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# SYNCHRONOUS PRIMARY CLEAR CELL CARCINOMA OF THE FALLOPIAN TUBE: AN EXTREMELY RARE OCCURRENCE AND POTENTIAL DIAGNOSTIC PITFALL

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ABSTRACT

Primary fallopian tube carcinoma (PFTC) is by far the rarest malignancy of the female genital tract, with an incidence of 0.41 per 100000 women - but even rarer is its association with other gynecologic malignancies. In this paper we report the case of a primary clear cell carcinoma of the fallopian tube associated with a synchronous endometrioid carcinoma of the uterine corpus and discuss the main immunohistopatological aspects of both neoplasms. The difficulty of this case resides in establishing the correct diagnosis for the secondary tumor present in the fallopian tube and distinguishing between a synchronous primary tumor, a mixed endometrial carcinoma extending to the adnexa, an ovarian tumor extending to the fallopian tube or a metastasis. Moreover, we highlight the importance of always taking into consideration the diagnosis of PFTC in postmenopausal women with abnormal vaginal bleeding, when endometrial sampling and cervical biopsy are not diagnostic, even if there is no pelvic mass.

## INTRODUCTION

Endometrial carcinoma is the most common gynecologic cancer in developed countries, with endometrioid subtype accounting for 60% of all cases. At the other end of the spectrum, primary fallopian tube carcinoma is extremely rare, accounting for only 0.14%-1.8% of all female genital malignancies (approximately 1/150 as common as ovarian cancer) [1-3].

This assumption has been due, considering the strict criteria classically used for ascribing a primary fallopian tube neoplasm, including all of the following: the bulk of the tumor must be present in the tube; any tumor present in the ovary, peritoneum, or endometrium must be of smaller quantity then that in the tube; and early cancer must be identified in the tube. However, there currently is compelling evidence to suggest that a significant proportion of cases of high-grade serous carcinoma classified as either ovarian or peritoneal in origin using conventional classification schemes have an origin in the distal fallopian tube. No scientific data is available for clear cell carcinoma, but the current agreement is that primary ovarian and fallopian tube carcinomas evolve in the same manner [4]. Clear cell carcinoma of the fallopian tube is extremely rare, representing only 2% of all fallopian tube carcinomas.

To our knowledge (which is based on a thorough literature review), there are only five previous case reports of gynecologic malignancies synchronous with primary fallopian tube carcinoma. This paper presents the sixth case report of a gynecologic malignancy coexisting with a primary fallopian tube carcinoma and the first one to involve this particular histologic subtype (primary clear cell carcinoma of the fallopian tube).

## MATERIAL AND METHOD

We report the case of a postmenopausal, 63-year-old female presenting to the Department of Obstetrics-Gynecology at the University Emergency Hospital in Bucharest, Romania for abnormal vaginal bleeding. The patient was married, with parity index G3P2L2 and no significant personal family history. Physical examination was not conclusive. Speculum investigation revealed minimal bleeding with a healthy cervix and vagina. Upon transabdominal ultrasound examination the uterus presented normal echostructure, measuring 75/54/42mm, with an endometrial thickness of 11mm. A diagnostic curettage was performed and after the initial workup, the patient underwent radical hysterectomy with bilateral salpingo-oophorectomy and the specimen was sent to the Department of Pathology for evaluation.

## RESULTS

Gross examination of the specimen revealed a normal-sized uterus with a soft and relatively well-circumscribed intrauterine tumor measuring 2/1/0.5cm, which had grey-yellowish color and ulcerated surface. The cervix and uterine corpus featured no other notable changes. The right fallopian tube was slightly enlarged and presented a solid, white-grey intraluminal mass of 1/1/1cm, which appeared to have no relation to the tumor identified in the uterine corpus (figure 1). The distal end of the salpinx was occluded, resembling chronic salpingitis and the serosal surface was smooth without any adhesions. The endosalpinx presented florid papillary growths filling and expanding the lumen, which

could not be traced to the proximal margin. Multiple samples have been subjected for histopathological examination. Peritoneal cytology was not performed.

