ANTICANCER RESEARCH *37*: 2557-2564 (2017)
doi:10.21873/anticanres.11599

Clinicopathological Characteristics of Mitotically-active Cellular Fibroma of the Ovary: A Single-institutional Experience

JI-YE KIM, KIYONG NA and HYUN-SOO KIM

Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract. *Mitotically-active cellular fibroma (MACF) is a rare form of ovarian fibromatous tumor. Although it is generally acknowledged to have indolent biological behavior, its rarity and overlapping histopathological features with more common and aggressive entities make MACF prone to misdiagnosis and overtreatment. The clinicopathological characteristics of ovarian MACF have not been clearly established. Our 10-year review of cellular fibromatous tumors of the ovary diagnosed at a single institution revealed four cases of cellular fibroma (CF) and three cases of MACF. The mean age of patients with MACF was 46 years (range=20-71 years). Patients presented with symptoms related to pelvic masses, such as abdominal pain and discomfort and flank pain. Serum levels of cancer antigen 125 was increased in two patients with MACF. All cases of MACF were a single unilateral tumor. Magnetic resonance imaging revealed solid or mixed solid and cystic ovarian masses with diameters of 7.3-14.9 cm. The radiological impressions included benign stromal tumor, benign epithelial tumor, and borderline epithelial tumor. Grossly, MACFs exhibited yellow-to-tan fleshy cut surfaces, without necrosis or hemorrhage. Extensive hyaline degeneration, resulting in a fibrotic cut surface, was observed in one case. Histologically, MACF displayed frequent mitotic figures, as well as increased cellularity and mild cytological atypia. The mean mitotic count was 8.7 per 10 high-power fields. MACF is a newly-recognized subtype of ovarian cellular fibromatous tumor. Pathologists and clinicians should be aware of this rare entity to prevent misdiagnosis of MACF as fibrosarcoma or adult granulosa cell tumor and resultant overtreatment.*

Correspondence to: Hyun-Soo Kim, Department of Pathology, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Tel: +82 222281794, +82 23620860, e-mail: hyunsookim@yuhs.ac

Key Words: Ovary, cellular fibroma, mitotically active cellular fibroma, fibrosarcoma.

Cellular fibroma (CF) of the ovary is an uncommon fibromatous tumor characterized by increased cellularity compared to fibroma of the conventional type. In 1981, Prat and Scully suggested increased mitotic activity as the most important morphological criterion to differentiate CF from fibrosarcoma (1). According to the 2003 World Health Organization (WHO) Classification of Tumours of the Female Genital Organs (2), ovarian CF is distinguished from fibrosarcoma on the basis of low mitotic activity (<4 per 10 high-power fields [HPFs]) and the absence of diffuse moderate-to-severe cytological atypia (3). However, previous studies noted a remarkably favorable prognosis for the subset of CF with particularly high mitotic activity (4-6).

The 2003 WHO Classification designated ovarian fibromatous tumor with markedly increased cellularity, increased mitotic activity (≥4 per 10 HPFs), and diffuse moderate-to-severe cytological atypia as fibrosarcoma (2). Since tumors with increased mitotic activity but no diffuse moderate-to-severe cytological atypia have not been categorized (7), this kind of tumor has been diagnosed mostly as fibrosarcoma. However, it has been suggested that the clinicopathological characteristics of CF with increased mitotic activity are significantly different from those of fibrosarcoma. In 2006, Irving and colleagues (4) first defined this kind of ovarian tumor as mitotically active cellular fibroma (MACF). The 2014 WHO Classification of Tumours of Female Reproductive Organs recognized a separate entity of CF that displays particularly high mitotic activity but no diffuse moderate-to-severe cytological atypia as MACF. The revised version of the WHO Classification also emphasized that MACFs reveal a characteristically indolent clinical behavior and should be distinguished from fibrosarcoma (8).

The histopathological diagnosis of ovarian fibromatous tumor is usually unequivocal due to their distinct spindle-cell morphology and fascicular growth pattern. Both ovarian CF and MACF are essentially tumors of fibroblastic origin. Amongst the family of ovarian fibromatous tumors, CF is regarded as a distinct entity and allocated a great deal of attention in the revised 2014 WHO Classification, whereas

MACF is only briefly mentioned (8). We recently experienced some cases of ovarian MACF, which initiated a comprehensive review of previously published cases (6, 7, 9-12) and the 10-year experience at our Institution. In this study, we thoroughly describe the clinical features, imaging findings, and pathological features of ovarian MACF. Our observations support the notion that the clinicopathological characteristics of ovarian MACF are significantly different from those of fibrosarcoma. Both pathologists and gynecologists should readily recognize differences in clinical and histopathological features among CF, MACF, and fibrosarcoma in order to prevent excessive treatment that may result from over-diagnosis.

