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Hibernoma Mimicking Atypical Lipomatous Tumor: 64 Cases of A Morphologically Distinct Subset

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Abstract

Hibernoma is a benign adipocytic tumor with predilection for subcutaneous tissue of the thigh, upper trunk, and neck of middle-aged adults. 11q13 rearrangement resulting in *MEN1/AIP* codeletion is characteristic. Hibernomas are composed, in varying proportions, of brown fat cells, mature adipocytes, and microvacuolated lipoblast-like cells. Examples containing predominantly multivacuolated lipoblast-like cells are uncommon and distinction from atypical lipomatous tumor (ALT) is important for clinical management. We herein present the clinicopathologic features of 64 hibernomas histologically mimicking ALT. MDM2 and CDK4 immunohistochemistry as well as *MDM2* fluorescence in-situ hybridization (FISH) were performed in a subset of cases. Clinical and follow-up information were obtained from referring pathologists. Thirty-four patients were male and 30 female, with a median age of 43 years (range, 24–78 years). The tumors were well-circumscribed and mostly deeply located (53/64 cases, 83%) with a median tumor size of 12.9 cm (range, 3.5–23 cm) and predilection for the thigh (42/64 cases, 66%). Histologically, large cells with prominent lipoblast-like cytoplasmic fatty vacuoles and small central nuclei were present to a prominent degree in all cases, along with mature univacuolated adipocytes and smaller numbers of large, finely vacuolated cells with eosinophilic granular cytoplasm. Nuclear atypia and mitoses were absent. None of the 39 cases tested showed CDK4 and MDM2 overexpression or *MDM2* amplification. Follow-up, available for 16/64 cases (median, 47 months; range, 1–165 months), revealed no recurrences or metastases. Hibernoma mimicking ALT shows predilection for deep soft tissue, especially in the thigh. These tumors behave in a benign fashion and MDM2/CDK4 negativity may be useful in excluding ALT.

Keywords

Hibernoma; brown fat; atypical lipomatous tumor; liposarcoma

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Introduction

Hibernoma, a benign brown fat tumor, was first described as “pseudolipoma” by Merkel in 1906¹ and was termed “hibernoma” by Gery in 1914 because of its morphologic resemblance to the brown fat observed in hibernating animals.² Hibernomas are uncommon and account for <2% of benign lipomatous tumors and 1% of all adipocytic tumors.³ They mostly occur in middle-aged adults with equal gender distribution, tend to be large with an average tumor size of 9.3 cm (range, 1–24 cm), and show a predilection for subcutaneous tissue of the thigh, upper trunk, and neck.⁴ Deep seated hibernomas account for <15% of cases.⁴ Hibernomas are benign tumors that do not recur after complete resection and no metastases have been reported.⁴ 11q13 rearrangement resulting in *MEN1* and *AIP* co-deletion is a characteristic finding.^{5, 6} Only a single case of hibernoma with (9;11)(q34;q13) translocation has been reported.⁷ Hibernomas are composed, in varying proportions, of three cell types which include large, finely vacuolated cells with eosinophilic granular cytoplasm (brown fat cells), cells with larger fatty vacuoles resembling lipoblasts, and mature adipocytes. In addition, rare myxoid, lipoma-like, and spindle cell variants of hibernoma have been described.⁴ Immunohistochemically, most hibernomas are positive for S-100 protein and usually negative for CD34.⁴

We herein present the clinicopathologic features of 64 cases of a distinct morphologic subset of hibernomas containing predominantly multivacuolated lipoblast-like cells, which may therefore be confused histologically with atypical lipomatous tumor (ALT).

Materials and Methods

Sixty-four cases diagnosed as hibernoma mimicking ALT between 2000 and 2017 were retrieved from the consultation file of one of the authors (C. D. M. F.). Hematoxylin and eosin stained sections were reviewed when available, and pathologic features were re-evaluated by at least two of the authors. Immunohistochemical staining was performed on 4- μ m-thick formalin-fixed paraffin-embedded tissue sections, using monoclonal antibodies directed against MDM2 (EMD Millipore, Billerica, MA, clone 1F2, 1:15, citrate buffer pressure cooker) and CDK4 (Cell Signaling, Danvers, MA, clone D9G3E, 1:400, citrate buffer pressure cooker). Appropriate controls were used throughout. *MDM2* fluorescence in-situ hybridization (FISH) was performed in a subset of cases at the time of diagnosis. Clinicopathologic and follow-up data, when available, were kindly provided by the referring pathologists and clinicians (see Acknowledgements).

