

The Morphologic Spectrum of Hibernoma

A Clinicopathologic Study of 170 Cases

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Hibernoma, an uncommon tumor of brown fat, has been described only in a few case reports and small series. The authors reviewed 170 cases of hibernoma and evaluated the morphologic features and the behavior of this tumor. The records from the Soft Tissue Registry of the Armed Forces Institute of Pathology from 1970 were searched for cases coded as "hibernoma." Clinical information and available slides from 170 hibernomas were reviewed. Immunohistochemical staining for S-100 and CD34 was performed on select cases. Follow-up information was obtained from the patients' medical records, the patients' physicians, and the patients themselves. Of 170 patients with hibernoma, 99 were men and 71 were women. The tumor occurred most commonly in adults, with a mean age of 38.0 years (age range, 2–75 years). Nine tumors occurred in pediatric patients. The most common anatomic locations included the thigh (n = 50), shoulder (n = 20), back (n = 17), neck (n = 16), chest (n = 11), arm (n = 11), and abdominal cavity/retroperitoneum (n = 10). The average duration of the tumor was 30.6 months. Tumor size ranged from 1 to 24 cm with an average dimension of 9.3 cm. All tumors were composed partly or principally of coarsely multivacuolated fat cells with small, central nuclei and no atypia. Four morphologic variants of hibernoma were identified: typical, myxoid, spindle cell, and lipoma-like. "Typical" hibernoma (n = 140) included eosinophilic cell, pale cell, and mixed cell types based on the tinctorial quality of the hibernoma cells. The myxoid variant (n = 14) contained a loose basophilic matrix. Spindle cell hibernoma (n = 4) had features of spindle cell lipoma and hibernoma; all occurred in the neck or scalp. The lipoma-like variant (n = 12) contained only scattered hibernoma cells. Immunohistochemically, 17 of 20 cases (85%) were positive for S-100 protein. Only one hibernoma of 20, a spindle cell variant, was positive for CD34, whereas other hibernoma variants were negative. Follow-up was obtained for 66 cases (39%) over a mean period of 7.7 years (range, 6 months–28 years). None of the patients with follow-up had a recurrence or metastasis, including eight with intramuscular tumors. No patient died of

disease. Hibernoma is a tumor found most often in adults and most commonly in the thigh, with several morphologic variants. It is a benign tumor that does not recur with complete excision. Hibernomas should not be confused with atypical lipomas or well-differentiated liposarcoma.

Key Words: Hibernoma—Brown fat—Soft-tissue neoplasm—Benign—Adult—Child.

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Hibernoma is an unusual tumor of brown fat. Thought to mimic morphologically the brown fat of hibernating animals, it has been previously called adenoma of sebaceous gland and pseudolipoma.^{4,16,23,26} Since its first description in 1906, only a few case reports and small series have described this rare, somewhat peculiar, tumor. We present 170 cases of hibernoma, report the spectrum of morphologic features, and confirm its benign behavior.

MATERIALS AND METHODS

The records from the Soft Tissue Registry of the Armed Forces Institute of Pathology (AFIP) in Washington, DC, USA, from 1970 to the present were searched for cases coded as hibernoma. Clinicopathologic and demographic information was obtained. Available slides from 175 cases were reviewed. Of the 175 cases, four neck masses from young adults showed a dominant neck mass of reactive lymph nodes surrounded by residual brown fat and were reclassified as non-neoplastic brown fat. One tumor was reclassified as a chondroid lipoma. The remaining 170 cases had features diagnostic of hibernoma (i.e., an integral brown fat component). Immunohistochemical staining was performed using the avidin-biotin complex system with diaminobenzidine as the chromogen in 20 cases. These tumors were evaluated for S-100 protein (polyclonal; dilution, 1:1600; Dako) and CD34 (Qbend; dilution, 1:40; Biogenex). Follow-up

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TABLE 1. *The anatomic distribution of hibernomas*

Anatomic location	No. of cases
Head and neck	23
Upper extremity	37
Trunk	39
Abdomen and retroperitoneum	16
Lower extremity (thigh)	55

information was obtained from the patients' medical records, the patients' physicians, and, occasionally, the patients themselves.

