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## Case Report

# Intraosseous hibernoma: Two case reports and a review of the literature ☆,☆☆

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## ABSTRACT

Intraosseous hibernomas are exceedingly rare tumors with only 35 cases reported worldwide. They are composed of vestigial brown adipose tissue and require biopsy and pathologic analysis for definitive diagnosis. Given their propensity to mimic more insidious malignant neoplasms, early and accurate identification may spare the patient both anxiety and invasive therapeutic interventions. In this report, we present two cases of intraosseous hibernomas and provide a review of current literature to further characterize the clinical, radiographic, and histopathologic parameters of these lesions. Clinicians should consider the diagnosis of intraosseous hibernoma when evaluating patients with characteristic presentations as it may be more prevalent than currently reported.

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## Introduction

Hibernomas are rare, benign soft tissue tumors composed of brown adipocytes. They were first described by Merkel in 1906 as a “pseudo lipoma” [1]. It wasn’t until 1914 when Gery correlated the histopathological findings of brown adipocytes with that of hibernating mammals, thus coining the phrase “hibernoma” [2]. These well-described soft tissue tumors most commonly present as an insidious and painless soft tissue mass within the 4th decade of life [3]. They usually occur

in the thigh, shoulder, back, and neck and can be described as typical (82%), myxoid (8%), lipoma-like (7%), and spindle cell (2%) [4]. Though benign, these lesions are definitively managed with surgical excision with a low risk of recurrence irrespective of the morphological variety diagnosed [5]. Hibernomas do not have the propensity to undergo malignant transformation, with only a single reported case in the literature describing a patient with Turner’s syndrome in 1967 [6].

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Until recently, hibernomas were thought to exclusively occur within the soft tissue. The first known case of an intraosseous aggregate of brown adipose tissue was discovered during a trephine bone biopsy as part of a clinical work-up for essential thrombocytopenia in 2006 [7]. Currently, only 35 total cases of intraosseous hibernomas have been reported within international literature [7–28]. Similar to their soft tissue counterparts, they are usually found incidentally while working up a different clinical scenario, although occasionally they present with pain. While it is debated if any of the reported intraosseous hibernomas were the true cause of the reported pain at presentation, most lesions may be treated conservatively with analgesics. Our review of the literature identified 2 patients who underwent successful treatment of symptomatology with radiofrequency ablation [13, 27] and 2 patients who required surgical excision of the lesion [20, 22].

In this report, we present 2 cases of intraosseous hibernomas including their clinical, radiographic, and histopathologic characteristics to broaden the current knowledge surrounding these rare bone tumors. We encourage all orthopedists, radiologists, and pathologists to consider intraosseous hibernoma among their differential diagnoses when faced with a non-specific presentation incorporating the aforementioned characteristics.

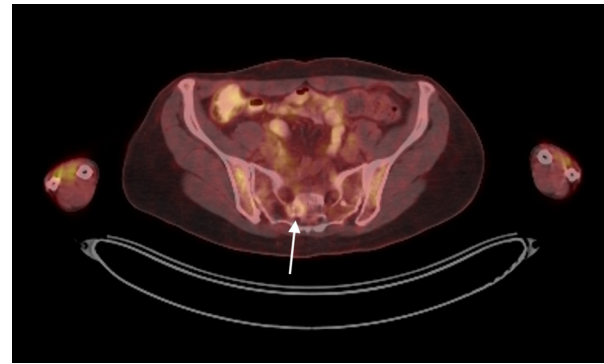
## Case reports

### Patient 1

A 52-year-old woman with past medical history significant for dermatofibrosarcoma protuberans and melanoma in situ presented to orthopedic oncology for consultation of chronic right hip pain. The patient described constant aching pain of her lateral right hip for 9 months duration that worsened at night and caused her to wake from sleep. Although extremely active, she denied exacerbation of pain from her regular activities of running, cycling, or skiing. There was no history of trauma to the region, nor constitutional symptoms.

Given her cancer history, the patient underwent a thorough diagnostic work-up to evaluate for potential malignancy. Blood work, including a complete blood count, prothrombin time, and partial thromboplastin time, were ordered and determined to be within normal limits.

