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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 196–200
www.tjog-online.com

Case Report

Meigs' syndrome with elevated serum cancer antigen 125 levels in a case of ovarian sclerosing stromal tumor

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Accepted 12 February 2010

Abstract

Objective: Meigs' syndrome presenting as an ovarian tumor with elevated serum cancer antigen 125 (CA 125) levels is unusual. Only 37 cases have been reported, including three cases of ovarian sclerosing stromal tumor (SCT). Many reports have suggested that the presence of ascites is the major factor inducing mesothelial expression of CA 125.
Case Report: An 18-year-old woman presented with massive ascites, elevated serum CA 125 levels, and radiographic evidence of ovarian tumor. The histological and immunohistochemical examinations revealed a benign SCT.
Conclusion: SCT is a benign ovarian tumor and complete excision is curative. We also review all 37 cases and discuss possible mechanisms of Meigs' syndrome and elevated serum CA 125 level.

Keywords: CA 125; Meigs' syndrome; Ovary; Sclerosing stromal tumor

Case report

An 18-year-old woman presented to the gastroenterology and hepatology outpatient department with a 6-month history of abdominal fullness, poor appetite, body weight loss, and irregular menses. Physical examination revealed abdominal distension, shifting dullness, and herniation of the umbilicus. There was no clinical or laboratory evidence of active excess hormone secretion. Ultrasonography revealed a 16.5-cm pelvic mass and massive ascites (Fig. 1). Computed tomography revealed right pleural effusion with atelectasis in the right lower lung (Fig. 2A), a rounded mass in the pelvic region measuring 15 cm × 14 cm × 10 cm in size, and massive ascites (Fig. 2B). There was no evidence of lymphadenopathy or metastatic lesions. Laboratory tests revealed high serum cancer antigen 125 (CA 125) levels (4,208.3 IU/mL); other tumor markers (alpha fetoprotein: 1.17 ng/mL; carcinoembryonic antigen: 0.7 ng/mL; and cancer antigen 19-9: 22.86 U/mL) were within normal limits. Large-volume paracentesis procured 9,000 mL of clear yellow transudate. Cytologic analysis of ascitic fluid was negative for malignant cells. Exploratory laparotomy revealed a large right ovarian tumor with a smooth surface without intrabdominal carcinomatosis. Intraoperative examination of frozen sections of the right ovarian tumor demonstrated a benign stromal tumor, and a right salpingo-oophorectomy was performed. On gross examination, the specimen consisted of a 890-g ovarian tumor measuring 14.5 cm × 13 cm × 9.5 cm attached to an unremarkable fallopian tube. The external surface was grayish white and glistening. The solid-cystic tumor was yellow, white, and solidly firm, with areas of myxoid and cystic change (Fig. 3A). No necrosis was present. Microscopically, the ovarian tumor was composed of a pseudolobular arrangement of tumor cells with alternating hypercellular and hypocellular areas (Fig. 3B). The tumor cells were spindle to polygonal in shape with eosinophilic to vacuolated cytoplasms, bland nuclei, and low levels of mitotic activity (Fig. 3C). Hemangiopericytoma-like vessels, myxoid to fibrotic stroma, and focal cystic

