Immunohistochemical findings in primary fallopian tube cancer. Case report

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Summary

Primary fallopian tube carcinoma is a rare malignancy, representing about 1% of female genital tract malignancies. We present a case report and compare the medical performance with accessible data from the literature as well as present immunohistochemical analysis of estrogen, progesterone, and proliferative together with basic cytokeratin reactions. We found that immunohistochemical expression of ER-β was dominant over ER-α which encourages further evaluations to be performed on a larger number of samples, especially taking into account the very scant progesterone receptor expression we noted. On the basis of the course of disease under study, etiological problems and the possibility of clinical misdiagnosis have been discussed. The low prevalence rate and lack of clear symptoms of this type of carcinoma makes the final clinical diagnosis almost impossible without an intraoperative histopathological study. Multicenter studies are needed to improve the understanding of possible risk factors.

Key words: Primary fallopian tube cancer; Oncogenes; ERα; ERβ; CK7; CK20.

Introduction

Primary fallopian tube cancer is a rare disease, representing about 1% of all female genital tract malignancies [1]. Its etiology is poorly known. Moreover, little is known about its risk factors, prophylaxis or prognostic factors. Formerly it was thought that risk factors were similar to the ones defined in fallopian tube cancer, nonetheless more and more reports proving their distinction appear [2]. The incidence of primary fallopian tube cancer has risen over the last decades, predominantly among women of higher economic status [3]. Difficult preoperative diagnostics is a clinical problem. Only 4% of cases are correctly diagnosed before an operation. Treatment is based on radical or as comprehensive as possible cytoreductive surgery followed by chemotherapy (cisplatin, paclitaxel). A five-year survival rate ranges from 22 to 57% [3].

As a matter of fact immunohistochemical markers used to distinguish ovarian carcinoma, such as cytokeratin 7 (CK7) or cytokeratin 20 (CK20), are virtually the same for tubal cancer.

Until now, it has also been controversial whether ovarian epithelium carcinomas possess steroidogenic enzymes, but several studies have previously shown that ovarian epithelial normal and tumor cells expressed progesterone and estrogen receptors α and β (ERα and ERβ) and are thus potential targets of ER-mediated effects on proliferation [4, 5].

The aim of our study was to describe medical performance in a case of fallopian tube cancer as well as perform immunohistochemical detection of estrogen receptors (ERα and Erβ), progesterone receptor (PgR), and proliferation marker Ki67 as well as basic cytokeratin CK7 and CK20 markers.

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Case Report

Clinical Summary

A 72-year-old woman with a BMI of 24.6 presented with pain in the hypogastrium of two months duration. Her history included two natural deliveries and she had her last menses at the age of 49 years. She had been treated due to arterial hypertension for 20 years and there was no family history of oncological diseases.

The following were found on examination: mobile resistance of 4-5 cm diameter in the right uterine adnexa. An outgrowth of heterogeneously risen echogenicity and irregular contour, measuring 42 x 45 mm, was found in the right adnexa by ultrasonography (US). The remaining organs of the small pelvis and abdominal cavity were unchanged. Free fluid in the peritoneal cavity was not found. On magnetic resonance imaging (MRI) with intravenous contrast medium, a heterogeneous signal was detected connected to the uterus from the posterior and right side (a well-restricted oval area - 42 x 27 x 40 mm), which amplified after the administration of contrast medium, possibly originating from the right ovary. No spread of the lesion to neighbouring organs was visualized. CA-125 marker level was: 86.70 U/ml and chest X-ray showed no focal lesions. A diagnosis of an adnexal tumor was made – probable ovarian cancer. The patient underwent laparotomy.

The suspicion of malignant infiltration, approximately 5 cm in diameter, was intraoperatively found in the right fallopian tube, while fallopian serosa was found to be smooth. The ovaries were bilaterally visually unchanged. A single adhesion of the urinary bladder peritoneum to the sigmoid colon was seen on the surface of about 8 mm. There was a the suspicion of a neoplastic lesion of metastatic potential in the adhesion. The remaining organs of the pelvis and abdominal cavity were visually intact.

