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Primary Malignant Melanoma Arising in an Ovarian Mature Cystic Teratoma – A Case Report and Literature Review –

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Ovarian primary malignant melanoma is very uncommon with only 44 reported cases in the literature. A 71-year-old woman with an ovarian mass and multiple nodules in the liver presented to our hospital. She was treated with bilateral salpingo-oophorectomy, and malignant melanoma was found in the mature cystic teratoma of the ovary. Malignant melanoma cells were also found in the ascitic fluid. She died 5 months later. Here we report a very uncommon case of malignant melanoma arising in an ovarian mature cystic teratoma with a review of the literature.

Key Words: Melanoma; Teratoma; Ovary

Malignant melanoma involving the ovary is uncommon. Most of the reported ovarian malignant melanomas are metastatic, and only 44 cases are primary.[1-18] Teratoid elements must be identified in the ovary for the diagnosis of primary malignant melanoma because ovaries normally do not contain melanin-producing cells.[4] However, it is challenging to assess the primary site of ovarian malignant melanoma because it is almost always found in an advanced state, replacing entire ovarian structures, and this makes it difficult to determine whether the lesion is a primary ovarian melanoma.

Mature cystic teratoma is the most common benign germ cell tumor of the ovary, and it constitutes 15-25% of ovarian tumors overall. A wide variety of malignant tumors may arise within a mature cystic teratoma, including squamous cell carcinoma (75%), adenocarcinoma (7%), undifferentiated carcinoma, basal cell carcinoma, and various sarcomas (7%). Malignant melanoma arising from mature cystic teratoma has also been reported, but it is very rare.

Here, we report on an uncommon case of primary malignant melanoma arising from a mature ovarian cystic teratoma with multiple metastatic lesions.

CASE REPORT

Clinical and radiological findings

A 71-year-old woman presented with general weakness, weight loss of three kilograms over a three-month period, and a one-month history of lower back pain. Past medical and family histories were unremarkable. Physical examination revealed a palpable mass in the lower abdomen. Laboratory findings on admission showed anemia (hemoglobin 8.4 g/dL), markedly elevated lactate dehydrogenase (LDH, 1,935 IU/L; normal range,

0 to 480 IU/L), and mildly increased cancer antigen 125 (47.3 U/mL) and carcinoembryonic antigen (8.3 ng/mL). Abdominal computed tomography revealed numerous hypodense nodules in the liver (Fig. 1A), a small nodule in the left adrenal gland, and a 15 cm sized septate cystic mass with multiple internal fatty components in the pelvic cavity. Magnetic resonance imaging findings of the pelvic mass were suggestive of ovarian mature cystic teratoma (Fig. 1B) but the nodules in the liver

