© Pediatr Med Rodz 2023, 19 (2), p. 135–139
DOI: 10.15557/PiMR.2023.0024

Received: 31.05.2023
Accepted: 15.06.2023
Published: 28.08.2023

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Krukenberg tumour in a patient with secondary infertility – case report

Guz Krukenberga u pacjentki z niepłodnością wtórną – opis przypadku

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Abstract

A patient with secondary infertility, diagnosed with an endometrial polyp and right ovarian cyst, was referred for hysterolaparoscopy treatment. The woman reported no symptoms. During the hospitalisation, in addition to the aforementioned issues, left ovarian lesions and ascites were identified. A 10 cm lesion in the right ovary exhibited abundant vascularity. Tumour markers (AFP, CEA, HE4, CA-125) and the ROMA algorithm were assessed and found to be within the normal range. Laparotomy revealed a high-grade malignant tumour of unknown origin confirmed by histological examination. Uterine resection with unchanged greater omentum was performed. Immunohistochemical tests revealed positive cytokeratin (CK) reaction, including CK7 and focal CK20, as well as a marker of proliferation Ki-67 in some cells (20–30%). Signet ring cells and positive mucicarmine stain reaction were detected. The histological evaluation confirmed a Krukenberg tumour originating most likely from the stomach. The patient was referred to the Maria Skłodowska-Curie Greater Poland Cancer for further treatment.

Keywords: diagnostics, stomach cancer, Krukenberg tumour

Streszczenie

Pacjentka z niepłodnością wtórną, u której ambulatoryjnie stwierdzono obecność polipa endometrium i torbieli jajnika prawego, została skierowana do szpitala w celu leczenia drogą histerolaparoskopii. Chora negowała objawy kliniczne. W trakcie hospitalizacji wykryto, oprócz opisanych zmian, również zmiany w jajniku lewym i wodobrzusze. W jajniku prawym, o wielkości prawie 10 cm (96 × 54 × 90 mm), stwierdzono bogate unaczynienie. Oznaczono markery nowotworowe (AFP, CEA, HE4, CA-125) oraz algorytm ROMA – wartości nie były podwyższone. Wykonano laparotomię. W histologicznym badaniu śródoperacyjnym wykryto nowotwór złośliwy o niskim stopniu zróżnicowania i niewiadomego pochodzenia. Wykonano wycięcie macicy z przydatkami oraz siecią większą, która makroskopowo była niezmieniona. Przeprowadzono badania immunohistochemiczne, które wykazały pozytywną reakcję na cytokeratyny (CK), w tym CK7 i ogniskowo CK20, a także w części komórek (20–30%) marker proliferacji Ki-67. Ponadto stwierdzono obecność komórek sygnetowatych oraz dodatnią reakcję barwną z mucykarminem. Histologiczna ocena końcowa – guz Krukenberga ze zmianą pierwotną najprawdopodobniej w żołądku. Chorą skierowano na dalsze leczenie w Wielkopolskim Centrum Onkologii.

Słowa kluczowe: diagnostyka, rak żołądka, guz Krukenberga

INTRODUCTION

Metastatic ovarian tumours account for 2.3–25% of all ovarian tumours. Their incidence depends on the geographic region, with higher rates in Asia than in Europe[1–4].

Cancers metastasising to the ovary may arise from various organs, including the breast, stomach, colon, and appendix. However, these tumours mostly arise from gastrointestinal malignancies (about 70% of cases), gastric cancer in particular[5–7]. A metastatic ovarian malignancy originating from gastric cancer was first described by a German gynaecologist and pathologist Friedrich Krukenberg in 1896; hence the name "Krukenberg tumour"[8].

After multiple histological analyses conducted mainly to differentiate primary mucinous ovarian adenocarcinoma from metastatic carcinoma, the World Health Organization established diagnostic criteria for Krukenberg tumours, which include the presence of mucin-producing signet ring cells with stromal invasion and fibrous sarcoma-like stromal proliferation[1,7,9,10].

