BOHR Journal of Obstetrics and Gynaecology
2023, Vol. 1, No. 1, pp. 10–16
DOI: 10.54646/bjog.2023.02
www.bohrpub.com

CASE REPORTS AND LITERATURE REVIEWS

Meigs syndrome: a case report and literature review

Algeri Paola[1], Seca Marta[2,3]*, Manzoni Marco[4], Clemente Francesco[1], Adorni Marco[1] and Ciammella Massimo[1]

[1]Department of Obstetrics and Gynaecology, Bolognini Hospital, ASST Bergamo EST, Bergamo, Italy
[2]University of Milano-Bicocca, Monza, Italy
[3]Department of Obstetrics and Gynaecology, San Gerardo Hospital, Monza Italy
[4]Department of Pathology, Bolognini Hospital, ASST Bergamo EST, Bergamo, Italy

***Correspondence:**
Seca Marta,
m.seca@campus.unimib.it

Received: 18 July 2023; **Accepted:** 28 July 2023; **Published:** 08 August 2023

Introduction: Meigs syndrome is defined by the presence of an ovarian benign tumor, ascites, and pleural effusion. The restoration of normal conditions following the removal of the ovarian mass is typical. Although an increase in CA 125 has been reported in association with Meigs syndrome, a level above 1000 IU/mL is unusual, and there is no clear association between patients' or tumor/cancer characteristics and CA 125 increment to the best of our knowledge.
Materials and methods: We conducted a review of Meigs syndrome cases associated with high CA 125 levels and then divided and compared all cases found in the literature and the one described in the text, taking into account the increase of CA 125 = 1000 IU/mL, to identify any possible factor influencing the CA 125 increase.
Results: A 55-year-old woman with Meigs syndrome (hydrothorax, ovarian fibroma, and ascites) presented CA 125 of 1713 IU/mL. In our review, we found 43 articles that collected 55 cases of Meigs syndrome with an increase in CA 125 of 25% or more than 1000 IU/mL. Considering two groups, divided considering the CA 125 value of 1000 IU/mL, we found that the presence of bilateral masses and ascites over 2 L represented independent risk factors for high elevation of CA 125.
Conclusion: The presence of bilateral mass and an increase in ascites were associated with an increase in CA 125 of 1000 IU/mL, which could be useful in maintaining a benign lesion hypothesis even if the definitive diagnosis could not be made until after surgery, at histological evaluation.

Keywords: cancer antigen 125, ovarian fibroma, Meigs syndrome, adnexal mass, ascites

Introduction

Meigs syndrome is a rare condition, with 1% of benign ovarian tumors (1). The diagnostic criteria are the presence of a benign mass of the ovary, ascites, and pleural effusion with the restoration of normal conditions after the removal of adnexal formation (2–5); 2–5% of the surgically removed ovarian mass was revealed to be a fibroma, which was associated with ascites in 10–15% and with pleural effusion in 1% of cases (6). The entity of ascites is variable (7), and its origin seems to be correlated to irritation of the peritoneal surfaces, or to pressure on lymphatics or vessels, or to hormonal stimulation, or to release of factors increasing vessel permeability, even if the effective patho-genesis remains unclear (6). The pleural effusion is usually unilateral and is on the right side. A hypothesis regarding its origin, reported in the literature, suspected the passage of ascitic fluid to the pleural space, even if its quantity is independent of the amount of ascites (8). Meigs syndrome is typical of the post-menopausal period, with a peak of incidence at 70 years old; however, there are also cases reported in fertile women (3, 9)). Usually, these patients remain asymptomatic for a long period of time, but, sometimes, virilization, abnormal vaginal bleeding, menstrual irregularity, and precocious puberty could be reported in case of tumors secreting sexual hormones. Furthermore, in the case of a