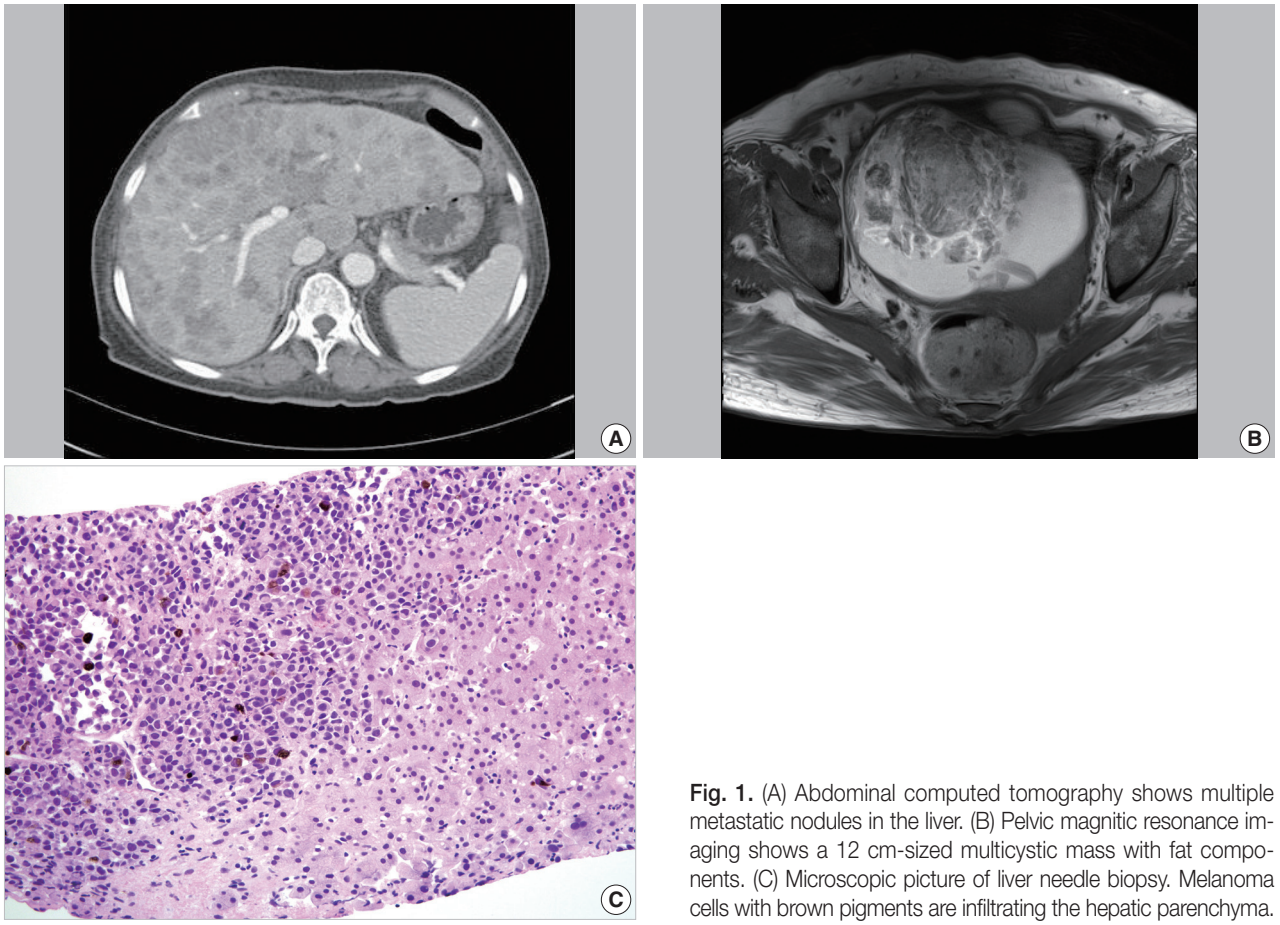

Fig. 1. (A) Abdominal computed tomography shows multiple metastatic nodules in the liver. (B) Pelvic magnitic resonance imaging shows a 12 cm-sized multicystic mass with fat components. (C) Microscopic picture of liver needle biopsy. Melanoma cells with brown pigments are infiltrating the hepatic parenchyma.

