

## Meigs' syndrome with elevated CA-125 and HE-4: a case of luteinized fibrothecoma

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### Abstract

Presence of fibrothecoma is not usually accompanied by elevated levels of tumor markers. In recent years, however, there have been isolated reports of fibrothecoma and Meigs' syndrome, accompanied by an increase in tumor markers. We present a case of fibrothecoma with Meigs' syndrome and elevated levels of both CA-125 (cancer antigen 125) and HE-4 (human epididymis protein 4).

In this paper, we present a case of Meigs' syndrome associated with an increased CA-125 and HE-4 level due to ovarian fibrothecoma.

**Key words:** Meigs' syndrome, CA-125, HE-4, fibrothecoma.

### Introduction

Meigs' syndrome in the classical form consists in benign solid ovarian tumors (fibrothecoma) accompanied by ascites and pleural effusion; its causes are unknown and it occurs almost always on the right side [1]. The characteristic feature of the syndrome is complete disappearance of ascites and/or the fluid in the pleura following the surgical removal of the tumor. The syndrome, so defined, was first described by Meigs and Cassa in 1937, even though first records describing cases of ovarian tumors and ascites were written already in 1728 [2, 3]. Before 1880, the publications were limited only to clinical and anatomical descriptions [3]. In 1887-1902, Demos noted for the first time that removing the tumor results in a complete remission of ascites, and postponing surgery constitutes an improper therapeutic procedure. In 1937, Meigs formulated the classic definition of the syndrome, which was originally called Demon-Meigs' syndrome and since 1954, only Meigs' syndrome [1, 2].

If the clinical symptoms (ascites, pleural or pericardial effusion) are accompanied by other benign or malignant tumors of the sex organs, the condition is defined as pseudo-Meigs' syndrome [3]. Pseudo-Meigs' syndromes were also described as accompanying colon cancer, collagenoses, thyroid cancer, breast cancer, angioleiomyoma [4-7]. Usually fibrothecoma does not result in increased levels of tumor markers. Over the last few years, however, there have been single reports of cases of fibrothecoma and Meigs' syndrome accompanied by increased levels of tumor markers [8]. We present a case of fibrothecoma with Meigs' syndrome and

increased levels of both CA-125 (cancer antigen 125) and HE-4 (human epididymis protein 4).

### Case report

The patient, 50 years old, was admitted to the First Oncological Gynecology and Gynecology Clinic in Lublin in January 2014. The following data were obtained from the interview: first menstruation at the age of 15, last menstruation at the age of 49; the patient gave birth twice vaginally, did not miscarry. The BMI was 27.0.

Speculum examination revealed that the front vaginal wall was protuberated as well as a deformed, columnar cervix with numerous Naboth cysts, macroscopically without abnormalities, moved to the left. Bimanual pelvic examination determined an anteverted and anteverted uterus, and a big, 10 cm × 9 cm, immovable tumor filling the pelvis, whose point of origin was difficult to determine. Groin lymph nodes were not examined.

Abdominal ultrasonography revealed free fluid in large quantities. It was difficult to assess the condition of abdominal organs due to the domination of the free fluid. A circular structure was found in the center of the pelvis minor, 106 mm × 92 mm in size, with a large fluid cavity inside and a smaller one in the thick wall on the left.

Ultrasonography of the pelvis minor conducted by 3D transvaginal and 2D transabdominal probes (the device was GE Voluson E8 Expert) revealed an anteverted uterus with an even outline and homogenous echogenicity, 54 mm × 42 mm × 36 mm in size. The uterine cavity had an even outline. The endometrium was typical of

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the second half of the cycle, with increased echogenicity and both layers 6.6 mm thick (the norm is < 16 mm). The left-sided image of the adnexa and the whole pelvis minor showed a solid tumor of about 100 mm × 93 mm × 90 mm in size, 450 ml in volume and an oval fluid area of about 34 mm in diameter. In the solid area of the tumor there were found numerous chaotically located vessels visible in the 3D "Power" color exam by angio-Doppler. The duplex-Doppler exam revealed low-resistance arterial and venous flow in the tumor's wall (PI = 0.67; RI = 0.42; PSV = 18.96 cm/s), typical of neo-angiogenesis. The ovaries as separate structures were not visualized. An increased quantity of free fluid was found behind the uterus and in the image of the adnexa. The fluid pocket behind the uterus was measured to be 36 mm in AP (< 5 mm being the norm). The ultrasound image suggested a proliferative process probably originating in the ovary/ovaries. But meta-type lesions could not be ruled out.

Results of peripheral blood laboratory tests were as follows: WBC 13.02 K/ml, RBC 4.79 M/ml, HGB 14.6 g/dl, HCT 43.7%, PLT 592 K/ml, sodium 138 mmol/l, potassium 4.54 mmol/l, chlorides 102.5 mmol/l, total proteins 6.26 g/dl, ASPAT 22U/l, and ALAT 17 U/l.

The concentration of tumor markers was very high. The concentration of CA-125 was 2310 U/ml, the norm being < 35 U/ml, while the concentration of HE-4 was 116.2 pmol. The risk assessed by means of the ROMA test (87.10) was very high.