The uterine corpus together with the adnexa was removed in a typical way followed by omentectomy and appendectomy. The common iliac, inner and obturator lymph nodes were collected bilaterally. Final postoperative outcome was serous pap-

illary carcinoma of the right oviduct G2 (the cancer did not infiltrate the serosa). There was metastatic focus in the sigmoid-bladder adhesion but the iliac and obturator lymph nodes (12 pieces in total) were intact. Neoplastic cells were present in the cytological smear from the peritoneal cavity.

The postoperative course was uncomplicated. The patient underwent supplementary treatment (chemotherapy). At the 26-month follow-up period after the oncological therapy there was no neoplastic relapse.

Method

The resected specimen was fixed in 10% buffered formaldehyde solution for 24 hours and embedded in paraffin blocks at 56°C. For routine histology, hematoxylin-eosin staining was performed. For immunohistochemical studies, a representative section from the resected specimen was selected. The following biological markers were investigated: cytokeratin (CK), CK 7, CK 20, estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), progesterone receptor (PGR) and proliferation marker Ki-67. CK was assessed using monoclonal mouse antibody, Clone AE1/AE3 (Dako, Denmark) at 1:100 dilution; CK 7 was assessed using monoclonal mouse antibody, Clone OV-TL 12/30 (Dako, Denmark) at 1:100 dilution; CK 20 was assessed using monoclonal mouse antibody, Clone K_S20.8 (Dako, Denmark) at 1:100 dilution; ERα was detected with a mouse monoclonal antibody, Clone 1D5 (Dako, Denmark) at dilution 1:200; ERβ was detected with a mouse monoclonal antibody, Clone EMR02 (Novocastra) at dilution 1:150; PGR was detected with a mouse monoclonal antibody, Clone PgR 636 (Dako, Denmark) at dilution 1:100; Ki-67 was detected with a mouse monoclonal antibody, Clone MIB-1 (Dako, Denmark) at dilution 1:150. The sections were deparaffinized in xylene and hydrated through graded alcohol. Antigen unmasking was performed using heat treatment in a microwave oven at 750 W for 7 min. Sections were allowed to cool in the buffer at room temperature for 30 min and were rinsed in deionized H_20 three times for 2 min each. Endogenous peroxidase activity was blocked with 1% hydrogen peroxide for 20 min. After rinsing in PBS, the sections were incubated with studied primary antibodies for one hour at room temperature. Antibody-antigen reaction was revealed with EnVision system (Dako, Denmark). Staining was routinely developed using 3,3'-diaminobenzidine as a chromogen (Dako, Denmark). Sections were counterstained with hematoxylin. The expression of studied proteins was evaluated with the use of light microscopy. Appropriate positive and negative immunohistochemical controls were done.

Final pathological findings

Histopathological examination of the studied tumor revealed serosal papillary carcinoma of the right side of the oviduct, grade 2 according to the WHO classification.

Immunostaining for ERα, ERβ, PGR and Ki-67 was restricted to the nucleus of the tumor cells, whereas CK and CK 7 staining was membrane and cytoplasmic. ERα was observed in 30% (focally to 50%) of the cancer cells, ERβ in > 90% of the cancer cells, PGR < 5% of the cancer cells (only focally), and Ki-67 in 60% of the cancer cells; CK and CK 7 were positive in the cancer cells and CK20 was negative.

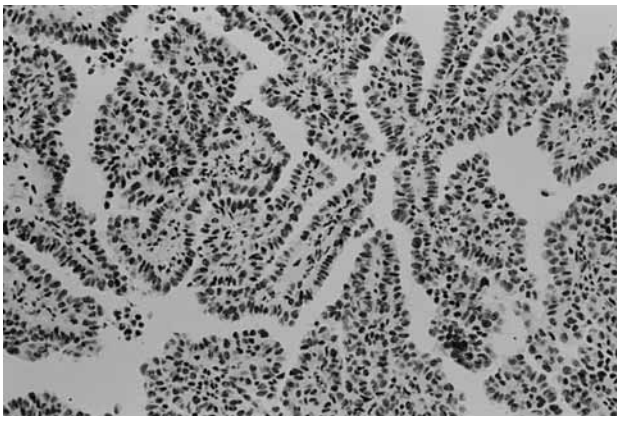

Figure 1. — Positive strong nuclear immunostaining for ERβ assessed in the majority of cancer cells (original magnification - 200x).