large mass, symptoms associated with the compression of neighboring organs could be detected. The clinic could be influenced also by the entity of ascites and pleural effusion, demonstrating compressive symptoms, dyspnea, cough, asthenia, and tachycardia (7). There isn't a specific blood test that could guide the diagnosis. An elevation of CA 125 is frequently described. It is expressed not only by the epithelium of the genital tract but also by the pleural and peritoneal mesothelium (6, 10). Although an increase of CA 125 has been reported in association with Meigs syndrome, a level above 1000 IU/mL is exceptional, and nowadays, there is no information about the possible factors influencing this elevation (6). Some studies hypothesized that this increase could be correlated with different mechanisms concerning its mesothelial production, such as the peritoneum irritation due to the compression by the ovarian mass or the pressure exerted by ascites (11–17). A retrospective study, comparing 580 patients with benign ovary mass, found a possible association between an increase of CA 125 > 35 IU/mL, ascites, hydrothorax, and tumor size > 10 cm. In addition, they underlined the likely production of CA 125 by the peritoneal mesothelium (18). In 2009, Benjapabal et al. conducted a literature review that analyzed all cases of Meigs syndrome associated with CA 125 elevation between 1989 and 2007. They reported 18 studies describing 28 cases in which only 6 patients presented CA 125 levels over 1000 IU/mL; however, the authors did not report any hypothetical cause of this increment (6). To the best of our knowledge, there isn't a clear association reported between patients or tumor characteristics and CA 125 over 1000 IU/mL in the literature. Therefore, we decide to share our case, considering the rarity of Meigs syndrome, with the presence of a big adnexal mass, ascites, and a high elevation of CA 125 elevation, suspected to be an ovarian malignancy. Moreover, we conducted a literature review of cases of Meigs syndrome in which an elevation of CA 125 was found, and subsequently, we performed a comparison between the cases (reported in the literature and our study) to evaluate any influencing factor that elevates the increase of CA 125.

Methods

First, we described our case report of an ovary fibroma determining a Meigs syndrome associated with an increment of CA 125. Subsequently, we conducted research in literature in PubMed, EMBASE, Cochrane Library, and Medline, starting with individual case reports, retrospective case series, and reviews concerning Meigs syndrome associated with CA 125 levels over the normal range in peer-reviewed journals. The publication range was from January 1989 to March 2022. Pseudo-Meigs syndrome without ovarian mass or associated with malignancies is not included. Then, we divided all cases found in the literature and our study, considering the increase of CA 125 = 1000 IU/mL or <1000 IU/mL, and we compared the two groups to find the possible factors influencing a high increment of CA 125. Comparisons between the two study groups were performed using Pearson's chi-square test for categorical variables and the one-way ANOVA test for continuous ones. Subsequently, a multivariate analysis was performed, considering the most clinically relevant parameters or the ones significantly different between the two study groups. We used SPSS version 22.0 and the R software version 3.2.20, and a p-value < 0.05 was considered significant.

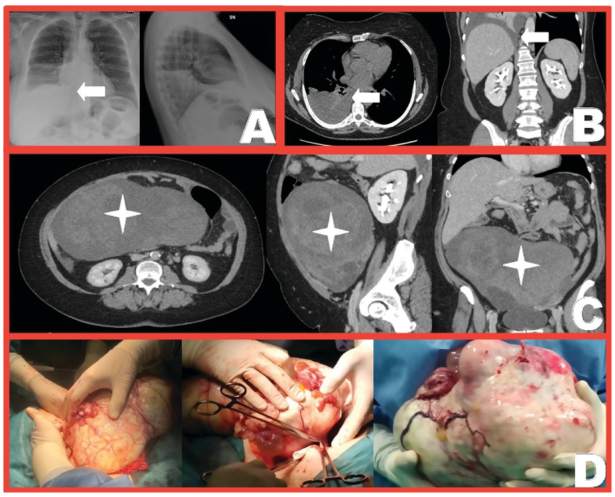

FIGURE 1 | (A) Chest radiography demonstrated a right hydrothorax. **(B)** A CT scan confirmed the right pleural effusion, with atelectasis. **(C)** CT scan detected an adnexal mass of 26 × 14 × 19 cm. **(D)** Surgical images of left mass resulted in a fibroma of 3304 g.