This study was performed with approval of the Institutional Review Board at Brigham and Women’s Hospital.

Results

Clinicopathologic Findings

Table 1 summarizes the clinicopathologic data of 64 cases of hibernoma mimicking ALT. Thirty-four patients were male and 30 female (M:F=1.1:1), with a median age at diagnosis of 43 years (range, 24–78 years). Grossly, the hibernomas were well-circumscribed and

mostly subfascial (i.e., deeply located) (53/64 cases, 83%) or superficial (11/64 cases, 17%). The majority of tumors occurred in the thigh (42/64 cases, 66%), followed by buttock (8/64 cases), inguinal region/groin (6/64 cases), trunk (3/64 cases), and less commonly axilla, foot, popliteal fossa, leg (not specified), and stomach (one case each). Most patients presented clinically with a painless palpable mass. The median tumor size was rather large, with a median largest dimension of 12.9 cm (range, 3.5–23 cm).

Grossly, the tumors were lobulated, well circumscribed, and surrounded partially or completely by a thin capsule in a subset of cases (21/64 cases), whereas the remaining cases were circumscribed but not clearly encapsulated. The cut surface varied from yellow to brown, and only 5/64 cases showed focal “necrosis”. Microscopically, the tumor cells were arranged in lobules separated by thin fibrous septa and were composed of three cell populations, to varying degrees (Fig. 1): finely microvacuolated cells with clear cytoplasm and central or less frequently eccentrically located small vesicular nuclei with single central nucleolus (lipoblast-like cells) without scalloping of the nuclei (Fig. 2), mature adipocytes, and brown fat cells with granular eosinophilic cytoplasm. The relative proportions of lipoblast-like cells per case ranged from 10% to 80%, but in areas of all cases these cells were strikingly predominant. No cytologic atypia, mitoses, or areas of necrosis were observed histologically in any of the cases. The hibernomas contained variable numbers of thin-walled, blood vessels of varying size and 7/64 cases contained occasional thick-walled vessels. Resection margins were positive in 12/64 cases (19%). None of the tumors tested expressed MDM2 (0/33) or CDK4 (0/34) by immunohistochemistry (Fig. 3) and FISH, performed in six cases, revealed no *MDM2* amplification.

Follow-up

Following a benign diagnosis, follow-up information was available for only 16/64 (25%) cases with a median follow-up time of 47 months (range, 1–165 months) and revealed that none of the patients developed local recurrence or metastasis, emphasizing the benign behavior of hibernoma. At the time of follow-up, all patients were alive without evidence of disease. Most patients had not been seen again after initial treatment.

Four cases were considered recurrent by the referring institution, two of which had known positive margins in the initial resection, suggesting incomplete resection rather than true recurrence.

Discussion

Hibernoma is an uncommon benign tumor composed of brown fat and most frequently arises in the thigh, upper trunk, and neck. Rare cases occurring in the axilla, groin, supraclavicular area, buttock, scalp, abdominal wall, breast, flank, pleura, adrenal, spine, larynx, bone, and spermatic cord have been described.^{4, 8–22}

We present herein the clinicopathologic findings in 64 cases of hibernoma with predominant microvacuolated lipoblast-like cells, referred in consultation with a diagnostic concern for ALT in 42/64 (66%) of cases, leading to preoperative radiation therapy in one case (#52). In addition to the classical variant of hibernoma, accounting for ~80% of cases, myxoid (9%),

lipoma-like (7%), and spindle cell (2%), variants have been described in the literature⁴, but tumors with such striking ALT-like features have not been emphasized previously. Because of the biased nature of consultation material, among which “classical” hibernomas are rare, it is not possible to determine or estimate the proportion of hibernomas which mimic ALT. It is also impossible for us to reliably assess the extent of lipoblast-like cells in these 64 cases, given the variability in sampling and number of slides submitted in the setting of consultation cases. It is abundantly clear, however, that most of the referring pathologists were concerned about excluding ALT, suggesting that, in the slides they saw, lipoblast-like cells were a major and striking component (which was often mentioned in the referral letters).