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2011.01.011

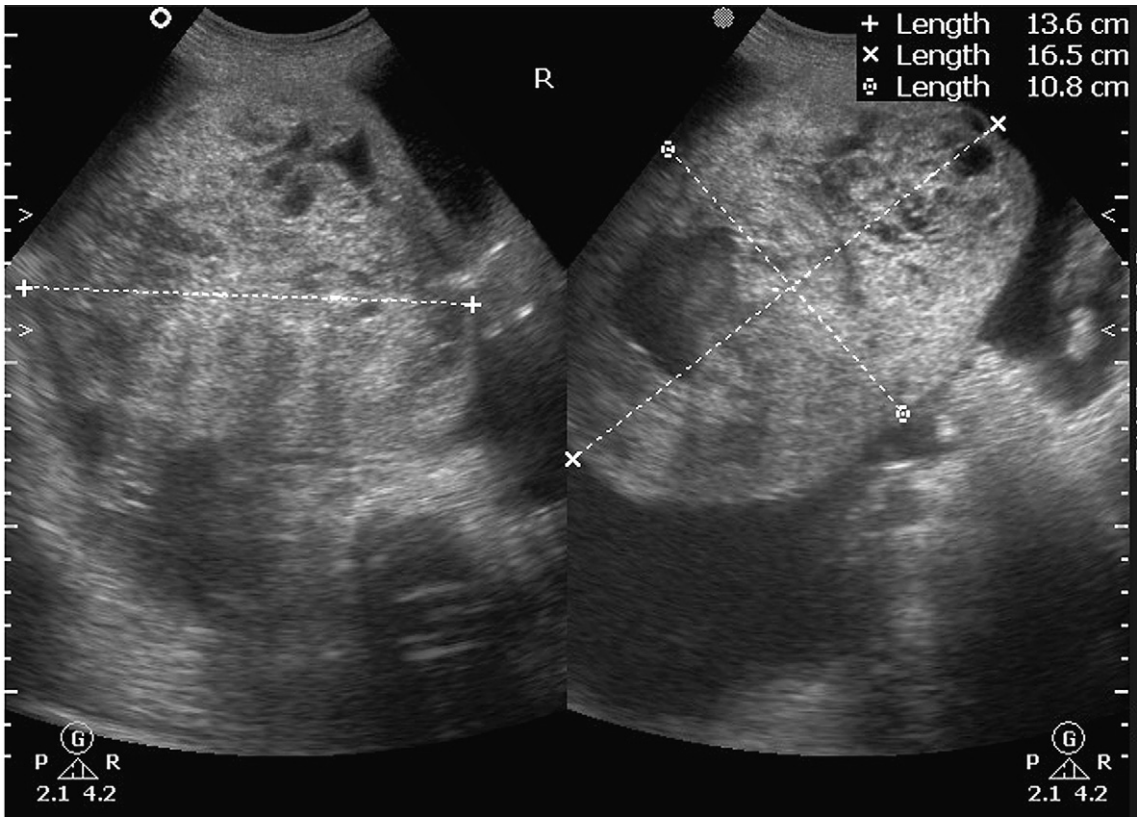

Fig. 1. Abdominal ultrasonography shows a 16.5 cm × 13.6 cm × 10.8 cm solid mass in the right adnexa with focal cysts inside the tumor. A large volume of ascitic fluid is also visible.

change were noted. The tumor was immunopositive for α-inhibin (Fig. 3D) and immunonegative for CA 125 and cytokeratin. The pathologic diagnosis was a sclerosing stromal tumor (SST).

The postoperative course was uneventful; the serum CA 125 level returned to normal and the ascites resolved.

Discussion

In 1989, Jones and Surwit [1] reported on a patient with Meigs' syndrome associated with fibroma-thecoma of the ovary and elevated CA 125 levels. Since then, 37 cases have been reported [1–26], including three with SSTs (Table 1).

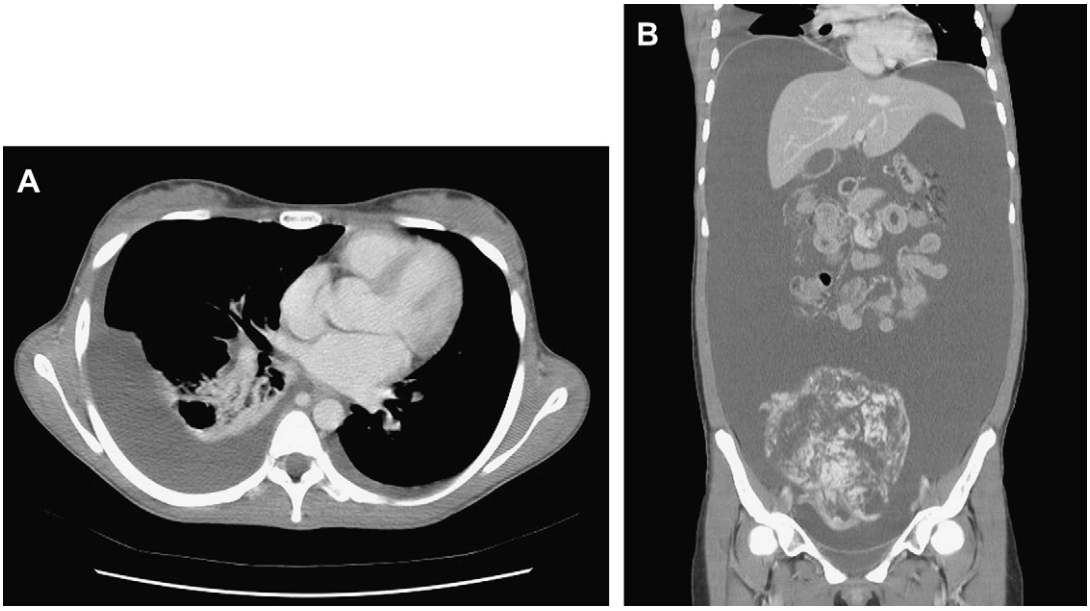

Fig. 2. Right-sided pleural effusion with atelectasis in the right lower lung. (A) Contrast-enhanced computed tomography scan demonstrates a 15 cm × 14 cm × 10 cm rounded pelvic mass with a solid component and (B) hypodense areas accompanied by massive ascites.

