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Short Communication
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The Lardaceous Ochre – Hibernoma

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Short Communication

Preface: Adipose tissue tumors are frequently discerned soft tissue neoplasia which delineates an enhancing prevalence with increasing age. Demarcation betwixt benign and malignant adipose tissue tumors and common or exceptional lipomatous neoplasia can be challenging and necessitate cogent clinical examination or imaging studies [1].

Hibernoma is described as a benign neoplasm composed of "brown fat" and was initially scripted as a "pseudolipoma" by Merkel in 1906. The neoplasm was nomenclated as a "Hibernoma" by Gery in 1914 on account of morphologic simulation to brown fat accumulated within hibernating animals [1,2]. Hibernoma can be designated as a lipoma configured of prominent, brown adipocytes which recapitulate normal brown fat, identical to classic lipoma incorporating white fat. Cogent microscopy and immune reactivity is sufficient to categorically elucidate Hibernoma, although it can be misinterpreted as a malignant neoplasm [1,2].

Disease characteristics: Hibernoma is an uncommon neoplasm accounting for an estimated <2% of benign lipomatous neoplasia and around 1% of adipocytic tumors, although actual prevalence remains undetermined. The tumefaction frequently occurs in middle aged adults with a mean age of disease emergence varying from 26 years to 38 years. The neoplasm is associated with a slight male predominance wherein approximately 60% of inflicted individuals are males [3,4]. Average tumour magnitude is around 9.3 cm and varies from 1 cm to 24 cm. Remnants of brown adipose tissue usually emerge within specific regions such as the neck, shoulder, peri-scapular region or infrequently upon trunk or retroperitoneum. Occasionally, sites such as lower and upper extremities are incriminated or intra-osseous, peri-renal, peri-adrenal, peri-pancreatic, para-aortal or intracranial neoplasia are cogitated [3,4]. Hibernoma is frequently located within the axilla, dorsal trunk, mediastinum, shoulder, thigh, abdominal cavity, arm, breast, para-glottic space, para-sacral region, retroperitoneum or spermatic cord.

Multiple neoplasias can arise in a singular individual [4]. Majority of tumefaction are sub-fascial whereas around 83% tumors are deep-seated and around 17% lesions are detected at a superficial site. The thigh is a frequent site of neoplastic occurrence with an estimated range of 21% to 76% of hibernomas, buttock roughly 13%, inguinal region or groin around 9% and trunk exemplifies an estimated 5% of tumors. Deep-seated or intramuscular Hibernoma rises in approximately 11% to 83% individuals [3,4].

Infrequently, Hibernoma appears within the groin, supraclavicular region, buttock, scalp, abdominal wall, flank, pleura, adrenal glands, spinal segments, larynx, bone, foot, popliteal fossa, hind- leg, stomach or spermatic cord [4]. Hibernoma demonstrates a predilection for subcutaneous tissue, especially with lesions discerned upon the thigh, upper trunk and neck. Deep-seated Hibernoma is encountered in approximately <15% subjects. Genomic rearrangement of 11q13 chromosome with consequent emergence of Multiple Endocrine Neoplasia (MEN1) and AH receptor-Interacting Protein (AIP) combined genetic deletion is a characteristic feature of Hibernoma. Genetic translocation of (9;11) (q34;q13) can be observed.

Hibernoma is devoid of incriminating factors of possible emergence [3,4].

Clinical elucidation: Majority of incriminated individuals present with a painless, palpable mass. The tumefaction is enlarged with a median tumor diameter of 12.9 cm and appears as a painless, elastic, firm, slightly mobile nodule upon the incriminated site. The neoplasm is devoid of cogent clinical symptoms or sensory or motor dysfunction [5,6].