The median patient age of 43 years and a slight male predominance observed in our study are in concordance with the findings in a large series of 170 hibernomas described by Furlong et al.⁴ In their study, the authors find that only 30% of all hibernomas occurred in the thigh and 11% were deep-seated.⁴ In our series, hibernoma mimicking ALT shows a clear predilection for the thigh (66%) and deep/intramuscular location (83%). Of note, in two smaller case series of hibernoma, the thigh was reported as the most common location (in 21% and 76% of cases, respectively).^{18, 19}

All cases in our series were diagnosed based on morphologic features and additional immunohistochemical workup is generally not needed to establish the diagnosis of hibernoma. None of the cases tested (in total 39) showed MDM2/CDK4 overexpression or *MDM2* amplification which is useful to rule out ALT as the main histologic differential diagnosis in this hibernoma subtype.

ALT frequently occurs in the lower extremities and is a locally aggressive tumor that comprises adipocytic (or lipoma-like), sclerosing, inflammatory, and spindle cell histologic subtypes.³ The designation ALT is used for lesions that are considered amenable to surgical resection, whereas well-differentiated liposarcoma is used to designate lesions at non-extremity sites, e. g. retroperitoneum, which require more radical surgery in order to achieve clear margins. ALT does not have the potential to metastasize and in the extremities, rarely undergoes dedifferentiation, but local recurrence is observed in 20–30% of cases.

Histologically, ALT is composed of a mature adipocytic component to varying degrees, showing significant variation in cell size and at least focal nuclear atypia and hyperchromasia, usually in both adipocytes and stromal cells. The presence of scattered hyperchromatic, often multinucleate, stromal cells or multivacuolated lipoblasts (defined by the presence of single or multiple sharply marginated cytoplasmic vacuoles scalloping an enlarged hyperchromatic nucleus) contributes to the morphologic diagnosis.³ In contrast, the multivacuolated lipoblast-like cells observed in hibernoma exhibit small nuclei which are neither hyperchromatic nor atypical, the vacuoles tend to be smaller than those observed in true lipoblasts and the scalloping of the nuclei is minimal. Furthermore, in ALT, true multivacuolated lipoblasts are usually not as numerous as the lipoblast-like cells in hibernoma mimicking ALT. An additional morphologic feature favoring hibernoma is the presence of scattered cells with more granular eosinophilic cytoplasm (brown fat cells). It is

worth noting that exceedingly rare examples of well-differentiated liposarcoma (with *MDM2* gene amplification) exhibiting hibernoma-like areas have been reported.²³

MDM2 and *CDK4* overexpression resulting from ring or giant marker chromosomes and high level 12q13–15 amplification (including the *MDM2*, *CDK4*, and *HMGA2* loci) help distinguish ALT from hibernoma, which instead shows 11q13 rearrangements involving *AIP* and *MEN1*. Recently published data have shown that loss of *AIP* is likely responsible for the brown fat phenotype.²⁴

Distinction of hibernoma from ALT is clinically important as ALT requires complete resection and harbors a risk of local recurrence in ~30% of cases, whereas none of the hibernomas mimicking ALT in our series recurred locally. However, two thirds of cases were initially diagnosed as ALT (or had a differential diagnosis that included ALT) and the fact that one patient received preoperative radiation highlights the importance of establishing the correct diagnosis to prevent unnecessary and potentially harmful treatment.

In summary, hibernoma consisting predominantly of multivacuolated lipoblast-like cells, shows predilection for the thigh and other deep locations, and may be confused histologically with ALT. Negativity for *MDM2* and *CDK4* by immunohistochemistry and lack of *MDM2* amplification are useful in the distinction of these lesions.

