Case Report

A Case Report and Discussion of Hibernomas: Pathology, Genetics, Diagnosis, and Treatment

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Abstract

A hibernoma is a rare benign tumor found in brown fat, compared to white fat, where most tumors arise. Hibernomas can usually be surgically removed without complication. Some genetic markers may exist for development of hibernomas, particularly genetic deformities occurring in genes situated on chromosome 11. In addition, different types of hibernomas tend to present based on the area of the body in which they form. Hibernomas are often undiagnosed unless they pose a particular problem to the patient, i.e. pain or pressure. Hibernomas can be surgically removed in order to relieve these symptoms, as seen in the case study for this report.

Introduction

Hibernomas are rare benign soft tissue tumors that arise from brown fat that persists beyond fetal life. The most common soft tissue tumors arise from white fat.[1,2,3] These tumors were initially described in the early 1900s by Merkl as being composed of brown fat. In 1914, the term hibernoma was proposed by Gery due to the morphological similarities of this tumor to the brown fat present in hibernating animals.[4] There are four subtypes of hibernomas that have been described previously and were recently added to the WHO Classification of tumors.[9] These tumors occur more commonly in adults and are seen in the interscapular-periscapular area, neck, axilla, thigh, brain, intrathoracic, and retroperitoneal area, as these are some of the places that brown fat will persist into adult life.[5] These tumors usually present as slow, painless growths, most common in the third and fourth decades of life.[2,6,7] There is some debate over gender predominance, and it has been noted previously that hibernomas are more common in one gender or another, although in previous reporting these numbers are very close to each other.[2,8]

Case Report

A 30-year-old man was referred to Surgical Specialists of Alabama because of a mass in the right shoulder. He had previously presented to the Northport DCH Emergency Room complaining of pain and limited range of motion. The mass had been present in the right shoulder, proximal deltoid area for years and over the last two to three months had been increasing in size rapidly. The patient stated that he smokes one pack of cigarettes per day and was otherwise healthy. MRI of the shoulder and chest was obtained, pre- and post-contrast.

On imaging, there was a large fatty mass seen in the anterior right chest/shoulder measuring 18 X 7.8 X 4.5cm. It contained multiple thin internal septations and a thin well-defined capsule. STIR images showed mild scattered edema around and within the mass. Post-contrast, the capsule and septa enhanced. The mass was noted to abut the pectoralis muscle with pos-

sibility of invasion. The mass also abutted the right shoulder and upper arm musculature. These findings were found to be consistent with lipomatous neoplasm, specifically benign fibrolipoma and liposarcoma. Suspicion for liposarcoma was high due to significant recent enlargement and associated pain.

The mass was completely excised down to the fascia. It was found to involve the right deltoid muscle and extend onto the area of the pectoralis muscle. A portion of the pectoralis muscle was excised with the specimen. The specimen was encapsulated and not infiltrating and was completely excised and sent for pathology and inking of margins. The patient had an uneventful operative course and was discharged home the same day with follow-up appointment in one week.

Macroscopically, the mass was tan-pink to tan-yellow, lobular, soft, irregularly surfaced, encapsulated, and vascular. The mass measured 21 X 11 X 6cm. After fixation there was no color, texture, or architectural change noted. It was composed of abundant brown fat, and no lipoblasts were seen. The specimen was determined to be a hibernoma.

Discussion

The human body contains two types of fat: brown fat and white fat. Brown fat participates in thermogenesis and regulation of metabolism. While it is commonly found in animals that hibernate, the theory that it is involved in hibernation has been disproved. Brown fat also exists in animals that do not hibernate and in humans during gestation.[8] It becomes recognizable in humans after the 21st week of gestation and is slowly replaced with white fat as maturation occurs.[2] However, it does persist in humans in specific areas of the body, particularly the neck, axilla, mediastinum, periaortic area, and perirenal area. Brown fat constitutes 1% of body mass in adults.[8,11]

Furlong et al. completed a review of 170 hibernoma cases and found that hibernomas are more common in men than women, though that distinction is debated. The average age of diagnosis for the four histological subtypes of hibernomas occurs at 38.8 years.[11] The study found that this tumor is most common in the lower extremities, followed by the upper extremities, head and neck, abdomen, and retroperitoneal.[9] The overlying skin can be warm to the touch due to the extensive vascularity of the tumor.[11]

Typically, these masses present as painless, progressive, slow growth, and only become symptomatic when they compress adjacent structures.[2] On imaging, they should clearly light up on contrast CT due to their fatty solid structure. Angiography can also be used, as these tumors are vascular. Blood flow through and within the mass can confuse the picture and cause it to look similar to a malignant process.[2,6] On T1 weighted MRI they show up as hypointense to fat, and on T2 images they are usually found to be isointense to subcutaneous fat.[11] These tumors can mimic the appearance of other lipomatous tumors, such as liposarcoma, increasing the need for index of suspicion and knowledge of the tumor type prior to surgery.[1,11] Gross specimen is well defined, encapsulated, soft, and a tan to reddish brown color depending the amount of intracellular lipids present.[2,7] Microscopically, it has large multivacuolated cells with eosinophilic cytoplasm and eccentric nuclei, univacuolated cells with peripheral nuclei, and smaller round cells with a granular cytoplasm.[5,6]

