Myolipoma of Soft Tissue
Clinicopathologic Analysis of 34 Cases

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Abstract: Myolipoma of soft tissue, which was first described by Meis and Enzinger (1991), is a rare benign neoplasm characterized by the admixture of mature adipocytes and well-differentiated smooth muscle cells. Recently, cytogenetic alteration of the *HMGA2* gene has been reported in 2 myolipomas. We present the clinicopathologic features of 34 cases of myolipoma of soft tissue, study immunoreactivity for HMGA2, and review the previous literature. In our series, there were 32 women and 2 men, with age at presentation ranging from 35 to 94 years (median, 55 y). The most frequently affected site was retroperitoneum (47%), followed by pelvis (15%), abdominal wall (12%), and intra-abdominal sites (9%). Follow-up information was available for 17 patients (50%), ranging from 1 to 202 months (mean, 41 mo). None has developed local recurrence or metastasis. Grossly, tumors were well circumscribed, and the cut surface showed an admixture of yellowish adipose tissue and tan-whitish nodules. The size ranged from 2.4 to 60 cm (median 10.5 cm). Histologically, the tumors were composed of an intimate admixture of mature fat cells and bland spindle-shaped cells with brightly eosinophilic cytoplasm, arranged in fascicles. Some cases showed the following unusual features focally: hypercellular fascicular pattern (N = 2), degenerative nuclear atypia (N = 1), round cell morphology (N = 1), hemosiderin deposition (N = 1), metaplastic cartilage (N = 1), metaplastic bone (N = 1), and eosinophil infiltrates (N = 1). Immunohistochemically, spindle cells showed strong and diffuse positivity for desmin (26/26 cases), SMA (20/21), and ER (13/15). Nuclear positivity for HMGA2 was identified in 15 of 25 cases (60%). MDM2 and CDK4 were usually negative (14/15, 8/9, respectively). In summary, myolipoma of soft tissue is a distinctive benign tumor composed of mature fat cells and smooth muscle cells and arises most commonly in deep-seated locations of middle-aged women. In our study, 60% of cases showed nuclear staining for HMGA2 by immunohistochemistry, which supports the possibility that these tumors harbor aberration of the *HMGA2* gene, as seen in lipomas and leiomyomas elsewhere.

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Key Words: myolipoma, soft tissue, *HMGA2*, benign tumor

(*Am J Surg Pathol* 2017;41:153–160)

Myolipoma of soft tissue is a rare benign neoplasm characterized by the admixture of mature adipocytes and well-differentiated smooth muscle cells. It is classified as a variant of lipoma of extrauterine sites in the World Health Organization classification,[1] thereby being distinguished from uterine "lipoleiomyoma." Myolipoma of soft tissue more often occurs in adults with a female predominance, tends to be large, and arises in deep-seated locations. This distinct entity was first fully described by Meis and Enzinger in 1991,[2] in which they reported 9 cases of myolipoma of soft tissue. To date, < 50 cases have been reported.

Cytogenetic alteration of the high-mobility group AT-hook 2 (*HMGA2*) gene has been reported in 2 cases of myolipoma.[3,4] HMGA2 is an architectural transcription factor located at 12q14-15, usually expressed only in early development, and plays an important role in the tumorigenesis of various epithelial and mesenchymal tumors. Rearrangement of *HMGA2* is well recognized in both adipocytic and smooth muscle tumors,[3,5–10] including conventional lipoma, atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS), leiomyoma, and leiomyosarcoma (LMS). In these tumors, overexpression of HMGA2 can be detected by immunohistochemistry,[5,9–11] but data regarding HMGA2 immunoexpression in myolipoma are still limited. To date, only 1 case has been published, which was negative for HMGA2.[11] In this study, we present the clinicopathologic features of 34 cases of myolipoma of soft tissue, study their immunoreactivity for HMGA2, and review the previous literature.

MATERIALS AND METHODS

Thirty-four cases diagnosed as myolipoma between 1992 and 2015 were retrieved from the consultation file of 1 of the authors (C.D.M.F.). One additional case was excluded when follow-up data revealed origin from female gynecologic organs. Hematoxylin and eosin–stained sections were reviewed when available, and pathologic features were reevaluated. Immunostains were performed on 4-μm-thick formalin-fixed paraffin-embedded tissue sections, using the following antibodies and conditions: desmin (Sigma-Aldrich, St Louis, MO, DE-U-10, 1:5000, citrate buffer pressure cooker), SMA (Sigma-Aldrich, 1A4, 1:20,000, no pretreatment), h-Caldesmon (Dako,

Carpinteria, CA, h-CD, 1:300, citrate buffer pressure cooker), MDM2 (EMD Millipore, Billerica, MA, 1F2, 1:15, citrate buffer pressure cooker), CDK4 (Cell Signaling, Danvers, MA, D9G3E, 1:400, citrate buffer pressure cooker), estrogen receptor (ER) (Dako, ER-1D5, 1:100, citrate buffer pressure cooker) and HMGA2 (BioCheck, Foster City, CA, HMGA2-P1, 1:1000, citrate buffer pressure cooker). Immunostained sections that had been performed at the time of diagnosis were reviewed, except ER and HMGA2, which were added for this study in all cases with available unstained slides. Appropriate controls were used throughout. Clinical course and follow-up data, when available, were kindly provided by the referring pathologists and clinicians (see the Acknowledgements section). This study was performed with the approval of the Institutional Review Board at the Brigham and Women's Hospital.