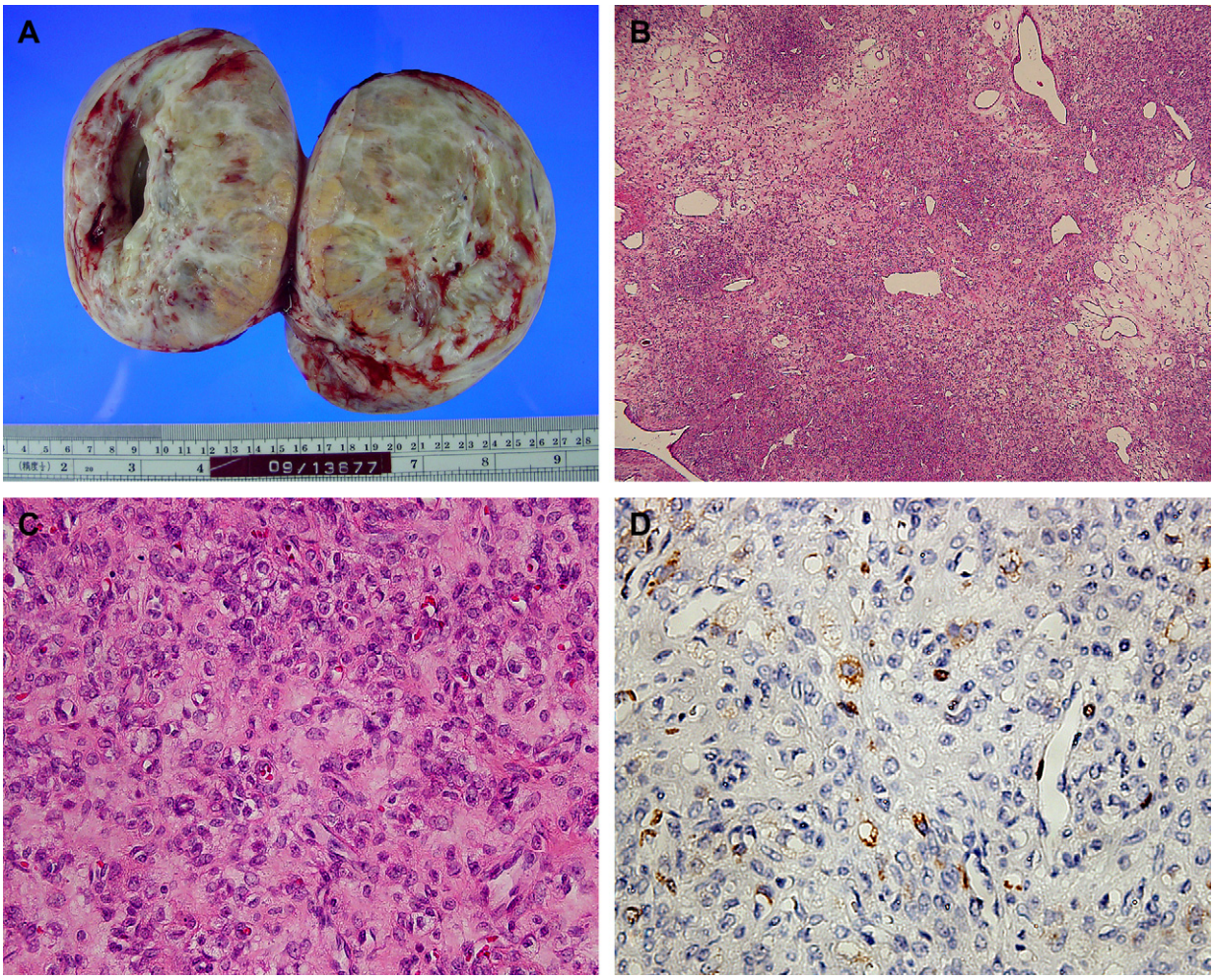

Fig. 3. (A) Gross examination of the sclerosing stromal tumor reveals a primarily solid tumor with grayish-white and yellow nodular areas with edematous change. (B) Pseudolobular pattern with cellular nodules separated by less cellularly dense fibrous or edematous areas and hemangiopericytoma-like branching vessels [hematoxylin and eosin (HE) stain ×40]. (C) Cellular nodules composed of fibroblast-like cells and rounded vacuolated cells (HE stain ×400). (D) Tumor cells were immunopositive for α-inhibin.