Patients and Methods

Case selection. The cases were selected from the computerized files of Severance Hospital. A thorough search was performed using the key words "ovary", "stromal tumor", "fibroma", "cellular fibroma", and "mitotically active cellular fibroma" among the archival surgical pathology cases. During the period from October 2007 to September 2016, 176 patients were diagnosed as having ovarian fibromatous tumors. Of these, 169 (96.0%) patients were diagnosed as having conventional fibroma. Of the remaining seven patients, four (2.3%) were diagnosed as having CF, and three (1.7%) were diagnosed as having MACF. Clinical and pathological information were obtained from the electrical medical information systems and pathology reports. Clinical details that were reviewed included age of patient at diagnosis, obstetric history (gravidity, parity, live children, dead children, abortion), serum levels of tumor markers, presenting complaint, previous gynecological history, associated medical condition, imaging findings [magnetic resonance imaging (MRI), computed tomographic (CT) or positron-emission tomography (PET), treatment, and current status. The pathological characteristics that were collected included gross appearance, presence of grossly identifiable necrosis or hemorrhage, presence of moderate-to-severe cytological atypia, presence of fascicular growth pattern, mitotic count (per 10 HPFs), presence of atypical mitotic figures or coagulative tumor cell necrosis, and co-existing histopathological findings. This study was reviewed and approved by the Institutional Review Board at Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea (2016-0481-001).

Histopathology. The resected specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin blocks. From each formalin-fixed, paraffin-embedded block, 4-μm sections were cut and stained with hematoxylin and eosin. Among these, the most representative slide containing an appropriate volume of tumor was chosen for reticulin staining and immunohistochemical staining.

Literature review. The Medline database was thoroughly searched using the PubMed retrieval service. Searches were performed in September 2016 using the key words "ovary", "cellular fibroma", "mitotically active cellular fibroma".

Results

Case report. *Case 1:* A 71-year-old Korean woman (gravida, 14; para, 3; live children, 3; dead children, 0; and abortion, 11) presented with intermittent low abdominal pain for the previous 7 years. She was on medication for hypertension and dyslipidemia. MRI revealed a 7.3-cm, well-defined, solid and cystic mass in the right ovary. On T2-weighted images the solid portion displayed dark signal intensity, and the cystic portion had peripheral nodular enhancement, showing the same signal intensity as the solid portion. No evidence of peritoneal seeding, lymphatic metastasis, or hematogenous metastasis was detected. The radiological impression was benign or borderline ovarian epithelial tumor. Serum tumor markers were within normal limits. Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy was performed. Grossly, the external surface was smooth, glistening, and pink-to-gray. The mass consisted of a well-circumscribed, solid tumor and a unilocular cystic lesion. No hemorrhage or necrosis was identified. In the inner aspect of the cystic lesion a slightly elevated, solid mural tumor was observed. The cut surface of the solid tumor was fleshy and tan-to-white. Histologically, the periphery of the ovarian mass predominantly consisted of fibroblast-like spindle cell proliferation but a fascicular growth pattern characteristic of fibroma was not apparent. Cellularity was significantly increased compared with conventional fibroma, and intervening collagen fibers were seldom observed. The center of the mass displayed extensive hyalinization and scattered thick-walled blood vessels. The neoplastic spindle cells showed mild cytological atypia, including mild nuclear enlargement, minimal nuclear membrane irregularity, and fine chromatin. Nuclear hyperchromasia or severe pleomorphism was not identified. The tumor cells exhibited a higher mitotic count than that of conventional fibroma (up to 10 per 10 HPFs), whereas atypical mitotic figures or coagulative tumor cell necrosis was absent. Reticulin staining revealed numerous, delicate, black-staining strands that surrounded individual tumor cells. Representative images and photomicrographs are shown in Figure 1. The right ovarian mass was diagnosed as MACF with extensive hyaline degeneration and cystic change. The patient remains alive without recurrence 4 months after surgery.