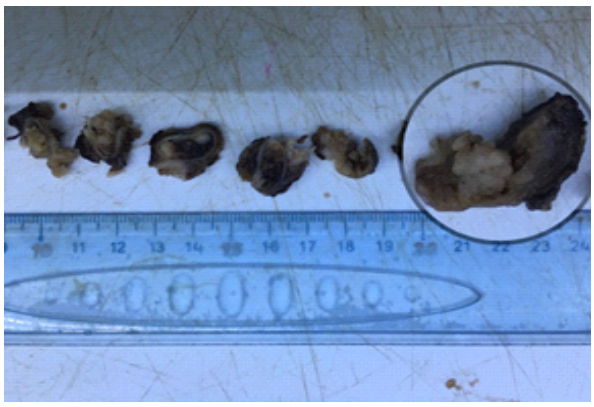

**Figure 1.** Gross aspect of the right fallopian tube showing an intraluminal mass of 1/1/1cm

Microscopic examination of the intrauterine tumor revealed a well-differentiated (G1), FIGO stage IA endometrial endometrioid carcinoma with villoglandular pattern, confined to the uterine cavity, presenting focal squamous differentiation and no lymphovascular emboli (figure 2).

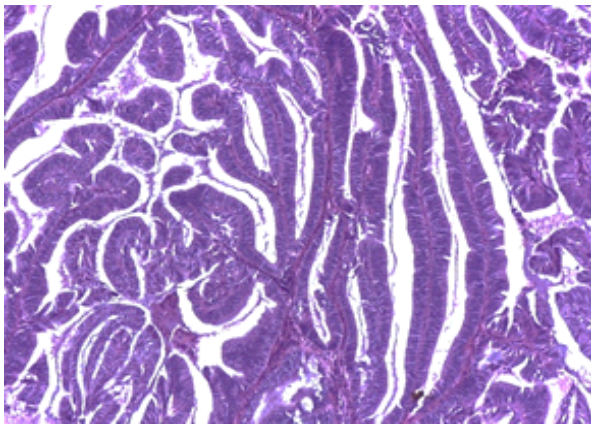

**Figure 2.** Histopathological aspect of the endometrial endometrioid carcinoma with villoglandular pattern, H.E., 100x

Microscopic examination of serial sections through the fallopian tube mass revealed an invasive proliferation with an admixture of solid and papillary growth patterns composed of rounded or polyhedral cells with clear or pale-eosinophilic cytoplasm, distinct cell borders, eccentric and rounded nuclei with prominent nucleoli. Rare hobnail cells with bulbous dark nuclei, tubulo-cystic areas and mucoid stroma expanding the cores of the papillae were focally present. Atypical mitotic figures were extremely rare, with less than 2 mitoses per 10 HPF (figures 3-4).

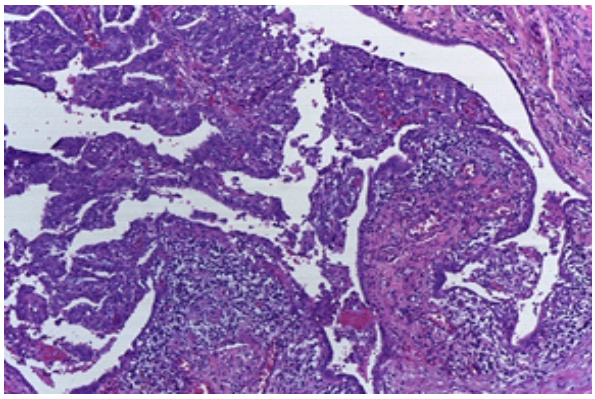

**Figure 3.** Histopathological aspect of the right fallopian tube featuring a papillary proliferation of atypical cells with bulky hyperchromatic nuclei and optically clear cytoplasm, H.E., 40x.

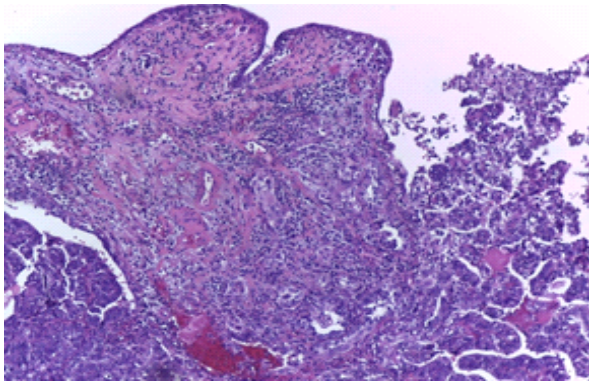

**Figure 4.** Histopathological aspect of the right fallopian tube showing transitional areas between the normal and invasive neoplastic salpingeal epithelium, H.E., 100x

Routine H&E staining suggested divergent histogenetic origin of the two identified tumors. Therefore, immunostaining was performed in order to confirm this hypothesis and establish the final histotype of the fallopian tube neoplasm.

