion cyst of the coelomic epithelium, and the left salpinx had a cystic Walthard's nest. There were no significant histomorphological alterations in the parameters. A Brenner tumour (CK7+, p63+, GATA3+, EMA-, CEA-, CA125-, ER-, PR-, WT 1-, p53 wild type) was observed in the right ovary with areas of calcification and bone metaplasia (Figure 4).

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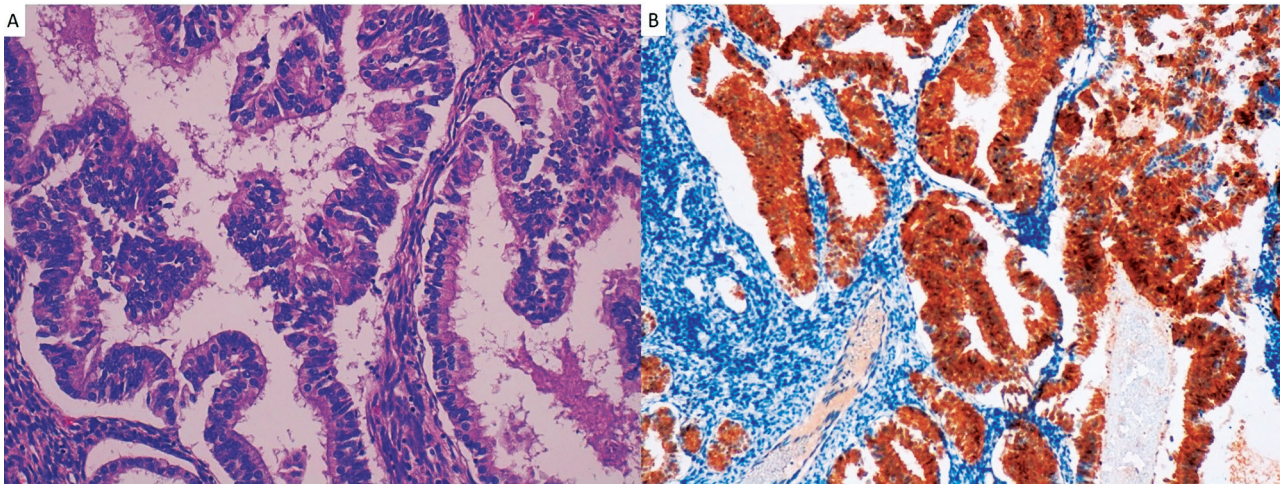


Figure 3. (A) Endometrial endometrioid carcinoma of the uterus arisen on polyp, FIGO grade 1 (20x EE). Confluent and back-to-back glands in absence of intervening stroma with villoglandular architecture. Mild cytologic atypia: nuclear rounding with some large nucleoli, cytoplasmic eosinophilia and loss of polarity; (B) Diffuse expression of p16 in the endometrial endometrioid carcinoma of the uterus arisen on endometrial polyp (20x p16 IHC).

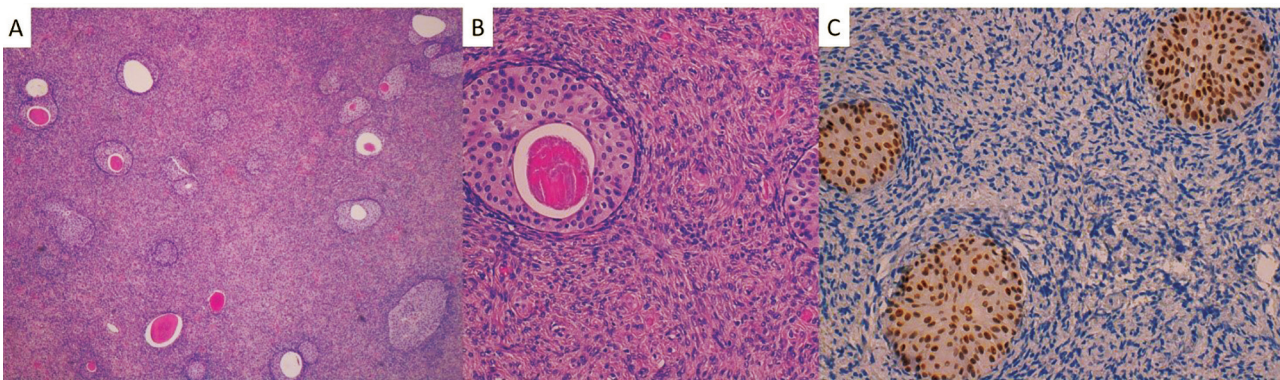


Figure 4. (A) Brenner tumour (4x EE). Benign Brenner tumour composed of nests of bland transitional urothelial-like epithelium embedded in fibromatous stroma; (B) Brenner tumour (20x EE). Benign nests of transitional epithelial cells with nuclear grooves and microcyst formation; (C) Brenner tumour (20x GATA3 IHC). GATA3 nuclear positivity in the transitional urothelial-like epithelium of Brenner tumour.