Tumor evolution is gradual and clinical manifestations ensue in enlarged tumors which compress adjacent neurovascular structures or irritate localized soft tissues. Hibernoma can produce steroid hormones [4]. Morphologically, adipose tissue cells with multiple vacuoles and miniature nuclei are discerned. Hibernoma demonstrates diverse histological appearances and staining characteristics

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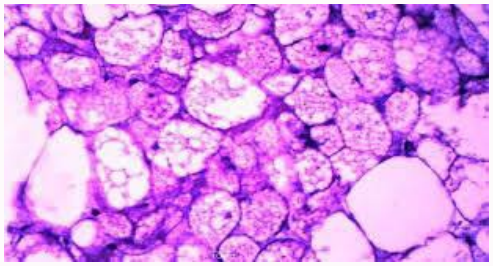

Figure 1: Hibernoma demonstrating enlarged, multi-vacuolated cells with miniature, centric nuclei and absence of mitotic.

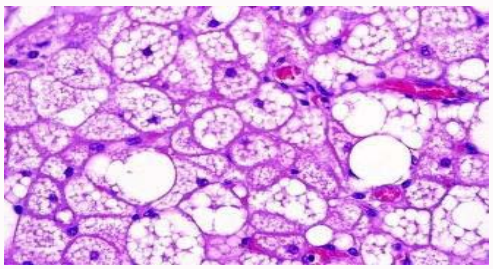

Figure 2: Hibernoma displaying multi-vacuolated adipocytes with several fat-filled spaces, miniature centroidal nuclei and a subdivision by mature, fibrous tissue septa.

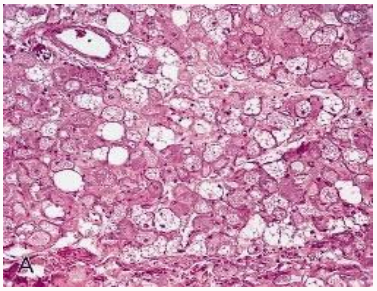

Figure 3: Hibernoma exhibiting granular and multi-vacuolated cytoplasm impacted with adipose tissue, fibrous tissue septa, numerous patent capillaries and miniature, uniform nuclei.

with the enunciation of subcategories such as typical, myxoid, mixed, lipoma- like or spindle cell. Aforesaid subtypes delineate divergent prevalence contingent to specific features such as anatomic location of neoplasm, gender predilection and age of neoplastic emergence. Diverse pertinent histological manifestations designate distinction betwixt Hibernoma and liposarcoma challenging, especially with imaging assays [5,6].

Hibernoma is comprised of varying proportion of three pertinent cellular subtypes described as enlarged, finely vacuolated cells with eosinophilic granular cytoplasm or brown fat cells, cells delineating enlarged fat vacuoles simulating lipoblasts and mature adipocytes. In addition, infrequent variants of Hibernoma described as myxoid, lipoma-like and spindle-shaped cells are discerned. Hibernoma is composed of specific subcategories as the classic variant (80%), myxoid variant (9%), lipoma- like (7%) or spindle cell variant (2%) - which is immune reactive to CD34 [5,6].