RESULTS

Clinical Findings

The clinical data for the 34 patients are summarized in Table 1. There were 32 women and 2 men (F:M = 16:1). Patient age at diagnosis ranged from 35 to 94 years (median, 55 y); two thirds of patients were in the fifth or sixth decades. All tumors presented in deep-seated locations, most frequently occurring in retroperitoneum, including pelvic retroperitoneum (16 cases, 47%), followed by pelvic cavity/pelvis not otherwise specified (5 cases, 15%), abdominal wall (4 cases, 12%), intra-abdominal sites (including stomach) (3 cases, 9%), inguinal/vulval/groin region (3 cases), lower extremity (2 cases), and buttock (1 case). Patients had either no symptoms, pain, or abdominal distension. Some patients noticed an enlarging mass. The tumors were occasionally found incidentally by computed tomography imaging or during abdominal surgery for another disease.

Follow-up information was available for 17 of 34 patients (50%), ranging from 1 to 202 months (mean follow-up, 41 mo). None has developed local recurrence or metastasis, emphasizing the benign clinical behavior of myolipoma. Fifteen of 17 patients (88%) were alive without evidence of disease after 1 to 115 months (mean, 32 mo), and 2 patients had died from other causes after 20 and 202 months, respectively. For many patients there were no follow-up data, as patients were often discharged from care after the benign diagnosis.

Pathologic Findings

The tumor size ranged from 2.4 to 60 cm (median, 10.5 cm). Grossly, tumors were nodular or lobulated, well

TABLE 1. Clinicopathologic Characteristics of 34 Cases of Myolipoma of Soft Tissue

Case No.	Age	Sex	Site (Side)	Size (cm)	Resection Margins	SMA	Desmin	Caldesmon
1	42	F	Retroperitoneum	3	R0	Positive	Positive	NA
2	60	F	Retroperitoneum (R)	13	R1	Positive	Positive	NA
3	75	F	Retroperitoneum	10.5	NA	Negative	Positive	NA
4	66	F	Abdominal wall	6.5	NA	NA	Positive	NA
5	61	F	Pelvic cavity	6.9	NA	Positive	Positive	NA
6	68	F	Abdomen/pelvis	NA	NA	NA	NA	NA
7	70	F	Pelvis (L) (Extraperitoneal)	8	R0	Positive	Positive	NA
8	51	F	Retroperitoneum	NA	NA	Positive	Positive	NA
9	54	F	Retroperitoneum (R)	9	NA	NA	NA	NA
10	57	F	Retroperitoneum (R)	24	R0	Positive	Positive	NA
11	35	F	Retroperitoneum/Pelvis	5.2	NA	NA	Positive	NA
12	49	F	Pelvic cavity (L)	15.2	R0	NA	Positive	NA
13	64	F	Abdominal wall	NA	NA	Positive	Positive	NA
14	79	F	Abdominal wall	6	R0	Positive	Positive	Positive
15	50	F	Retroperitoneum/Pelvis	18	R0	NA	Positive	NA
16	67	F	Retroperitoneum	NA	NA	Positive	Positive	Positive
17	53	F	Retroperitoneum/pelvis	28	R0	NA	NA	NA
18	60	F	Stomach	2.4	NA	Positive	Positive	Positive
19	64	M	Thigh (R)	13	R0	Positive	Positive	NA
20	54	F	Abdominal wall	8.5	NA	NA	Positive	NA
21	50	F	Retroperitoneum	15	NA	Positive	Positive	Positive
22	45	F	Retroperitoneum/pelvis	12.5	NA	Positive	Positive	Positive
23	65	F	Retroperitoneum	12	NA	NA	NA	NA
24	52	F	Inguinal region (L)	16	R0	NA	NA	NA
25	54	F	Vulva/inguinal canal (R)	10.5	NA	NA	NA	NA
26	94	F	Pelvis NOS	9	NA	Positive	Positive	NA
27	59	F	Omentum	3.5	NA	Positive	Positive	NA
28	53	F	Retroperitoneum	30	R0	Positive	Positive	NA
29	55	F	Retroperitoneum	14	R1	Positive	Positive	NA
30	38	F	Buttock	25	R0	Positive	Positive	NA
31	50	F	Intra-abdominal	60	R0	Positive	Positive	NA
32	60	F	Pelvic cavity	NA	NA	Positive	Positive	NA
33	36	M	Calf	NA	NA	NA	NA	NA
34	55	F	Groin	5	NA	NA	NA	NA

ANED indicates alive with no evidence of disease; DOC, died of other causes; NA, not available.

circumscribed, and usually surrounded by a thin capsule. The cut surface showed an admixture of yellowish adipose tissue and variably sized, whorled, tan-whitish nodules, which depended on the amount and distribution of the smooth muscle component (Fig. 1). Some tumors contained myxoid areas. There was no evident hemorrhage or necrosis except in 1 case with focal infarction (case #28).

