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Endometriosis and carcinosarcoma – a hypothetical correlation or a proven pathogenetic pathway? Colon carcinosarcoma with origin in endometriotic foci – a case report

Endometrioza i mięsakorak – hipotetyczny związek czy udowodniona wspólna ścieżka patogenetyczna? Opis przypadku mięsakoraka jelita grubego wychodzącego z ogniska endometriozy

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Abstract

We present the first case of a patient with a synchronic occurrence of three neoplasms: non-small cell lung cancer, serous cancer of the ovary, and carcinosarcoma of the colon. Moreover, the possible origin of the carcinosarcoma is an endometriotic focus, which is an extremely rare occurrence, especially in women with no history of endometriotic treatment. Immunohistochemical staining of the carcinosarcoma was positive for CD10, estrogen receptors and desmin – typical markers for endometriotic foci.

The growth of endometriosis depends on estrogen, which is produced at reduced levels after menopause. However, in some cases endometriosis could be diagnosed de novo in postmenopausal women.

On the basis of the reported patient we discuss possible correlations between endometriosis and carcinosarcoma, as well as treatment methods of carcinosarcoma.

Key words: **endometriosis** / **carcinosarcoma** / **ovarian adenocarcinoma** /

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Streszczenie

Prezentujemy pierwszy na świecie przypadek pacjentki, u której rozpoznano synchroniczne występowanie trzech nowotworów: niedrobnokomórkowego raka płuc, raka surowiczego jajnika oraz mięsakoraka jelita grubego. Co więcej, najbardziej prawdopodobnym punktem wyjścia mięsakoraka jelita grubego jest ognisko endometriozy. Niesłychanie rzadko opisuje się karcynogenezę związaną z endometriozą u pacjentek, które wcześniej nie leczyły się z powodu endometriozy. Badanie immunohistochemiczne mięsakoraka ujawniło ekspresję CD10, desminy oraz receptorów dla estrogenów – typowych markerów endometriozy. Aktualnie uznaje się, że endometrioza – mająca podłoże estrogenne, może być diagnozowana de novo nawet po menopauzie.

Na podstawie przedstawionego opisu przypadku przedyskutowaliśmy możliwy związek endometriozy i mięsakoraka oraz dostępne opcje terapeutyczne mięsakoraków.

Słowa kluczowe: **endometrioza** / **mięsakorak** / **rak surowiczy jajnika** /

Background

The diagnostic process of pelvic tumors in menopausal women should include genital neoplasms as well as endometriosis. Endometriosis, defined as the presence of endometrial tissue (stroma and glands) outside the uterus, can occasionally be diagnosed *de novo* after the last period. Endometriosis could also be a risk factor for well-known neoplasms detected mainly after menopause [1]. Adenocarcinoma endometrioidale of the ovary and clear cell carcinoma are typical cancers correlated with endometriosis. Carcinosarcomas derived from endometriotic foci outside the uterus are extremely rare. Thus, there is no standard treatment for this kind of tumor and few case reports in the literature. Agito MD et al., reported a case of carcinosarcoma arising from intestinal endometriosis [2], and Noel JC et al., presented a case of a 75-year-old woman who developed an urethral malignant Müllerian carcinosarcoma arising from endometriotic foci [3]. Uterine and ovarian carcinosarcomas are associated with a worse prognosis than high-grade papillary serous carcinomas of the ovary [4]. The difference is not FIGO (FIGO – The International Federation of Gynecology and Obstetrics) stage related [5]. Gynecologists agree that surgical excision should be the first-line treatment for carcinosarcomas.

We report a rare case of a patient with carcinosarcoma of the colon with a likely origin in endometriosis. In addition, the woman presented with two other neoplasms: non-small cell lung cancer and serous adenocarcinoma of the ovary. To the best of our knowledge, it has been the first case of cancer originating from endometriosis in a patient with no history of endometriosis, but who presented also with disseminated non-small cell lung cancer.