Results

Case presentation

A 55-year-old Caucasian woman was admitted to the emergency room for fever and dyspnea. There were no anamnestic features except for obesity (BMI: 36.5 kg/m^2). She reported two pregnancies with regular course, namely, one delivered vaginally and the other delivered through cesarean. Menopause started 2 years before. The last gynecological evaluation, 8 years earlier, was regular. Her blood test demonstrated an increment of white cell count (12.6 × 10^9/L), C-reactive protein (25.6 mg/dL), and platelets (437 × 10^9/L). Blood culture results were negative. The molecular SARS-CoV19 swab was negative. The electrocardiogram was normal. A thromboprophylaxis therapy and an antibiotic therapy were started. A chest radiography showed a right hydrothorax (**Figure 1A**). A CT scan excluded pulmonary infection and embolism, confirmed the right pleural effusion with atelectasis (**Figure 1B**), and detected an adnexal mass of 26 × 14 × 19 cm (**Figure 1C**). A gynecological visit combined with ultrasound was

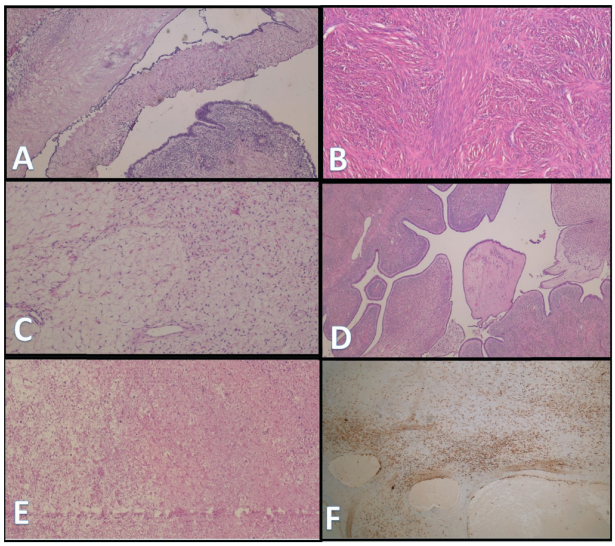

FIGURE 2 | Histopathological evaluation of the ovarian mass. **(A)** Frozen section with a key field to render a diagnosis of cystadenofbroma. **(B)** The fibromatous component was composed of densely stromal areas, and **(C)** more edematous ones. **(D)** Cystadenofbroma had some wide papillae, with bland stroma and regular epithelial lining. **(E)** An area with ischemic and hemor-rhagic changes, possibly due to compression of this part of the mass. **(F)** An active chronic inflammatory infiltrate is evident close to such areas, shown by CD45 (LCA) immunostain.

performed and reported a normal uterus and right ovary, while in the left, dishomogeneous adnexal mass, multilocular, solid, with vascularization at Doppler evaluation was confirmed. Accordingly, she was admitted to the Gynecological Department. CA 125 was 1713 IU/mL. During the hospitalization, she performed a thoracentesis, which removed 1400 mL of pleural effusion, showing a negative result for malignancies. She underwent a colonoscopy, which showed negative findings. After the administration of antibiotics, the fever disappeared, and the blood test improved. She underwent a laparotomy surgery: 700 mL of ascites was detected and sent for cytology, which showed a negative result. The surgeons performed a hysterectomy with bilateral ovariectomy and the intraoperative diagnosis of the removed left adnexal mass was consistent with a cystadenofbroma of 3304 g (**Figure 1D**). Blood loss was 50 mL. The postoperative course was regular. The follow-up was negative, with a normalization of CA 125.