Microscopically, the tumors were composed of an intimate admixture of mature fat cells and spindle-shaped cells in very variable proportions (Fig. 2; Table 1). The spindle cells were generally characterized by brightly eosinophilic cytoplasm, blunt-ended nuclei, and inconspicuous nucleoli and were arranged in fascicles (Fig. 2B). The appearance of thin spindle cell bundles interdigitating with adipocytes was characteristic (Fig. 2C). There were variable amounts of edematous or hyalinized stroma, in which spindle cells were sparse (Fig. 2D). Focal lymphocytic infiltrates and scattered mast cells were usually seen in the spindle cell areas. Mitoses were present in only 1 case (case #33), numbering $<1/10$ HPF. Tumor cells were cytologically bland in typical cases, whereas some examples showed the following unusual features focally: hypercellular fascicular pattern of spindle cell component (cases #10 and 34) (Fig. 3A), degenerative nuclear atypia (case #5) (Fig. 3B), round cell morphology (case #10) (Fig. 3C), focally prominent hemosiderin deposition (case #34) (Fig. 3D), metaplastic cartilage (case #17) (Fig. 3E), metaplastic bone (case #33) (Fig. 3F), and eosinophil infiltrates (case #10). There was no necrosis, but 2 tumors showed hyaline change due to infarction (cases #5 and 28). The lesions usually contained variable numbers of small blood vessels and uterine leiomyoma-like thick-walled vessels but never showed more granular eosinophilic cytoplasm, epithelioid morphology, or perivascular orientation, as would be expected in angiomyolipoma.

Immunohistochemically, spindle cells showed strong and diffuse positivity for desmin (26/26 cases, 100%) (Fig. 4A) and SMA (20/21 cases, 95%) (Fig. 4B), indicating smooth muscle differentiation. H-Caldesmon was also positive (5/5 cases, 100%). In addition there was diffuse nuclear positivity for ER, mainly in smooth muscle cells but focally in adipocytes, in 13/15 cases, among which 2 of the 15 were male patients. The ER-negative cases occurred in 1 female and 1 male. Nuclear positivity for HMGA2 was identified in both spindle cells and fat cells in 15 of 25 cases (60%) (Fig. 4C), although positivity of adipocytes was less than in spindle cells. MDM2 and

TABLE 1. *(continued)*

MDM-2	CDK-4	HMGA-2	Myomatous/Lipomatous Component (%)	Recurrence	Follow-up Status (mo)
Negative	NA	Negative	50/50	None	ANED (6)
Negative	NA	Negative	35/65	None	ANED (1)
NA	NA	NA	NA	None	ANED (4)
Negative	Negative	Positive	30/70	NA	NA
Negative	Negative	Negative	40/60	None	NA
NA	NA	NA	NA	NA	NA
NA	NA	Positive	50/50	None	ANED (3)
Negative	Negative	Positive	90/10	NA	NA
NA	NA	NA	NA	None	ANED (41)
Positive (scattered cells)	Negative	Positive	80/20	None	ANED (43)
NA	NA	NA	NA	NA	NA
Negative	Negative	Positive	70/30	None	ANED (1)
Negative	Equivocal	Positive	50/50	NA	NA
Negative	Negative	Negative	10/90	None	ANED (1)
NA	NA	Positive	60/40	None	ANED (16)
Negative	NA	Positive	80/20	NA	NA
Negative	Negative	Positive	50/50	None	ANED (2)
Negative	NA	Positive	40/60	NA	NA
Negative	Negative	Negative	80/20	None	ANED (112)
Negative	NA	Negative	20/80	NA	NA
Negative	NA	Positive	60/40	None	ANED (115)
NA	NA	Negative	80/20	None	ANED (106)
NA	NA	NA	50/50	NA	NA
NA	NA	NA	NA	None	NA
NA	NA	NA	80/20	NA	NA
NA	NA	Negative	10/90	NA	NA
NA	NA	Positive	60/40	NA	NA
NA	NA	Negative	20/80	None	ANED (24)
NA	NA	Positive	50/50	None	DOC 20)
NA	NA	Positive	40/60	None	ANED (1)
NA	NA	Positive	90/10	None	DOC (202)
NA	NA	Negative	40/60	NA	NA
NA	NA	NA	50/50	NA	NA
NA	NA	NA	60/40	NA	NA