RESULTS

Clinical Features

Of 170 patients with hibernoma, 99 (58%) were male and 71 (42%) were female. The tumor occurred usually in adult patients with an average age of 38 years (age range, 2–72 years). Nine patients were younger than 18 years, two boys and seven girls. The age distribution is shown in Figure 1. The anatomic locations in order of frequency included the thigh (n = 50), shoulder (n = 20), back (n = 17), neck (n = 16), chest (n = 11), arm (n = 11), abdominal cavity and retroperitoneum (n = 10), axilla (n = 6), groin (n = 5), supraclavicular area (n = 4), buttock (n = 4), scalp (n = 3), abdominal wall (n = 4), breast (n = 3), spermatic cord (n = 2), spine (n = 2), and scrotum and perirectum (n = 1 each). A summarized list of anatomic locations is presented in Table 1. Of the nine pediatric tumors, three occurred in the thigh, whereas others were present in the back, chest, neck, breast, abdominal wall, and spine. The average preoperative duration of all tumors was 30.6 months (range, 10 days–10 years). The majority of tumors presented as slowly growing, progressively enlarging, painless masses. Occasionally, there was rapid growth of the tumor. One patient with a large retroperitoneal mass

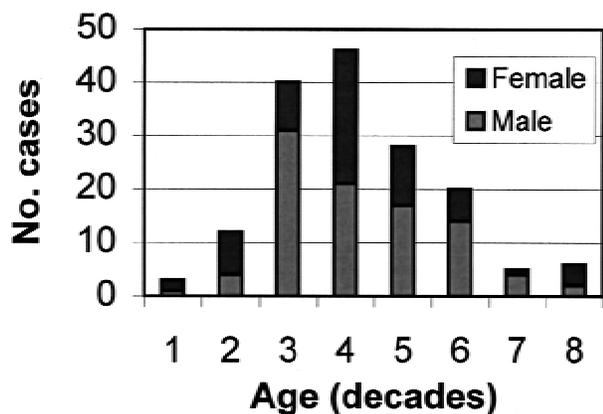


FIG. 1. Age and gender distribution of 170 cases of hibernoma.

complained of shortness of breath, anorexia, and weight loss.

Pathology

The mean tumor size was 9.3 cm (range, 1–24 cm). Grossly, the tumors were well circumscribed, partially encapsulated, and lobulated (Fig. 2). The cut surface varied from yellow to brown and was occasionally mucoid with rare areas of hemorrhage.

Common to all tumors microscopically was the presence of multivacuolated fat cells with small, central nuclei. The appearance and relative small numbers of these cells varied and, according to this, several histologic variants were recognized based on the tinctorial quality of hibernoma cells, the nature of the stroma, and the presence of a spindle cell component.

The most common type of hibernoma, collectively, was the typical variant (n = 140). Within this variant, a range of pale staining and eosinophilic hibernoma cells was identified. The pale cell subtype (n = 75) was composed of pale, multivacuolated cells seen in various numbers mixed with univacuolated white fat (Fig. 3). Often, approximately equal numbers of pale and eosinophilic multivacuolated cells were identified comprising a mixed cell subtype (n = 41). The eosinophilic cell subtype (n = 24) was composed of at least 50% of hibernoma cells that had deeply eosinophilic granular cytoplasm (Fig. 4). This subtype occurred more often in the upper extremity, whereas the pale and mixed cell subtypes occurred more frequently in the thigh and trunk respectively.

Fourteen tumors, representing the "myxoid variant," were composed of multivacuolated brown cells with a slightly eosinophilic cytoplasm separated by acellular myxoid stroma (Fig. 5). This variant occurred predominantly in men (13 of 14 tumors). The head and neck



FIG. 2. The macroscopic appearance of hibernoma. This encapsulated tumor has a lobular, greasy, yellow–brown cut surface.

