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1930s. According to the most recent systematic review of the literature, the risk is small and is 1.32–1.7 (95% CI) [7]. There are many publications on the relationship of endometriosis with ovarian clear cell carcinoma, however, it is not known whether these two diseases have a common aetiology and whether the relationship is sequential in nature, i.e. endometriosis developing into cancer through malignant transformation [8].

The aim of this study was to investigate the relationship of clear cell carcinoma with endometriosis and analysis of possible common risk factors for both of these disease entities in respect of data from available literature. The study was based on data collected in a retrospective analysis of clinical material from 2004-2014.

**Material and methods**

In a retrospective study done by the Department of Operative and Oncological Gynaecology at the Medical University of Lodz, histopathological data of ovarian cancer from 2004-2014 were analysed. The search terms in PubMed and Web of Science were the words or phrase “clear cell carcinoma, ovarian cancer, clear cell, sophisticated histopathological findings but dealt with an organ other than the ovary”. Of the 394 ovarian cancers found, 9 had dealt with histopathology. These 9 papers formed the basis of our patient selection, and we then analysed their data on menstrual history, diversity, comorbidities, data from the physical examination and operational protocols and histopathological diagnosis. Prospective data from follow-up were obtained from 7 patients. Each patient gave her consent to anonymously publish her data. Statistical analysis was performed using Microsoft Excel 2013.

**Results**

Among the 394 patients operated for ovarian cancer in our clinic in 2004-2014, the patients with ovarian clear cell carcinoma (OCCC) type accounted for 0.02% (9/394). In our study group of OCCC, the mean age at diagnosis was 57.6 years and a mean BMI of 27.2 kg/m². The study showed that 77.8% of respondents have gone through pregnancy (n = 7) and that most of the patients were multiparous (85.7%) 66.7% of all analysed patients. OCCC was detected mostly in the stage Ia (n = 4) (Fig. 1). The concentration of Ca125 in the study group averaged 142.75 U/ml; median 69.3 U/ml (Table I). None of the patients had clinically or histologically confirmed coexistence of endometriosis. The most common morbidities in the study group were hypertension and obesity affecting 33% of patients in both cases, and thrombocythemia which was seen in 22% of patients. Follow-up was achieved in 77.8% of patients (n = 7), 42.8% of which remained in remission (n = 3) after radical treatment operations and first-line chemotherapy (Table II). One patient managed to stabilize her disease but suffered from progression after a year, subsequently being placed on second-line chemotherapy. In another patient, upon completion of first-line treatment, remission was achieved for a year until relapse of a vaginal tumour, which was then treated with brachytherapy. Death from cancer was confirmed in one patient who was operated on with stage Ia ovarian cancer. This patient suffered a recurrence of her cancer one year from diagnosis which led to her death.

**Discussion**

In recent years, the world has observed an increase in incidence of ovarian cancer. Peak incidence coincides with the postmenopausal period with the age of 40-70 years [2]. This age distribution is also present in our study group. Ovarian cancers due to their histopathological structures are divided into: serous, mucinous, endometrioid, clear cell, mixed and undifferentiated carcinoma (source: WHO; http://webcache.googleusercontent.com/search?q=cache:sxun1BsGqPMJ:https://www.seap.es/documents/228448/528821/01_Prat.pdf+&cd=1&hl=pl&ct=clnk&gl=pl). The OCCC represent...
sents a small percentage of ovarian cancers (approx. 112%/11.2%) [9, 10]. In our study, of 394 patients operated within a 10-year period, pathologists recognized OCCC in < 1% of patients with ovarian cancer. Only the Japanese population, wherein the ovarian cancer is less common than in the other populations, is characterized by a greater proportion of OCCC of 15-25% [11]. The prognosis of this tumour type is described as worse than those of other histological subtypes with a 5-year survival of around 30% [12-14]. One of the reasons for the poor prognosis is the late diagnosis of the disease. Therefore, the determination of the genetic relationship between endometriosis and OCCC could be helpful to patients with endometriosis by closely monitoring them as well as the possibility of applying preventative measures [15]. This cancer is difficult to be detected and even small primary lesions may result in distant metastasis. It spreads contiguously in the peritoneal cavity and through lymph vessels, as opposed to the more common route of blood vessels [2]. In the early stages of OCCC, the symptoms are nonspecific and become more noticeable with the progression of the disease [15]. These include, among others: abdominal distension, pelvic pain, ascites, and dysuria [15-17]. Chronic and especially severe endometriosis may also have this characteristic pelvic pain making it a part of our differential diagnosis [18]. The differential diagnosis of cancer takes into account: physical examination, imaging investigations: transvaginal and transabdominal ultrasound, CT, MRI, concentration of Ca125, and the risk calculated in the algorithms RMI and ROMA (called risk of malignancy index; risk of ovarian malignancy algorithm) (http://xemamedica.com/eng/calc/) [2, 19]. Definitive diagnosis is made based on the histological examination of stretch material taken during surgery. The treatment of choice is radical surgery with inter- or post-operative cytoreduction by chemother-apy. Clear cell carcinomas are biologically aggressive cancers and mostly resistant to conventional platinum-based chemotherapy. However, the early stages of clear cell cancer have a good prognosis and may not require adjuvant therapy [20]. Thrombosis occurs more often in patients with OCCC as demonstrated in our study group with a thrombocythemia occurring in 22% of patients, although no serious thrombotic complication were observed.