Chest radiological examination revealed lungs without active local abnormalities with lung parenchymas of average breadth, unenlarged heart, even diaphragmatic domes and free angles.

Results of the examination of the fluid collected by puncture of the peritoneal cavity (4 l) were as follows: color: straw-colored, transparency: unclear, cell-density: 900 cells/ml, alkaline, protein: 4 g/dl, glucose: 128 mg/dl, LDH: 102 U/l, neutrophils: 60%, lymphocytes: 40%, and amylase: 10 U/l. Fluid culture revealed no cancer cells. After 48 hours of incubation, no microorganisms were found. Broth culture was negative.

On the basis of conducted examinations it was decided to perform surgery. Due to the unknown advancement stage of the disease and the suspicion that metastasis may have occurred, the patient's consent was obtained to broaden the scope of the operation and perform the following procedures: hysterectomy, omentectomy, appendectomy and removal of a part of the intestines with possible creation of a so-called artificial rectum.

Description of the surgery: the abdominal cavity was opened by median incision elongated to the navel. About 5 l of fluid was removed from the abdominal cavity (some was collected for histopathological examination). There was found an ovarian tumor 12-15 cm in diameter, with an uneven but smooth surface. The tu-

mor was partly attached to the peritoneum parietale. The left adnexa were of normal size, macroscopically and palpably normal. The uterus was slightly enlarged. On the peritoneum parietale of the recto-uterine pouch there was an infiltration or a pressure ulcer after freed tumor adhesions. No other pathological lesions in the abdominal cavity were found – the intestines, omentum and liver macroscopically and palpably without lesions. The tumor on the left ovary was freed from adhesions and removed. Next, the uterus, left adnexa and vaginal cuff were removed in the typical manner. The remainder of the vagina was closed. Omentum majus and appendix were removed (retrocaecal appendix about 12 cm in length). The abdominal cavity was carefully rinsed with Braunol solution. Homeostasis was checked, the abdominal wall closed and the drain removed. There were no postoperative complications.

The patient was discharged from the clinic on the fifth day following the operation. The results of the histopathological examination (no. 93658): tumor in the right adnexa – luteinized fibrothecoma (solid, cohesive, gray, 13 cm × 9 cm × 9 cm in size, external surface damaged in places). No cancer cells were found in the postoperative material. The postoperative control examination was conducted 4 weeks after the procedure. Gynecological and ultrasound examination did not reveal any pathological lesions in the pelvis minor. No fluid was found in the abdominal cavity. CA-125 and HE-4 levels were normal.

## Discussion

Fibrothecoma is a rare, benign ovarian tumor. The incidence of fibrothecoma among all ovarian tumors is estimated to be 1-4% [3, 9]. Clinically, it may resemble ovarian cancer and be confused with it [10]. Only in 50% of cases, fibrothecoma is correctly diagnosed as benign before the operation [8].

Fibrothecoma is a sex-cord stromal tumor. According to the WHO classification of ovarian tumors, it is in the subgroup of granulosa-theca cell tumors and the thecoma-fibroma group. The average age of women in whom fibrothecoma is diagnosed is 47 and 90% of the patients are 30 years old or younger. In 10-15% of cases, fibrothecoma is accompanied by ascites, in 1% with hydrothorax, and in 40% the tumor is over 10 cm in size [11].

Many case reports notwithstanding, the etiopathogenesis of the syndrome still is not clearly defined [3, 4, 6]. Mechanisms that are suggested, including peritoneum irritation, direct pressure upon lymph nodes, hormonal stimulation, release of inflammatory mediators, are not able to explain the pathogenesis fully [12]. There are reports suggesting that proinflammatory cytokines – interleukin (IL) 6, IL-1β, IL-8, vascular endothelial growth factor (VEGF) and fibroblast growth

factor (FGF) – play an important role in ascites, hydrothorax or pleurocardia [13]. Numerous Meigs' syndrome cases were described as related to increased levels of CA-125 [14]. CA-125 is a glycoprotein, in humans encoded by the MUC16 gene on chromosome 19 [3]. The antigen CA-125 is a tumor marker produced by many human tissues, including the epithelium of the oviduct, ovaries, cervix, uterus and the mesothelial cells of the peritoneum, pericardium and pleura [3]. A slight CA-125 increase in the serum is possible in ovarian fibrothecoma, and its increase is proportional to the advancement of ascites. In the cases of fibrothecomas, very high levels of CA-125 are observed exceptionally rarely. Scholars believe that a CA-125 increase in the serum may be caused by CA-125 expression in the mesothelium rather than by the fibrothecoma.

In the case we report, apart from CA-125, we tested also human epididymis protein 4, HE-4, and assessed the risk of malignancy by means of the ROMA program, which was high. This is the first case in Polish- and English-language literature where a high risk of malignancy in Meigs' syndrome suggested a malignant ovarian tumor. Therefore, the authors suggest that Meigs' syndrome should be remembered in all cases of ovarian cancer accompanied by ascites and/or pleuritis and high CA-125 and HE-4 levels.

## Conclusions

The diagnosis of an ovarian tumor with accompanying ascites and substantially increased levels of tumor markers does not necessarily have to prove ovarian cancer and in rare cases may concern benign lesions of the fibrothecoma type.

## Disclosure

Authors report no conflict of interest.

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