Case 2: A 47-year-old Korean woman (gravida, 3; para, 1; live child, 1; dead child, 0; abortion, 2) presented with abdominal distension and right flank pain. She denied significant medical history. Laboratory examination revealed an increased serum cancer antigen (CA)-125 level of 66.4 IU/ml; MRI revealed a 14.9 cm, well-defined, solid mass in the right ovary and a moderate amount of ascites. The ovarian mass was suspected to be fibrothecoma. Bilateral salpingo-oophorectomy was performed. Grossly, the mass displayed fleshy, tan-to-yellow cut surfaces, without necrosis or hemorrhage. Histologically, the tumor uniformly consisted of spindle-to-ovoid fibroblastic cells. The individual tumor cells had mild cytological atypia and a mitotic count of 8 per 10 HPFs. No evidence of atypical mitotic figures or

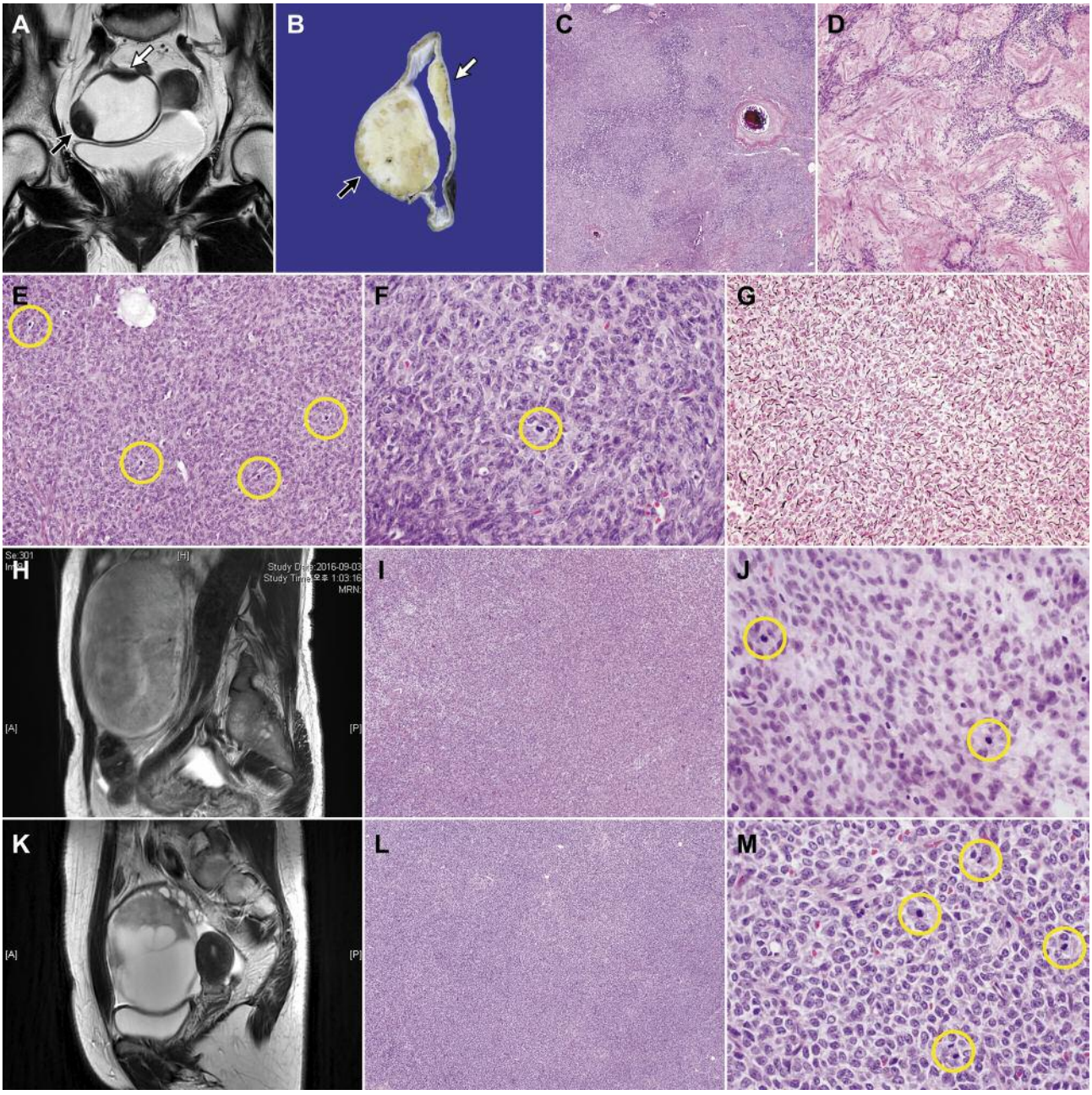

Figure 1. *Mitotically-active cellular fibroma: Case 1. A: Magnetic resonance imaging revealed a 7.3 cm, well-defined, solid and cystic mass (black arrow) in the right ovary. An additonal mural nodule (white arrow) was noted within the cystic mass. B: Grossly, a well-circumscribed, ovoid solid tumor mass (black arrow) and a unilocular cystic mass with slightly elevated mural nodule (white arrow) corresponding to image A. C: Histopathologically, proliferation of fibroblast-like spindle cells was evident. D: Areas of extensive hyaline degeneration were observed. E: A fascicular growth pattern, characteristic of fibroma, was not apparent. Yellow circles highlight mitotic figures. F: The tumor cells displayed oval to spindle-shaped nuclei with fine chromatin, mild atypia, mild nuclear enlargement, minimal irregularity of the nuclear membrane, and small, central nucleolus. Intervening collagen fibers were seldom observed. G: Reticulin stain revealed delicate, black-staining collagen fibers surrounding individual tumor cells. Original magnification, C and D, ×40; E, ×100; F and G, ×200. Case 2. H: Magnetic resonance imaging revealed a 14.9-cm, well-circumscribed, ovoid, solid ovarian mass. I: Histopathologically, the tumor consisted of diffusely growing fibroblastic cells. J: The tumor cells demonstrated mild cytological atypia and frequent mitotic figures (yellow circles). Similarly to case 1, fascicular