An AP radiograph of the pelvis with 2 views of the right hip demonstrated a 2.5 cm sclerotic cortical lesion in the right supra-acetabular aspect of the bony pelvis with minor degenerative changes and acetabular spurring. Further investigation via positron emission tomography (PET) scan demonstrated subtle radiotracer uptake overlying the right mid-sacrum (Fig. 1). No abnormal radiotracer uptake was seen in the region of the right acetabular sclerotic focus identified on the radiographs. Given the incomplete characterization of the lesion, further imaging with MR was pursued. Corresponding to the focus of radiotracer uptake on radionuclide bone scan, the MRI demonstrated a 2.1 cm T1 hypointense, T2 hyperintense lesion in the right sacral wing with moderate enhancement on post contrast sequences (Fig. 2).



**Fig 1 – Case 1. Positron emission tomography (PET) demonstrates subtle radiotracer uptake within the right mid-sacrum (arrow).**

Given the non-specific imaging characteristics and history of malignancy, a percutaneous CT-guided needle biopsy was performed (Fig. 3). Immunohistochemical staining demonstrated intraosseous brown adipocytes positive for S100 without concomitant PanCK (AE1/AE3) staining, consistent with an intraosseous hibernoma. Due to lack of symptoms, the patient elected to forgo further intervention in favor of conservative management and was ultimately lost to follow-up.

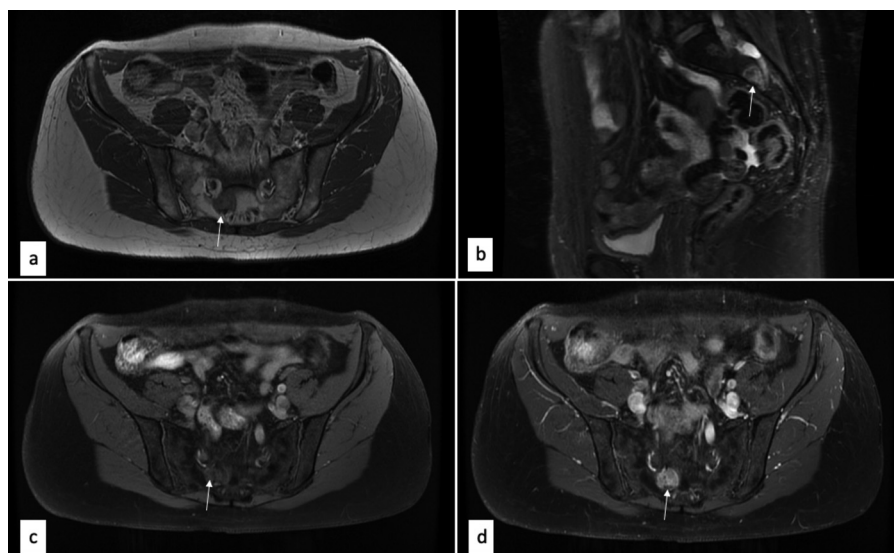
### Patient 2

A 68-year-old woman with past medical history significant for atypical squamous cells of undetermined significance of the cervix and basal cell carcinoma presented to orthopedic oncology for consultation regarding a right sacral ala lesion discovered during a work-up of chronic midline lumbar back pain of ten years duration. The aching pain localized to her lower back, was made worse with prolonged sitting or standing, and was not associated with any radicular symptomatology, numbness, paresthesias, or changes in bowel or bladder control. There was no history of trauma to the region or of constitutional symptoms including fever, chills, night sweats, or weight loss. The patient had attended eight weeks of physical therapy without improvement in her symptoms, at which point an MRI of the lumbar and sacral spine was ordered.

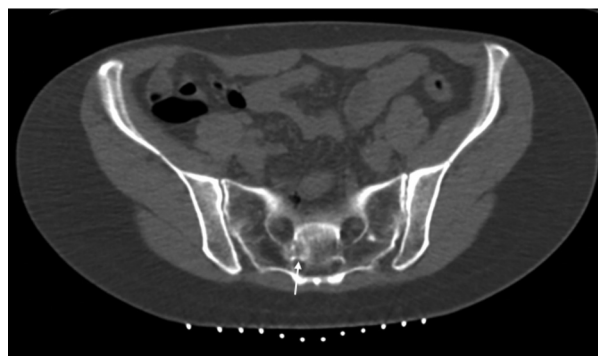
There was no reported family history of cancer. All relevant laboratory studies, including CBC, CMP, thyroid studies, prothrombin time, and partial thromboplastin time were within normal limits.