Case report

A 65-year old female (gravida 1, para 1, vaginal delivery) presented to our clinic with an abdominal mass recognized on a CT scan performed for the diagnosis of pulmonary lesions and was scheduled for a gynecological surgery. Half a year earlier she had undergone fibro-bronchoscopy with biopsy which revealed non-small cell lung carcinoma. Due to small (up to 9 mm) disseminated lesions she was not operated for lung cancer. After the CT scan, the patient immediately consulted a gynecologist. Ca125 levels were determined and ultrasound testing of the ovaries was performed. Blood Ca125 concentration was 240 U/ml, indicating the presence of an ovarian tumor, and ascites was diagnosed. The preoperative diagnosis presented a challenge because the abdominal tumor, primarily visible on CT, was not diagnosed on intravaginal ultrasound examination, but small hypoechoic cysts of the right ovary were discovered. The patient was promptly referred to the hospital. On admission she was in good overall condition, without pelvic pain and body mass loss, but she reported a history of abdominal distention for a few months. The patient had no history of surgeries, endometriosis, or any gynecological diseases. She was scheduled for an exploratory laparotomy (longitudinal incision). The intraoperative consultation revealed a malignant lesion of the right ovary, 10 cm in diameter. Ascites in the amount of 7 liters was evacuated. Total hysterectomy with bilateral adnexectomy and omentum excision were performed. A large colon tumor (6 cm in diameter), which was revealed on CT, was also removed, with surgical margins clear of cancer. Finally, a tumor of the right ovary was diagnosed as serous adenocarcinoma (stage G3), and the left ovary was also affected by cancer. An endometrial cyst (5 cm in diameter) was present on the right side. The colon tumor was composed of two components, with a spindle cell sarcomatous part and a glandular part. The glandular part showed CKAE1/AE3 (cytokeratin AE1/AE3), CK7 (cytokeratin 7), PAX8 (paired box gene 8), and ER (estrogen receptor) expression, the spindle cells were positive for CD10, WT1 (Wilms' tumor protein gene), and desmin (Figures 1, 2 and 3). Immunohistochemical stains indicated a carcinosarcoma, with a high probability that the neoplasm had its origin in endometriotic foci.

The ovarian cancer tissue of the patient was included in a comparative study in which the immunosuppressive microenvironment was investigated (the results are to be published elsewhere). More than 20 parameters were determined, including types of immune suppressor cells, gene expression levels, and cytokine production of *ex vivo* tissue cultures. Interestingly, the tumor tissue of our patient showed the highest score for several parameters among the 21 ovarian cancer samples included in the study. In *ex vivo* tissue cultures, where small tissue pieces were cultivated in cell culture medium for 3 days, the highest concentration of VEGF (vascular endothelial growth factor) was measured. The value was almost 4 times higher than the median of the whole group. Furthermore, an unusually high infiltration of NK (natural killer) cells was observed. Also, the number of regulatory T cells expressing CD8 (cluster of differentiation 8), but lacking the co-stimulatory CD28 (cluster of differentiation

28) receptor, was the highest among the examined samples (approximately twice the value of the median). In tissue culture, the cells grew more aggressively than cells derived from other samples, eventually resulting in an emergence of a new ovarian cancer cell line.

After the surgery, the patient was given two courses of Carboplatin with paclitaxel. She was referred to the palliative care unit when her condition worsened. The patient died 4 months after the gynecological surgery due to increasing ascites, hydrothorax and respiratory failure.