Herein, we report on the fourth known case of Meigs' syndrome associated with SST of the ovary.

SSTs account for only 2.5% of ovarian sex cord-stromal tumors. Unlike other sex-cord stromal tumors, which typically develop in the fifth and sixth decades of life, SSTs often present in the second and third decades of life and approximately 80% of cases present in patients younger than 30 years. Most cases of SST are benign and unilaterally right sided. No cases of recurrent disease after complete excision have been reported.

In 1937, Meigs and Cass [27] published a report on seven patients presenting with a triad of findings: ovarian tumor, pleural effusion, and ascites characterized by resolution of symptoms with removal of the tumor. In 1954, Meigs [28] proposed that the classification of Meigs' syndrome be restricted to benign and solid ovarian tumors with the gross appearance of a fibroma (fibroma, thecoma, granular cell tumor, or benign Brenner tumor) in patients with nonmalignant ascites or/and hydrothorax that resolves after removal of the tumor. When other ovarian tumors (metastatic or primary malignant tumors or uterine or fallopian tube tumors) are found in association with the criteria of Meigs' syndrome, the term pseudo-Meigs' syndrome is used.

The mechanisms by which peritoneal and pleural effusion develop in both Meigs' and pseudo-Meigs' syndromes are not fully understood. Meigs and Cass [27] suggested that irritation of the peritoneal surface by a hard, solid ovarian tumor or leakage from the edematous stroma of a tumor could stimulate the production of peritoneal fluid. Other possible mechanisms described by other investigators include active fluid secretion by the tumor, obstruction or congestion of peritoneal lymphatics and veins by the tumor [12], and increased permeability of the neovasculature and transudation through the tumor surface that exceeds the capacity for reabsorption. More recently, reports have suggested that the mesothelium is the main factor in the production of ascites [7].

CA 125, identified in 1981 by Bast et al [29], is an antigenic determinant of a high–molecular weight glycoprotein and is now the most widely studied serum biomarker for ovarian tumors. Although as many as 50% of Stage I and more

Table 1
Reported cases of Meigs' syndrome with preoperative serum CA 125 levels

Author	Year	Patient age	Histopathology	Tumor size (cm)	CA 125 (U/mL)	Ascites (mL)
Jones and Surwit [1]	1989	70	Fibroma/thecoma	11 × 9 × 8	226	1,200
Hoffman [2]	1989	32	Thecoma	11 × 11 × 7	498	NR
Martin et al [3]	1990	NR	Granulosa cell tumor	NR	307	NR
Walker et al [4]	1990	52	Cellular fibroma	16 × 4 × 8	>5,000	4,500
		67	Cellular fibroma	18 × 15 × 10	104	3,000
Le Bouëdec et al [5]	1992	66	Fibroma/thecoma	15	645	NR
		76	Fibroma/thecoma	12	286	NR
Williams et al [6]	1992	74	Luteinized thecoma	15 × 10 × 9	329	300
Lin et al [7]	1992	74	Fibroma	20 × 12 × 12	2120	7,000
		72	Fibroma	14 × 8 × 7	7,000	6,000
Turan et al [8]	1993	63	Thecoma	18 × 9 × 5	744	NR
Timmerman et al [9]	1995	71	Fibroma	30 × 20.5 × 10	484.5	1,000
		73	Fibroma	19 × 17 × 9	42.3	500
Aoshima et al [10]	1995	33	Brenner tumor	NR	71	NR
Siddiqui and Toub [11]	1995	73	Cellular fibroma	15 × 13 × 10	1,780	NR
Abad et al [12]	1999	51	Cellular fibroma	6 × 5	577	5,000
Chan et al [13]	2000	13	Fibroma	20 × 19 × 10	970	2,100
Patsner [14]	2000	62	Fibroma	10	185	300
		57	Fibroma	14	850	1,000
		52	Fibroma	16	520	1,500
		60	Fibroma	14	64	100
		72	Fibroma	18	1,200	1,500
		58	Fibroma	18	80	100
Bretelle et al [15]	2000	71	Fibrothecoma	7 × 6.6	2,610	NR
Buttin et al [16]	2001	67	Brenner tumor	11 × 9 × 6	759	3,500
Massoni et al [17]	2001	33	Fibrothecoma	17.5 × 11.5	752	3,200
López et al [18]	2002	78	Fibroma	22 × 8.5 × 20	498	NR
		68	Fibroma	18 × 14 × 10	265	NR
Huang et al [19]	2003	31	Sclerosing stromal tumor	7 × 6 × 6	396	1,300
Vieira et al [20]	2003	65	Thecoma	14 × 12 × 8	319	NR
Bildirici et al [21]	2003	17	Sclerosing stromal tumor	25 × 18 × 15	193	400
Cissé et al [22]	2004	25	Fibroma	15 × 11 × 9.8	482	NR
Choi et al [23]	2005	69	Granulosa cell tumor	12 × 10 × 6	82	2,500
Jung et al [24]	2006	50	Sclerosing stromal tumor	19 × 13 × 10	1,476	NR
Morán-Mendoza et al [25]	2006	46	Fibroma	25 × 23 × 19	1,808	500
Kaur et al [26]	2009	12	Juvenile granulosa cell tumor	10 × 10	708	NR
Current report	2009	17	Sclerosing stromal tumor	14.5 × 13 × 9.5	4,208	9,000