Krukenberg tumours occur in middle-aged women (about 45 years of age). An analysis conducted by Chinese researchers in 130 patients with Krukenberg tumours showed the median age of 41 years; 40.8% and 59.2% of patients were <40 years and >40 years old, respectively[3]. Based on 48 studies from an electronic database of 3,025 women with Krukenberg tumours, Lionetti et al. reported that 39.7% of patients were ≥50 years of age[11]. Rare cases of Krukenberg tumours in pregnant women have also been described[12,13].

Bilateral and synchronous Krukenberg tumours account for about 60–80% and over 63% of cases, respectively. Krukenberg tumours often develop asymptomatically; the symptoms are usually correlated with the tumour size and may sometimes reach about 10 cm. Weight loss, bloating, abdominal pain, and ascites have also been reported. Some of these symptoms are associated with extraovarian tumour dissemination as a result of cell detachment from the parent tumour[1,3,7,9,11].

Research on the mechanisms underlying the spread of Krukenberg tumours revealed three pathways involving, among others: integrins, microRNAs, numerous growth factors (epidermal growth factor receptor, EGFR; mitogen-activated protein kinase, MAPK; vascular endothelial growth factor, VEGF), as well as increased expression of some matrix metalloproteinases (MMPs)[2,9,14]:

- hematogenous spread – metastasis associated lung adenocarcinoma transcript 1 (MALAT1), a long non-coding RNA, plays the key role in this process;
- lymphagenous spread – this process depends on the VEGFR-3 receptor and endothelin 1 (ET-1) and is most likely related to tumour recurrence in the lymph nodes;
- transcoelomic spread – a passive process in which cells detached from the parent tumour travel in naturally flowing fluid (also in the case of ascites).

Krukenberg tumour poses a diagnostic challenge; it is impossible to find the primary malignancy in approximately 15% of cases[1,2,3,9]. Many imaging modalities (ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography combined with computed tomography) are used in the diagnosis. Histological diagnosis is based on immunohistochemistry and multiple molecular factors, e.g. cytokeratins (e.g. CK7 and CK20), tumour markers and homeobox proteins (e.g. CDX2)[1–3,5,15,16].

Krukenberg tumour is associated with poor prognosis; survival is approximately 1 year and seems to depend on the location of the primary tumour, the size of the ovarian tumour, and the management (ovariectomy vs. non-ovariectomy). The prognostic role of the coagulation system (fibrinogen, D-dimers) is also emphasised[1,2,17].

Additionally, follow-up is important, as even in the case of complete remission of the disease, recurrence may occur after many years[18].

CASE REPORT

A 38-year-old patient with secondary infertility was admitted to the Gynaecology and Obstetrics Clinical Heliodor Święcicki Clinical Hospital of the Poznan University of Medical Sciences for hysterolaparoscopy treatment of right ovarian cyst and endometrial polyp. She had a history of hypothyroidism, past spinal surgery for disc herniation and spontaneous abortion at 10 weeks gestation.

Gynaecological speculum examination on admission found bloody discharge and a small, smooth vaginal part. Intravaginal examination showed an anteverted uterus with normal size and mobility. A palpable, hard resistance was detected to the right, located adjacent to and connecting with the uterus. Laboratory findings on admission were as follows: alpha-fetoprotein (AFP) 1.75 ng/mL, carcinoembryonic antigen (CEA) 0.80 ng/mL, human epididymis protein 4 (HE4) 38.66 pmol/L, carcinoma antigen 125 (CA-125) 13.12 U/mL. ROMA (Risk of Ovarian Malignancy Algorithm) was estimated at 4.15%.

An ultrasound (US) scan performed in the hospital showed an anteverted uterine corpus measuring 57 × 50 mm. Phase 2 endometrium with a thickness of 14 mm. A 15 mm long endometrial polyp was found in the uterine cavity. The left ovary, 43 × 37 mm, irregular in shape, with a solid-cystic mass. The right ovary completely transformed into a richly vascularised solid-cystic tumour measuring 96 × 54 × 90 mm (Figs. 1, 2). A significant amount of fluid in the rectouterine pouch and between the bowel loops, with the largest pouch 6 cm in diameter.