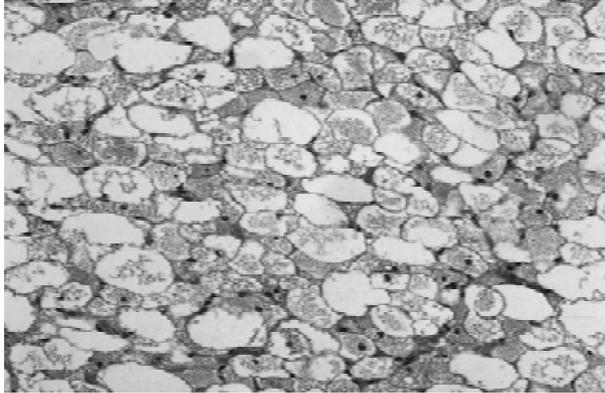


FIG. 3. Pale-staining hibernoma cells with less eosinophilic cytoplasm are identified in the pale cell subtype of typical hibernoma together with some white fat cells.

region, including the scalp and shoulder, were the most common sites for this variant.

Twelve hibernomas, the lipoma-like variant, contained predominately univacuolated cells and only scattered granular or pale multivacuolated hibernoma cells (Fig. 6). No atypia was identified in any case. The thigh was the site of the majority of these hibernomas.

Four of the hibernomas had combined features of spindle cell lipoma and hibernoma. These tumors contained an admixture of hibernoma cells and bland spindle cells, thick bundles of collagen, mast cells, myxoid stroma, and mature adipocytes (Fig. 7). All four spindle cell variants of hibernoma occurred in the posterior neck or scalp. Detailed clinicopathologic characteristics for each variant are listed in Table 2.

Only the "typical" and lipoma-like morphologic variants were represented in the nine pediatric patients. Nearly half the pediatric tumors were the pale cell subtype.

At least 19 tumors were intramuscular, most commonly the typical variant. Four of the intramuscular tumors were the lipoma-like variant. No tumor with a

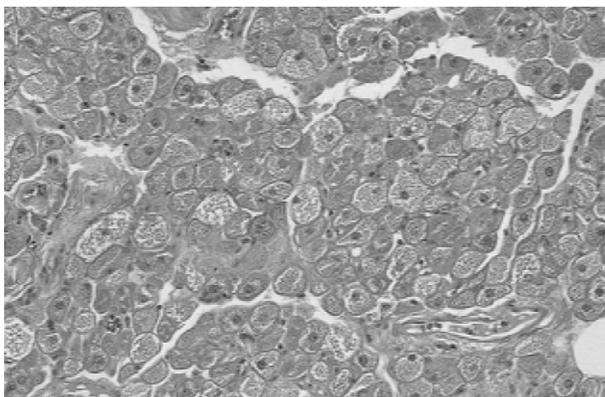


FIG. 4. The eosinophilic subtype of typical hibernoma is composed predominantly of granular-appearing brown fat cells with prominent nucleoli.

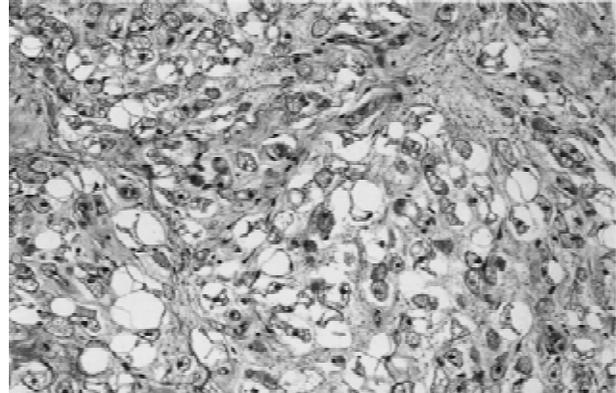


FIG. 5. The myxoid variant has hibernoma cells floating in a loose myxoid matrix.

spindle cell component was intramuscular. Additional noteworthy cases included two hibernomas arising in the breast, one in a fibroadenoma and one with associated microcalcifications. These patients were 20 and 71 years old, respectively.