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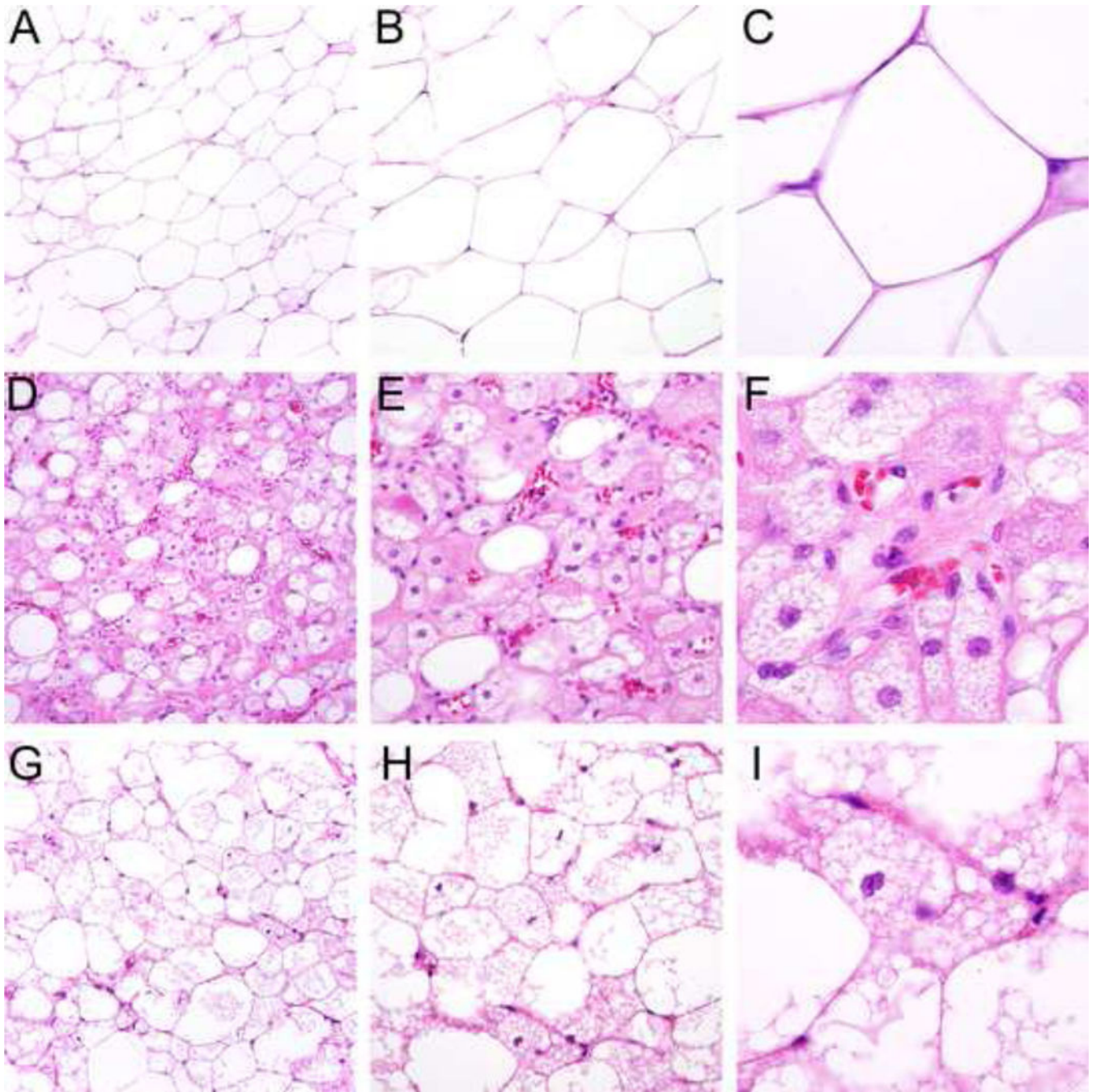


Figure 1. Morphologic spectrum of hibernoma: tumors consist in variable proportions of mature adipocytes containing a single cytoplasmic vacuole (A-C), large, finely vacuolated cells with eosinophilic granular cytoplasm (hibernoma cells) resembling brown fat (D-F) and multivacuolated lipoblastlike cells with small central nuclei (G-I), which were especially prominent in this case series (see Figure 2).