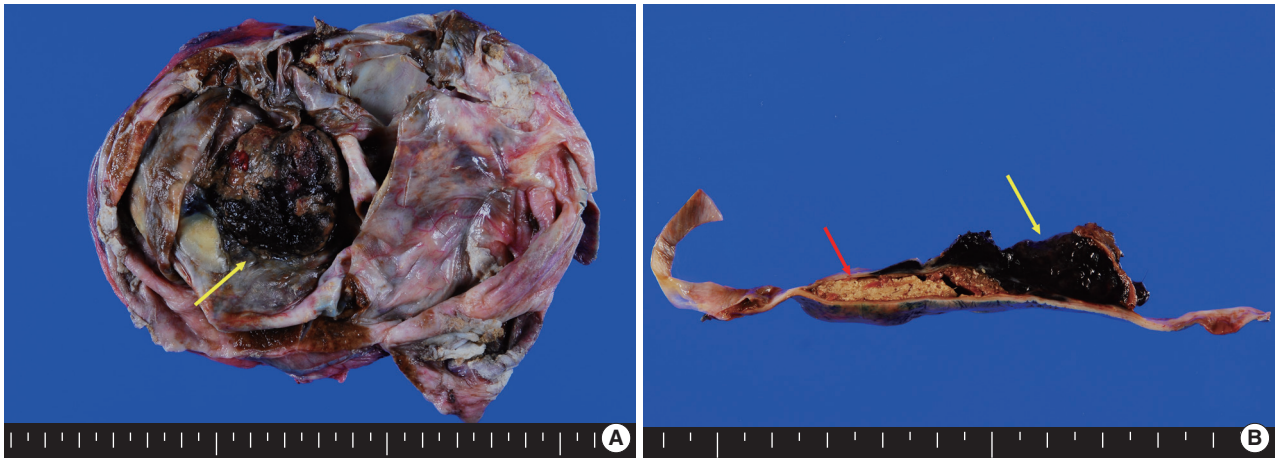

Fig. 2. (A) Internal surface of the ovarian cyst. A dark black elevated mass (arrow), measuring 6.5×6 cm, is seen. Adjacent cystic wall is of the mature cystic teratoma. (B) The cut surface of the mass. Dark pigmented area (yellow arrow) is seen with fatty area of the teratoma component (red arrow).

and adrenal glands were more likely metastatic. The possibility of ovarian malignancy arising in a mature teratoma was considered. A liver biopsy was performed, and in order to determine the primary tumor site and tumor stage, the patient underwent bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, left adrenalectomy, and appendectomy.

Pathologic findings

Liver biopsy

The histologic features of the liver biopsy revealed a proliferation of spindle-shaped cells showing pleomorphism, prominent nucleoli, and black-brown pigments (Fig. 1C). On immunohistochemical staining, the tumor cells expressed S-100, Melan A, human melanoma black-45 (HMB-45) and vimentin, but the cells were negative for leukocyte common antigen, cytokeratin, and hepatocyte antigen. The morphological and immunophenotypic features were consistent with metastatic malignant melanoma, but no mass or pigmented lesion was found on her skin. Therefore, the differential diagnosis included clear cell sarcoma of the soft tissue and primary ovarian malignant melanoma arising from a mature cystic teratoma.

Ovary

The right ovary showed an unruptured cystic mass, measuring 15×12×11 cm and weighing 920 g. The cyst contained dark brownish fluid with whitish-gray keratin and sebum-like materials. The internal surface of the cyst showed an elevated, black-colored solid mass, measuring 6.5×6 cm (Fig. 2A). On section, the black-colored mass was connected to the cystic lesion (Fig. 2B). The ometum showed several conglomerated nodules along with a dark black nodule in adrenal gland, measuring 2×1 cm. The uterus, left ovary, left salpinx, and appendix were unremarkable.

Microscopically the cystic portion of right ovarian mass revealed typical features of mature cystic teratoma, and the black solid portion was composed of large epithelioid cells with abundant eosinophilic cytoplasm, prominent nucleoli, frequent mitoses, and dark brownish pigments. The tumor had abundant vascular structures with central coagulative necrosis. The majority of the epidermal lining cells around the solid mass were denuded, so the relationship with epidermal lining or junctional activity could not be evaluated (Fig. 3A, B). On immunohistochemical staining, the tumor cells were positive for S-100, Melan A, HMB-45, B cell lymphoma-2 (bcl-2), c-kit, and phosphatase and tensin homolog (PTEN), but negative for cytokeratin, estrogen receptor, and progesterone receptor (Fig. 3C). The tumor cells were also positive for Fontana-Masson staining (Fig. 3D). These findings were consistent with malignant melanoma.

Metastatic lesions were found in the omentum, left adrenal gland, serosal surface of the appendix, peritoneum of the cul-de-sac, and uterosacral ligament. However, the uterus, left ovary, and salpinx were uninvolved.

Peritoneal washing fluid

The peritoneal washing fluid collected during the operation contained many atypical cells. These discohesive cells were round to oval in shape and had irregular nuclei, prominent nucleoli, vacuolated cytoplasm, and cytoplasmic melanin pigments in a background of reactive mesothelial cells (Fig. 3E, F).