The endometrial carcinoma revealed typical endometrioid immunophenotype, with strong and diffuse nuclear positivity for ER and PR in more than 95% of all tumoral cells, diffuse cytoplasmic positivity for Vimentin in virtually all tumoral cells, a low Ki-67 proliferation index of approximately 15% and normal expression of p53. On the other hand, the fallopian tube neoplasm featured a high Ki-67 proliferation index of 85%, abnormally strong and diffuse immunoexpression of p53, diffuse cytoplasmic positivity for Napsin A and complete absence of nuclear expression for ER, PR and WT-1 (figures 5-7). Moreover, both tumors showed intense and diffuse cytoplasmic positivity for CK7 and complete absence of p16.

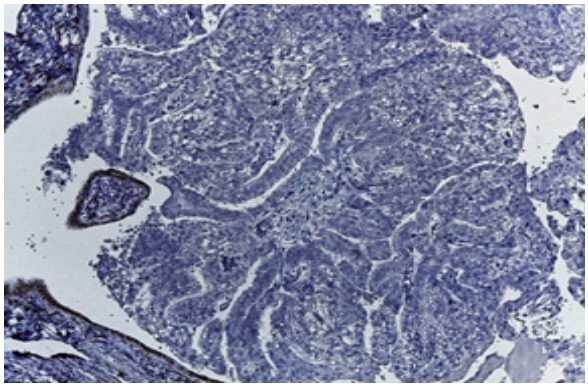

**Figure 5.** Immunostain showing complete loss of nuclear expression for ER in the fallopian tube tumor, IHC with DAB chromogen, 40x

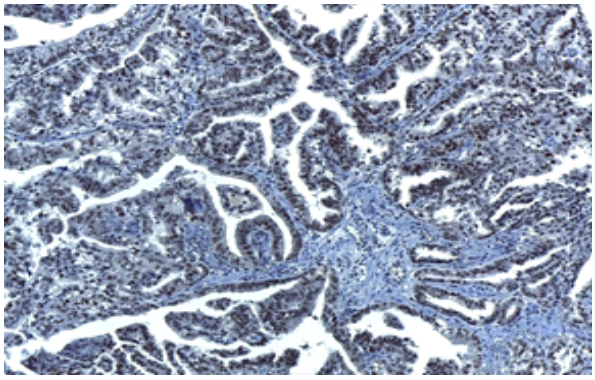

**Figure 6.** Immunostain showing mutation-type p53 overexpression in the fallopian tube tumor, IHC with DAB chromogen, 40x

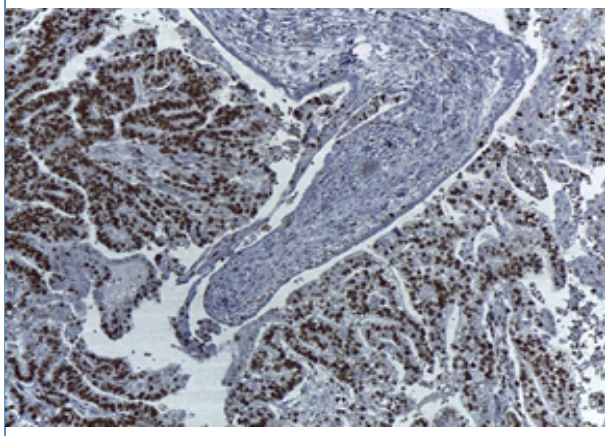

**Figure 7**. Immunostain showing a very high Ki67 proliferation index of the fallopian tube neoplasm, IHC with DAB chromogen.

The final histopathological diagnosis was invasive primary clear cell carcinoma of the fallopian tube, with adjacent in situ areas, chronic salpingitis and synchronous endometrial endometrioid carcinoma. Postoperative evolution was uneventful, and the patient was referred to the Department of Oncology for adjuvant chemotherapy.

## DISCUSSION

Primary fallopian tube carcinoma (PFTC) represents the rarest malignancy of the female genital tract, with an incidence of 0.41 per 100000 women [5], which was first described by Renand in 1897 [2]. Rokitansky documented the first histopathologic description in 1861 and Orthman published the first case report in 1888 [6]. Clinically and histologically, primary fallopian tube carcinoma resembles epithelial ovarian cancer (EOC), from which it is difficult to distinguish. While ovarian cancer is usually diagnosed in advanced stages, PFTC is often found earlier due to abdominal pain from tubal distension and shorter history of symptoms in PFTC than in EOC. However, PFTC is an extremely difficult pre-operative diagnosis, rarely perceived clinically due to the scarcity of symptoms and absence of an efficient screening method [7]. Patients with fallopian tube carcinoma may present with pain, pelvic mass and white or bloodstained vaginal discharge. These symptoms are known as Latzko's Triad [8] and are found in only 23% of patients [9]. The association between high resolution transvaginal ultrasound and serum levels of the tumour marker CA-125 could help identify primary fallopian tube carcinoma, but is difficult to distinguish it from ovarian carcinoma, which is much more common [10-14]. Our patient did not undergo pre-operative serum CA-125 testing and the fallopian tube mass was discovered incidentally. Regardless, histopathological examination represents the gold standard method for diagnosis.