The lumbar and sacral spine MR images demonstrated two adjacent lesions within the right sacrum (Fig. 4). This MRI demonstrated a 1.3 × 1.2 cm lesion centrally located within the S1 vertebral body and an adjacent 1.5 × 1.9 cm lesion within the right sacral ala. These lesions both demonstrated T1 hypointense and heterogeneously hyperintense T2 signal with mild enhancement on post-contrast sequences. The smaller lesion was unchanged from the prior lumbar MRI, while the larger lateral lesion had increased in size. Further imaging was pursued with radiographs; however, no definitive lesion was identified.

Given the increase in size of the lateral lesion, a CT-guided needle biopsy was performed (Fig. 5). The pathology revealed



**Fig. 2 – Case 1. (A) Axial T1 pelvis MRI demonstrating a T1 hypointense lesion within the right sacrum (arrow). (B) Sagittal fat-saturated T2 weighted image demonstrating the hyperattenuating lesion within the right sacrum (arrow). (C) Axial fat-saturated T1 pre-contrast image demonstrating the T1 hypointense lesion within the right sacrum (arrow). (D) Axial fat-saturated T1 post contrast MRI demonstrating the 2.1 cm enhancing lesion within the right sacrum (arrow).**



**Fig. 3 – Case 1. Axial CT image obtained during CT guided percutaneous biopsy demonstrating mixed sclerotic lesion within the right sacrum (arrow), which was targeted for biopsy.**

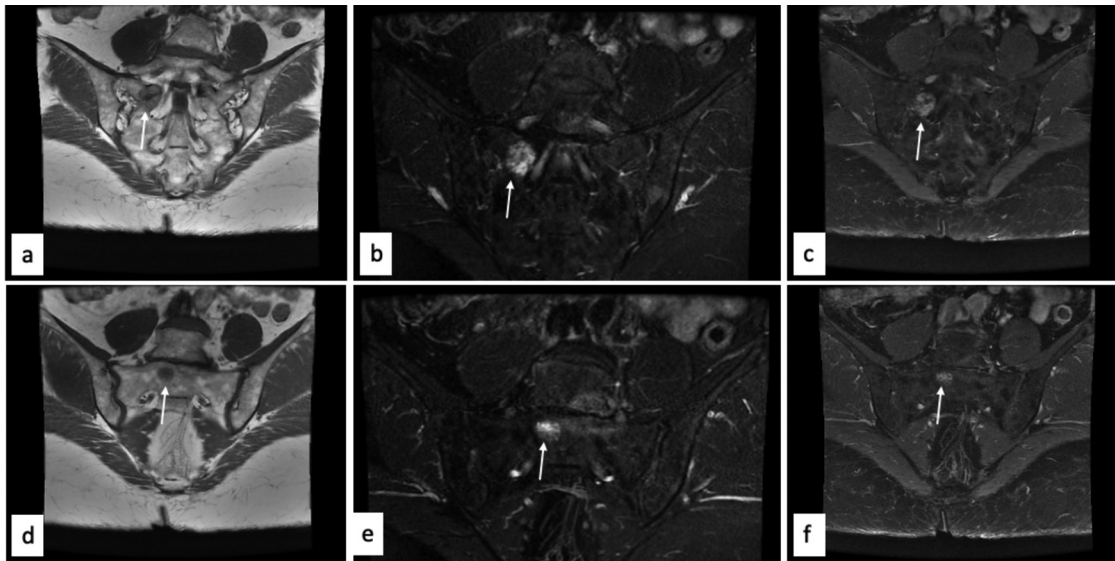
components of bone and marrow with large adipose cells resembling brown fat with coarsely granulated cytoplasm. Immunohistochemical stains show the lesional cells were positive for S100 and negative for PanCK (AE1/AE3) and CD163 (Fig. 6), supporting the diagnosis of an intraosseous hibernoma.

