

## The Impact of Uterine Neoplastic Tissue in Accurately Examined Fallopian Tubes on Pathological Diagnosis and Clinical Management

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### Abstract

The presence of intraluminal uterine neoplastic tissue or neoplastic cells in accurately examined Fallopian tubes can pose serious diagnostic problems for pathologists.

Indeed, this finding, with the simultaneous presence of neoplastic cells in the intraoperative cytology of peritoneal washing, might suggest the retrograde transtubal spread of a uterine malignancy and, consequently, can be responsible for its upstaging, with an impact on the therapeutic approach.

In a comment on our previously paper, in which we demonstrated this unusual mechanism of metastasis in a case of USC (Uterine Serous Carcinoma), and by a mini-review of the retrograde transtubal spread of uterine carcinoma, we discuss the pathological criteria for this findings and its impact on the management of patients affected by all subtypes of minimally invasive uterine carcinomas.

**Keywords:** Retrograde transtubal neoplastic spread; Laparoscopic hysterectomy; Hysteroscopy; Technical artifact

### Abbreviations

EC: Endometrial Carcinoma; ESGO: European Society of Gynecological Oncology; ESMO: European Society of Medical Oncology; ESTRO: European Society for Radiotherapy and Oncology; LH: Laparoscopic Hysterectomy; USC: Uterine Serous Carcinoma

### Description

EC is the sixth most common cancer in women worldwide, with the highest incidence observed between the ages of 55 and 64 years [1,2].

The main risk factors for the development of EC are diabetes, obesity, nulliparity, early-onset menarche, late-onset menopause, and exposure to unopposed oestrogen or tamoxifen therapy [3,4].

Typically, these malignancies are classified based on clinical, morphological, histological and genetic features into two major groups, type I and type II.

Type I Ec, referred to as endometrioid tumours, is the more frequent subtype; it is considered a low-grade tumour that often occurs in perimenopausal obese women. Characteristically, this neoplasm is hormone-dependent, and its prognosis is favourable [1,4].

In contrast, type II Ec, which corresponds to a serous histotype, is less common and occurs in elderly women. Type II Ec is hormone-independent and associated with a higher stage of development at diagnosis and a higher risk of recurrence; consequently, its prognosis is worse than that of type I Ec [1,4].

Numerous mechanisms have been proposed to explain why serous carcinoma of the uterus often coexists with intraperitoneal diffusion even in cases with superficial infiltration of the myometrium. These mechanisms include neoplastic embolization of the lymphatic vessels and multifocal neoplastic transformation that can simultaneously involve the endometrial ovarian and peritoneal surface [5-8].

Multifocal papillary serous carcinoma of the peritoneum, in addition to breast and ovarian carcinoma and endometrial serous carcinoma, have usually been suggested in patients with BRCA1

mutations [9].

However, in a recently published paper, we reported an example of a minimally invasive USC in a BRCA1-mutated patient with a history of breast carcinoma and demonstrated that subsequent peritoneal metastases were not related to concomitant ovarian or tubal lesions, but to an unusual mechanism of metastasis that can be considered retrograde transtubal spread [10].

This unusual mechanism of metastasis in serous carcinoma of the endometrium is rare and has an important impact on prognosis but, in our opinion could be underestimated [11-13].

In fact, to identify the presence of uterine carcinoma in the Fallopian tube an accurate histological examination is required with adequate sampling of the adnexa [10,14,15].

Additionally, it is important to perform an immune histochemical analysis with specific markers to demonstrate the serous phenotype and the endometrial origin of neoplastic cells in the tubal lumen [10].

In cases of USC and all high-grade EC (Type II), the presence of neoplastic cells in the Fallopian tubes likely represents a propensity for transtubal dissemination of aggressive subtypes of uterine carcinoma [11-13].

Although transtubal spread is more common among women with the serous subtype and other aggressive EC, data in the literature suggest that this mechanism can also be observed in cases of low-grade EC [16].

In these examples, the spread of endometrial neoplasms to the

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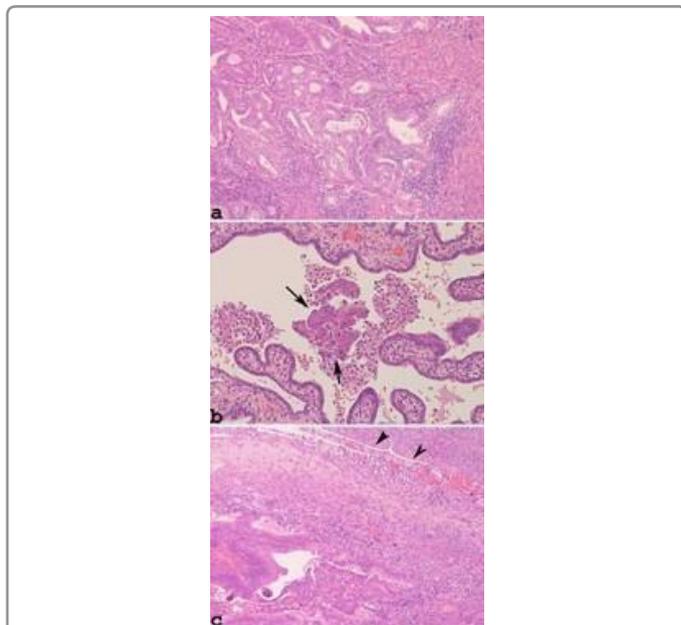
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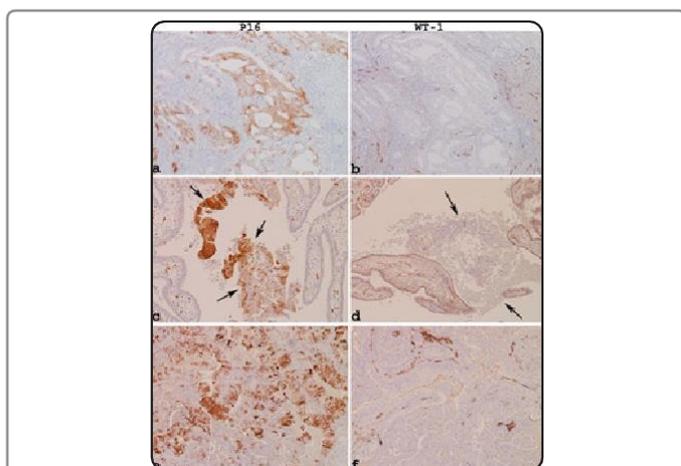
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peritoneal surface, even in the absence of accurate sampling of the Fallopian tubes was demonstrated by the presence of atypical cells in the intraoperative cytology of peritoneal washing and by the presence of peritoneal keratin granulomas in cases of EC with squamous differentiation [16].

