Serous endometrial cancer confined to a polyp with malignant pleural effusion

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DR MAURO: **CASE PRESENTATION**
A 66-year-old woman in good general health was admitted to the emergency unit with dyspnea and a wheezing cough. The patient’s past medical history was unremarkable and she did not have a history of prior surgery. Menopause was reached at 54 years of age and she had never taken hormone replacement therapy. She did not have a family history of gynecological cancer and she did not report any gynecological symptoms including abnormal uterine bleeding. On physical examination, the tactile vocal fremitus was reduced, dullness on percussion, with shifting dullness absent on the right side, and absence of breath sounds on the right side, reduced on the left.

The uterus was increased in size due to leiomyomata and the fundus of the uterus was palpated just below the transverse umbilical line. In the emergency unit, a right pleural effusion was found on chest x-rays (Figure 1A, B), therefore a thoracentesis with cytologic examination was performed. (Figure 2). No ascites was present at admission either clinically or by ultrasound. There was no evidence of malignancy during the gynecological evaluation. The cervix was normal and no atypical vaginal discharge was found.

**DR FILIPPELLO: WHAT DID ANALYSIS OF THE PLEURAL EFFUSION SHOW?**
Cytological examination of the pleural fluid showed many clusters of neoplastic cells with marked nuclear pleomorphism and hyperchromatic nuclei on a background of reactive mesothelial and inflammatory cells (Figure 2A). The neoplastic cells were widely immunoreactive for cytokeratin AE1/AE3, BerEP4, TEB72.3, and Paired-box gene 8 (PAX-8) (Figure 2B), focally positive for Wilms tumor protein-1 (WT-1) and negative for calretinin, podoplanin, thyroid transcription factor-1 (TTF-1) and GATA binding protein 3 (GATA-3). The immunophenotype of the cells in the pleural fluid was suggestive of Mullerian-derived malignancy.

**DR TRIPODI: CONSIDERING THE FINDINGS OF THE CYTOLOGICAL RESULT, WHAT OTHER EXAMINATIONS WERE PERFORMED?**
We completed the work-up with a transvaginal ultrasound which showed diffuse leiomyoma hampering appropriate evaluation of the endometrium. The left ovary showed a 20×20mm solid multilocular lesion, with more than 10 loculi (color score 2). A unilocular non-vascularized cyst was found on the right ovary. No ascitic fluid was present. A diagnostic hysteroscopy was performed showing the uterine cavity entirely filled by a sessile polypoid formation with a large flat base, absence of a stalk, with non-atypical surface vessels. The endometrial biopsy performed on the polyp surface was negative for malignancy. The blood tests showed increased CA19.9 and fibrotic striae appeared reduced on the CT scan (Figure 3).

**DR DI GUARDIA: CAN YOU COMMENT ON THE CHEST X-RAY IMAGES AT ADMISSION?**
The chest x-ray examination in two projections shows extensive radio-opacity of the right hemithorax due to the presence of abundant pleural effusions (Figure 1A, B). After placement of a right pleural drainage tube, discrete reduction of the ipsilateral pleural effusion was observed on x-ray examination performed the next day (Figure 1C, D). After removal of the pleural drain, both the pleural effusion and fibrotic striae appeared reduced on the CT scan (Figure 3).
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(49.9 IU/mL), CA125 (268.3 IU/mL), and CA15.3 (34.4 IU/mL), hence a CT scan of the abdomen, pelvis and chest was performed.

**DR DI GUARDIA: WHAT WERE THE RESULTS OF THE CT SCAN?**

The CT scan showed an enlarged uterine body with multiple nodular formations with inhomogeneous density, the largest of which was approximately 60×44 mm in the axial plane, in the presence of diffuse leiomyomata (Figure 4A–C). The endometrial cavity appeared dilated and diffusely inhomogeneous, with a density of about 24 Hounsfield Units (HU) in basal conditions, which increased to 65 HU in the portal phase after administration of iodinated contrast medium (Figure 4B).

The left ovary was enlarged (approximately 54×39 x 54 mm) with multiple cystic formations of pluri-concamerated appearance with thick septa and some contextual calcifications. A nodular formation with inhomogeneous enhancement of about 29×25 mm adherent to the anterior margin of the right ovary and adherent to the posterior profile of the uterine body was also detected (Figure 4A,B).