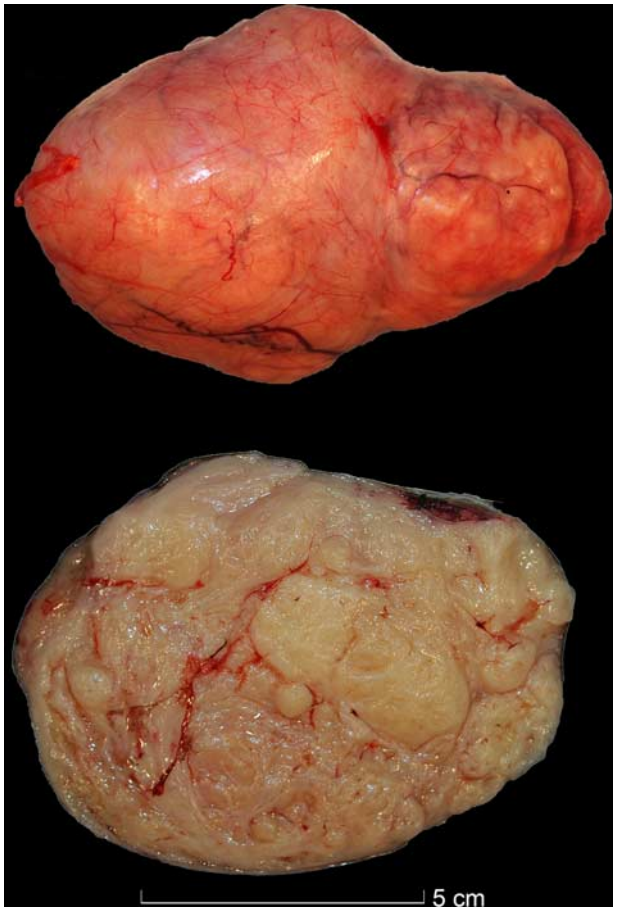

FIGURE 1. Myolipoma is usually thinly encapsulated and has a variably fatty or more tan-colored, fleshy cut surface (Image courtesy of Dr Richard Cheney, Roswell Park, NY).

CDK4 were usually negative (14/15 cases, 8/9 cases, respectively), with 2 exceptions: 1 tumor stained focally MDM2-positive and CDK4-negative (case #10), and the other stained CDK4-weakly positive (equivocal) and MDM2-negative (case #13). Both cases exhibited immunoreactivity for HMGA2. The case with nuclear atypia (case #5) was negative for MDM2, CDK4, and HMGA2.

DISCUSSION

Since Meis and Enzinger[2] described 9 cases of myolipoma in 1991, 32 additional convincing cases have been reported.[3,4,12–40] We have excluded the following cases from our literature review: (1) sacral myolipoma, (2) Müllerian-type myolipoma (lipoleiomyoma), and (3) those reports lacking a clear description or illustration. The first, sacral myolipoma, is a lesion that consists of fat cells and skeletal muscle cells, likely representing a developmental anomaly[41,42]; although the name is the same as "myolipoma," it completely differs from myolipoma of soft tissue, which consists of fat and smooth muscle cells. The second, Müllerian-type myolipoma, is better to distinguish from myolipoma of soft tissue, because Müllerian-origin myolipoma involving round ligament, broad ligament, or fallopian tube is generally considered the same as or close to uterine "lipoleiomyoma." The reported cases with little or no description or illustration could not easily be verified as myolipoma.

In the previously reported cases, there were 32 female and 9 male patients (F:M = 3.5:1), ranging from 4 to 83 years in age (median 53 y). The affected sites were retroperitoneum (10 cases, 24%), intra-abdominal sites (7 cases, 17%), pelvis (5 cases, 12%), abdominal wall (5 cases, 12%), inguinal region (2 cases), and trunk (1 case), but rare unusual sites have also been reported, specifically subcutaneous tissue of trunk or head/neck (3 cases), orbit (2 cases), nose (1 case), tongue (1 case), breast (1 case), pericardium (1 case), spinal-intramedullary (1 case), and anus (1 case). Tumor size ranged from 2 to 35 cm, but the tumors in superficial locations were smaller (2.8 to 5.5 cm, median 3.25 cm) than deep-seated tumors (2 to 35 cm, median 16 cm). Histologically, all cases showed an admixture of mature fat cells and smooth muscle cells. Only 1 reported case showed bizarre nuclei in the smooth muscle component,[32] as in 1 of our cases. Immunohistochemical studies were performed in 29 previously reported cases (70%). Most of the cases were positive for SMA and/or desmin (28/29 cases, 97%). MDM2 was negative (1/1 case, 100%). To date, only 1 case has been reported that was negative for HMGA2,[11] whereas cytogenetic aberration of *HMGA2* has been reported in 2 cases.[3,4] HMB-45 was consistently negative (13/13 cases, 100%). ER and progesterone receptor were examined in 6 and 5 cases and positivity was found in 4 (67%) and 3 (60%) cases, respectively. Follow-up data were available in 16 reported cases (39%, from 1 to 120 mo, mean 38 mo). There was no recurrence except 1 incompletely excised case, which needed further debulking of the tumor.