Histopathological finding

Grossly, the huge mass was characterized by a predominantly solid component, with a few small superficial cysts filled with citrine limpid fluid, with occasional small vegetations. The cut surface was fasciculated and whitish, with only small cystic spaces inside. A minor part of the mass was slightly darker, with seemingly bland ischemic features, possibly consequent of compression due to the large size. On frozen sections, depicted in **Figure 2A**, the findings were consistent with a cystadenofbroma. The histological finding showed a spindle cell tumor with bland cytological features, often with edematous stromal areas. Sections of the cysts showed a benign-looking lining epithelium with regular papillae (**Figure 2A**). On permanent sections, depicted in **Figures 2B–F**, the histological findings confirmed the intraoperative diagnosis of papillary cystadenofbroma. As said, part of the fibroma had a dense stroma, and other areas were frankly edematous (**Figures 2B, C**). The small cysts, both superficial and internal, were lined by a bland-looking epithelium consistent with that of a cystadenoma, often with some papillae (**Figure 2D**). The grossly suspected ischemic features were confirmed (**Figure 2F**), with a small part of the fibromatous cells showing necrosis, ischemic changes, and a moderate chronic active inflammatory infiltrate [**Figure 2F**, CD45 (LCA) immunostaining]. In this approach, combine all your researched information in the form of a journal or research paper. In this, the researcher can take the reference of already accomplished work as a starting building block of the paper.

Literature review

Our literature review found 43 articles (41 full texts and 2 abstracts), collecting 55 cases of Meigs syndrome with an increment of CA 125, resumed in **Table 1**. In addition to our patient, we reported 56 cases. The mean of the CA 125 level was 1112.35 ± 944.20 IU/mL, with 14 (25%) cases presenting an increment over 1000 IU/mL. The mean age of patients was 53.48 ± 16.97 years. In 27 (48.2%) cases, a unilateral adnexal mass was reported, with a mean of bigger tumor diameter of 15.73 ± 5.94 [other 10 cm in 44 (78.6%) cases]. Different histological types of mass such as fibroma and fibrothecoma (39 cases, 69.6%) were found. The ascites was found in 51 (91.1%) cases, while pleural effusion was found in 31 (55.4%) cases; moreover, in 23 (41.1%) cases, it was observed on the right side.

Retrospective analysis

We compared two groups, divided considering the CA 125 values: 42 patients with CA 125 < 1000 IU/mL were grouped under the first group, and 14 patients with CA 125 = 1000 IU/mL were grouped under the second group. **Table 2** shows the characteristics of the two study groups; they reported similar age, mass diameters, presence of ascites and hydrothorax, hydrothorax localization and its quantity. The groups did not differ significantly in the histological classification of ovarian masses. The group with elevated CA 125 = reported a higher incidence of the bilateral lesion (21.4 vs 2.4%, p = 0.04) and a bigger amount of ascites

TABLE 1 | Literature review.