**DR TRIPODI: CONSIDERING THE COMPREHENSIVE EVALUATION, WHAT DID YOU PROPOSE TO THE PATIENT TO CONFIRM THE SUSPICIOUS MULLERIAN ORIGIN OF THE MALIGNANT CELLS DISCOVERED IN THE PLEURAL FLUID?**

The patient underwent surgery after completion of the pre-operative work-up. A diagnostic laparoscopy was performed showing suspicious pelvic carcinomatosis and bilateral encapsulated cystic

**Figure 1** Chest x-rays showing right pleural effusion at different stages of treatment. (A,B) Coronal and sagittal images showing large pleural effusion at onset. (C,D) The pleural cavity and the pulmonary coronal and sagittal scan after removal of the pleural drain.

**Figure 2** Pleural effusion showing the presence of serous carcinoma cells. (A) Pleural effusion. (B) PAX-8 immunohistochemistry (IHC) reaction. Clusters of carcinoma cells are readily appreciable in the pleural effusion (A: 400×, hematoxylin and eosin, H&E) which was immunoreactive for PAX-8 (B: 200×, PAX-8 IHC).
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formations of the right ovary with a leiomyomatous uterus. Therefore, due to the overall volume of the enlarged uterus and because of the suspicion of pelvic malignancies, an open approach with peritoneal washing, bilateral salpingo-oophorectomy en bloc with the pelvic peritoneum, simple extrafascial hysterectomy, infra-colic omentectomy, and peritoneal biopsies was performed. Intra-operative frozen section ruled out the presence of malignant lesions in both the ovaries and in the pelvic nodules in the presence of benign cystadenomas and endometroid cysts on both ovary and pelvic peritoneum.

DR FILIPPELLO: CAN YOU DESCRIBE THE RESULTS OF THE FINAL PATHOLOGY OF THE SURGICAL SPECIMENS?

Cytologic examination of the peritoneal washing showed the presence of neoplastic cells was morphologically and by

Figure 3  Chest CT scan of the pleural cavity after pleural drainage. After removal of the pleural drain, both the pleural effusion and fibrotic striae appear reduced.

Figure 4  Abdominal CT images showing the leiomyomatous uterine body and the ovarian suspicious lesions. (A,B) Transverse and sagittal scans showing an enlarged uterine body with multiple nodular formations in the presence of diffuse leiomyomata. (B) The endometrial cavity appears dilated and diffusely inhomogeneous. (C) The left ovary is enlarged (arrow) with the largest lesion measuring about 54 mm in diameter, with multiple cystic formations of pluri-concamedated appearance with thick septa and some contextual calcifications.
immunohistochemical analysis comparable with the findings in the pleural fluid.

Macroscopic evaluation of the surgical specimen showed an enlarged leiomyomatous uterus of 14×8×7 cm weighing 408 g. The uterine cavity was filled with a voluminous polypoid lesion of 7 cm largest diameter, grayish, with firm consistency, originating from the uterine fundus. Microscopically, the uterine polyp was composed of atrophic and cystically dilated endometrium with interspersed microscopic tumor glands with glandular and papillary growth and high-grade nuclear features, morphologically corresponding to serous endometrial carcinoma (Figure 5A–C). The tumor superficially infiltrated the polyp’s endometrial stroma and the final stage corresponded to stage IA based on the International Federation of Gynecology and Obstetrics (FIGO) classification of 2009 and to pT1a based on the 8th Edition of the American Joint Committee on Cancer (AJCC) of 2017. The 2023 FIGO stage classifies this tumor as a stage IC.

Immunohistochemistry (IHC) showed strong and wide positivity for estrogen and p53, corresponding to mutation-type labeling (Figure 5D), and negativity for progesterone. Human epidermal growth factor receptor (HER2) IHC showed moderate basolateral stain in about 80% of the neoplastic population (2+ score) and fluorescence in situ hybridization (FISH) confirmed gene amplification. Mismatch repair protein IHC analysis showed preserved expression of all four markers (MLH1, PMS2, MSH2, MSH6), excluding microsatellite instability. Biopsies from the recto-uterine pouch, rectal serosa, broad ligaments, and the omentum were negative for tumor involvement. The right parametrium, the broad ligament, and the rectal serosa were occupied by foci of endometriotic cyst consisting of endometrial glands surrounded by endometrial stroma (Figure 6).