Discussion

Endometrial stromal sarcomas at extrauterine sites may be primary or metastatic, derived from an uterine tumor [6]. To the best of our knowledge, the presented case has been the first report of a synchronic occurrence of non-small cell lung cancer, serous adenocarcinoma of the ovary and carcinosarcoma of the colon with origin in endometriosis (Figures 1, 2, 3). Endometriosis enhances the risk for ovarian cancer (1.32-1.9 95% CI) according to the latest systematic review [7, 8]. Increased concentrations of a variety of inflammatory and angiogenic factors in the peritoneal fluid are typical for both, endometriosis and ovarian cancer [9]. VEGF, one of the most potent angiogenic factors, was found to be highly expressed in cell cultures of the ovarian tumor in our patient. VEGF also exerts immunosuppressive functions in ovarian cancer by inhibiting the maturation of dendritic cells and the generation of regulatory T cells [10]. The massive infiltration of the ovarian tumor mass with regulatory T cells indicated that anticancer immune reactions were efficiently suppressed in case of our patient. The immediate attachment and proliferation of the ovarian cancer cells in cell culture was unique among 21 samples examined and underlines a highly aggressive character of malignant cells in this particular case. Ectopic endometrium can transform into atypical and further into malignant lesions, with high probability due to pathological inflammatory reactions at the site of the ectopic foci. The same events are thought to cause spindle cell sarcoma. Spindle cells occur as a response to injury, infection or inflammation [11]. The cell of origin of ovarian cancer and the mechanisms by which cancer develops are still open to debate. For a long time ovarian surface epithelium (mesothelium) was believed to be the first participant in ovarian carcinogenesis [12]. An alternate theory proposes that tumors with a Müllerian phenotype (serous, endometrioid and clear cell) are derived from Müllerian-type tissues but not from the mesothelium [13]. However, there are some doubts concerning the first theory and recent molecular studies have supported the Müllerian-type tissue theory. The progression from benign endometrial lesions to atypical and then invasive cancer lasts about a dozen years and is triggered by accumulation of genetic changes such as loss of heterozygosity or mutation of suppressor genes like tp53, ARID1A (AT-rich interactive domain-containing protein 1A) or PTEN (Phosphatase and tensin homolog) [8, 14, 15]. Yamamoto et al., demonstrated that mutation of the PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene could be one of the first steps in the progression from endometriosis to clear cell cancer [16]. Immunohistochemical studies proved that sarcomas with the origin in uterine tissue (carcinosarcoma, endometrial stromal sarcoma) express the same markers as endometriotic foci (CD10, desmin) [17, 18]. CD10 is known to be expressed by endometrial

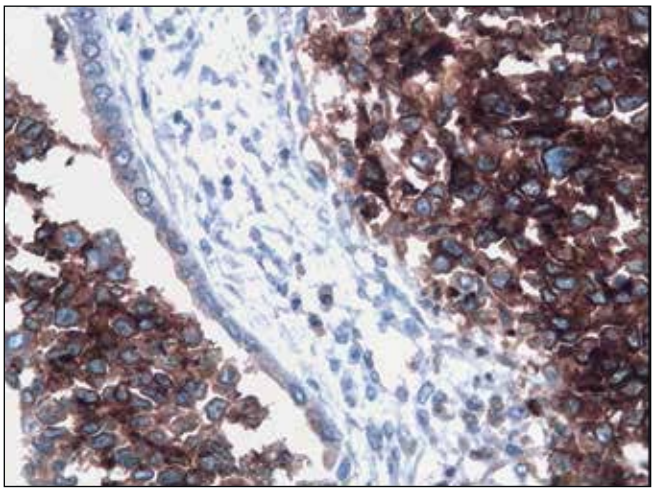

Figure 1. Positive staining for CD-10 (magnification 200x) in the spindle cell part of carcinosarcoma of the colon. Brown colored cells – positive staining for CD-10 what suggests endometrial origin of carcinosarcoma cells (CD-10 is a sensitive immunohistochemical marker of normal endometrial stroma); blue cells – negative staining for CD-10 indicating colon cells.