PFTC may be an incidental finding in patients with BRCA1 and BRCA2 mutation undergoing prophylactic salpingo-oophorectomy as reported by Hartley et al. [15]. Even if it is well known that primary fallopian tube carcinomas can manifest as a consequence of hereditary breast-ovarian cancer syndrome, there are few scientific reports which document rarer histopathological subtypes, such as clear cell carcinoma. Also, it seems that immunohistochemical or PCR-based positivity for p53 alterations is a hallmark of some fallopian tube carcinomas and correlates with poorer survival rates [16-17]. However, not all primary fallopian clear cell carcinomas are related to BRCA1 or BRCA2 mutations, some cases being reported in non-BRCA carriers with peculiar presentation related to pregnancy [18-19]. Our patient was not screened for BRCA1 or BRCA2, but presented aberrant p53 immunostaining indicative of an aggressive tumour behaviour, as suggested by the abovementioned authors.

The difficulty of this case resides in establishing the correct diagnosis for the secondary tumor present in the fallopian tube and distinguishing between a synchronous primary tumor, a mixed endometrial carcinoma extending to the adnexa, an ovarian tumor extending to the fallopian tube or a metastasis. This is increasingly difficult, as the fallopian tube mass was completely asymptomatic and discovered incidentally. A neoplasm can be classified as primary fallopian tube when it is either restricted to this anatomical structure, or when the fallopian tube is most affected, whereas co-locations such as the ovary and uterus show lesser involvement or a different histology. In our case, although the fallopian tube mass was not significantly larger than the uterine tumor, it had no macroscopic or microscopic connection to it and featured completely different histopathological and immunohistopathological aspects.

To our knowledge, primary clear cell carcinomas of the fallopian tube are extremely rare and the scientific data is very limited. However, they are thought to arise and have similar prognostic factors to clear cell carcinomas from other gynecologic areas.

Clear cell carcinomas of the ovary were initially thought to arise from mesonephric remnants, being originally described by Schiller as 'mesonephromas' or 'mesonephric carcinomas' due to their microscopic pattern [20]. However, it is now known that these neoplasms are of müllerian origin [4]. Most of them occur along the course of müllerian duct derivatives or within an ovary involved by endometriosis (which is commonly associated with clear cell carcinoma - up to 50% of cases). Clear cell carcinoma may also arise from müllerian-derived vaginal adenosis in girls and young women prenatally exposed to diethylstilbestrol [4]. The müllerian system commonly features metaplasias of one cell type to another, especially in the endometrium. Additionally, tumors of a specific müllerian type may also appear in various sites. Not only that clear cell carcinoma has often been described in association with endometriosis, it has also been noted a frequent association with endometrioid carcinoma and an admixture of serous and mucinous cell types. In our case, the tumor clearly developed from the tubal epithelium, which is of müllerian origin, and was not related to diethylstilbestrol exposure or endometriosis.

Similar to ovarian carcinoma, fallopian tube carcinoma metastasizes mainly by direct extension and lymphatic spread [21]. Distant metastases are rare, but involvement of the central nervous system has been previously documented [22]. The incidence of nodal involvement in fallopian tube carcinoma is unascertained. Tamini and Figge [21] cited two cases with apparent early stage disease, where periaortic nodes were the only sites of metastasis. Their total frequency of nodal involvement was 53%. They promoted nodal sampling, especially of the periaortic nodes at the time of surgery, and recommended treatment of areas beyond the pelvis.

## CONCLUSIONS

Primary fallopian tube carcinomas (PFTC) are extremely rare tumors and their association with a synchronous malignancy of the genial tract is even more extraordinary. To our knowledge, this case is the first report in the scientific literature of clear cell carcinoma of the fallopian tube associated with endometrial carcinoma.

The diagnosis of PFTC should always be considered in postmenopausal women with abnormal vaginal bleeding, when endometrial sampling and cervical biopsy are not diagnostic, even if there is no pelvic mass. While the significance of this rare histologic subtype of primary fallopian carcinoma remains unclear, their identification by conventional histopathological techniques would permit more elaborated studies in the future.

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