Histologically, myolipoma of soft tissue is composed of an intimate admixture of mature adipocytes and well-differentiated smooth muscle cells in very variable proportions. There is no cytologic atypia in typical myolipoma, whereas rare examples showed unusual features in our series. The following unusual findings could potentially mimic a malignant tumor: hypercellular fascicular pattern of spindle cells, degenerative nuclear atypia, and focal round cell morphology. While these morphologic variations may be seen in leiomyoma, mitotic activity and coagulative necrosis are the most important clues to a diagnosis of malignancy. In addition, 2 cases exhibited metaplastic cartilage or bone, which are also occasionally seen in lipoma (so-called "osteochondrolipoma").

In our study, 60% of the cases were immunoreactive for HMGA2. HMGA2 is an architectural transcription factor located between MDM2 and CDK4 on chromosome 12q, which regulates normal cell growth and differentiation, and plays an important pathogenetic role in various epithelial and mesenchymal tumors.[43] Upregulation of HMGA2 by translocation has been reported in benign mesenchymal tumors including conventional lipoma (eg, *HMGA2-LPP*)[7] and a subset of uterine leiomyomas (*HMGA2-RAD51B*).[8] In contrast, overexpression of HMGA2 in malignant tumors, such as liposarcoma and

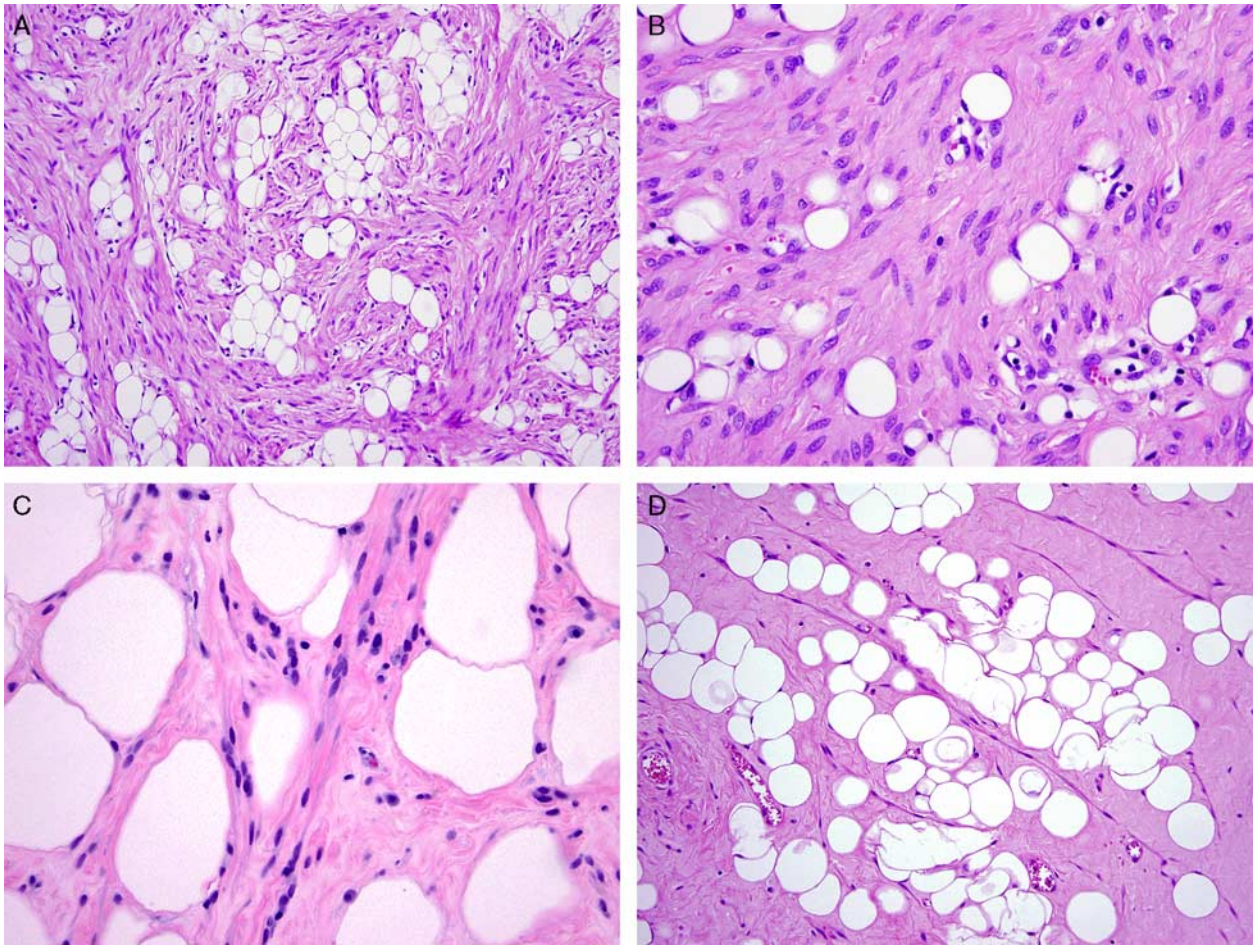

FIGURE 2. Myolipoma—note the circumscription, intimately admixed smooth muscle cells and adipocytes, generally bland cytomorphology, and occasionally hyaline stroma.