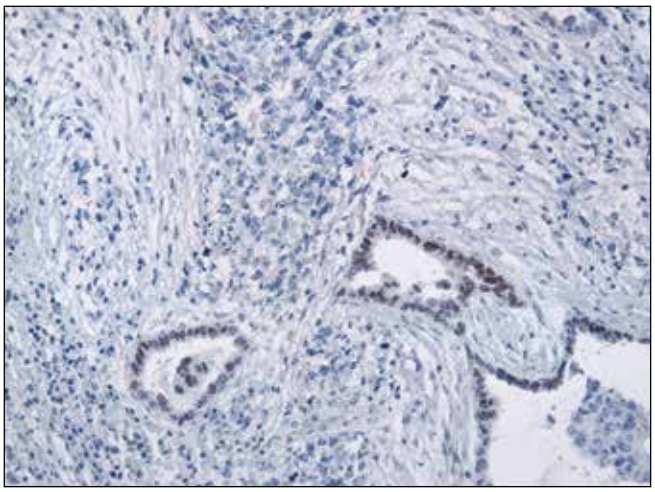

Figure 2. Positive staining for ER receptors. A small focus of endometriosis seen in the middle of the picture. Glandular epithelial tissue with nuclear expression of ER indicating for origin in endometrium are colored brown. Blue colored are non-epithelial cells, without ER expression (magnification 100x).

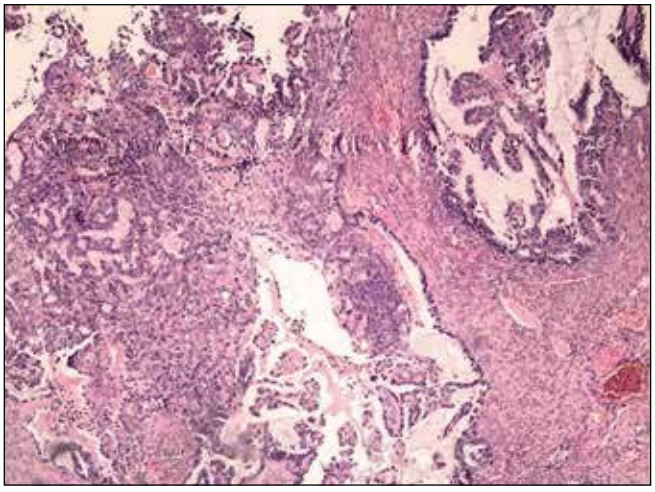

Figure 3. Hematoxylin-eosine staining; typical pathological image of ovarian serous adenocarcinoma (magnification 40x).

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and endometriotic stromal cells and may be induced by progestins [19]. Our patient also showed expression of CD10 in the colon tumor, suggesting that the carcinosarcoma could have originated from an extragenital endometriotic implant. Another indicator for that theory is the endometrioid cyst found in the right ovary. Endometrial ovarian cysts are known to be independent risk factors for ovarian cancer over the age of 45 [1]. Munksgaard et al., published epidemiological data concerning endometriosis and non-ovarian neoplasms. They found no obvious link between breast or endometrial cancer and endometriosis [8]. There is also no known association between lung cancer and endometriosis. Studies on pleuro-pulmonary endometriosis generated ambiguous results.

In summary, we report an extremely rare case of colon carcinosarcoma originating in endometriotic foci in a woman with no history of endometriosis and no known risk factors for the disease. The coexistence of three neoplasms implied that the patient could not receive the standard treatment for ovarian cancer. Surgical excision of the tumor, radical abdominal hysterectomy and bilateral salpingo oophorectomy constitute the first-line treatment for carcinosarcoma as well as ovarian cancer. Para-aortic and pelvic lymphadenectomy should be performed. Adjuvant radiotherapy and adjuvant chemotherapy could be considered. However, the role of chemotherapy in the treatment of carcinosarcoma remains questionable. Ifosphamide, cisplatin, adriamycin and paclitaxel with carboplatin are reported to be used by oncologists. Despite advances in the diagnosis and treatment, survival has not improved over the last 25 years [20]. Future research will show if a common origin for the coincidence of lung cancer and other neoplasms as reported in this paper will be demonstrated in more cases.

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The authors declare that they have no conflict of interest.

Statement

The patient reported in the manuscript gave an informed consent to publish her case.

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