growth pattern and collagenous stroma were subtle. Original magnification, I, ×40; J, ×100. Case 3. K: Magnetic resonance imaging revealed a 10.8-cm, well-defined, solid and multilocular cystic mass in the left ovary. The ovarian mass was suspected to be borderline epithelial tumor. L: Histopathologically, a fascicular growth pattern was not apparent. M: The tumor cells exhibited mild cytological atypia, with mild nuclear membrane irregularity and small nucleolus. Increased mitotic activity (yellow circles) was observed. Original magnification, L, ×40; M, ×100.*

Table I. *Clinical features of ovarian cellular fibroma (CF) and mitotically-active cellular fibroma (MACF).*

Histopathological diagnosis	Case	Age (years)	G-P-L-D-A	Increased tumor marker	Clinical presentation	Associated medical condition	Surgical treatment	Additional treatment	Follow-up duration (months)	Current status
MACF	1	71	14-3-3-0-11	None	Low abdominal pain	HTN, dyslipidemia	TLH+ BSO	None	4	NED
	2	47	3-1-1-0-2	CA-125: 66.4 IU/ml	Abdominal distension, right flank pain	None	BSO	None	5	NED
	3	20	0-0-0-0-0	CA-125: 42.6 IU/ml	None	PCOS	LSO	None	29	NED
CF	4	52	4-2-2-0-2	CA-125: 474 IU/ml	Abdominal pain	TB	TLH+ BSO	None	12	NED
	5	75	5-4-4-0-1	CA-125: 219.7 IU/ml	Abdominal pain	DM, HTN	TLH+ BSO	None	73	NED
	6	54	4-2-2-0-2	Not applicable	None	Thyroid cancer	TLH+ BSO	None	16	NED
	7	42	5-2-2-0-3	Not applicable	Abdominal pain	HTN, uterine LM, IUD *in situ*	BSO	None	4	NED

BSO: Bilateral salpingo-oophorectomy; CA-125: cancer antigen-125; DM: diabetes mellitus; G-P-L-D-A: gravidity-parity-live children-dead children-abortion; HTN: hypertension; IUD: intrauterine device; LM: leiomyoma; LSO: left salpingo-oophorectomy; NED: no evidence of disease; PCOS: polycystic ovarian syndrome; TB: tuberculosis; TLH: total laparoscopic hysterectomy.

coagulative tumor cell necrosis was identified. Similarly to Case 1, the fascicular growth pattern was subtle. Reticulin stain highlighted a fine meshwork of collagen fibers surrounding individual tumor cells, excluding the possibility of adult granulosa cell tumor (AGCT). Representative image and photomicrographs are shown in Figure 2. The right ovarian mass was diagnosed as MACF. The patient remains alive without recurrence 5 months after surgery.

