

## CASE REPORTS

# A case report of lipoma-like hibernoma in axilla: A rarely benign tumor of brown adipose tissue

Ricardo Rubini Costa\*<sup>1</sup>, Antonio Torregrosa Gallud<sup>2</sup>, José Miguel Rayón<sup>3</sup>, Jerónimo Forteza Vila<sup>4</sup>

<sup>1</sup>Universidad Católica de Valencia, Valencia, Spain

<sup>2</sup>La Fe University and Politechnic Hospital, Valencia, Spain

<sup>3</sup>Hospital 9 de Octubre, Valencia, Spain

<sup>4</sup>Instituto Valenciano de Patología, Universidad Católica de Valencia, Valencia, Spain

**Received:** December 13, 2017

**Accepted:** January 4, 2018

**Online Published:** January 9, 2018

**DOI:** 10.5430/css.v4n1p1

**URL:** <https://doi.org/10.5430/css.v4n1p1>

## ABSTRACT

**Background:** Hibernoma or lipoma of brown fat is a rare benign tumor, representing 1.6% of the neoplasms of this tissue. Because of its histological characteristics can be wrongly classified as liposarcoma, therefore a correct differential diagnosis is necessary to provide appropriate treatment.

**Case presentation:** The patient on which this case study is based is a 44-year-old male with a painless soft mass in his axilla located by his 4<sup>th</sup> and 5<sup>th</sup> ribs. The resected specimen did not have the classic macroscopic features of lipoma or fibrolipoma. Microscopically, the report described a proliferation of unilocular adipocytes with eccentric nucleus and, in less frequency, multilocular adipocytes with central nucleus. He had no recurrence after excision.

**Conclusions:** Despite radiology studies and other technologies such as magnetic resonance imaging, computerized axial tomography (CAT), etc., the clinical diagnosis of hibernoma could be difficult. Lipoma-like hibernoma only have a few multilocular cells and can be wrongly classified as liposarcoma. Well-differentiated liposarcoma resembles it on low-power examination. Due to this it is especially important to perform a differential diagnosis with lipoma, fibroma, and even with liposarcoma. In this study we describe the histological features, the molecular markers and cytogenetic aspects that contribute to differentiate hibernoma from others tumors.

**Key Words:** Hibernoma, Atypical lipoma, Fatty tumor

## 1. INTRODUCTION

Hibernoma or lipoma of brown fat is a benign tumor which derives from the brown adipose tissue, representing 1.6% of the neoplasms of this tissue.<sup>[1]</sup>

Brown fat has metabolic and thermogenic functions which is why it is abundant in hibernating animals. In the human body we find brown adipose tissue in newborns, decreasing considerably after the eighth week of life.<sup>[2]</sup> Histologically, brown adipose tissue is mainly characterized by the presence

of multilocular adipocytes with numerous mitochondria. The mitochondria of multilocular adipocytes are special because they do not have many of the enzymes for ATP production and therefore the energy generated is released as heat.

Hibernoma was described for the first time in 1906 by Merkel, who called it “pseudolipoma”.<sup>[3]</sup> In 1914 Gery called it Hibernoma due to the resemblance with the hibernating glands of hibernating mammals.<sup>[4]</sup> Furlong et al.<sup>[2]</sup> published the largest series with 170 cases of hibernoma, of which 99

\*Correspondence: Ricardo Rubini Costa, M.D.; Email: ricardo.rubini93@gmail.com; Address: Universidad Católica de Valencia, Valencia, Spain.

cases were men and 71 were women, with a mean age of 38 years (ages ranged from 2 to 75 years).

Hibernoma can be found mainly in axillae, the interscapular region and groin. Less frequently in jaw, neck, shoulder, back, chest, arm, and retroperitoneum.<sup>[2,5]</sup> It is a clinically well-defined tumor, soft, mobile, lobulated, encapsulated and it rarely infiltrates other structures. Hibernoma is warm to the touch and its average dimension fluctuates between 5 cm and 10 cm, although some hibernomas have been described as being 25 cm × 25 cm and 2,500 g in weight.<sup>[6,7]</sup>