Due to the suspicion of bilateral ovarian tumours in ultrasound, the patient was qualified for laparotomy surgery. After opening the abdominal cavity by a transverse incision just above the pubic symphysis, a significant amount of watery fluid was found; corpus uteri of normal size with a subserosal myoma on the anterior wall, about 1.5 cm in diameter. The ovaries bilaterally transformed into tumours

DOI: 10.15557/PiMR.2023.0024

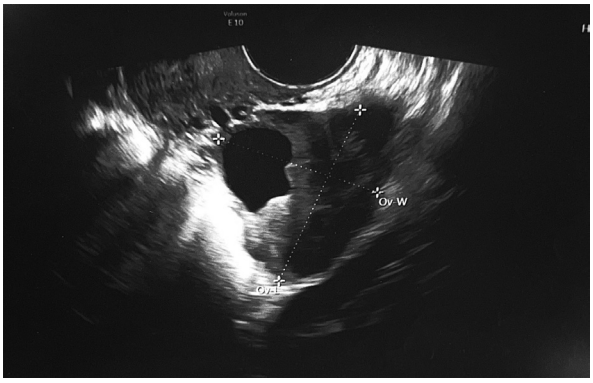

Fig. 1. Left ovarian pathology (US)

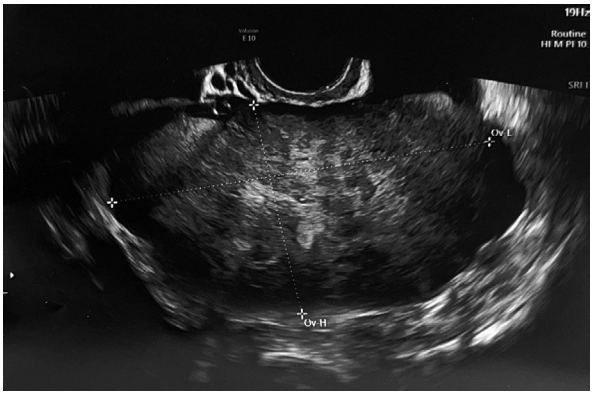

Fig. 2. Right ovarian pathology (US)

with an uneven surface and varying compactness, partly solid, partly cystic; the fallopian tubes without macroscopic changes, free rectouterine pouch, the greater omentum macroscopically unremarkable. A detailed inspection of the abdominal cavity was performed, revealing no suspicious lesions. The right ovary was resected and sent for intraoperative histopathology. The preliminary diagnosis was as follows: a high-grade malignant ovarian tumour of unknown primary origin. For this reason, the surgical treatment was extended to include hysterectomy with left salpingo-oophorectomy, as well as removal of the right fallopian tube and the greater omentum.

An immunohistochemical panel was performed to identify the primary source of the tumour. Cytokeratins (CK AE1/AE3+, CK7+, CK20+/–), non-epithelial cell markers (CD99+/–, alpha inhibin+/–), markers of melanocyte maturation (HMB-45), CD45, metastasis marker (vimentin) and Ki-67 proliferation marker, which was positive in 20–30% of cells, were measured. Histochemical mucicarmine staining for intracellular mucus was positive. Final histological diagnosis: poorly differentiated malignant ovarian tumour of unknown primary origin. Mucocellular carcinoma with signet-ring cells and focal necrosis. Endometrial glandular polyp; omentum without pathological findings.

Krukenberg tumour was diagnosed based on immunohistochemical and histochemical findings, with the primary lesion more likely to be located in the stomach than elsewhere in the gastrointestinal tract. The patient was referred to the Maria Skłodowska-Curie Greater Poland Cancer in Poznan for further treatment.

DISCUSSION

Metastatic ovarian tumours often pose a diagnostic challenge. In order to distinguish Krukenberg tumours from primary ovarian carcinomas, many diagnostic models have been developed that take into account clinical, biochemical and radiological features to accurately define these two types of cancer[5,19,20]. It is estimated that the primary source of Krukenberg tumour is unknown in approximately 15% of women[1]. Accurate histopathological assessment, which determines further therapeutic management and prognosis, plays a decisive role in the diagnosis[1,7,19,21].