The right ovary was partly replaced by a cyst of 3.2×1.5 cm total dimension filled with clear liquid. The left ovary showed a multilocular cyst extending into the mesovarium of 3.5 cm largest dimension partly filled with brownish material (Figure 7). The ovarian cysts histologically corresponded to serous cystadenoma in both the ovaries, including fibrous septa lined by columnar occasionally ciliated cells (Figure 8). In the left ovary adjacent to the serous cystadenoma an endometriotic cyst was also present. A firm, tan-white, well-demarcated nodule of 4×2.5 cm located in the right mesovarium was also observed (Figure 7A), corresponding to leiomyoma.

**DR TRIPODI: CONSIDERING THE FINAL PATHOLOGY, WHAT WAS THE RECOMMENDATION FOR FURTHER ADJUVANT TREATMENT?**

Based on the ESGO guidelines, in the presence of high-risk features external beam radiotherapy with concurrent chemotherapy is the treatment of choice in the adjuvant setting. Chemotherapy alone is an alternative option. Furthermore, the ESGO guidelines updated in 2020 encouraged the integration of the molecular classification to conventional pathologic analysis in all endometrial carcinomas.

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**Figure 5** Endometrial polypoid lesion with serous cell carcinoma. (A) Low-power view of endometrial polyp with atrophic, cystically dilated endometrium and serous carcinoma (arrows) (10×, H&E). (B,C) At higher magnification, serous carcinoma shows high-grade cytological features with glandular and papillary architecture and interspersed atrophic endometrium (50× and 100×, H&E). (D) Immunohistochemistry (IHC) for p53 resulted strongly positive in the carcinoma component, corresponding to mutation pattern labeling with wild-type labeling in the atrophic endometrium (40×, p53: IHC).
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especially high-grade tumors. In our patient we evaluated the loss of mismatch repair protein expression (MMRd), no specific molecular profile (NSMP), and abnormal p53. At the time the case was treated we were not yet equipped to perform the exonuclease domain hotspot mutation POLE. However, she was by default in the high-risk group, and considering the presence of aberrant p53 and the presence of malignant cells both in the peritoneal and the pleural fluid, the patient was recommended adjuvant chemotherapy with six cycles of carboplatin and paclitaxel with a 3-week schedule. Given the presence of HER2-positive serous carcinoma, trastuzumab was added to the standard two-drug combination with the same schedule. Trastuzumab has been shown to prolong survival of patients with HER2-positive advanced uterine serous carcinoma.3

DR BUDA: HAS THIS ATYPICAL ONSET OF APPARENT EARLY-STAGE ENDOMETRIAL CANCER ALREADY BEEN DESCRIBED IN THE LITERATURE?

Endometrial cancer is the most common gynecological malignancy and its incidence rate shows a significant upward trend.4 Generally, it has a favorable prognosis as it is confined to the uterus.5 However, the more aggressive sub-types such as clear cell, serous and mixed histotype have a high risk of distant metastasis.6 The lung is the most frequent site of distant involvement, occurring in about 5% of cases.7 Even more uncommon is the finding of a malignant pleural effusion without any lung lesions. To our knowledge, this is the first case of endometrial serous carcinoma limited to an endometrial polypoid lesion presenting with a malignant pleural effusion at onset.

Figure 6  Histologic image of endometriosis in the rectal serosa with endometrial glands made of non-ciliated columnar cells surrounded by a highly cellular stroma (200×, H&E).

Figure 7  Macrosopic views of the ovaries. (A) The right ovary shows many serous cysts connected to the ovary with a solid round and well-demarcated nodule corresponding to a leiomyoma. (B) The left ovary is enlarged and replaced by a multilocular cyst.
DR MAURO: WHAT ARE THE MOST TYPICAL SITES OF METASTASIS OF SEROUS ENDOMETRIAL CANCER AND WHAT CAN BE THE PATHOGENESIS OF PLEURAL EFFUSION IN THIS CASE?