Four variants of hibernoma were described by Furlong et al.<sup>[2]</sup> in 2001 and added to the WHO Tumor Classification in 2002: typical, myxoid, lipoma-like and spindle cell. Typical hibernoma had eosinophilic cell, pale cell and mixed cell types based on the tinctorial quality of the hibernoma cells. The myxoid variant contained a loose basophilic matrix. The lipoma-like subtype only had dispersed hibernoma cells. Spindle cell hibernoma had characteristics of spindle cell lipoma and hibernoma. The latter type is considered less common than the other three.<sup>[8]</sup> There are also variants which are more common in specific anatomical locations. For example, the myxoid type is more common in head and neck and the typical hibernoma is more common in the thigh.<sup>[9]</sup>

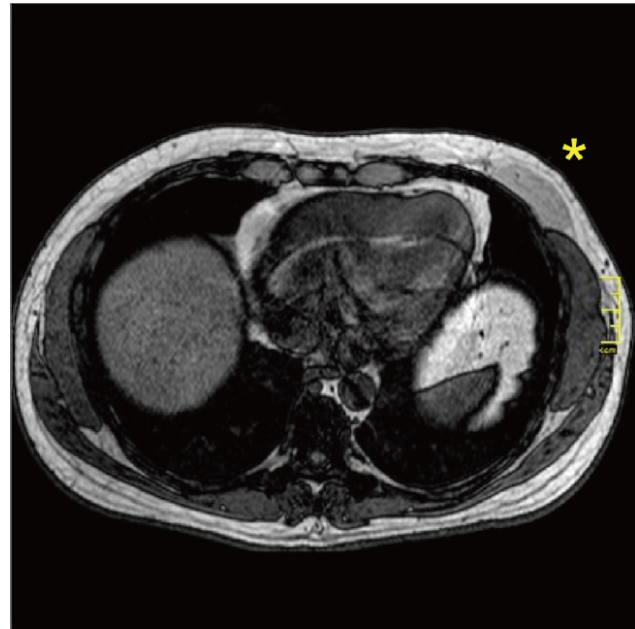
In the following section we report a case of lipoma-like hibernoma, a literature review and differential diagnosis with similar pathologies.

## 2. CASE PRESENTATION

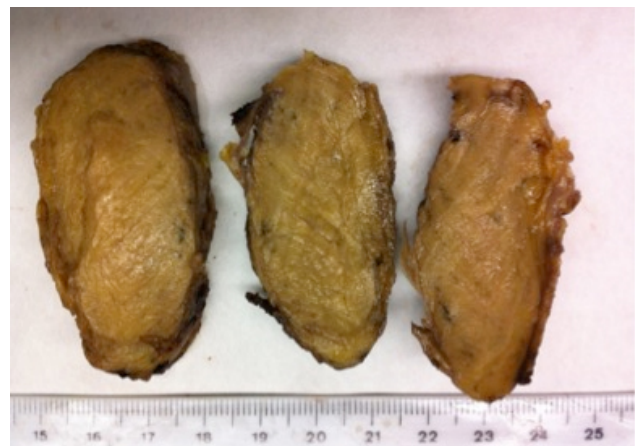
The patient on which this case study is based is a 44-year-old male, with no relevant medical history for this pathology. He was admitted to hospital with a lump in his axilla located by his 4<sup>th</sup> and 5<sup>th</sup> ribs which he had noticed a few months before. Medical exploration displayed evidence of a painless soft mass, detached from lower or superficial planes and slightly warm to the touch. The radiological screening with magnetic resonance imaging (MRI) (see Figure 1) showed a neoplasm with no infiltration of others structures. After medical and radiologic examinations, it was diagnosed as a probable lipoma or fibrolipoma with a diameter of 5 cm. A surgical intervention was conducted with the excision of the mass; so, under local anesthesia and sedation, excision and primary closure with resorbable material and skin staples were performed. The postoperative course was normal, with the staples being removed on the 10th postoperative day. The resected specimen did not have the classic macroscopic features of lipoma or fibrolipoma; it was brown and lobulated (see Figure 2).

Macroscopically, it consisted of a brownish mass with an ovoid appearance that had well-defined lipomatous charac-

teristics. The mass measured 5 cm × 3 cm. Microscopically, the report described a proliferation of unilocular adipocytes with eccentric nucleus and, in less frequency, multilocular adipocytes with central nucleus (see Figure 3A and B).