LMS, is thought to be induced by Let-7 microRNA repression[6,44–46] or by an unknown mechanism without translocation. Recently, Panagopoulos et al[4] described fusion of the *HMGA2* and *C9orf92* genes resulting from a t(9;12)(p22;q14) in 1 case of myolipoma. Our data support probable rearrangement of *HMGA2* in myolipoma. In addition, 2 cases showed either focal MDM2 positivity or weak CDK4 positivity, which was unconvincing and likely of no significance.

Given the striking predilection for retroperitoneal/abdominal locations, the question arises as to the potential relationship between myolipoma and deep-seated leiomyomas in these locations, which also show striking female predominance and frequent positivity for ER. Mature fat has been described as a component of some deep leiomyomas[47,48] but is not commonly as prominent as in the lesions described here, in which at least 50% of cases were composed of at least 50% fat and often more. Nevertheless, there is a distinct and credible possibility that these lesions represent the morphologic continuum of a single "entity," and hopefully this will become clearer with the future acquisition of additional molecular genetic data.

The histologic differential diagnosis of myolipoma is other soft tissue tumors characterized by the admixture of fat cells and spindle cells: spindle cell lipoma, mammary-type myofibroblastoma (MTMF), lipoleiomyosarcoma (L-LMS), dedifferentiated liposarcoma (DDLPS), and fat-forming solitary fibrous tumor (SFT).

Spindle cell lipoma (SCL) occurs typically in subcutaneous tissue of neck, shoulder, and back with a male predominance, being composed of an admixture of adipocytes, short spindle cells, and ropey collagen bundles. SCL often has myxoid stroma, and spindle cells have short stubby nuclei and indistinct, pale cytoplasm, easily distinguished from myolipoma morphologically. Immunohistochemically, SCL does not show diffuse positivity for desmin and SMA.

Mammary-type myofibroblastoma (MTMF) is a part of the 13q/Rb family of tumors closely related to SCL[49] and also resembles SCL morphologically. Affected site and age distribution are similar to myolipoma; furthermore, MTMF often shows diffuse immunoreactivity for desmin, indicating myofibroblastic differentiation.[50,51] However, it can be distinguished on the basis of morphology of the spindle cells and diffuse immunoreactivity