CA 125 = cancer antigen 125; NR = not reported.

than 90% of advanced-stage ovarian cancers are associated with an elevated serum level of CA 125, the specificity of the CA 125 determinant is low, as increased levels have also been found in cases of adenocarcinoma of the endocervix, endometrium, and fallopian tube; nongynecological malignancy (e.g. pancreas, colorectum, breast, lung, and liver); multiple benign diseases; and conditions, such as endometriosis, uterine myoma, pelvic inflammatory disease, early pregnancy, ascites, liver cirrhosis, heart failure, and inflammation of the pleura and peritoneum [30].

The precise mechanism of serum CA 125 level elevation is still unclear. Some tumors express CA 125, which is absorbed into the circulation resulting in elevated serum levels. Insult to or inflammation of the peritoneum or pleura have been observed to give rise to elevated serum CA 125 levels, possibly through the stimulation of mesothelial cells to produce CA 125. Increased intrabdominal pressure caused by tumor growth may also elicit mesothelial expression of CA 125 [9]. In our review of the 37 reported cases of Meigs' syndrome with elevated serum CA 125 levels in which immunohistochemical staining of the tumor for CA 125 was performed, we found that none of the tumor specimens were positive for that determinant. Immunohistochemical analysis revealed that CA 125 was expressed at the peritoneal and omental surface, rather than in the tumor bed, in most cases [7,9,16]. Therefore, mesothelial expression of CA 125, rather than expression by the tumor itself, may be a major factor resulting in elevation of serum CA 125 levels in patients with Meigs' syndrome.

Ascites and pleural effusion have also been found to be correlated with elevated serum CA 125 levels. In a study of patients undergoing chronic hemodialysis, serum CA 125 levels were significantly higher in patients with the presence of serosal fluid than in patients without the presence of serosal fluid [31]. Zuckerman et al [32] also noted that in liver cirrhotic patients with ascites, elevated serum CA 125 levels were correlated with ascitic volume, and rapid decline in this marker was observed after large-volume paracentesis. Reports of CA 125 assessment in patients with benign stromal tumors without ascites describe levels lower than 35 U/mL; however,

in patients with ascites, the CA 125 levels are much higher (range 500−5,000 U/mL) [33]. Mezger et al [34] found a significant linear correlation between volume of effusion and serum CA 125 values in both benign and malignant diseases, including some tumor types not known to produce the antigen. Patsner [14] also described a correlation between CA 125 elevation and volume of ascites in patients with Meigs' syndrome. After reviewing the 25 of the 37 cases of Meigs' syndrome with elevated serum CA 125 levels in which ascitic fluid volumes were reported, we found that the volume of ascites was positively correlated with higher levels of CA 125 (mean 1,577 U/mL *vs.* 337 U/mL when using 1,000 mL as the cutoff point), but that tumor size was not linearly associated with CA 125 values. With the exception of one case of Meigs' syndrome with underlying systemic lupus erythematosus, peritoneal or pleural effusion was the only factor contributing to the elevated CA 125 levels in the reported cases. That evidence indicates that effusion is also a major factor influencing serum CA 125 level. In conclusion, although elevation of serum CA 125 in association with a solid pelvic mass and ascites is suggestive of an ovarian malignancy, SST of the ovary associated with Meigs' syndrome is also a diagnostic possibility, especially in young patients. The mechanism by which effusion develops in Meigs' syndrome is not fully understood. In Meigs' syndrome, the elevation of serum CA 125 levels may result from mesothelial expression rather than tumor expression of that tumor marker. The presence of ascites is a major factor contributing to mesothelial expression of CA 125, and expression level is correlated with ascites volume.

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