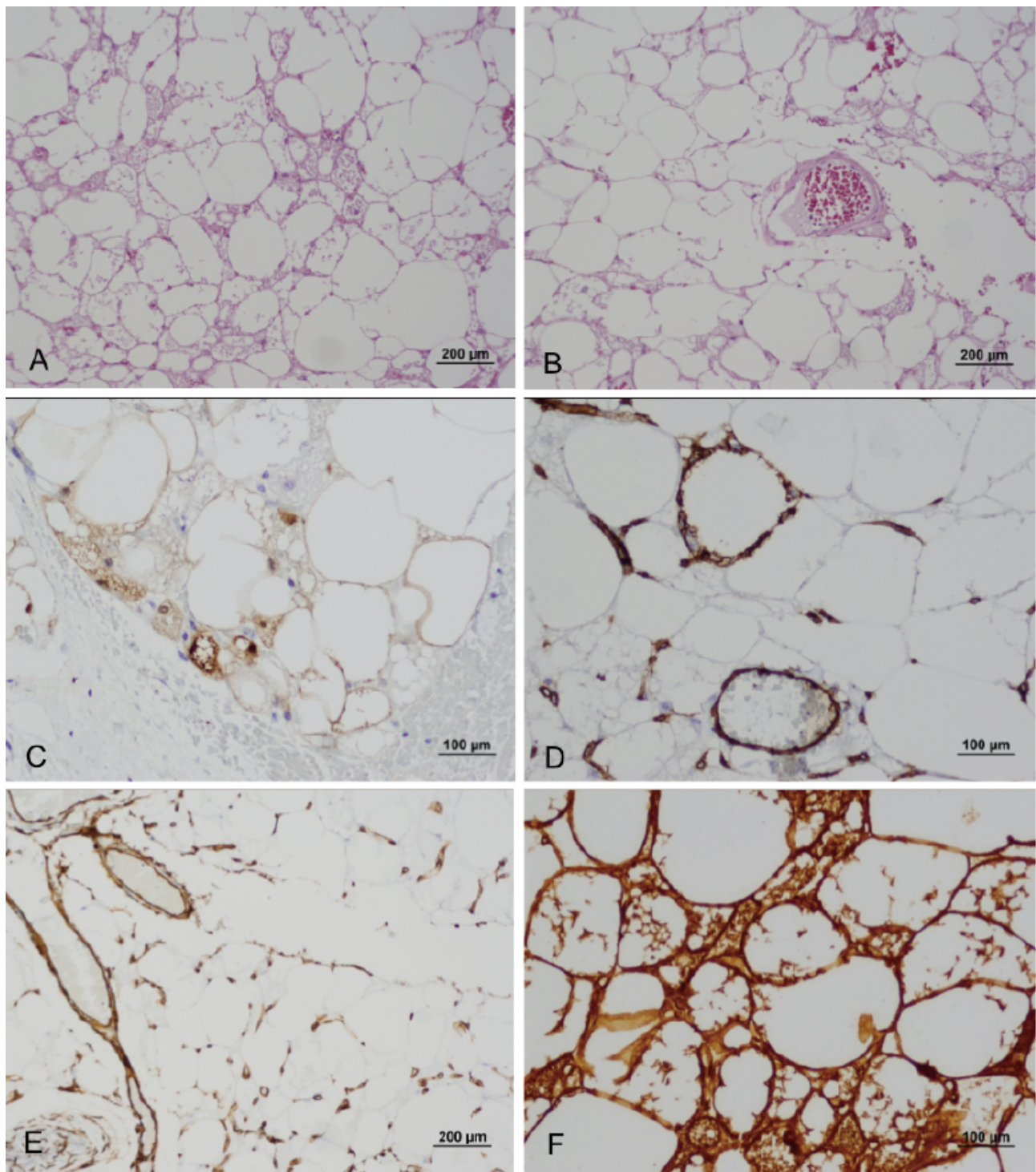


**Figure 1.** Magnetic resonance imaging of the thorax demonstrates a mass in the anterior part of the axilla (axial view)



**Figure 2.** Macroscopic image of the resection piece

The tumor cells were stained with S100 protein (see Figure 3C). CD31, CD34 and Vimentin markers also stained the cells (see Figure 3D, 3E and 3F). Regarding the cytogenetic issues, Fluorescence in situ hybridization (FISH) detected deletions on chromosome 11q13 (see Figure 4). We did not have evidence of malignancy and the final diagnosis was lipoma-like hibernoma. The patient did not report signs of recurrence after ten months from its extirpation.