Studies on the transformation of endometrial lesions into malignant neoplasm indicate that oncogenesis occurs most often in foci located in the ovaries. This transformation can be described as loss of heterozygosity, tumour suppressor genes p53 mutation and PTEN [21]. It seems that the progression from the benign lesion of endometriosis to invasive tumours, through the atypia and metaplasia and to the frank borderline tumours takes several years and is due to the accumulation of genetic changes [21]. Yamamoto et al. proved that mutations of the PIK3CA gene (phosphatidylinositol3 kinase) may be one of the first events that initiate the transformation of endometriosis into OCCC [22]. This mutation was detected in approximately 33% of OCCC [23]. An interesting fact is that another mutation characteristic of endometriosis, endometriosis carcinoma, as well as of clear cell carcinoma is a tumour suppressor gene mutation ARID1A (AT rich interactive domain containing protein 1A) [4]. This gene regulates transcription of p53 dependent proteins. It has been shown that mutations in this gene promote the development of carcinogenesis in mice. The presence of this mutation in both endometriosis and in OCCC may suggest a cause-and-effect relationship of these two diseases [24].

Tumours originating from endometriosis have some common features: they are most common in younger patients as compared to patients with squamous cell carcinoma of the ovary, as they are detected in the lower stages with a higher degree of differentiation, and thus have a better prognosis [24]. Although we failed to find a relationship between OCCC and endometriosis in the study group, we drew attention to the fact that they have a better prognosis – 42.8% of patients with a 5-year survival after diagnosis. According to the statistical data, the survival of patients with epithelial ovarian can-

| Tab. II. Follow-up after initial diagnosis of clear cell ovarian cancer |
|-------------------------------------------------------------|
| Patient | Date of diagnosis | Treatment | Observation | Adjuvant therapy |
|---------|-------------------|-----------|-------------|-----------------|
| 1       | 17.10.2007        | radical operation | remission | chemotherapy    |
| 2       | 28.06.2011        | operation (non-radical) | progression in the abdomen | chemotherapy    |
| 3       | 22.08.2011        | radical operation | lost to follow-up (FU) | –               |
| 4       | 21.05.2012        | radical operation | remission | chemotherapy    |
| 5       | 02.07.2010        | radical operation | neoplastic infiltration of the urinary bladder suspected – chemotherapy; metastasis in vagina – operation | chemotherapy + brachytherapy |
| 6       | 10.11.2010        | radical operation | alive | chemotherapy    |
| 7       | 07.12.2011        | radical operation | remission | chemotherapy    |
| 8       | 15.06.2012        | radical operation | death 16 months after diagnosis | radiotherapy    |
| 9       | 04.11.2004        | operation – not radical | lost to FU | –               |
Endometriosis is 46% (source: http://www.cancerresearchuk.org/cancerinfo/cancerstats/types/ovary/survival/ovarian-cancersurvivalstatistics). Zafrakas et al. reviewed the literature concerning the association between endometriosis and ovarian cancer. On the basis of the collected literature, they were unable to perform a meta-analysis. Their research yielded only one prospective cohort study, some case control studies and most of them were retrospective cohort ones [25]. The main limitation of most publications was the lack of operative confirmation of endometriosis. The risk of ovarian cancer in patients with endometriosis, in most of the retrospective studies, was determined at OR 3.05-3.41 [26-28]. However, a prospective study of Olson et al., which analysed 1392 patients with reported endometriosis in 13 years of observation has not found any association between endometriosis and ovarian cancer including OCCC (RR 0.8, 95% CI: 0.2-2.4) [29]. Zafrakas et al. conclude that the link of endometriosis and OCCC is still debatable on the basis of the above analysis of the literature [25]. The new discoveries of common genetic basis of endometriosis and OCCC have not been yet translated into the clinic and oncologic screening among patients with endometriosis.

Conclusions

In our clinical material, OCCC is a rare histopathological specimen with prognosis comparable to that of serous ovarian cancer. Establishing the cause-and-effect relationship between this histopathological subtype and endometriosis cannot be proved based on clinical material of only one clinic or operative ward. This issue requires statistical studies of available publications targeted at comparing the clinical and molecular groups of patients with endometriosis and OCCC.

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Disclosure

Authors report no conflict of interest.

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