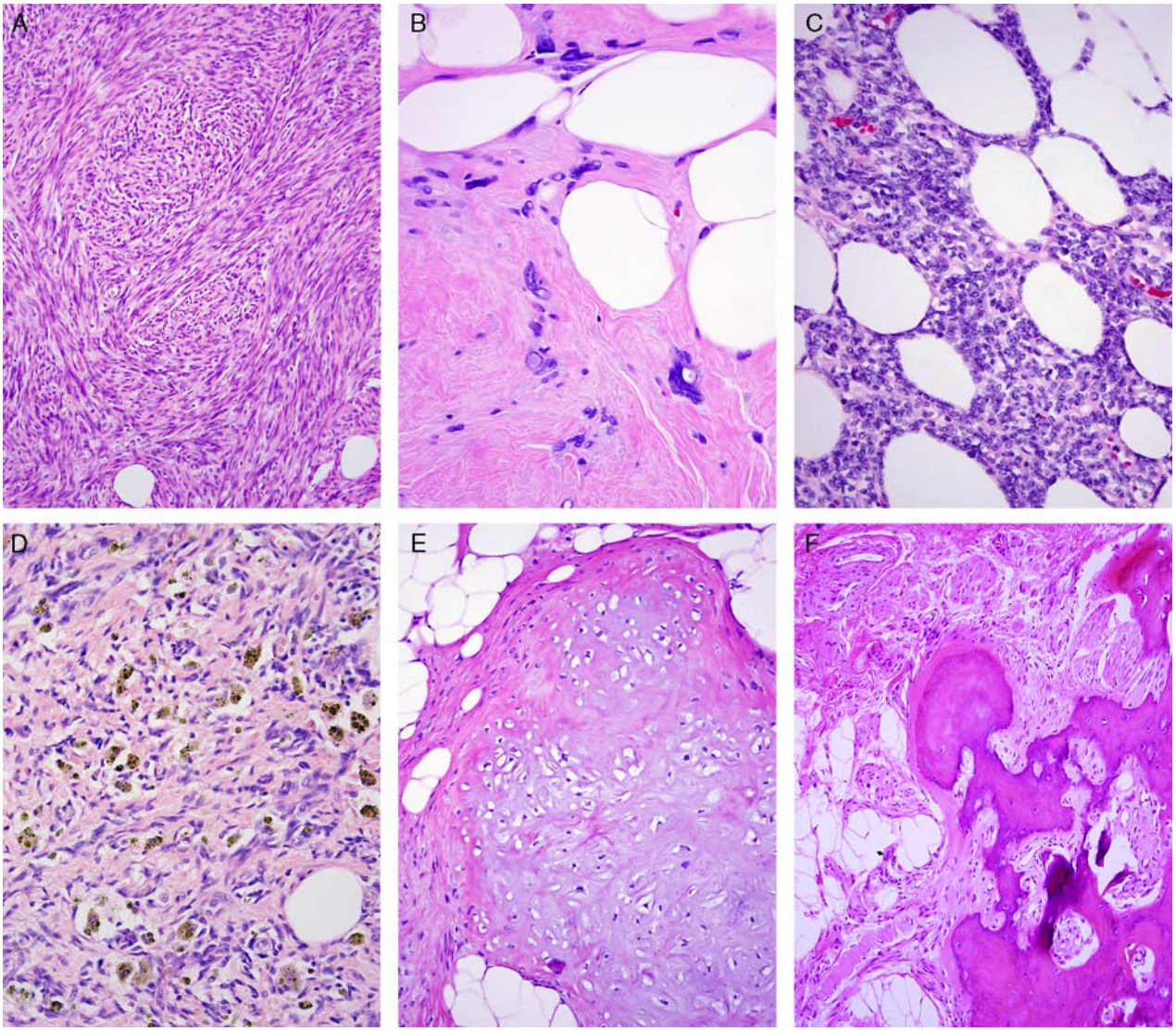

FIGURE 3. Myolipoma—occasional features showed unusual features such as hypercellularity (A), degenerative nuclear atypia (B), focal round cell morphology (C), prominent stromal hemosiderin (D), and either cartilaginous (E) or osseous (F) metaplasia.

for CD34 in MTMF. Furthermore, MTMF often shows Rb loss.[49,50]

L-LMS is composed of WDLPS and a well-differentiated smooth muscle component.[52,53] It arises in middle-aged adults, tends to be large, and occurs in deep-seated locations. The smooth muscle component is benign-looking or low-grade LMS with mild nuclear atypia, so the appearance may resemble myolipoma. L-LMS is a variant of WDLPS; adipocytes vary in size, and the lesion contains lipoblasts or atypical cells with hyperchromatic nuclei in irregular fibrous septa. Immunohistochemically, positivity for MDM2 and CDK4 has been reported in both liposarcoma and smooth muscle components.[54]

DDLPS sometimes shows heterologous smooth muscle differentiation in the areas of dedifferentiation.[55] The component of LMS has obvious nuclear atypia and high mitotic activity. Although HMGA2 is usually positive in DDLPS, MDM2 and CDK4 are also positive in almost all cases.

Fat-forming SFT is a variant of SFT, characterized by an admixture of fibroblastic spindle cells and fat cells. The spindle cells are arranged in a "patternless pattern" with branching hemangiopericytoma-like vessels and nuclear expression of STAT6, which is useful for the diagnosis of fat-forming SFT, as in conventional SFT.[56–58]

In addition, myolipoma may be confused with angiomyolipoma, because the name is similar. Angiomyolipoma is part of the PEComa family, caused by *TSC1* or *TSC2* mutation, and often affects the kidney in patients with tuberous sclerosis. The lesions consist of mature fat cells, smooth muscle cells, and thick-walled vessels. The smooth muscle cells often show epithelioid morphology with eosinophilic granular cytoplasm, typically surrounding