Case 3: The third case was a 20-year-old Korean woman (gravida, 0; para, 0; live child, 0; dead child, 0; abortion, 0) who had been on regular gynecological follow-up for polycystic ovarian syndrome. Pelvic ultrasonography revealed an 11.0 cm, septated ovarian cystic lesion. Serum CA-125 level was increased (42.6 IU/ml). MRI revealed a 10.8 cm, well-defined, solid and multilocular cystic mass in the left ovary and a small amount of ascites. The ovarian mass was suspected to be borderline epithelial tumor. In consideration of her age and fertility preservation, she received left salpingo-oophorectomy. Grossly, the cut surface of the mass was fleshy and tan-to-gray. No necrosis or hemorrhage was observed. Histopathologically, a spindle cell neoplasm showed significantly increased cellularity. The tumor cells exhibited mild cytological atypia. No diffuse moderate-to-severe cytological atypia or coagulative tumor cell necrosis was noted. A fascicular growth pattern was relatively unapparent. On high power, increased mitotic activity (up to 8 per 10 HPFs) was noted. Atypical mitotic figures were absent. Representative image and photomicrographs are shown in Figure 3. The left ovarian mass was diagnosed as MACF. The patient remains alive without recurrence 29 months after surgery.

Clinical features and imaging findings. During the study period, four patients were diagnosed as having CFs and three as having MACFs at our Institution. The patients' age at diagnosis ranged from 20-75 years (mean=51.6 years). The patients ranged from premenopausal to postmenopausal, and all but one patient had multiple gravidity and parity. Five out of the seven patients presented with abdominal pain or distension or right flank pain, and the other two patients had adnexal masses incidentally discovered during follow-up for pre-existing clinical conditions. Six patients were tested for serum tumor markers at the time of diagnosis and four patients had elevated serum CA-125 level, raising the suspicion of ovarian malignancy. All but one patient was treated with bilateral salpingo-oophorectomy; the remaining patient was treated with unilateral salpingo-oophorectomy in consideration of her young age (20-year-old) and fertility preservation. Coexisting gynecological lesions included adenomyosis, endometriosis, endometrial polyp, cervical low-grade squamous intraepithelial lesion, and tubal hyperplasia. Follow-up data were available for all patients. The mean follow-up duration was 20.4 months (range=4-73 months). No recurrence or tumor-related death was noted. Detailed clinical features of the seven patients with CF or MACF are summarized in Table I.

Imaging findings of ovarian CFs and MACFs are shown in Table II. One patient had bilateral cellular fibromas. Six patients displayed at least small amounts of pelvic fluid at the time of discovery. A well-circumscribed tumor border was observed in six cases. Five cases exhibited cystic change within the mass. There was a disagreement between radio-

Table II. *Imaging findings of ovarian cellular fibroma (CF) and mitotically active cellular fibroma (MACF).*

Histopathological diagnosis	Case	Location	Greatest dimension	Component	Tumor border	Amount of ascites	Radiological impression
MACF	1	Right ovary	7.3 cm	Solid and cystic	Well-defined	None	Benign or borderline epithelial tumor (MRI)
	2	Right ovary	14.9 cm	Solid	Well-defined	Moderate	Benign stromal tumor (MRI), benign stromal tumor (CT)
	3	Left ovary	10.8 cm	Solid and cystic	Well-defined	Small	Borderline epithelial tumor (MRI), Borderline epithelial tumor (PET)
CF	4	Left ovary	16.0 cm	Solid	Well-defined	Moderate	Malignant stromal tumor (MRI), benign stromal tumor (PET)
	5	Bilateral ovaries	12.8 cm (right), 3.0 cm (left)	Solid and cystic	Well-defined	Small	Malignant epithelial tumor (MRI)
	6	Right ovary	5.3 cm	Solid and cystic	Ill-defined	Small	Benign stromal tumor or malignant epithelial tumor (MRI), borderline epithelial tumor (PET)
	7	Right ovary	4 cm	Not applicable	Well-defined	Small	Benign epithelial tumor (CT)

CT: Computed tomography, MRI: magnetic resonance imaging; PET: positron-emission tomography.

Table III. *Pathological features of ovarian cellular fibroma (CF) and mitotically active cellular fibroma (MACF).*

Histopathological diagnosis	Case	Gross finding			Histopathological finding					Coexisting histopathological finding
		Appearance	Necrosis	Hemorrhage	Cytological atypia	Fascicular growth	Mitotic count (per 10 HPFs)	Atypical mitosis	CTCN	
MACF	1	Fleshy cut surface	Absent	Absent	Mild	Subtle	10	Absent	Absent	Extensive hyalinization, cervical LSIL
	2	Fleshy cut surface	Absent	Absent	Mild	Subtle	8	Absent	Absent	None
	3	Fleshy cut surface	Absent	Absent	Mild	Subtle	8	Absent	Absent	None
CF	4	Fibrotic, firm	Absent	Absent	Mild	Marked	0	Absent	Absent	Uterine adenomyosis
	5	Fibrotic, firm	Absent	Absent	Mild	Marked	0	Absent	Absent	Uterine adenomyosis
	6	Fibrotic, firm	Absent	Absent	Mild	Marked	2	Absent	Absent	Ovarian endometriosis, endometrial polyp
	7	Not applicable	Absent	Absent	Mild	Marked	1	Absent	Absent	Ovarian hemorrhagic follicle cyst