Immunohistochemical studies for S-100 and CD34 were performed on 20 select cases, representing most morphologic variants. Most hibernomas, 17 of 20 (85%) showed positivity for S-100, ranging from focal to diffuse (Fig. 8). Multivacuolated hibernoma cells more often demonstrated stronger positivity than the univacuolated white fat cells. CD34 was analyzed in 20 hibernomas, including one spindle cell hibernoma and representative cases of all other morphologic subtypes. CD34-positive spindle cells were present in the spindle cell variant. All other morphologic variants were negative for CD34.

Follow-up was obtained for 66 cases (39%) over a mean interval of 7.7 years (range, 6 months–28 years). None of the patients with follow-up had a recurrence or metastasis, including eight with intramuscular tumors. No patient died of disease related to hibernoma. Three

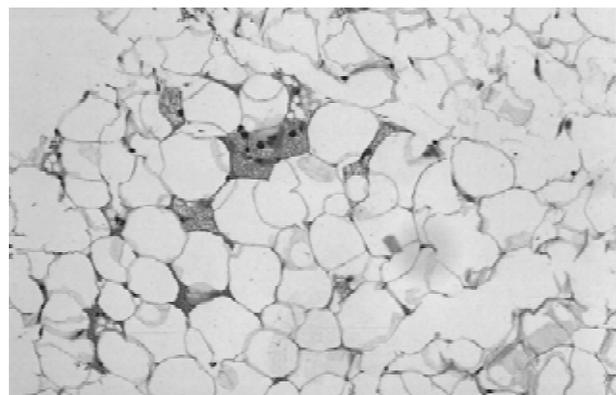


FIG. 6. Only rare hibernoma cells are identified in the lipoma-like subtype.

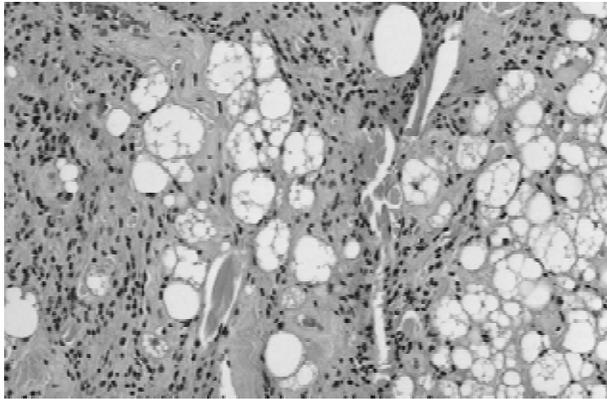


FIG. 7. Bland spindle cells, ropy collagen, myxoid stroma, scattered mast cells, and multivacuolated pale hibernoma cells are features of this peculiar hybrid spindle cell hibernoma.

patients died of other disease, including two with malignant tumors and one with congestive heart failure.

DISCUSSION

Hibernoma, an unusual tumor mimicking brown fat, has been well recognized since the turn of the century.^{4,16,23} Although, the ultrastructural features have been reviewed extensively,^{2,9,13,15} histologic studies are limited to few cases or small series.¹⁵ We describe a large series of hibernomas, expand the morphologic spectrum, and confirm the benign behavior of this tumor.

Several demographic characteristics differ in our review from the known literature. Of 170 patients with hibernomas, 99 tumors occurred in male and 71 in female patients. Previously, there has been a slight female predominance.^{17,20} Additionally, it was thought that the most common site of occurrence of hibernomas is in areas of residual brown fat; namely, the neck, axilla, back, and mediastinum.^{1,4,11,13,29,31} Scattered case reports have described such tumors in the thigh.^{2,3,20} The current study shows a clear predilection for the tumor to arise in the thigh, with 30% of cases occurring in this anatomic location. It is unclear, however, whether the extremities are sites of residual brown fat in adults,⁵ or whether hibernoma represents altered programming of the neoplastic fat cells toward brown fat differentiation.