References	Age	Ovarian mass diameters	Right (R) or left (L) ovarian mass	Ascites (Yes/No); entity (ml)	Pleural Effusion (Yes/No); Entity (ml)	CA 125 levels (IU/mL)	Histology of ovarian tumor
Hoffman 1989 (only abstract available)	32	Large	\	NR	NR	498	Thecoma
Jones 1989	70	8 × 8 cm	\	NR	Y (right); 1200	226	Fibrothecoma
Martin 1990	**55**	14 cm	R	N	Y(right); N/V	307	Granulosa cell tumor
Walker 1990	52	16 × 4 × 8 cm	R	Y; 4500	Y (bilateral); N/V	5000	Fibroma
	67	18 × 15 × 10 cm	\	Y; 3000	N	104	Fibroma
Le Bouedec 1992 (only abstract available)	**66**	NR	\	NR	NR	645	Fibroma
	76	NR	\	NR	NR	286	Thecoma
Lin 1992	74	15 × 10 × 10 cm	L	Y; NR	Y; NR	2120	Fibroma
	72	13 × 10 × 9 cm	\	Y; 6000	Y(right); small amount	7000	Fibroma
William 1992	74	15 × 9 × 10 cm	\	Y; 300	N	329	Thecoma
Turan 1993	63	18 × 9 × 15 cm	L	Y; NR	Y(bilateral); NR	743.6	Thecoma
Siddiqui 1995	73	10 × 15 × 13 cm	\	Y; NR	Y (right); NR	1780	Fibroma
Timmerman 1995	71	3 × 2 × 1 cm	L	Y; 1000	Y(right); NR	484.5	Fibroma
	73	19 × 17 × 9 cm	L	Y; 500	NR	42.3	Fibroma
Abad 1999	51	5.6 × 5 cm and 4.4 × 4 cm	Bilateral	Y; 5000	Y(bilateral); NR	577	Fibroma
Chan 2000	13	20 × 19 × 10 cm	L	Y; 2000	Y (right); NR	970	Fibroma
Patsner 2000	62	10 cm	\	Y; 300	NR	185	Fibroma
	57	14 cm	\	Y; 1000	NR	850	Fibroma
	48	11 cm	\	Y; 30	NR	36	Fibroma
	52	16 cm	\	Y; 1500	NR	520	Fibroma
	60	14 cm	\	Y; 100	NR	64	Fibroma
	72	18 cm	\	Y; 1500	NR	1200	Fibroma
	58	18 cm	\	Y; 100	NR	80	Fibroma
Buttin 2001	67	12 × 10 × 6 cm	L	Y; 3500	Y (right); NR	759	Brenner tumor
Lopes Sanchez 2002	78	20 × 8 × 20 cm	L	Y; 500	Y (right); 1500	498	Fibroma
	68	14 × 10 × 18 cm	\	Y; NR	Y (right); 1300	265	Fibroma
Vieira 2003	65	14 × 12 × 8 cm	L	Y; NR	Y (left); NR	319	Thecoma
Moran Mendoza 2006	46	25 cm	\	Y; NR	Y; NR	1808	Fibroma
Benjapibal 2009	56	14 × 12 cm	R	Y; 2500	Y (right); 1500	1.064	Fibroma
Rana 2009	70	9.4 × 9.1 × 6.8 cm	L	Y; NR	Y(bilateral); NR	284	Bilateral struma ovarii
Amorim Costa 2010	63	6 cm and 4 cm	Bilateral	Y; 8000	Y; NR	2168	Sclerosing stromal tumor of the right ovary; Serous cystadenoma of the left ovary
Jia-Hung Liou 2011	18	16.5 cm	R	Y; 9000	Y (right); NR	4208.3	Sclerosing stromal tumor
Monteiro 2012	13	16 × 15 cm	R	Y;3000	Y (right); 1600	453	Fibroma
Anastasilakis 2013	49	15 cm	R	Y; NR	Y; NR	444.7	Teratoma
Iyer 2013	28	13.5 cm	L	Y; NR	Y; NR	368	Fibroma
Riker 2013	54	11.8 × 13.4 cm	\	Y; NR	Y (right); NR	238	
Serges Loué 2013	35	23.3 × 20 cm and 11.5 × 9 cm	Bilateral	Y; 7000	Y; 500	1835	Fibrothecoma
Su 2013	53	12.2 × 9 × 10.7 cm	\	Y; small amount	Y (right); NR	222	Fibrothecoma

(Continued)

TABLE 1 | (Continued)