Clinical course

After the operation, the patient was stable and was able to undergo two rounds of chemotherapy (cisplatin-dacarbazine-vincristine). However, the patient's general condition deteriorated, and there was no evidence of the therapeutic effect. She suffered from ascites and respiratory discomfort, and then died five months after initial presentation.

DISCUSSION

Malignant melanoma involving the ovary is uncommon. Most cases are metastatic lesions, and primary ovarian tumors are very rare. According to one study, only one case of primary ovarian melanoma was identified among 23 cases of malignant melanoma involving the ovaries, and the melanoma originated from a mature cystic teratoma.[19]

Boughton *et al.*[1] and Cronje and Woodruff[3] proposed the following criteria for the diagnosis of primary ovarian melanoma: 1) no other possible sites of a primary tumor; 2) unilateral tumor within the ovarian teratoma; 3) good correlation of the patient's age and symptoms with those of well-documented cases in the literature; and 4) demonstration of junctional activity (desirable but not necessary for diagnosis).

In our case, other possible primary sites of melanoma, such as the skin, intestine, and eyeball were examined but no pigmented lesions were found. The malignant melanoma arose in a unilateral ovarian teratoma. As in previously reported cases, the patient was relatively old (71 years) and had general weakness, weight loss, and a palpable abdominal mass.[1,6,14,16,18] These findings