CTCN: Coagulative tumor cell necrosis, HPF: high-power field; LSIL: low-grade squamous intraepithelial lesion.

pathological interpretations. Different imaging modalities (MRI, CT, or PET) were used to establish a preoperative clinical diagnosis. In two CF cases, the interpretation results were conflicting. In one case the radiological impressions were malignant stromal tumor on MRI and benign stromal tumor on PET scan, and in the second case the impression was benign stromal tumor or malignant epithelial tumor on MRI and borderline epithelial tumor on PET scan. In addition, the imaging findings failed to closely match the final histopathological diagnosis. Three out of the four CFs and all MACFs were preoperatively evaluated using MRI. All cases of CF evaluated were interpreted as malignancy, and two cases of MACF as borderline epithelial tumor.

Pathological features and immunohistochemical findings. Pathological features of ovarian CFs and MACFs are shown in Table III. Grossly, both CFs and MACFs were predominantly solid or mixed solid and cystic lesions. The tumor size ranged from 4.0-14.6 cm (mean=10.2 cm). Histologically, all cases displayed similar morphological

features to those of conventional fibroma. The degree of cytological atypia was minimal to mild; some of the tumor cell nuclei possessed a small, single nucleolus but diffuse moderate-to-severe cytological atypia suggestive of malignancy was not observed. Instead, there were significant differences in cellularity, presence of fascicular growth pattern, and mitotic count. Both CF and MACF exhibited increased cellularity. A fascicular growth pattern was obvious in CF. In contrast, MACF displayed a predominantly diffuse growth pattern throughout the tumor, and reticulin staining confirmed the presence of individually wrapped collagen fibers. Whereas CF exhibited mitotic counts of ≤2 per 10 HPFs, frequent mitotic figures (≥8 per 10 HPFs) were identified in all cases of MACF. No moderate-to-severe cytologic atypia or atypical mitotic figures were detected in CF or MACF. Coagulative tumor cell necrosis was not observed.

Discussion

Many ovarian tumors composed primarily of fibroblastic cells are fibromas of conventional type and generally do not pose a diagnostic challenge. Most contain spindle- to ovoid-shaped cells as the principal cell type, with variable amounts of extracellular collagenous matrix. A small subset of fibromatous tumors, however, exhibit increased cellularity and mitotic activity, and the presence of either or both features leads to classification as CF or MACF. We investigated the clinicopathological characteristics of ovarian MACF through a retrospective review of our 10-year institutional experience. Age and clinical presentation of patients with MACF were similar to those of previously published cases. In our series, the patient age ranged from 20–71 years, with mean and median age of 46 and 47 years, respectively. The mean age of patients with MACF reported in a previous large study was 41 years (4). Most patients diagnosed as having MACF presented with symptoms associated with an abdominal or pelvic mass, which was the usual presentation of patients reported in the literature. We observed that more than half of the cases presented as mixed solid and cystic lesions in imaging studies, indicating the nature of frequent cystic change in these tumors. There were disagreements between different imaging modalities and radio-pathological interpretations. The radiological impressions of two CFs were discordant between MRI and PET. Furthermore, all CFs evaluated by MRI were interpreted as malignancy and two MACFs were interpreted as borderline epithelial tumor. Our observations suggest limitations of imaging studies in predicting the diagnosis of ovarian CFs and MACFs, and indicate that surgical excision and subsequent histopathological examination are required to make an accurate diagnosis.

Grossly, MACF had a softer, fleshier cut surface than conventional fibroma, which is typically hard, chalky, and white or yellow-to-white, with a vaguely whorled cut surface that resembles uterine leiomyoma. In contrast, all CFs had grossly fibrotic-firm appearances. We assume that the difference in gross appearance of MACF is due to differences in the proportion of collagenous stroma. In CF the collagen fibers were easily recognized at low-power magnification, and an appreciable number of collagen fibers were dissecting and separating tumor cells into bundles. As a result of the relatively large amount of collagen fibers, there was obvious and pronounced fascicular growth of tumor cell bundles. MACFs tended to have subtler evidence of fasciculation due to fewer collagen fibers. They were distinctively more cellular than CFs and allowed little space between the tumor cells. The collagen fibers were not easily identified in conventional hematoxylin and eosin staining but their presence could be confirmed through reticulin staining. This feature might easily deceive a pathologist into misdiagnosing MACF, especially as AGCT. In this situation, reticulin staining is fundamental for differentiating the two entities as it confirms fibroblastic collagen production in MACFs by demonstrating collagen fibers surrounding individual cells.