Discussion

Primary fallopian tube cancer is a rare female sex organ tumor, similar to ovarian carcinoma but characterized by a worse prognosis [1]. Therefore, it should be treated as a separate disease entity that is independent of other pathological processes of the minor pelvis in women. Primary serous neoplasms in women are found within the borders of the ovaries, fallopian tubes and peritoneum. The above-mentioned three neoplasms could be considered to constitute merely a variety of the same carcinogenesis process, but in fact little is known about primary fallopian tube cancer [2]. It is assumed that hormonal contraception, similarly to parity and breast-feeding, reduces the risk of primary fallopian tube cancer as well as ovarian carcinoma, in contrast to serous peritoneal carcinoma [2, 3]. This may indicate a different route of development for peritoneal carcinoma. The findings of a multicenter clinical case control study published by Moore *et al*. [4] did not prove any differences in survival rates between patients treated for one of the two above-mentioned neoplasms. A problematic issue in case of primary fallopian tube cancer is the difficult differential diagnosis. It can often be clinically misinterpreted as a fallopian tube abscess [5]. According to Riska and Leminen [6], only 4% of fallopian tube cancers are correctly diagnosed before surgery. A similar problem occurred in the case presented here. Based on the interview, physical examination, laboratory diagnostics, US and MRI with contrast, the following diagnosis was made: adnexal tumor – probable ovarian cancer. This diagnosis, however, was confirmed by the intraoperative procedure. Genetic mutations associated with the presence of the BRCA gene may play a key role in this cancer pathogenesis [7]. According to Callahan *et al*. [8], the presence of the BRCA gene enables carcinogenesis in the fimbriae of the oviduct to a greater extent than in the ovary. Moreover, in women with primary fallopian tube cancer a drop in the expression of genes coding for p53

and p27 (kip1) proteins responsible for apoptosis, has been found. On the other hand, in 57% of female patients with advanced stage of the disease, an elevated expression of HER-2/neu oncogene (human epidermal growth factor receptor 2), encoding a receptor protein for cellular growth factor has been found [9]. In ovarian tumor samples the level of ER-α mRNA were similar or slightly higher than those in normal ovaries, while ER-β mRNA was decreased [10]. In another study both ER-α and ER-β mRNAs were expressed in 80% of ovarian cancer samples, however, the ER-α to ER-β ratio was higher suggesting that overexpression of ER-α relative to ER-β mRNA could be a marker of ovarian carcinogenesis [11]. So far no study has shown either gene or protein estrogen and progesterone receptor expression in tubal carcinoma. Although this was only a case study it has been clearly shown that the immunohistochemical expression of ER-β was dominant over ER-α which encourages us to perform further confirmatory evaluations on a larger number of samples, especially taking into account very scant progesterone receptor expression.

Among different cytokeratin combinations, different patterns of CK7 and CK20 staining have so far been mostly used to distinguish between different histological subtypes of ovarian carcinoma [11]. We also attempted to used them to see whether any similarities exist in tubal and ovarian cancers as to the expression of characteristic histological markers. Indeed, absence of CK20 expression with concomitant positive CK7 immunostaining can be characteristic of serous ovarian carcinomas [12], which would not indicate the effectiveness in distinguishing between tubal and ovarian cancer. It is also not surprising that the majority (60%) of cancer cells exhibited high Ki-67 staining since the proliferative potential of these types of tumors is widely accepted.

A deeper understanding of the potential risk factors for primary fallopian tube cancer requires multicenter studies. Furthermore, a need exists for the identification of prognostic factors regarding the treatment at various stages of disease progression.

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