Histological elucidation: Macroscopically, the tumor is lobulated, well circumscribed with partial to complete circumscription and a thin, fibrous tissue capsule, discerned in around one third of lesions. Also, tumefaction can be circumscribed and un-encapsulated. Cut surface of Hibernoma varies from brown to yellow in combination with an adipose tissue matrix and focal necrosis is discerned in approximately 8% of neoplasms. Hibernoma demonstrates quantifiable thin walled blood vessels of diverse magnitude wherein around 10% instances delineate thick walled vasculature [4,6]. On cogent cytological examination, miniature, spheroidal, brown fat- like cells demonstrating minute, uniform cytoplasmic vacuoles and regular, spherical, tiny nuclei are observed. Additionally, an intermingling of delicate, branching capillaries and variable quantities of mature fat cells are exemplified [5]. Microscopically, tumor cells configure distinct lobules demarcated by thin, fibrous tissue septa and are comprised of an admixture of distinctive cellular populations designated as cells with fine micro-vacuoles, clear cytoplasm, centric or infrequently eccentric, miniature, vesicular nuclei with singular, centroidal nucleolus devoid of nuclear scalloping in addition to lipoblast-like cells, mature adipocytes and brown fat cells impacted with granular, eosinophilic cytoplasm. Proportion of preponderant lipoblast-like cells is variable and ranges from 10% to 80%. The neoplasm is devoid of cellular or nuclear atypia, enhanced mitotic activity or areas of necrosis [4,6]. On histological examination, cellular neoplasm composed of multi-vacuolated cells with granular cytoplasm and centric, miniature nuclei is discerned, a characteristic feature of brown fat cells. Few uni-vacuolated adipocytes are observed [6]. The tumor demonstrates an organoid configuration created by aggregates of uniform, enlarged cells simulating brown fat cells impacted with eosinophilic or pale-staining, multi-vacuolated cytoplasm and coarse granules. Miniature vacuoles are imbued with neutral fat which can be appropriately stained. Nucleus is miniature, centric and devoid of atypia. Cells imbued with brown fat are frequently admixed with white, pale-staining fat. The neoplasm can be circumscribed by a loosely configured, basophilic intercellular matrix. Nodules situated within neck or scalp can demonstrate features of a spindle cell lipoma. Also, singularly disseminated Hibernoma cells can be observed [5,6] (Figures 1-10).

Immune histochemical elucidation: Hibernoma is immune reactive to S100 protein in around 85% instances. Hibernoma cells can be stained with Oil red O and Sudan Black. Immune reactivity to CD31 and Uncoupling Protein1 (UCP-1) is discerned. Hibernoma is immune non reactive to CD34 and p53 [7]. Hibernoma is immune non reactive to Mouse Double Minute 2 Homolog (MDM2) and Cyclin-Dependent Kinase 4 (CDK4). Amplification of MDM2 is absent, as evaluated by Fluorescent in Situ Hybridization (FISH) technique, a feature which excludes the presence of an atypical lipomatous tumour [7,8]. On ultrastructural examination, Hibernoma is akin to brown fat. Individual tumor cell is encompassed with a basal lamina.

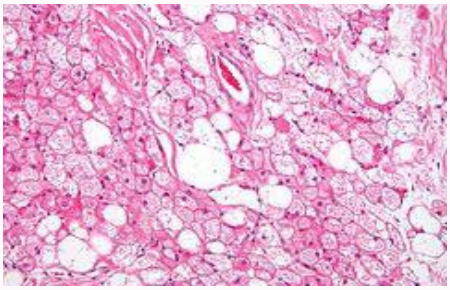

Figure 4: Hibernoma enunciating accumulation of multi-vacuolated, lipid rich cells imbued with brown fat and granular cytoplasm, red cell extravasations, congested capillaries and mature adipocytes.

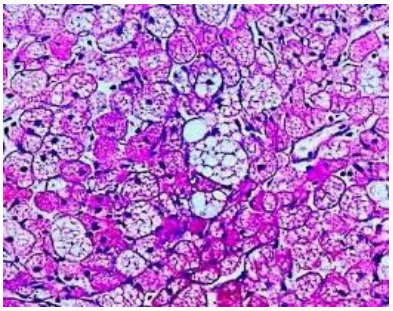

Figure 5: Hibernoma delineating aggregates of cells with granular cytoplasm, miniature nuclei and multiple vacuoles, mature adipocytes and red cell extravasations.

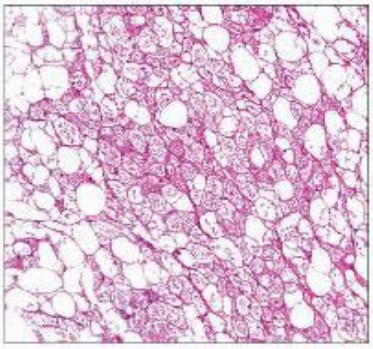

Figure 6: Hibernoma exhibiting cells with granular cytoplasm, multiple vacuoles, and cells imbued with adipose tissue, lack of atypia, uniform nuclear characteristics, red cell extravasations and congested capillaries.