Histologically, MACF exhibited dense cellularity, sometimes with translation to small hypocellular areas that were accompanied by extensive hyaline degeneration or edema (1, 4, 5). The fascicular arrangement of tumor cells and collagenous stroma that is characteristic of conventional fibroma was subtle in MACFs. The nuclei were oval to spindle-shaped, with relatively smooth nuclear contours and a small nucleolus. All MACFs had mild cytologic atypia. Most importantly, all MACF cases displayed significantly increased mitotic activity. The number of mitotic figures observed ranged from 8-10 per 10 HPFs, without atypical forms. Consistent with previous data, our cases of cellular fibromatous tumors with four or more mitotic figures per 10 HPFs but no diffuse moderate-to-severe cytological atypia warranted designation as MACF. Attention to these histopathological features facilitates the correct diagnosis and avoids potential overdiagnosis as the rare and clinically aggressive fibrosarcoma.

In terms of pathological examination, caution should be applied regarding malignant tumors showing overlapping histopathological features with MACFs. Importantly, in our 10-year single-institutional experience there was no case diagnosed as ovarian fibrosarcoma. Clinicians should be aware of the overlapping features of frequent mitoses between fibrosarcoma and MACF to prevent overdiagnosis of an ovarian cellular fibromatous tumor as fibrosarcoma. At the initial discovery of fibrosarcoma by Prat and Scully (1), it was suggested that a mitotic index of more than 4 per 10 HPFs is sufficient for the diagnosis of fibrosarcoma. However, subsequent observations amended the diagnostic criteria for fibrosarcomas to additionally require nuclear pleomorphism

and severe cytologic atypia rather than only a high mitotic index (4). In regard to the higher prevalence of MACF compared to fibrosarcoma demonstrated in this study, the majority of particularly cellular fibromatous tumors with frequent mitoses of the ovary may be MACFs rather than fibrosarcomas. In fact, fibrosarcoma is exceptionally rare. Grossly, these tumors are typically large and overtly malignant with extensive coagulative necrosis and hemorrhage (1, 5). In contrast to CF and MACF, on microscopic examination they show diffuse moderate-to-severe cytological atypia and brisk mitotic activity with a typical mitotic count of up to 25 per 10 HPFs (1, 5, 13). Fibrosarcomas have often spread beyond the ovary at presentation and have been fatal in more than half of reported cases, with death usually occurring within less than 2 years from diagnosis (1, 5, 13, 14). Occasional tumors can show areas of fibrosarcoma in a background of MACF, thus thorough histological sampling is essential in all cellular fibromatous tumors.

AGCT should also be distinguished from MACF. Ovarian AGCT, an aggressive sex cord-stromal tumor, is more common than MACF. AGCT that exhibits a prominent fibromatous stromal component may resemble MACF. The fibroblastic origin should be confirmed using reticulin staining, which highlights individually wrapped tumor cells by collagen fibers (15). In contrast, reticulin staining in AGCT demonstrates aggregation of tumor cell groups, clusters, or nests by collagen fibers. In tumors with a diffuse growth pattern, an extensive search may be required to show insular, follicular, or other typical patterns of adult granulosa cell tumor. Attention to the pale, vesicular nuclear characteristics of AGCT and the presence of nuclear grooves can be helpful. However, the latter finding is not required for diagnosis, and is by no means exclusive to AGCT. Leiomyosarcomas involving the ovary, whether primary or metastatic, should be readily distinguished from CF and MACF by their high-degree of nuclear pleomorphism and atypical mitotic figures. Metastatic gastrointestinal stromal tumor (GIST) has important prognostic and therapeutic implications and may enter into differential diagnoses of a cellular fibromatous tumor. Histologically, metastatic GIST to the ovary may show pure spindled cell morphology, with mitotic activity in the range of that seen in MACFs. Furthermore, skeinoid fibers, brightly eosinophilic globules and plaques frequently present in the stroma of GISTs of small bowel origin, may be mistaken for the wavy collagen fibers and hyaline plaques seen in fibromas and thecomas (4, 16). Skeinoid fibers are densely staining and have irregular hard edges, in contrast to hyaline plaques, which have more fibrillary, wavy collagen fibers coalescing into larger aggregates. Although skeinoid fibers are believed to be nonspecific, in the context of a spindled-cell neoplasm of the ovary their presence should raise the index of suspicion for metastatic GIST.