**Figure 3.** (A) Unilocular adipocytes with eccentric nucleus and multilocular adipocytes with central nucleus (Hematoxylin and eosin 10 $\times$ ); (B) Multilocular and unilocular adipocytes. A blood vessel in the centre (Hematoxylin and eosin 10 $\times$ ); (C) Staining with S100 protein (20 $\times$ ); (D) Immunohistochemical staining was performed to show the tumor cells are positive for CD31 (20 $\times$ ); (E) Immunohistochemical staining with CD34 (10 $\times$ ); (F) Immunohistochemical staining with Vimentin (20 $\times$ ).

### 3. DISCUSSION

In most mammals there are two varieties of adipose tissue, which are differentiated by their color, distribution, vascularization and metabolic activity, in white fat and brown fat.<sup>[10]</sup>

White adipose tissue constitutes most of the fat component of the fat organism.<sup>[10,11]</sup>

Hibernoma is a rare benign tumor composed of brown fat;<sup>[2,10]</sup> this brown adipose tissue is only found in some

areas of the body and is stored, providing insulation against heat loss; even plays a metabolic role by guaranteeing the storage of energy reserves.<sup>[10,11]</sup> Primarily the region with the highest amount of brown fat in fetuses and newborns is the retroperitoneum, and it decreases after 2 months of age.<sup>[11,12]</sup>



**Figure 4.** Fluorescence in situ hybridization analysis confirms the chromosome deletion within the band 11q13. The deletion is a mutation where a part of a chromosome or a sequence of DNA has been lost during DNA replication, here we can see a red spot that marks the deletion.

Despite radiology studies and other technologies such as MRI, computerized axial tomography (CAT), etc., the clinical diagnosis of hibernoma could be difficult; as an infrequent tumor reported in the third and fourth decades of life, without predominance of sexes. Their clinically characteristics are a mobile palpable mass, usually in the extremities, with slow and painless growth, founded simultaneously in several locations. No cases of metastasis or local recurrence are reported after surgical excision.<sup>[11,13]</sup>

To establish a differential diagnosis with other pathologies with adipose component, such as lipoblastoma or lipoblastomatosis, made up of white fat like Lipoblastoma that has a focal presentation, or lipoblastomatosis with a diffuse distribution.

The most common site of origin are the extremities, followed by the trunk, retroperitoneum, neck, and inguinal and perineal regions.<sup>[14,15]</sup> Pelvic and abdominal localization is rare.<sup>[16]</sup>

Magnetic Resonance images show some distinctive features between white fat tumors (lipoblastomas, lipomas) and hi-

bernomas; but it's not very easy to identify.<sup>[11,13]</sup>

Sometimes the features of hibernoma are seen mixed with those of ordinary lipoma or of spindle cell lipoma, and other hibernomas are accompanied by a myxoid matrix.<sup>[2,17]</sup>

This brown adipose tissue has smaller cells of different size, with a multilocular appearance; and the greater number of mitochondria present in brown fat is related to the exothermic function, which constitutes a unique property of brown adipose tissue.<sup>[15,18]</sup>

Also, the connective tissue surrounding these cells has abundant blood supply, which gives hypervascular characteristics in imaging studies.<sup>[10,11]</sup>

Lipoma-like hibernoma only have a few multilocular cells and can be wrongly classified as liposarcoma. Well-differentiated liposarcoma resembles it on low-power examination, but closer inspection shows scattered tumor cells with large, deep-staining nuclei.<sup>[20]</sup>

Due to this it is especially important to perform a differential diagnosis with lipoma, fibroma, neurofibroma, angiolipoma, and even with liposarcoma, by clinically and radiologically studies, making a differential diagnoses with myxoid liposarcoma, angiomyolipoma and mesenteric panniculitis;<sup>[12]</sup> so myxoid liposarcoma may present a clinical picture and radiological findings similar to hibernoma and lipoblastoma, but it is associated with infiltrating growth, presenting cellular atypia and is extremely infrequent in the pediatric age;<sup>[20]</sup> the angiomyolipoma is a vascular tumour with striated muscle cells and adipose tissue,<sup>[18,21]</sup> and characteristically found at the renal level.