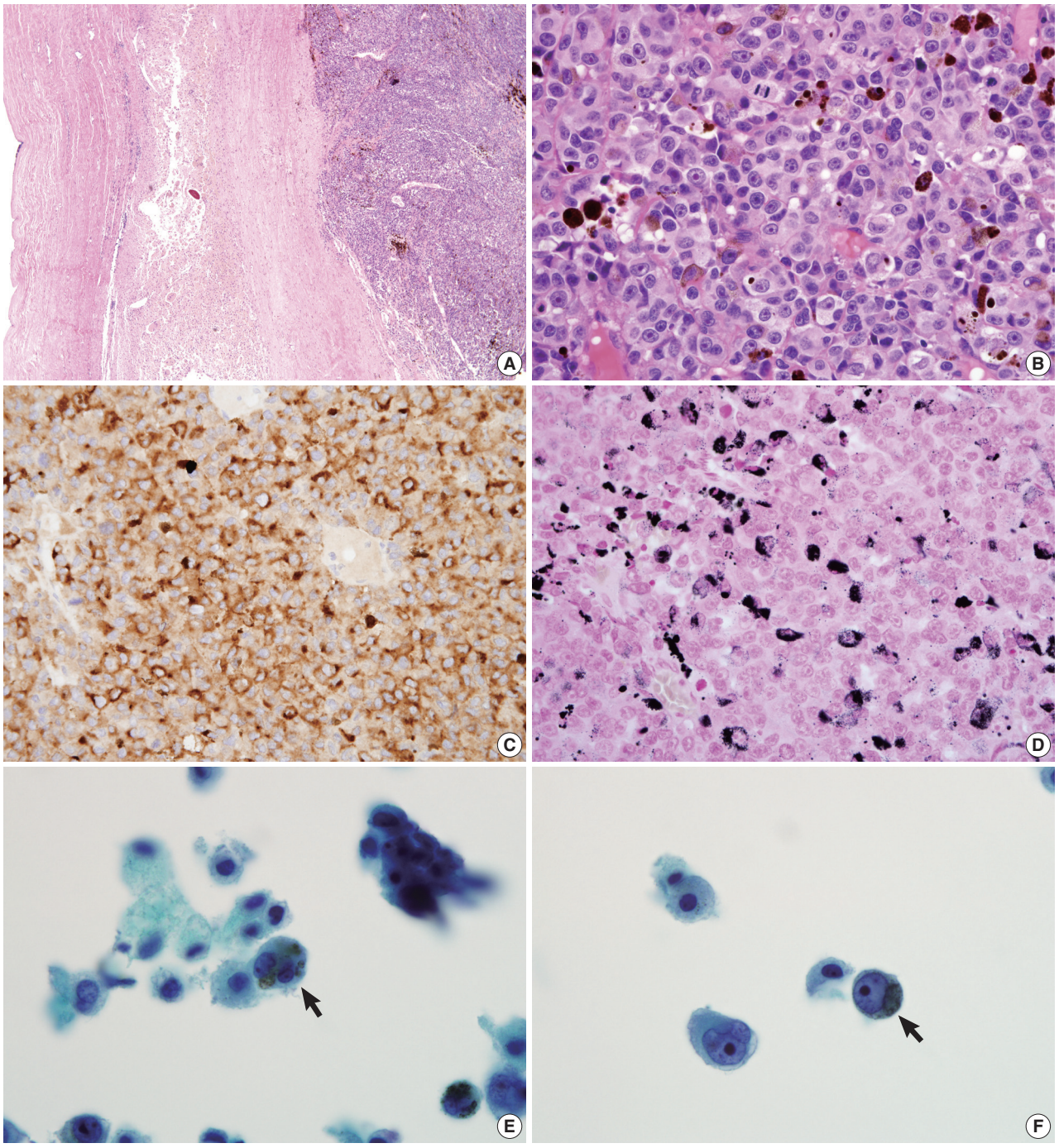

Fig. 3. (A) Malignant melanoma cells are located amongst the keratin material in the teratoma components. (B) Malignant melanoma cells have large nuclei, prominent nucleoli, and dark brown pigments. (C) Positive immunohistochemical staining of the tumor cells with human melanoma black-45. (D) Positive Fontana-Masson staining of the tumor cells. (E, F) Liquid-based cytology of the ascitic fluid. The tumor cells have enlarged eccentric nuclei, prominent nucleoli, and dark intracytoplasmic pigmentation (arrow) (Papanicolau stain).

all supported a diagnosis of primary ovarian malignant melanoma. To date, only 44 cases of primary malignant melanoma arising in a mature ovarian cystic teratoma have been reported. From these, we reviewed 17 cases, and the clinicopathologic features are shown in Table 1.

Junctional activity was not observed in our case, but the presence of junctional activity is not necessary for diagnosis and does not exist in every case (only in 5 of 11 cases with the available

Table 1. Clinicopathologic features of previously reported primary ovarian malignant melanomas arising in mature cystic teratomas

Author	Age (yr)	Symptom	Operation	Additional therapy	DEJ activity	Serum LDH (IU/L)	Serum CA-125 (U/mL)	Distant metastasis	Follow-up time	Patient outcome
Cronje and Woodruff[3]	74	Abdominal distension	Salpingo-oophorectomy	No	Yes	ND	ND	Yes	18 mo	DOD
Boughton *et al.*[1]	27	Pelvic mass	Cystectomy	No	Yes	ND	ND	No	2 yr	NED
Carlson and Wheeler[2]	20	Abdominal pain	TAH-BSO, rectosigmoid resection	CTx	ND	ND	ND	Yes	5 yr	NED
O'Leary and Tejura[9]	79	Abdominal pain	TAH-LSO	No	No	ND	ND	No	2 mo	DOD
Ueda *et al.*[13]	86	Autopsy	Autopsy	No	No	ND	ND	No	No	DOD
Watanabe *et al.*[16]	55	Ovarian mass	TAH-BSO	No	No	ND	Normal	No	6 mo	NED
McNeilage *et al.*[7]	19	Back pain	TAH-BSO	CTx, RTx	No	2,346	93	Yes	37 days	DOD
Vigliani *et al.*[14]	67	Abdominal pain	Myomectomy and BSO	No	Yes	1,290	ND	Yes	3 mo	DOD
Vimla *et al.*[15]	42	Abdominal pain	Ovarian cystectomy	CTx	ND	ND	ND	Yes	18 mo	NED
O'Gorman and Olaitan[8]	49	Abdominal distension	BSO	No	Yes	Normal	Elevated	No	ND	NED
Zarbo *et al.*[17]	60	Abdominal distension	TAH-BSO	CTx	No	ND	203	Yes	4 mo	DOD
Takubo *et al.*[10]	65	Abdominal distension	TAH-BSO	No	Yes	Normal	Normal	No	24 mo	NED
Gök *et al.*[5]	67	Abdominal distension	TAH-BSO	No	ND	ND	ND	No	7 mo	DOD
Tsukamoto *et al.*[12]	46	Abdominal distension	TAH-BSO	CTx	No	ND	ND	Yes	12 mo	NED
Gao *et al.*[4]	53	Abdominal distension	BSO	CTx	ND	ND	351.7	Yes	6 mo	DOD
Lee *et al.*[6]	46	Pelvic mass	TAH-BSO	CTx	ND	ND	260	Yes	2 mo	DOD
Choi *et al.*[18]	45	Pelvic mass	TAH-LSO	CTx	ND	ND	ND	Yes	37 mo	NED
Present case	71	Abdominal mass	TAH-BSO	CTx	No	1,935	47.3	Yes	5 mo	DOD