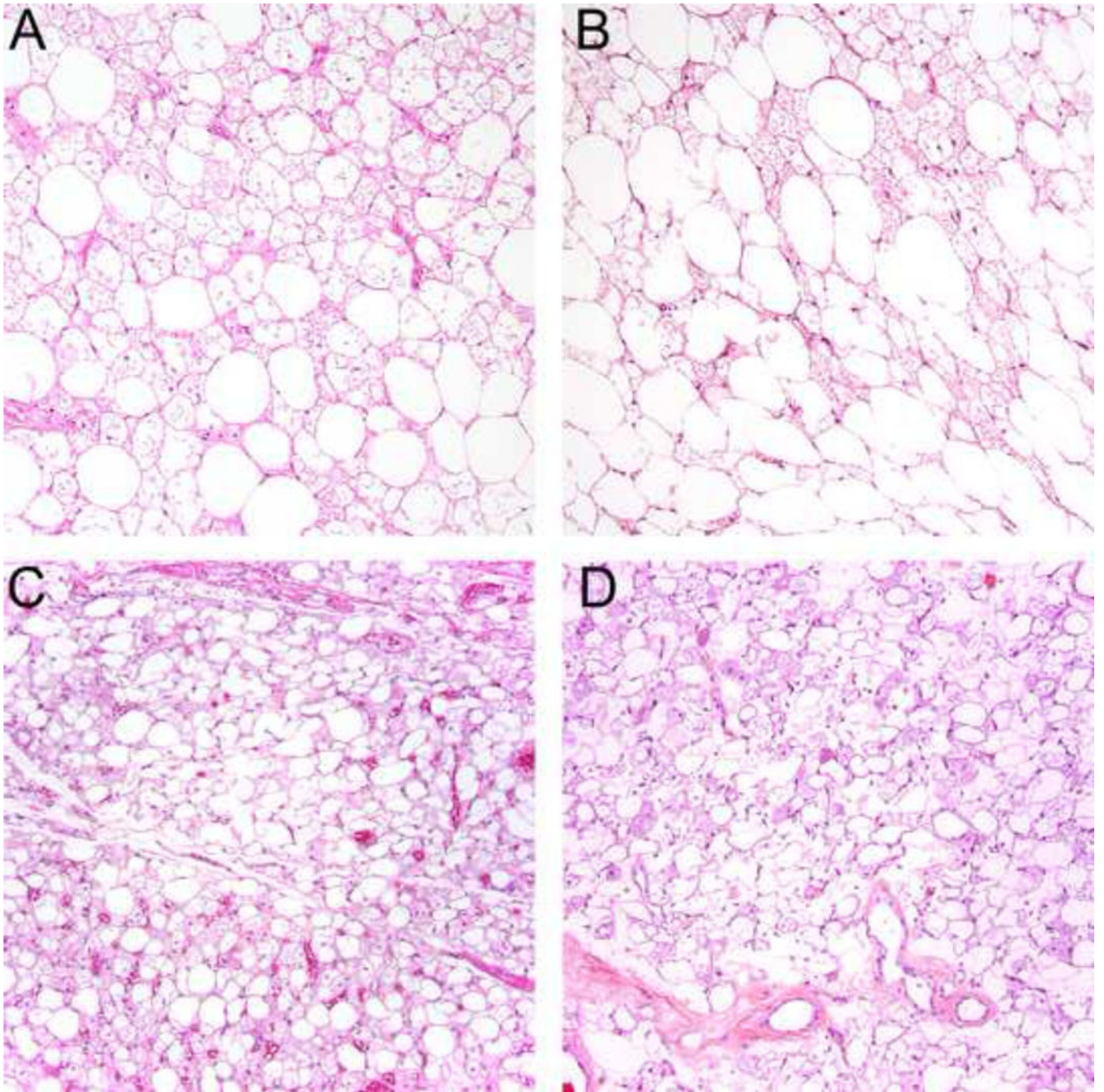


Figure 2. Areas of each tumor contained numerous multivacuolated lipoblast-like cells, often in sheets (A,B), but in others areas admixed brown fat cells and mature adipocytes were admixed (C-D).