The ultrastructure of hibernoma consists of a brown colored mass structured in lobes, as well as a wide vascular net. Microscopically, it contains multilocular adipocytes with a centric nucleus.

The immunohistochemical analysis technique of labeling with CD31 is a good tool to differentiate lipoma and hibernoma in paraffin sections. The CD31 glycoprotein cell surface is involved in the process of angiogenesis. The CD31 antigen is positive in unilocular and multilocular adipocyte surfaces of hibernoma and normal brown fat.<sup>[17]</sup>

However, CD31 is not expressed in normal adipocytes of white fat, in neoplastic cells of lipoma or in lipoblasts of well-differentiated and myxoid liposarcomas.<sup>[22]</sup>

Regarding cytogenetic aspects, hibernoma frequently presents chromosome deletion within the 11q13 band; where a part of a chromosome or a sequence of DNA are lost during DNA replication. This deletion was found in our case study. It is thought that deletions of AIP and MEN1

tumor suppressor genes are related to the development of hibernoma.<sup>[23,24]</sup>

Complying with the criteria of benignity, hibernoma rarely recurs after excision. In our patient's case there have been no signs of recurrence or any other complications 10 months after the excision.

#### 4. CONCLUSIONS

Despite radiology studies and other technologies such as MRI, CAT, etc., the clinical diagnosis of hibernoma could be difficult. Lipoma-like hibernoma only have a few multilocular cells and can be wrongly classified as liposarcoma.

Well-differentiated liposarcoma resembles it on low-power examination. Due to this it is especially important to perform a differential diagnosis with lipoma, fibroma, and even with liposarcoma. In this study we describe the histological features, the molecular markers and cytogenetic aspects that contribute to differentiate hibernoma from others tumors. CD31 antigen is positive in unilocular and multilocular adipocyte surfaces of hibernoma and it is not expressed in normal adipocytes of white fat, in neoplastic cells of lipoma or in lipoblasts of well-differentiated and myxoid liposarcomas.

#### CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

#### REFERENCES

- [1] Miettinen MM, Fanburg-Smith JC, Mandahl N. Hibernoma. In: Fletcher CDM, Unni KK, Merthens F, ed. WHO classification of tumour of soft tissue and bone. Lyon: Farcpress; 2002. 33-4 p.
- [2] Furlong MA, Fanburg-Smith JC, Miettinen M. The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. *Am J Surg Pathol.* 2001; 25: 809-814. PMID: 11395560. <https://doi.org/10.1097/00000478-200106000-00014>
- [3] Merkel H. Uber ein pseudolipom der mamma (About a pseudolipom of the chest). *Beitr Path Anat.* 1906; 36: 152-7.
- [4] Gery L, Bonnel MF. Discussion du Tumeur du Creux de l'Aisselle (Discussion of the tumor of the axilla). *Bull Men Soc Anat (Paris).* 1914; 89: 110-112.
- [5] Vidal N, Tirapequi S, Máximo T, et al. Presentación de dos casos clínicos (Presentation of two cases). *Rev. Chilena de Cirugía Junio.* 2004; 56(3): 279-282.
- [6] Enzinger FM, Weiss SW. *Soft Tissue Tumors. USA: Mosby Company; 1983.c*
- [7] Ersozlu S, Sahin O, Ozgur AF, et al. Sciatic neuropathy from a giant hibernoma of the thigh: a case report. *Am J Orthop (Belle Mead NJ).* May 2008; 37: 103-6.
- [8] Moretti VM, Brooks JS, Lackman RD. Spindle-Cell Hibernoma: A Clinicopathologic Comparison of This New Variant. *Orthopedics.* Jan 2010; 33(1): 52-5. <https://doi.org/10.3928/01477447-20091124-29>
- [9] Balaguera J, Fernandez I, Aquiriano L, et al. Axillary Hibernoma: An Unusual Benign Soft-Tissue Tumor. *Int Jour of Surg.* 2010; 22: 11.
- [10] Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev.* 2004; 84(1): 277-359. PMID: 14715917. <https://doi.org/10.1152/physrev.00015.2003>
- [11] Bancroft LW, Kransdorf MJ, Peterson JJ, et al. Benign fatty tumors: classification, clinical course, imaging appearance, and treatment. *Skeletal Radiol.* 2006; 35(10): 719-33. PMID: 16927086. <https://doi.org/10.1007/s00256-006-0189-y>
- [12] Baskurt E, Padgett DM, Matsumoto JA. Multiple hibernomas in a 1-month-old female infant. *AJNR Am J Neuroradiol.* 2004; 25(8): 1443-5. PMID: 15466349.
- [13] Sansom HE, Blunt DM, Moskovic EC. Large retroperitoneal hibernoma - CT findings with pathological correlation. *Clin Radiol.* 1999; 54(9): 625-7. [https://doi.org/10.1016/S0009-9260\(99\)90027-2](https://doi.org/10.1016/S0009-9260(99)90027-2)
- [14] Ritchie DA, Aniq H, Davies AM, et al. Hibernoma-correlation of histopathology and magnetic-resonance-imaging features in 10 cases. *Skeletal Radiol.* 2006; 35(8): 579-89. PMID: 16642344. <https://doi.org/10.1007/s00256-006-0114-4>
- [15] Nagano A, Ohno T, Nishimoto Y, et al. Lipoblastoma mimicking myxoid liposarcoma: a clinical report and literature review. *Tohoku J Exp Med.* 2011; 223(1): 75-8. PMID: 21212605. <https://doi.org/10.1620/tjem.223.75>
- [16] Treppiedi E, Zimmitti G, Manzoni A, et al. Extra peritoneal giant pelvic hibernoma: a case report. *J Surg Case Rep.* 2017 Dec 15; 2017(12). PMID: 29255590. <https://doi.org/10.1093/jscr/rjx250>
- [17] Chiriac LR, Dekmezian RH, Ayala AG. Characterization of the myxoid variant of hibernoma. *Ann Diagn Pathol.* 2006; 10: 104-106. PMID: 16546046. <https://doi.org/10.1016/j.anndiagpath.2005.04.007>
- [18] Craig WD, Fanburg-Smith JC, Henry LR, et al. Fat-containing lesions of the retroperitoneum: radiologic-pathologic correlation. *Radiographics.* 2009; 29(1): 261-90. PMID: 19168848. <https://doi.org/10.1148/rg.291085203>
- [19] Rosai J, Ackerman LV. *Surgical Pathology.* 10a. ed. Philadelphia: Mosby Elsevier; 2011.
- [20] Kumazoe H, Nagamatsu Y, Nishi T, et al. Dumbbell-shaped thoracic hibernoma: computed tomography and magnetic resonance imaging findings. *Jpn J Radiol.* 2009; 27(1): 37-40. PMID: 19373530. <https://doi.org/10.1007/s11604-008-0289-9>
- [21] Shin NY, Kim MJ, Chung JJ, et al. The differential imaging features of fat-containing tumors in the peritoneal cavity and retroperitoneum: the radiologic-pathologic correlation. *Korean J Radiol.* 2010; 11(3): 333-45. PMID: 20461188. <https://doi.org/10.3348/kjr.2010.11.3.333>
- [22] Rosso R, Lucioni M. Normal and neoplastic cells of brown adipose tissue express the adhesion molecule CD31. *Arch Pathol Lab Med.* Apr 2006; 130(4): 480-2. PMID: 16594742.
- [23] Nord KH, Magnusson L, Isaksson M, et al. Concomitant deletions of tumor suppressor genes MEN1 and AIP are essential for the pathogenesis of the brown fat tumor hibernoma. *Proc Natl Acad Sci USA.* Dec 2010; 107(49): 21122-7. PMID: 21078971. <https://doi.org/10.1073/pnas.1013512107>
- [24] Maire G, Forus A, Foa C, et al. Genes Chromosomes Cancer. 11q13 alterations in two cases of hibernoma: large heterozygous deletions and rearrangement breakpoints near GARP in 11q13.5. *Genes Chromosomes Cancer.* 2003; 37(4): 389-95. PMID: 12800150. <https://doi.org/10.1002/gcc.10223>