Magnitude of lipid droplets is inversely proportional to quantifiable mitochondria per unit of cytoplasm. Pleomorphic mitochondria with dense matrices or enlarged, spherical mitochondria with transverse lamellar cristae are discerned. Additionally, undulations and invaginations of plasma-lemma, micro-pinocytotic vesicles and periodically appearing, miniature plasma-lemmal densities are discerned. A conspicuous lack of systematic occurrence of cytoplasmic membranes is enunciated [7]. Hibernoma is associated with chromosomal rearrangements of 11q13-21 genes, a feature which is also enunciated in lipoma and liposarcoma.

Certain tumor cells display a trisomal or tetrasomal genome [7,8].

Differential diagnosis: Hibernoma requires segregation from neoplasia such as well differentiated liposarcoma which emerge as deep-seated tumors displaying cellular and nuclear atypia and specific chromosomal translocations.

A classic lipoma is devoid of vacuolated lipocytes [7,8]. Also, remnants of brown fat can be discerned encompassing cervical or axillary lymph nodes, especially in children wherein the accumulation may not represent a definitive tumefaction [8].

Investigative assay: An incisional tissue specimen can confirm the presence of a Hibernoma [7]. Conventional plain radiographs depict a soft tissue neoplasm with an absence of intra-tumoral calcification. Imaging studies demonstrate a soft tissue tumor with characteristic accumulation of adipose tissue. Plain radiographs delineate radiolucent zones in the absence of calcification or concomitant osseous anomalies.

Ultrasonography can confirm the presence of neoplasm akin to

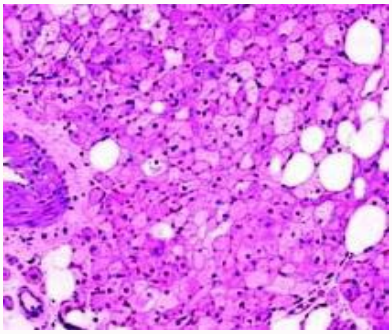

Figure 7: Hibernoma enunciating enlarged cells with granular cytoplasm, multiple vacuoles, scanty lymphocytic infiltrate, mature adipocytes, prominent vasculature and lack of atypia.

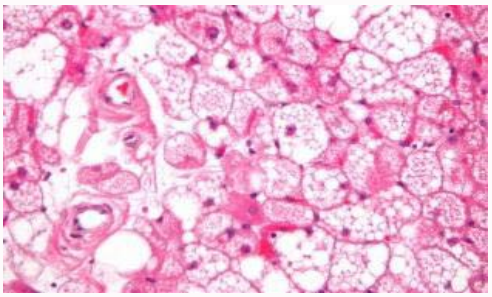

Figure 8: Hibernoma exemplifying enlarged cells with abundant granular cytoplasm, multiple intracellular vacuoles, centric, miniature, uniform nuclei, intermingled adipocytes and lack of atypia, necrosis or mitosis.

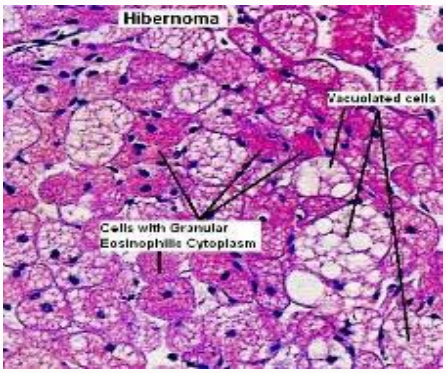

Figure 9: Hibernoma depicting aggregates of vacuolated cells with clear, finely vacuolated cytoplasm and an admixture of enlarged cells with granular, eosinophilic cytoplasm, uniform, centroidal, miniature nuclei and absence of mitosis [18].