Moreover, the transtubal spread of EC can be observed in cases of minimally invasive low-grade endometrioid carcinoma by accurate sampling of the Fallopian tubes and in the simultaneous presence of neoplastic noninvasive implants on the ovarian surface from a previous hysteroscopy (Figures 1 and 2).



**Figure 1:** Example of a well-differentiated endometrioid carcinoma previously diagnosed on endometrial biopsy by hysteroscopy and that had superficially infiltrated the myometrium (a: Haematoxylin and eosin stain  $\times 100$ ), associated with the presence of small fragments of neoplastic tissue in the tube lumen (b: Haematoxylin and eosin stain  $\times 200$ , Arrows: Fragments of neoplastic tissue) and a small peritoneal implant on the ovarian surface (c: Haematoxylin and eosin stain  $\times 100$ , Arrowheads: mesothelial lining on ovarian surface).



**Figure 2:** Immuno histochemical analysis of neoplastic tissue showing the same immunoreactivity in the uterine cavity (a: p16  $\times 100$  and b: WT-1  $\times 100$ ), in the salpinx (c: p16  $\times 200$ ; d: WT-1  $\times 100$ ; Arrows: Fragments of neoplastic tissue, in tubal lumen) and ovarian surface (e: p16  $\times 100$ ; f: WT-1  $\times 100$ ) with focal positivity for p16 and negativity for WT-1.

In these cases, in accordance with the recent ESMO-ESGO-ESTRO guidelines, these neoplasms should be placed in the “high” prognostic risk group; therefore, it is necessary to consider performing adjuvant therapy with chemotherapy and radiotherapy [17].

However, it should be noted that in cases of minimally invasive EC, the intraoperative cytology of peritoneal washing might represent a serious diagnostic problem for pathologists and might have important consequences on the patient because of the upstaging of the uterine neoplasm and the treatment approach.

Thus, it is necessary to consider other conditions that might explain this finding, such as uterine manipulation due to total LH, exfoliation of uterine neoplastic tissue produced during hysteroscopy and technical artifact due to the sampling of surgical specimens in the pathology laboratory [18-21].

To avoid the dissemination of neoplastic cells during LH, tubal ligation could be useful [22,23].

Hysteroscopy is a diagnostic method widely used in the diagnosis of endometrial neoplasms and pre neoplastic lesions that cause abnormal genital bleeding. This method, in fact, allows the evaluation of the morphology of the endometrium and the performance of biopsies of suspicious lesions for neoplasms.

The exfoliation of uterine neoplastic tissue and neoplastic diffusion produced during hysteroscopy, as suggested by some authors, could be facilitated by irrigation of the uterus with fluid medium and increased pressure in the uterine cavity during the procedure [19,20].

These authors observed that this mechanism of neoplastic diffusion is more frequent in cases of aggressive subtypes of EC. Moreover, they demonstrated retrograde transtubal spread in the peritoneal cavity and the simultaneous presence of neoplastic cells in the intraoperative cytology of peritoneal washing [19,20].

Regarding histologic artifact, due to the sampling of surgical specimens in pathology laboratories, which represents a serious potential source for diagnostic error, it is necessary to recognize these artefacts, according to the useful data provided by Layfield et al. [21].

Essentially, these authors state that these artifacts can be recognized, taking into account that the foreign neoplastic tissue present in a histological section is usually observed at the periphery of non-neoplastic tissue or is sometimes located in a different plane; therefore, on microscopic examination, it has a different focus than the surrounding tissue.

## Declarations

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## Authors' Contributions

The authors declare that they participated in this study as described below and have read and approved the final manuscript. Prof Vito Andrea Capozzi acquired the data pertaining to the cases, reviewed the literature, and drafted the manuscript. Giovanna Giordano was responsible for the concept of the paper, reviewed the available literature, evaluated the pathological data, drafted and edited the manuscript. Dr Roberto Berretta contributed to the data acquisition. All authors agree to be accountable for all aspects of the work.

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## Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

## Declarations

Consent for publication the patients agreed to the publication of these cases.

## Competing Interests

The authors declare no conflicts of interest.

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