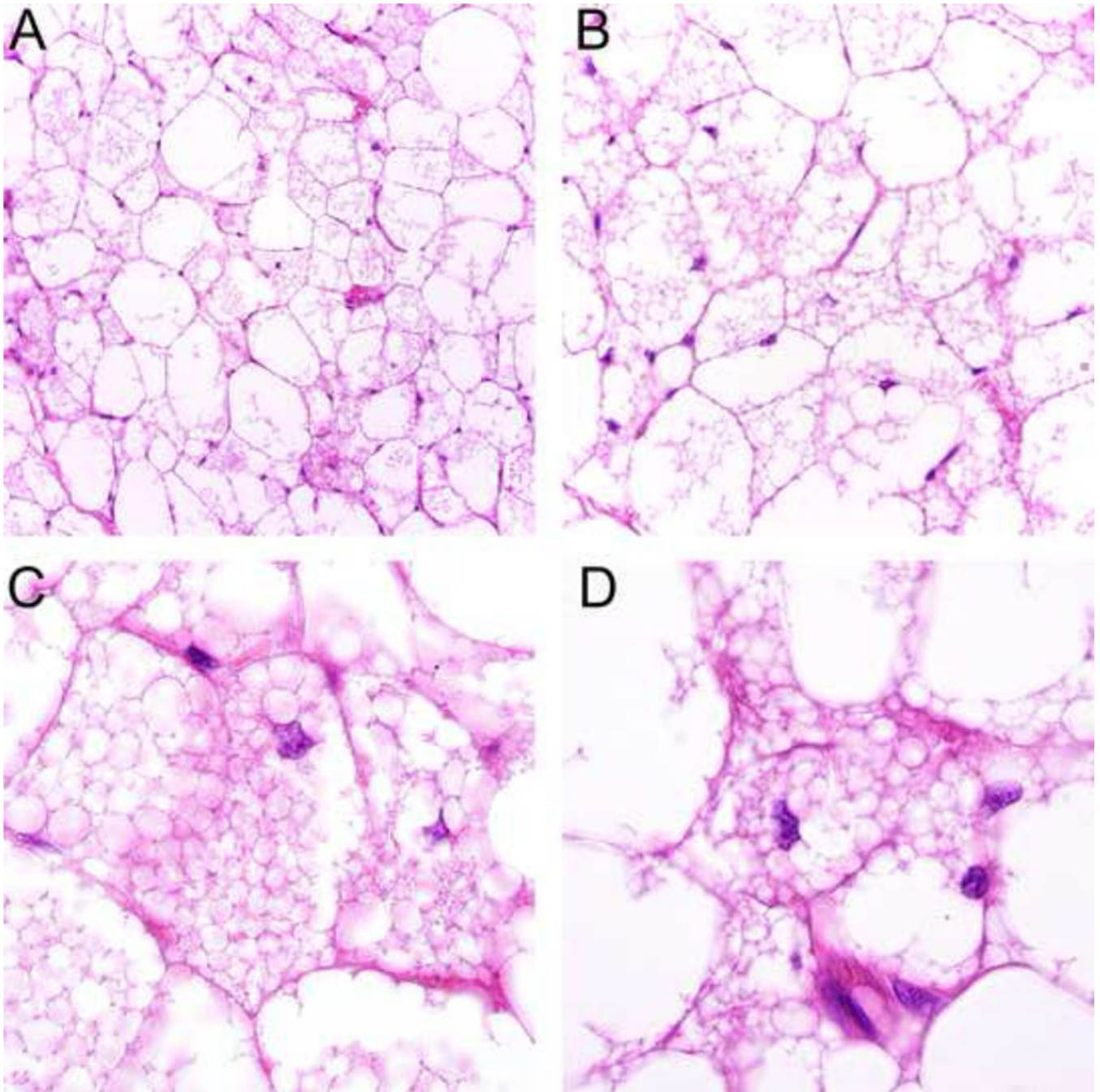


Figure 3. Prominent multivacuolated lipoblast-like cells in hibernoma mimicking atypical lipomatous tumor exhibit small nuclei without hyperchromasia or atypia and contain multiple small fatty vacuoles with minimal scalloping of the nuclei (A-D).