References	Age	Ovarian mass diameters	Right (R) or left (L) ovarian mass	Ascites (Yes/No); entity (ml)	Pleural Effusion (Yes/No); Entity (ml)	CA 125 levels (IU/mL)	Histology of ovarian tumor
Yueh-Yi Chen 2013	52	30 × 30 cm	\	Y; NR	Y (left); NR	269.8	Intestinal type mucinous borderline tumor
Cha 2014	52	18.5 × 17.5 × 17.3 cm	L	Y; 1400	Y (right); NR	319.2	Fibrothecoma
Yazdani 2014	50	9 × 10.9 cm	L	Y; NR	Y (left); NR	>600	Fibrothecoma
Danilos 2015	50	10 × 9.3 × 9 cm	L	Y; 5000	N	2310	Luteinized fibrothecoma
Fremed 2015	13	17 × 19 cm	R	N	Y (bilateral); NR	176	Fibroma
Jung-Woo Park 2015	61	12 × 11 cm	L	Y; NR	Y (right); NR	347	Thecoma
Sánchez-Torres 2016	55	15.7 × 8.6 × 10.7 cm and 4.9 cm	Bilateral	Y; NR			
Sofoudis 2016	61	10.9 × 10.9 × 9.6 cm	R	Y; NR	Y; NR	210.1	Fibroma
Yadav 2017	55	6 × 5 × 5 cm	L	Y; 500	N	258	*Struma ovarii*
Ayumi Yaguchi 2020	37	27 × 15 × 13 cm	\	Y; 8050	Y; NR	331.8	Mature teratoma
Navarro-Esteva 2020	59	21 cm and 3 cm	Bilateral	N	Y (right); NR	1000	Fibroma
	48	NR	R	Y; NR	Y; NR	526	Granulosa cell tumor
Dellaportas 2021	46	22 × 21 × 18 cm	L	Y; 4000	Y; NR	938	Fibrothecoma
Hou 2021	52	13 × 15 cm	R	Y; NR	Y (right); NR	663.3	Fibrothecoma
Li 2021	19	29.2 × 11.8 × 8.4 cm	L	Y; small amount	Y; large amount in right pleura; small one in left pleura	410.7	Dysgerminoma
Palmieri 2021	24	26 cm	\	Y; NR	Y (bilateral); NR	2124	Fibroma
Wu 2021	52	11.6 × 10 × 12.4 cm	\	N	Y (right); modest volume	150.8	Granulosa cell tumor

Y: yes; N: no; NR: not reported.

(4911.1 ± 2897.6 mL vs 1814 ± 2073 mL, p = 0.003). The results of the multivariate analysis are described in **Table 3**. In particular, the presence of bilateral masses and the ascites over 2 L represented independent risk factors for the elevation of CA 125 over 1000 IU/mL, while no influence seems to be reported by the tumor dimension, the presence of ascites or hydrothorax, and the histological origin of the mass. Specifically, bilateral masses increase the possibility to find an important increment of CA 125 over 1000 IU/mL of 13 times and the ascites quantity over 2 L of 6 times.

Discussion

Ovarian fibroma is the most common tumor found in the case of Meigs syndrome, associated with ascites in 10–15% and with pleural effusion in 1% of cases (1, 6). Our review of literature collecting 43 articles (55 cases) of Meigs syndrome with CA 125 over the normal range confirmed that this condition the post-menopausal period (3, 9) and that it is correlated most frequently with fibroma or fibrothecoma more than other histotypes. Only 14 out of 56 patients (55 cases reported in the literature and 1 case in our study) presented a CA 125 over 1000 IU/mL, which is a rare condition (6, 11–17). In our comparison, we associated the increment of CA 125 of over 1000 IU/mL with a higher incidence of the bilateral lesion and a bigger amount of ascites (over 2 L), even if the presence of ascites itself is not a risk factor for the increment of CA 125. At multivariate analysis, we confirmed the univariate results: we found that bilateral masses increment by 13 times and the ascites quantity over 2 L increment by 6 times the possibility, to detect an important increment of CA 125 over 1000 IU/mL. To the best of our knowledge, this is the first review that tried to define an association between patient/mass characteristics and high increment of CA 125.

We are aware that using data from the literature could be a bias, but the strength of our paper is to try to define a connection between the pelvic mass elevation of CA 125 and patients' characteristics in order to better understand the disease. Only a previous retrospective study that compared 580 patients with benign ovary masses showed an association between an increase of CA 125 > 35 IU/mL, ascites, hydrothorax, and tumor size > 10 cm, but it did not report possible factors determining a high increment of CA 125 (18). Our study is a comparison between masses collected by

TABLE 2 | Population characteristics.