DEJ, dermoepidermal junction; LDH, lactate dehydrogenase; CA-125, cancer antigen 125; ND, no data; DOD, dead of disease; NED, no evidence of disease; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; CTx, chemotherapy; LSO, left salpingo-oophorectomy; RTx, radiotherapy.

data). Junctional activity in primary ovarian malignant melanomas may be destroyed by tumor invasion, or the malignant melanoma may originate from a component of the cystic teratoma rather than from a dermoepidermal junction.[13]

Melanotic metastases mainly involve the surrounding structures or spread via the vascular or lymphatic systems. The most common sites of spread are the lymph nodes, liver, lung, and bones.[17] In this case, there was no evidence of ovarian rupture; therefore, vascular or lymphatic metastases could be the cause of the liver, omental, adrenal, and peritoneal involvement.

In many studies, an increased serum LDH level is correlated with decreased survival in patients with advanced malignant melanoma.[7,14,20] Our patient also had a high serum LDH level (1,935 IU/L), and she survived only 5 months after operation.

The immunohistochemical staining of tumor cells in previously reported cases revealed positivity for S-100, Melan A, and HMB-45.[2,4-7,9-11,13,14,16-18] There was also a case that was positive for c-kit and PTEN.[11] Some cases were positive for Fontana-Masson staining. Our case was positive for S-100, Melan A, HMB-45, bcl-2, c-kit, and PTEN, and Fontana-Masson, and negative for cytokeratin, estrogen receptor, and progesterone receptor, which were sufficient for a diagnosis of malignant melanoma. Common cytomorphologic features of malignant melanoma, such as discohesion, multinucleation, prominent nucleoli, and cytoplasmic vacuolization, were also observed in our case.

Surgical resection is the gold standard of treatment, but malignant melanoma arising in the ovary has a poor prognosis. In 17 reviewed cases, 10 cases had metastatic lesions[2-4,6,7,12,14,15,17] and 9 cases had died within the 18 months.[3-7,9,13,14,17] Chemotherapy was performed in some studies.[2,4,6,7,12,15,17] A study reported chemotherapy with intraperitoneal carboplatinum resulted in five-year disease-free survival;[2] however, the evidence for a chemotherapeutic benefit remains inadequate. In our case, the patient underwent chemotherapy using cisplatin, dacarbazine, and vinblastin, but the effect was not satisfactory, and the patient survived only five months.

In this case, the patient initially presented with multiple metastatic nodules in the liver and adrenal glands along with ascites. The metastatic nodules and the peritoneal washing cytology were morphologically consistent with malignant melanoma but no skin lesions were observed as a possible primary site. When metastatic malignant melanoma is found in biopsy specimens of internal organs or ascitic fluid cytology, the ovary should be considered a possible primary organ. In conclusion, we report a very uncommon case of primary ovarian malignant melanoma arising in a mature cystic teratoma.

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