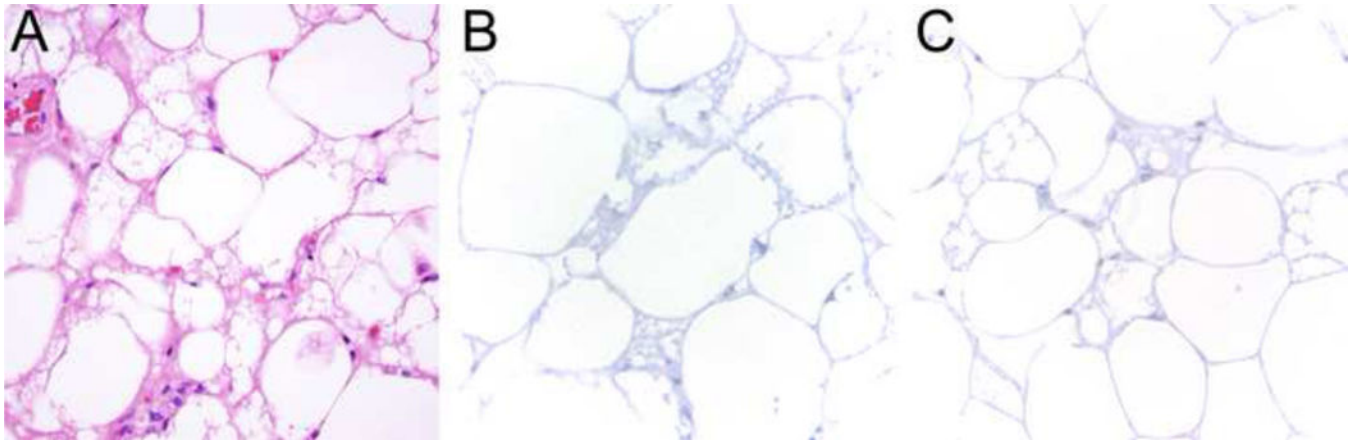


Figure 4.
The lipoblast-like cells in hibernoma mimicking atypical lipomatous tumor (A) are negative for MDM2 (B) and CDK4 (C) by immunohistochemistry.

Table 1

Clinicopathologic findings in 64 cases of hibernoma mimicking atypical lipomatous tumor.