In summary, we describe the clinicopathological characteristics of ovarian CF and MACF. This study highlights the potential danger of misdiagnosing ovarian cellular fibromatous tumors as malignant aggressive tumors such as fibrosarcoma and AGCT. Increases in both cellularity and mitotic activity raise the index of suspicion of malignancy, but the absence of diffuse moderate-to-severe cytological atypia or atypical mitotic figures does not support the diagnosis of fibrosarcoma. Our data support the notion that increased cellularity, mild cytological atypia, and frequent mitotic figures are suggestive of MACF. Surgical excision seems to be a curative treatment for ovarian MACF, although given its rarity, further investigation using a large patient cohort is necessary to establish its biological nature and clinical outcome.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B03935584).

References

1 Prat J and Scully RE: Cellular fibromas and fibrosarcomas of the ovary: a comparative clinicopathologic analysis of seventeen cases. Cancer *47*: 2663-2670, 1981.

2 Tavassoli FA and Devilee P: World Health Organization Classification of Tumours: Pathology and Genetics. Tumours of the Breast of Female Genital Organs. Lyon, France: IARC, 2003.

3 Tavassoli FA and Devilee P: WHO Classification of Tumours of the Breast and Female Genital Organs. Lyon, France: IARC, 2003.

4 Irving JA, Alkushi A, Young RH and Clement PB: Cellular fibromas of the ovary: a study of 75 cases including 40 mitotically active tumors emphasizing their distinction from fibrosarcoma. Am J Surg Pathol *30*: 929-938, 2006.

5 Tsuji T, Kawauchi S, Utsunomiya T, Nagata Y and Tsuneyoshi M: Fibrosarcoma versus cellular fibroma of the ovary: a comparative study of their proliferative activity and chromosome aberrations using MIB-1 immunostaining, DNA flow cytometry, and fluorescence *in situ* hybridization. Am J Surg Pathol *21*: 52-59, 1997.

6 Kaku S, Takeshima N, Akiyama F, Furuta R, Hirai Y and Takizawa K: A unique fibrous tumor of the ovary: Fibrosarcoma or mitotically active cellular fibroma? Anticancer Res *27*: 4365-4369, 2007.

7 Zong L, Lin M and Fan X: Mitotically active cellular fibroma of ovary should be differentiated from fibrosarcoma: a case report and review of literature. Int J Clin Exp Pathol *7*: 7578-7582, 2014.

8 Kurman RJ, Carcangiu ML, Herrington CS and Young RH: World Health Organization Classification of Tumours of Female Reproductive Organs. Lyon, France: IARC, 2014.

9 Bucella D, Limbosch JF, Buxant F, Simon P, Fayt I, Anaf V and Noel JC: Recurrence of mitotically active cellular fibroma of the ovary. Obstet Gynecol Int *2009*: 803062, 2009.

10 Monteiro SB, Costa A and Paiva V: Mitotically active cellular ovarian fibroma with Meigs' syndrome and elevated CA-125: towards fertility preservation. J Pediatr Adolesc Gynecol *25*: e107-109, 2012.
11 Wu H, Xie J, Huang W and Wu J: Mitotically active cellular fibroma of the ovary: a case report and a review of the literature. Eur J Gynaecol Oncol *35*: 81-83, 2014.
12 Yamada T, Hattori K, Satomi H, Hirose Y, Nakai G, Daimon A, Hayashi A, Terai Y, Ohmichi M and Fukunaga M: Mitotically active cellular fibroma of the ovary: a case report and literature review. J Ovarian Res *8*: 65, 2015.
13 Shakfeh SM and Woodruff JD: Primary ovarian sarcomas: report of 46 cases and review of the literature. Obstet Gynecol Surv 42: 331-349, 1987.
14 Celyk C, Gungor S, Gorkemly H, Bala A, Capar M, Colakodlu M and Akyurek C: Ovarian fibrosarcomas. Acta Obstet Gynecol Scand *81*: 375-376, 2002.
15 Burandt E and Young RH: Thecoma of the ovary: a report of 70 cases emphasizing aspects of its histopathology different from those often portrayed and its differential diagnosis. Am J Surg Pathol *38*: 1023-1032, 2014.
16 Zighelboim I, Henao G, Kunda A, Gutierrez C and Edwards C: Gastrointestinal stromal tumor presenting as a pelvic mass. Gynecol Oncol *91*: 630-635, 2003.

Received February 28, 2017
Revised March 17, 2017
Accepted March 21, 2017