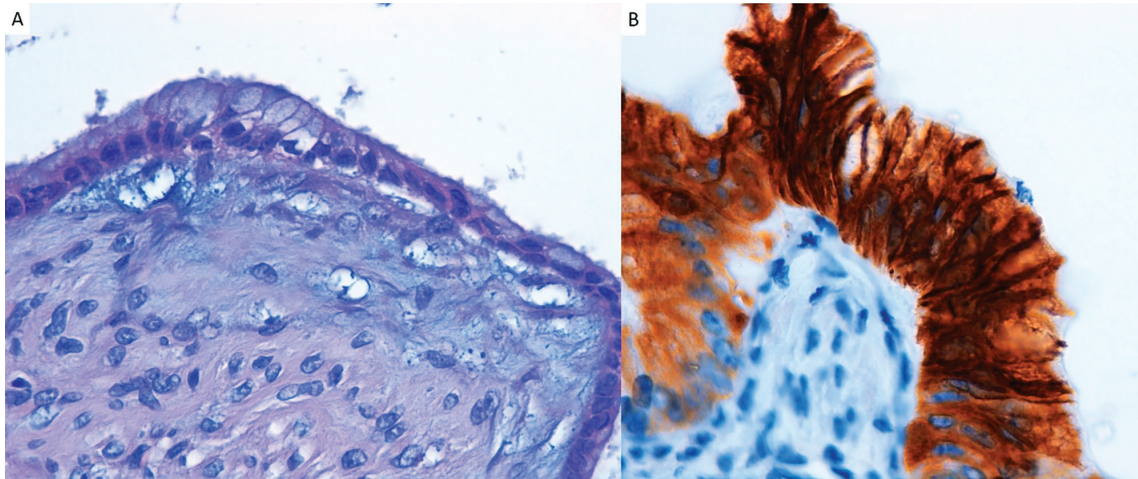


Figure 5. (A) Ovarian mucinous cystadenoma (60x EE). Benign multilocular cystic neoplasm lined by a single layer of bland mucinous epithelium - intestinal type with goblet cells; (B) Ovarian mucinous cystadenoma (60x CK20 IHC). Strong CK20 expression in simple non stratified mucinous epithelium resembling intestinal type epithelium.

In the same ovary, a mucinous cystadenoma (CK7+, CK20+, CDX2 focal+) coexisted with presence of large areas of ischemic-hemorrhagic necrosis from obstructed outflow (**Figure 5**). Right salpinx with presence of microcysts.

The cytology of the aspirated fluid in the Douglas was negative for presence of neoplastic cells. Also, peritoneal biopsies were negative. The omentum appeared with foci of chronic inflammation and reactive mesothelial hyperplasia.

Ultimately, our patient was simultaneously affected by Brenner tumour and mucinous cystadenoma at the ovarian level, by atypical endometrial hyperplasia with foci of intraepithelial endometrioid adenocarcinoma at the uterine level, and reactive mesothelial hyperplasia at the omental level. At 6-month follow-up, through total-body CT with and without contrast medium, the patient did not show recurrences of the disease. In November 2022 the patient died of decompensated Diabetes Mellitus.

DISCUSSION

The patient's clinical history is compatible with the favourable prognosis generally presented by patients with synchronous uterine-ovarian tumours. Contrary to the literature, our case appears anomalous in the association of the tumour histotype, in fact, the endometrioid carcinoma (probable degeneration of a coexisting hyperplasia), at the ovarian level, was associated with the Brenner tumour (benign) and with the mucinous cystadenoma. Usually, however, the association is

with ovarian endometrioid cancer. An adjuvant therapy was not considered necessary thanks to the benign nature of the ovarian neoformations and the low stage of the uterine malignancy. An annual transvaginal ultrasound check-up can be a valid means of early diagnosis given the low aggressiveness and progression of synchronous utero-ovarian tumours.

The clinical case in question shows us that there is still a lot to understand in the case of synchronous tumours. Complete genetic mappings are absolutely necessary. For this reason, it is important to report every single case and stimulate histological, histochemical and genetic investigations. Actually, their genotype is never perfectly superimposable. It must be considered that, so far, studies have never carried out a complete genetic mapping and could therefore have overlooked common bases. These tumours probably have a common starting mutated cell on which other random mutations accumulate in the two pelvic organs considered. Genetic analyses are missing in our study. The reflection of the clinical case and the review of the scientific Literature show how research in future cases cannot avoid carrying out in-depth genetic tests to discover the real origin of synchronous genital tumours.

It is also absolutely necessary to understand the mechanisms underlying the malignant degeneration of endometriosis or endometrial hyperplasia. These pathologies are not infrequently found in the patient's medical history [13, 14].

According to the IOTA model, the "easy descriptors" could not be considered because the ovarian cyst had a diameter greater than 100 mm. In light

of the “simple rules” of the IOTA model, however, malignant predictive factors were found in the absence of benign predictive factors (multilocular formation with solid component with a diameter greater than 100 mm, M3). This characteristic is sufficient to define the cyst as malignant.

Furthermore, calculating the risk according to Adnexal Mass Risk Prediction Models, the probability of malignancy was calculated at 75%. This prediction was also suggestive according to the “risk of malignancy Index”, its numerical value was 397 (> 200) favourable for the malignant nature.

In synchronous tumours, the IOTA model could reduce its sensitivity and specificity. Further case reports, however, are necessary to have certain deductions.

CONCLUSIONS

The theory of pseudo-metastases seems credible, and a more complete gene typing will probably give us the definitive confirmation in the future. Knowing the mutations underlying this particular category of tumours can guide us towards the most effective medical therapy. The primary endometrial origin would lead these tumours to a treatment area similar to that of the low-stage endometrial cancer.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

A.S.: Conceptualization, investigation, writing – original draft. A.T.: Data curation, validation. P.P.: Investigation, visualization. A.D.A.: Supervision, data curation. M.L.: Investigation, writing - review & editing. G.D.R.: Investigation. N.D.S.: Visualization. D.S.: Writing - review & editing. A.D.D.: Data curation. M.G.: Supervision, investigation. L.M.D.S.: Project administration.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

It was not necessary because the manuscript is a case report. The patient has consented to the processing of clinical data for scientific purposes.

Informed consent

An informed written consent was obtained from the patient before the writing of the case report.

Data sharing

Data are available under reasonable request to the corresponding author.

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