Case no.	Age	Sex	Tumor site (side)	Tumor size (cm)	Margin status	MDM2 IHC	MDM2 FISH	CDK4 IHC	Follow up (months)
1	78	F	Inguinal region (R)	6	-	Negative	-	Negative	-
2	53	M	Thigh	10	-	Negative	-	Negative	-
3	37	M	Thigh (L)	18	-	-	-	-	-
4	37	M	Thigh (L)	18	Negative	-	-	-	-
5	74	M	Thigh (L)	23	-	-	-	-	-
6	49	M	Thigh (R)	14	-	-	-	-	-
7	43	F	Thigh (L)	15	Positive	-	-	-	ANED (84)
8	56	M	Thigh (L)	19	-	-	-	-	-
9	50	M	Inguinal region (L)	3.5	Negative	Negative	-	Negative	ANED (165)
10	57	F	Thigh (L)	12.5	-	-	-	-	ANED (135)
11	42	M	Thigh (R)	10	Negative	Negative	-	Negative	ANED (76)
12	39	M	Thigh (L)	8.7	Negative	-	-	-	-
13	25	F	Axilla (L)	11	Negative	-	-	-	ANED (150)
14	39	M	Thigh (R)	20.5	Positive	-	-	-	ANED (118)
15	40	F	Thigh (R)	17	-	-	-	-	-
16	61	F	Thigh (L)	15	-	Negative	-	Negative	-
17	42	F	Thigh (L)	20	-	-	-	-	-
18	49	M	Thigh (L)	13	Negative	Negative	-	Negative	-
19	33	F	Thigh (R)	11	Negative	Negative	-	Negative	-
20	40	M	Thigh (R)	14.7	-	-	-	-	-
21	38	M	Popliteal fossa (L)	6	-	-	-	-	-
22	39	F	Thigh (R)	14	Positive	Negative	-	Negative	-
23	44	F	Lower back	4	-	Negative	-	Negative	-
24	28	M	Thigh (L)	14.2	Negative	-	-	-	-
25	42	M	Thigh (L)	18.5	-	-	-	-	-
26	24	M	Thigh (R)	8	-	-	-	-	ANED (48)
27	65	M	Foot (R)	7	-	Negative	-	Negative	-
28	28	F	Groin (R)	11	Negative	-	-	-	-
29	59	M	Thigh (R)	6.2	-	Negative	-	Negative	-
30	66	F	Thigh (L)	6	Positive	Negative	-	Negative	-
31	50	F	Thigh (R)	18	Positive	Negative	-	Negative	-
32	56	F	Thigh (L)	12.7	Negative	-	-	-	-
33	39	F	Thigh (L)	14	Positive	Negative	-	Negative	-
34	43	F	Thigh (L)	8.1	Positive	Negative	-	Negative	-
35	52	M	Thigh (R)	10	Negative	Negative	-	Negative	-
36	78	F	Inguinal region (L)	8	Negative	-	-	-	ANED (40)
37	39	M	Buttock (R)	17.3	Negative	Negative	-	Negative	-
38	58	F	Thigh (L)	13.5	-	Negative	-	Negative	-
39	50	F	Buttock (R)	15.5	-	Negative	-	Negative	ANED (1)

Case no.	Age	Sex	Tumor site (side)	Tumor size (cm)	Margin status	MDM2 IHC	MDM2 FISH	CDK4 IHC	Follow up (months)
40	40	M	Thigh (L)	15	Negative	Negative	-	Negative	ANED (45)
41	38	M	Thigh (L)	11	-	Negative	-	Negative	-
42	61	M	Abdominal wall (R)	14	-	-	-	-	-
43	43	F	Leg (L)	7	-	-	-	-	-
44	46	F	Thigh (L)	7.7	-	-	-	-	-
45	46	F	Thigh (R)	20	-	Negative	-	Negative	ANED (9)
46	26	M	Buttock (R)	14	Positive	-	Negative	-	-
47	47	M	Buttock/lower back	15	-	Negative	-	Negative	-
48	31	F	Thigh (L)	14	Positive	Negative	-	Negative	-
49	68	F	Thigh (L)	10	-	Negative	-	Negative	-
50	31	M	Thigh (R)	14	-	Negative	-	Negative	-
51	44	M	Thigh (L)	7.3	Positive	-	Negative	-	ANED (23)
52	43	F	Thigh (R)	10	-	Negative	-	Negative	-
53	34	F	Thigh (L)	9.5	-	Negative	-	Negative	-
54	47	M	Thigh (L)	12	Negative	Negative	-	Negative	-
55	45	F	Groin (L)	11	Positive	Negative	-	Negative	-
56	51	M	Buttock (R)	14	-	Negative	-	Negative	-
57	48	M	Buttock (R)	15.8	-	-	-	-	ANED (7)
58	30	F	Buttock (R)	14.5	Negative	-	-	-	ANED (2.5)
59	45	M	Thigh (L)	3.8	-	Negative	-	Negative	-
60	28	M	Thigh (L)	6.7	-	Negative	-	Negative	-
61	36	F	Inguinal region	23	-	-	Negative	-	-
62	69	M	Buttock (L)	23	-	-	Negative	Negative	-
63	41	M	Abdominal wall (L)	8.4	Positive	-	Negative	-	ANED (1)
64	38	F	Stomach	10	Negative	-	Negative	-	ANED (5)

ANED: alive, no evidence of disease; IHC: immunohistochemistry; L: left; R: right