The average age in our series was 37.1 years (range, 2–72 years), which is slightly higher than in the previous unpublished data from the AFIP.¹¹ Nine of our tumors occurred in patients younger than 18 years. Only one case report describes this tumor in a child, a 16-year-old boy.¹

A total of 170 cases were reviewed morphologically. Four variants were identified describing the key histologic appearance, each having the prototypical cell types of hibernoma described previously.^{9,15} They included, in

order of frequency, subtypes of “typical” hibernoma: a mixture of pale hibernoma cells and white fat (pale cell), evenly distributed pale and eosinophilic hibernoma cells (mixed cell), and a predominance of eosinophilic hibernoma cells (eosinophilic cell); the lipoma-like variant with only scattered hibernoma cells among white fat; the myxoid variant; and a spindle cell variant combining the features of hibernoma and spindle cell lipoma. The importance of these variants is that they all should be recognized in the spectrum of hibernoma.

All variants of hibernoma followed a benign course, but there was some difference in the clinicopathologic parameters of the variants. The median age for all variants occurred during the third decade; however, it was the highest for the typical variant (38 years) and lowest for the myxoid type (32 years). No myxoid or spindle cell variants occurred in pediatric patients. There was a slight male predominance for the typical and lipoma-like hibernoma variants. Only one each of the myxoid and spindle cell types occurred in a woman. Anatomic locations varied. The thigh was the most common site for typical hibernoma and the lipoma-like variant. The myxoid type was found most often in the head and neck region, and the spindle cell variant was found in the posterior neck and scalp.

Univacuolated cells are present in varying numbers in all variants, but are the predominant cell type in some hibernomas, especially the lipoma-like variant. Dardick⁹ suggests that normal brown fat and hibernomas can undergo maturation from an immature multivacuolated cell to a mature univacuolated cell, but remain distinct ultrastructurally from white adipose tissue. However, it remains somewhat controversial whether these univacuolated cells are brown fat in origin or the same as mature, white adipocytes.^{5,9,15} This variant seems to be the most troublesome for surgical pathologists because the multivacuolated “hibernoma” cells are often mistaken for lipoblasts. This differential diagnostic problem may occur especially with intra-abdominal fatty tumors, most of which are well-differentiated liposarcomas. In nearly one-fourth of our consult cases (23%), the contributing pathologist considered a diagnosis of atypical lipoma, well-differentiated liposarcoma, or myxoid liposarcoma. Furthermore, radiographs and conventional computed tomographic scans may also suggest a malignant process if more sophisticated studies, such as magnetic resonance imaging, are not available, compounding the diagnostic difficulty.^{3,20} The nucleus of the hibernoma cell may be indented, but is usually central or slightly eccentric and often has a prominent nucleolus, features distinguishing it from a lipoblast. Furthermore, it lacks the hyperchromasia and scalloping of a lipoblast. Atypia in a hibernoma is a rare find, and was described in a single case report in 1979.¹⁰ A possible malignant hibernoma was proposed at that time, yet this case never me-

TABLE 2. Clinicopathologic comparison of hibernoma variants

	Frequency (%)	Age (yr; median/range)	M/F	Anatomic locations	Intramuscular (no. of tumors)
Typical	82	38/8-75	77/63	Thigh, trunk, upper extremity	13
Myxoid	9	32/20-72	7/5	Head and neck, shoulder, trunk	2
Lipoma-like	7	36.5/2-50	13/1	Thigh, hip, trunk	4
Spindle cell	2	32.5/28-59	3/1	Posterior neck and scalp	0

tastized. We however, found no atypia within the fatty component in any of our 170 cases. Although hibernoma-like cells have been described in atypical lipomatous tumors, and myxoid and dedifferentiated liposarcomas,^{11,17,22,27} in our experience this is an extremely rare finding. In such cases, the presence of adipocytic atypia, typical vascular pattern, and dedifferentiated areas are decisive for the diagnosis. Tumors composed of malignant brown fat cells, by contrast, are virtually nonexistent. Furthermore, karyotypic findings would differentiate between atypical lipomatous tumors, myxoid liposarcomas, and hibernomas.²⁷