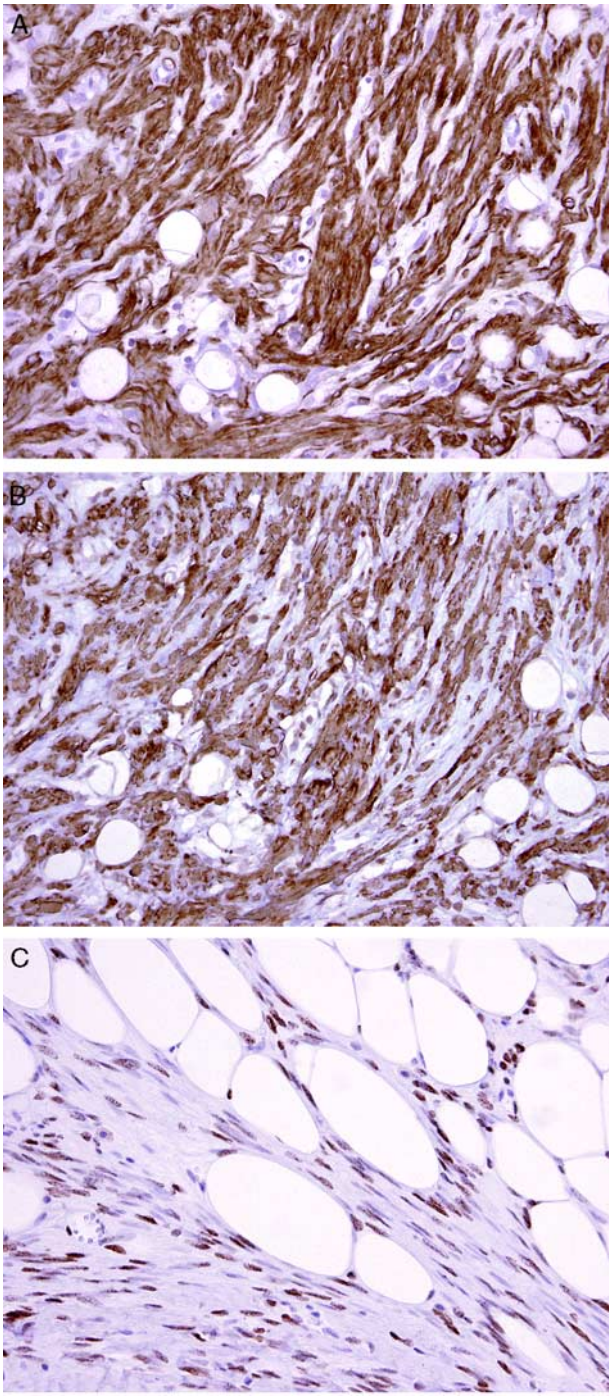

FIGURE 4. Myolipoma—showing diffuse positivity for desmin (A), smooth muscle actin (B), and nuclear positivity for HMGA2 in both smooth muscle cells and adipocytes (C).

vessel walls. Myolipoma seems never to show epithelioid morphology. Immunohistochemically, angiomyolipoma is positive for melanocytic markers such as HMB-45 and Melan A, whereas myolipoma is consistently negative.

In summary, myolipoma of soft tissue is a distinctive tumor characterized by the admixture of mature adipocytes and well-differentiated smooth muscle cells, arises most commonly in deep-seated locations especially retroperitoneum, pelvis, and intra-abdominal sites of middle-aged women, and the clinical course is completely benign. We found HMGA2 nuclear staining in 60% of cases by immunohistochemistry, suggesting possible *HMGA2* rearrangement. Further study is required to establish the molecular genetic pathogenesis of myolipoma of soft tissue and thereby hopefully to define the precise relationship with deep-seated leiomyomas in similar anatomic locations.

ACKNOWLEDGMENTS

The authors thank the following pathologists and clinicians who kindly provided case material and clinical follow-up when available: Dr N.P. Libbey, Providence, RI; Dr R.T. Cheney, Buffalo, NY; Dr D.K. van Horn, Newport Beach, CA; Dr E. Pham, Tustin, CA; Dr J.M. Hogan, Cork, Ireland; Dr L.D. Roanh, Ha Noi, Vietnam; Dr D.H. Kandil, Worcester, MA; Dr A. Tawil, Beirut, Lebanon; Prof. F. Bertoni, Bologna, Italy; Dr G. Mazzoleni, Bolzano, Italy; Dr E. Vlodavsky, Haifa, Israel; Dr W. Sanford, Manchester, NH; Dr J.T. Buchanan, Nashua, NH; Dr E. Sung, Sacramento, CA; Dr X.S. Liu, Albuquerque, NM; Dr P. Dalton, Harbor City, CA; Dr K.F. Forsthoefel, Columbus, OH; Dr F. MacSweeney, London, UK; Dr S. Ramachandra, London, UK; Dr T. Ardaman, Irving, TX; Dr J.L. Killeen, Honolulu, HI; Dr M. Kierson, Bethlehem, PA; Dr A. Mohanty, Pittsburgh, PA; Dr M. Lovell, San Antonio, TX; Dr R.L. Wolbarsht, New Bedford, MA; Dr J. Khorsand, New Bedford, MA; Dr W. Zhang, New Bedford, MA; Dr J.R. Slemmer, Cleveland, TN; Dr K. Dakin-Haché, Halifax, Canada; Dr F. Khalil, Tampa, FL; Dr K.G. Allen, Jackson, MS; Dr B.J. Williams, Plano, TX; Dr N. de Saint Aubain Somerhausen, Brussels, Belgium; Prof. M. Leader, Dublin, Ireland; Dr F. Ellinger, Marilia, Brazil; Dr D. Haynik, Scottsdale, AZ; Dr M. Demeure, Scottsdale, AZ; Dr S. M. Ismail, Cardiff, UK.

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