Serous endometrial cancer accounts for nearly 10% of all endometrial cancers and represents one of the most aggressive subtypes.\(^8\)\(^9\) It has a major ability to early spread by lymphatic and hematogenous routes, as well as by peritoneal diffusion. From the available literature, the incidence of lung metastasis from endometrial cancer is less than 5%,\(^7\) with only one case report describing the presence of a malignant pleural effusion at presentation.\(^10\) However, unlike this case, the tumor was in an advanced stage with disseminated peritoneal carcinomatosis.

In our case, the only positive specimens for carcinoma at the final pathologic evaluation, beyond the endometrial polyp, were the pleural effusion and the peritoneal washing. Therefore, we can assume that the tumor cells reached the pleural cavity through the circulation of peritoneal fluid.

The pathophysiology of the formation of pleural effusion in the presence of malignancy is largely unknown. The peritoneal fluid is produced and reabsorbed by the cells of the peritoneum. Its circulation facilitates the movement of the intestinal loops and carries the fluid itself to certain sites where it is reabsorbed. The sites where the fluid is most reabsorbed are the diaphragm, the pelvis, and the greater omentum. In selected regions of the abdominal cavity there is a slowdown in the circulation of peritoneal fluid, and this occurs at the sites of greatest reabsorption, or at the level of the appendix, and at the right and left colic angles.\(^11\) This circulation pathway can explain the presence of endometrial tumor cells in our patient’s pleural fluid.

DR BUDA: WHAT RECOMMENDATIONS DO YOU SUGGEST THAT EMERGED FROM THIS RARE CASE?

The uniqueness of the presentation of our case allows us to emphasize some peculiarities on the aggressive behavior of serous endometrial cancer. This was underlined also in the last version of the FIGO endometrial cancer classification,\(^4\) where all aggressive histological types including serous carcinoma limited to a polyp or confined to the endometrium are re-classified as stage IC. This differs from the previous 2009 classification in which aggressive histological types with any infiltration of the myometrium were classified as stage IIC. As shown in the PORTEC-3 study, the addition of adjuvant chemotherapy to radiotherapy provides significant benefit in women with serous carcinomas.\(^12\)

In this case, the multidisciplinary team decided to propose only adjuvant chemotherapy, considering the peritoneal spread to be a greater risk of recurrence in the presence of non-invasive microscopic cancer in a polypoid confined lesion. In the presence of malignant cells in the pleural fluid of patients, the Mullerian origin should also be investigated even if it is a rare presentation.

As shown by this case, a single polyp biopsy does not always allow the correct diagnosis, therefore menopausal endometrial polyps should be removed entirely to exclude malignancy that, although rare, may be present even in the absence of gynecological symptoms. All apparent early-stage endometrial cancers should be adequately staged surgically and the presence of tumor cells in the peritoneal fluid may represent a negative prognostic factor.

CONCLUSION

The presence of a pleural effusion as the only symptom at the onset of early-stage uterine serous carcinoma is very uncommon. IHC analysis is an important tool to discriminate between the different tumor sub-types but does not always allow for identification of the true origin of the malignancy. When we are faced with aggressive histology such as serous endometrial cancer, it is critical to investigate all possible gynecological tumor origins, even in a completely asymptomatic woman. In menopause, asymptomatic polyps must be entirely removed to avoid the risk of malignant degeneration.

Moreover, we underline the importance to add as staging criteria the complete molecular surrogate in all women with endometrial cancer, thus allowing a better prediction of prognosis. The performance of a complete molecular classification, including exonuclease domain hotspot mutation (POLE), loss of mismatch repair protein expression (MMRd), no specific molecular profile (NSMP), and abnormal p53, emerging from

**Figure 8** High-power view of a microscopic section of the left ovarian serous cystadenoma. The cyst consists of fibrous septa lined by a monolayer of columnar occasionally ciliated cells (200×, H&E).
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the gathered evidence is now recommended¹ and must be considered to better define the need for further adjuvant treatments.¹³

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Collaborators N.A.

Contributors All authors contributed to the study. Conception and design were performed by AB and JM. Material preparation, data collection and analysis were performed by FF and ET. The first draft of the manuscript was written by JM and FF, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. AB is the guarantor and supervisor of the tumor board.

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