The presented 38-year-old patient had no clinical manifestations suggestive of metastasis to the ovary. An analysis of the electronic database of over 3,000 patients with Krukenberg tumours has shown that 11.2% of women were asymptomatic[21]. Young women account for 80% of cases[19]. During a 10-year follow-up of patients with secondary ovarian tumours, Lin et al. found that the median age was 41 years[3]. A case of an 18-year-old woman with Krukenberg tumour has also been described[22].

Transvaginal ultrasound in the described patient showed that both ovaries were transformed into solid-cystic tumours. The right-sided tumour was almost 10 cm in size and had abundant vascularisation. There was also fluid in the rectouterine pouch and between the bowel loops. Retrospective studies conducted in the Mayo Clinic over a period of 22 years showed that ascites and bilateral nodular ovarian lesions were a poor prognostic factor[19]. Lionetti et al. reported ascites, which is also an unfavourable prognostic factor, in 51.7% of patients[11]. Similar data have been presented by other authors[7]. In the aforementioned analysis by Lionetti et al.[11], more than 40% of Krukenberg tumours reached a size of at least 10 cm. As pointed out by other researchers, the size of tumours and the stage of the disease correlate with symptoms[3,11].

Our patient was diagnosed for secondary infertility. Endometrial polyposis and ovarian cyst were considered to be the likely aetiology. The link between infertility treatment and ovarian cancer remains unclear[23]. A Cochrane review covering 28 years of research on the risk of ovarian cancer in women using infertility drugs (over 4,684,000 women) found this link to be debatable[24]. However, our patient had no history of infertility treatment.

Due to the detected ultrasound pathology, she was thoroughly screened for tumour markers, which were found to be normal. A 12-year study in a cohort of 1,696 women showed elevated CA-125 levels in patients with Krukenberg tumours, which decreased after its eradication[5]. Similarly, Aziz et al. reported an increase in CA-125 and CA-19-9 in Krukenberg tumours[21]. On the other hand, Nunes Pereira et al.[20] and Sørensen and Mosgaard[25] demonstrated the

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role of CA-125/CEA ratio, with ovarian cancer found in 80% of patients with a CA-125/CEA ratio >25. This ratio was 16.4 in our patient. Therefore, it can be considered that the patient was clinically and biochemically asymptomatic. An immunohistochemical panel, which is helpful in distinguishing a primary tumour from a metastatic lesion and often suggests the primary location, was performed in our patient[21,26–28]. Aziz et al. showed different CK7 and CK20 values in primary ovarian cancer, gastric and colorectal metastasis to the ovary. CK7 is strongly positive in primary ovarian cancer, less positive in gastric metastasis and negative in colorectal metastasis. On the other hand, CK20 is negative in primary ovarian cancer and colorectal metastasis, but positive in gastric cancer metastasis[21]. In the case of our patient, these values were not remarkable – CK7 was positive, while CK20 showed a focal positive reaction. Yang et al. considered CK7 to be the best marker differentiating gastric (positive in 93%) from colorectal cancer metastases to the ovary[26]. Some other reports indicate that immunohistochemistry positive for CK7 and negative for CK20 may indicate an unknown primary origin, including breast cancer. According to these studies, both of these cytokeratins were negative in 60% of cases with the primary tumour in the stomach[27].

Additionally, our patient was assessed for the presence of cells derived from the sex cords and other epithelial and non-epithelial tumours. It was found that she showed no vimentin, CD99, or HMB-45 expression, which is consistent with the findings of other researchers[21,28].

The investigations presented above are therefore inconclusive and further diagnostic tests are needed to determine the source of the primary cancer.

CONCLUSION

In the case of suspicious cystic-solid ovarian masses, even in young women, histological assessment should be sought. In ambiguous situations, clinical, biochemical, and immunohistochemical investigations, as well as ultrasound imaging should be supplemented with more precise methods (magnetic resonance imaging, computed tomography) or other diagnostic tools (gastroscopy or colonoscopy).

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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