Diagnosis

There tumors are generally painless and are often found incidentally during routine physical exams or following an injury.[8] There has been some association to weight loss due to the excessive thermogenesis produced by the brown fat. In some cases a fever and elevated inflammatory markers such as sedimentation rate, leukocytes, and C-reactive protein can be elevated.[8] At the time of diagnosis the tumor is usually ≥ 10 cm.[3] On radiography, the hibernoma is seen as a soft tissue swelling, with few other characteristics.[8] Ultrasound studies will show a hyperechoic mass with hypervascularity noted on Doppler studies.[5,8] Angiography will also show the hypervascularity of the hibernoma along with possible arteriovenous shunts.[8] The non-lipoma subtype is always heterogeneous, hypo- or isointense with hypervascularity on MRI.[3] On T1 weight MRI they show up as hypointense to fat, and on T2 images they are usually found to be isointense to subcutaneous fat.[11] On PET scanning these lesions typically light up due to an increased number of mitochondria and high rate of metabolism occurring in the brown fat.[8] This is not the only benign lesion that lights up on PET scan; other examples include: benign follicular thyroid adenomas, colonic adenomas, renal oncocytomas, and benign plexiform neurofibromas.[8] Typically, lipomas do not show uptake on PET scan, and liposarcomas show moderate uptake; however, there is some overlap in the definition of uptake values with little standardization so uptake potential does not accurately predict malignant potential.[8] Some have suggested CT guided biopsy, but due to the hypervascularity of the tumor, this has been controversial due to risk of hematoma or bleeding.[3] Therefore, core or percutaneous biopsies should be avoided to prevent these negative side-effects.[5] However, it has been noted that fine needle or percutaneous biopsy has a specificity of 100% and a sensitivity of 99% for diagnosis of this pathology.[8] Differential diagnosis of these tumors should include atypical lipoma, well differentiated liposarcoma, rhabdomyoma, fibroma, neurofibroma, angiolipoma, and granular cell tumor.[8]

Pathology

In 2001, four morphological subtypes of hibernomas were described by Furlong: typical, myxoid, lipoma-like, and spindle cell, and in 2002 they were added to the WHO Tumor Classification.[9,11] These four subtypes are determined based on ratio of multivacuolate adipocytes that are commonly seen in brown fat and univacuolate adipocytes that are commonly seen in white fat. Tumors with ≥ 70% multivaculoate adipocytes are considered to be non-lipoma hibernomas (typical), while < 70% multivacuolate adipocytes are considered lipoma-like hibernomas.[3,8,9,10,11] The non-lipoma or typical subtype is considered the

most common (82%) and has three histological appearances: the eosinophilic variant, the pale variant, and the mixed variant. The eosinophilic variant is the classic presentation.[3] The myxoid subtype (9%) contains a basophilic matrix.[8] Spindle cell hibernomas (2%) contain features of spindle cell lipomas and hibernomas.[8] The lipomas variant (7%) only contains lipomatous cells in a scattered arrangement.[8] Certain variants are more common in specific anatomical locations. For example, the thigh is most common for the typical hibernoma, while the myxoid type is most common in the head and neck, and the spindle cell variant is most common in the posterior neck and scalp.[8] Approximately 85% of all hibernomas were found to contain S100 protein on immunohistochemical staining.[11]

Genetics

Recent studies in Sweden suggest that there may be a genetic component to propensity to form hibernomas. Based on their research with 15 hibernomas, they found that these tumors typically present with a balanced translocation between the 11q13 chromosome and a variety of other chromosomes.[12] These translocations have been found to be associated with MEN1 and AIP genes. These two genes sit close to each other on chromosome 11. They found in all except for one of their tumors that one or both of the alleles were deleted. The translocations of chromosome 11 occur between many different partner chromosomes, unlike other translocations that typically occur between alternating chromosomal partners. The target genes involved in the translocation are well known tumor-suppressor genes that are involved in hereditary tumor syndromes. AIP mutations area associated with a predisposition to familial pituitary adenoma syndrome. MEN1 protein product menin is associated with transcription and genomic stability and involved in the MENI, multiple endocrine neoplasia type I. These patients have displayed some lipomatous tumors in addition to the endocrine neoplasias typical of the disorder.[12] MENI and AIP have been found to be connected to the formation of brown fat and its development. AIP is thought to repress peroxisome proliferator-activated receptor - alpha (PPAR alpha), and menin has been shown to have the same effect on peroxisome proliferator-activated receptor-gamma. PPAR-alpha and PPAR-gamma have been shown to be involved in the rate-limiting reaction for brown fat lipogenesis. Therefore, the loss of MENI and AIP's regulatory effect has been associated with overactivity of these enzymes leading to overproduction and development of brown fat.[12]

Treatment

Hibernomas are typically removed surgically because histology and pathology cannot be confirmed by imaging and can even mimic more ominous tumors on imaging studies. These tumors do not infiltrate surrounding structures but can grow to a large size and lead to compressive effects.[8] At the time of surgery, these tumors are found encapsulated and can be adhered to muscle or growing intramuscularly.[8] Hibernomas are considered benign tumors, and, therefore, marginal excision is considered curative. There have been no metastasis or deaths reported from these tumors, although there have been a few cases of nuclear atypic identified.[9,11] There has been evidence of recurrence in some cases, but that has been attributed to incomplete resection of the primary hibernoma.[8]

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