	CA 125 < 1000 IU/mL *n* = 42	CA = 1000 IU/mL *n* = 14	*P*-value
Patient age (years)	53.5 ± 16.9	53.5 ± 17.9	0.99
CA 125 level (IU/mL)	393.8 ± 237.2	2523.6 ± 1707.5	**0.000**
Maximum mass diameter	15.1 ± 5.8	17.5 ± 6.1	0.21
Diameter > 10 cm	32 (76.2%)	12 (85.7%)	1
Unilateral side of ovarian mass	22 (52.4%)	5 (35.7%)	**0.04**
Right localization	8 (19.0%)	2 (14.3%)	1
Bilateral ovarian masses	1 (2.4%)	3 (21.4%)	**0.04**
Histological classification			0.30
Teratoma	2 (4.7%)	0	
Dysgerminoma	1 (2.4%)	0	
Fibroma	19 (45.2%)	10 (71.4%)	
Fibrothecoma	8 (19.0%)	2 (14.3%)	
Thecoma	5 (11.9%)	0	
Borderline tumor	1 (2.4%)	0	
Brenner tumor	1 (2.4%)	0	
Granulosa cell tumor	3 (7.1%)	0	
Struma ovarii	2 (4.7%)	0	
Strumal tumor	0	2 (14.3%)	
Presence of ascites	37 (88.1%)	13 (92.9%)	1
Quantification of ascites (ml)	1814 ± 2073	4911.1 ± 2897.6	**0.003**
Presence of hydrothorax	20 (47.6%)	11 (78.6%)	0.17
Quantification of hydrothorax (ml)	1580 ± 432.4	1133.3 ± 550.8	0.25
Right hydrothorax	17 (40.5%)	6 (42.9%)	1
Bilateral hydrothorax	4 (9.5%)	2 (14.3%)	1

TABLE 3 | Multivariate regression analysis—influencing factors for CA 125 elevation over 1000.

	OR (95% CI)
Bilateral tumor	13.2 (1.13–154.92)
Tumor dimension over 10 cm	1.1 (0.19–6.36)
Presence of ascites	1.1 (0.10–11.05)
Ascites quantifications over 2 L	6.5 (1.05–40.13)
Presence of hydrothorax	3.58 (0.68–18.81)
Different histological origin	1.25 (0.70–2.24)
Fibroma at histological evaluation	1.88 (0.36–9.83)

33 years of literature review, with a lack of some patients' data and possible confounding factors in the older paper, which are certain study biases However, the power of the review and our analysis concerning the rarity of Meigs syndromes, moreover in case of high elevation of CA 125, with difficulties in the possibility to collect an adequate number of cases. Therefore, we think that our contribution could be helpful in pre-surgery hypothesis; even in case of bilateral mass and high amount of ascites, a possibility of benignity could be maintained considering our results. Certainly, the differential diagnosis must be performed after surgery, with histological evaluation of the mass, to exclude malignancies; however, in case of ascites, pleural effusion, ovarian mass, or high increment of CA 125, the physician should shift malignant and benign mass hypothesis, especially in the absence of malignancy characteristics of tumor at the ultrasound and the absence of pelvic and peritoneal metastasis, omental cake, and lymph nodes involvement.

Conclusion

Meigs syndrome is a rare condition, which frequently mimics ovarian cancer. However, a possible hypothesis of a benign tumor, even if ovarian cancer must be suspected, could be maintained, moreover if there are no other malignancies characteristics. Indeed, we found that the presence of a bilateral mass and an elevated amount of ascites, typically found in ovarian cancer, determine a high increase of CA 125 in a benign condition like Meigs syndrome. This article guides a stepwise walkthrough by experts for writing a successful journal or a research paper starting from the inception of ideas till their publication. Research papers are highly recognized in the scholar fraternity and form a core part of PhD curriculum. Research scholars publish their research work in leading journals to complete their grades. In addition, the published research work also provides a big weightage to get admissions in reputed varsity. Now, in this study, we enlist the proven steps to publish the research paper in a journal.

Author contributions

AP wrote the manuscript and collected the data. SM collected the data and revised the manuscript. MM gave pathological information and revised the manuscript. CF performed the surgical and clinical management of the patient. AM revised the manuscript and managed the patient. CM performed the surgical and clinical management of the patient.

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