adipose tissue tumors with a definitive tumor perimeter relatable to circumscribing skeletal muscle. Lesion perimeter depicts mildly enhanced perfusion within the tumefaction [9]. Combined ultrasonography and angiography can demonstrate enhanced perfusion of the neoplasm or arteriovenous shunts, although further demarcation betwixt Hibernoma and associated soft or adipose tissue tumors can be challenging. Magnetic Resonance Imaging (MRI) exhibits a well demarcated tumefaction with hyper-intense signal upon T2 weighted imaging and intermediately-intense signal upon T1 weighted imaging, ranging betwixt signal intensity of muscle and subcutaneous tissue.

Prominent fibrous tissue septa are accompanied by low-intensity signal. Adoption of intravenous gadolinium contrast exemplifies

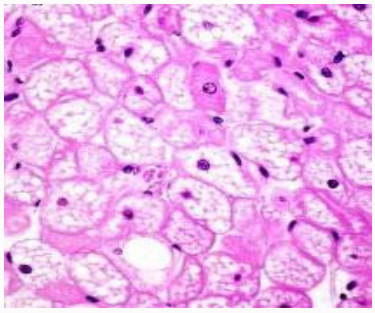

Figure 10: Hibernoma displaying aggregates of enlarged cells with granular, eosinophilic cytoplasm, uniform nuclei, multiple vacuoles, mature adipocytes and lipoblast-like cells with clear cytoplasm with absent mitosis [19].

variable or intense contrast enhancement [9,10]. Contrast enhanced Magnetic Resonance Imaging (MRI) exhibits a tumefaction with clearly defined tumor perimeter situated within specific sites. T1 weighted and T2 weighted images are hyper-intense. Inferior images are observed with subcutaneous adipose tissue upon T1 weighted resonance imaging.

Tumor periphery displays contrast enhancement [10]. Positron Emission Tomography (PET-CT) enunciates medium to elevated uptake of 18 Fluoro-Deoxy Glucose (18F-FDG) on account of amplified metabolic activity within brown fat tissue in addition to discernible standardized uptake levels akin to liposarcoma. Characteristically, hibernoma demonstrates fluctuating standard uptake values on account of inconstant metabolic activity within brown fat cells, a feature which can be triggered by variations in extraneous temperature [9,10]. Imaging characteristics of each neoplasm is variable as diverse subtypes of Hibernoma are comprised of varying quantities of adipose tissue and water. Contingent to tumour location, magnitude or signal characteristics upon cogent imaging, neoplastic differentiation within diverse lesions such as lipoma, well differentiated liposarcoma, atypical lipomatous tumor, myxoid liposarcoma or associated malignant adipose tissue tumors can be challenging [3,4].

Therapeutic options: Hibernoma as a benign tumor is devoid of distant metastasis or tumor reoccurrence following a comprehensive surgical resection. Cogent surgical excision of the tumefaction is indicated on account of emergence of localized clinical symptoms. Preferred treatment option is a comprehensive marginal resection of the neoplasm inclusive of pseudo-capsule and one centimeter margin of uninvolved, peritumoral soft tissue [9]. Comprehensive surgical extermination of the neoplasm is recommended, as the tumefaction can reoccur if excised inadequately. Essentially a benign neoplasm, Hibernoma is devoid of malignant metamorphosis or a metastatic dissemination. Nevertheless, surgical eradication is preferred in order to exclude a malignant neoplasm demonstrating Hibernoma -like differentiation, a feature which can be misrepresented in miniature lesions. Tumor reoccurrence is absent following a comprehensive excision [9,10]. Hibernoma can be detected within tumor perimeter in nearly 19% of surgical resection specimens. Median follow up of an average of 47 months is accompanied by negligible localized tumor reoccurrence or distant metastasis, thus emphasizing the benign nature of Hibernoma. As an exceptional tumefaction of brown fat, Hibernoma is associated with a superior prognostic outcomes [9,10].

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