Specifically, hibernomas with myxoid change may be confused with myxoid liposarcoma. The latter may have cells with abundant granular cytoplasm somewhat resembling the hibernoma cells. Interestingly, it was once thought histologically and ultrastructurally that myxoid liposarcomas might be derived from brown fat.^{12,19,28} In the case of myxoid liposarcoma, the hypervascularity and common presence of the prominent "plexiform" capillary pattern and characteristic molecular translocation t(12;16) help to diagnose accurately this type of liposarcoma.¹¹

Spindle cell features similar to spindle cell lipoma were seen in four hibernomas: bland spindle cells, a slightly myxoid background, scattered mast cells, and numerous bundles of rosy collagen. In addition to mature adipocytes, hibernoma cells were also present. Three cases occurred in the neck and one in the scalp, the typical location of spindle cell lipomas. Furthermore, one of these spindle cell hibernomas was positive for CD34, also found in spindle cell lipoma,³⁰ indicating that this variant has indeed a hybrid phenotype of hibernoma and spindle cell lipoma. The literature describes one case of another peculiar "hybrid" tumor in the uterus of a 24-year-old woman having a smooth muscle component and a hibernomatous component and was termed *leiomyohibernoma*.⁷ Additionally, two of our cases occurred in the breast, one within a fibroadenoma, a similar hybrid phenomenon. Although a histologically different lesion, an adenohibernoma has been previously described comprised of brown fat and benign mammary glands.⁸

Hibernoma cells are S-100 positive in all variants; however, positivity may range from focal to diffuse. S-100 positivity of hibernoma should not lead to confusion with granular cell tumor. Most hibernomas are nega-

tive for CD34, which may outline clusters of granular cells in granular cell tumor.

Characteristic cytogenetic abnormalities described in hibernoma include structural rearrangements of 11q13 and 11q21, as reported in the few cases of hibernomas reported to date.^{14,24,25} 11q13 rearrangements also have been identified in other lipomatous tumors such as typical lipoma and myxoid liposarcoma.^{14,24}

Several reports have questioned the benign behavior of hibernomas.^{2,10,21,26} Lowry and Halmos,²¹ in 1967, described a malignant hibernoma based on muscle infiltration. Enterline et al.,¹⁰ 10 years later described a deep-seated retropharyngeal tumor with atypia and a rare atypical mitosis, but indicated that these features and even an infiltrative pattern are not necessarily criteria for malignancy. We concur and believe that hibernomas are benign tumors. Although some investigators discuss a rare case of recurrence, the details, including the possibility of incomplete excision, remain unclear.^{2,31} No case in the current study recurred, including those tumors that were intramuscular. Furthermore, none of the hibernomas reported in the literature metastasized.^{1-3,6,7,10,15,18,26,31}

In summary, our morphologic review of hibernomas distinguishes four histologic variants: typical, myxoid, spindle cell, and lipoma like. The importance of this morphologic spectrum is that they should be recognized as hibernomas; the behavior is benign for all. Additionally, residual brown fat in the neck, often surrounding reactive lymph nodes, should not be considered neoplas-

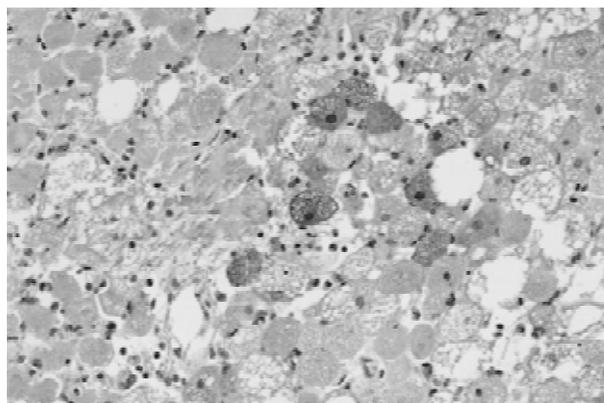


FIG. 8. At least focal S-100 positivity is found in most hibernomas.

tic brown fat. Hibernomas are benign tumors that are not expected to recur with complete local excision. □

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