Owing to the benign course of an intraosseous hibernoma, the patient elected to pursue conservative management with annual surveillance with orthopedic oncology. The patient will continue to follow up with her primary sports medicine physician regarding her chronic lumbar back pain and annually with orthopedic oncology for MRI surveillance of both sacral lesions. Her first follow-up visit has not yet occurred at time of this publication.

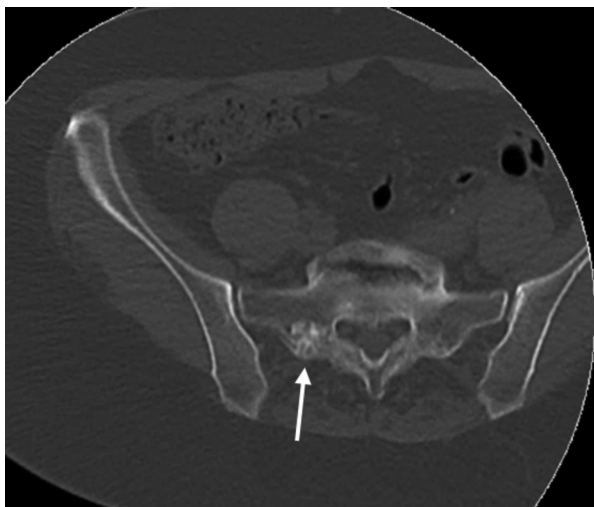
## Discussion

Classically, there are two varieties of adipose tissue found within the human body, brown and white adipocytes [29]. Adipocytes are derived from the same mesenchymal progenitor stem cells as osteoblasts [30, 31]. The retinoblastoma protein (pRb), a well-described tumor suppressor, has also been shown to play a key role in mesenchymal differentiation. When pRb is present in sufficiently high amounts, it induces the shared precursor cell to differentiate into an osteoblast; when pRb levels are sufficiently low, the common progenitor differentiates into an adipocyte. The prolonged absence of pRb produces a brown, metabolically active adipocyte, whereas its resurgence produces a white, storage adipocyte [32].

White adipocytes serve as an energy reservoir within adult human bone marrow and are termed “lipomas” when unregulated growth yields a soft tissue mass [33]. They consist of a single, large lipid droplet and are characteristically clear or white on visual inspection [34]. Conversely, brown adipocytes are abundant in newborns and hibernators where they provide non-shivering thermoregulatory functions via mitochondrial “uncoupling regulatory protein 1” (UCP1), which uncouples electron transport from ATP production, thereby converting chemical energy into thermogenesis [35]. They are composed of multiple small lipid droplets and numerous iron-containing mitochondria, giving rise to their characteristic tan color [34, 36]. Though the quantity of brown adipocytes decreases drastically over time, the increase in FDG-PET imaging in the clinical setting has demonstrated persistent brown adipose tissue reservoirs surrounding major arteries, in the upper trunk, axilla, cervical, paravertebral, perirenal, and adrenal regions in adults [37–39]. While tumors of brown adipose



**Fig. 4 – Case 2. (A) Coronal oblique T1 pelvis MRI demonstrating a heterogeneous T1 hypointense lesion within the right sacral ala (arrow). (B) Coronal oblique T2 pelvis MRI demonstrating a heterogenous T2 hyperintense lesion within the right sacral ala (arrow). (C) Coronal oblique fat-suppressed T1 post-contrast pelvis MRI demonstrating an enhancing lesion within the right sacral ala (arrow). (D) Coronal oblique T1 pelvis MRI demonstrating a T1 hypointense lesion within the S1 vertebral body (arrow). (E) Coronal oblique T2 pelvis MRI demonstrating a T2 hyperintense lesion within the S1 vertebral body (arrow). (F) Coronal oblique fat-suppressed T1 post-contrast pelvis MRI demonstrating an enhancing lesion within the S1 vertebral body (arrow).**



**Fig. 5 – Axial CT image obtained during percutaneous biopsy demonstrating a sclerotic right sacral ala lesion (arrow), which was targeted for biopsy.**

tissue are termed “hibernomas,” it is important to note that a small proportion of hibernoma cells are white adipocytes intermixed among the much more numerous brown adipocytes [40].

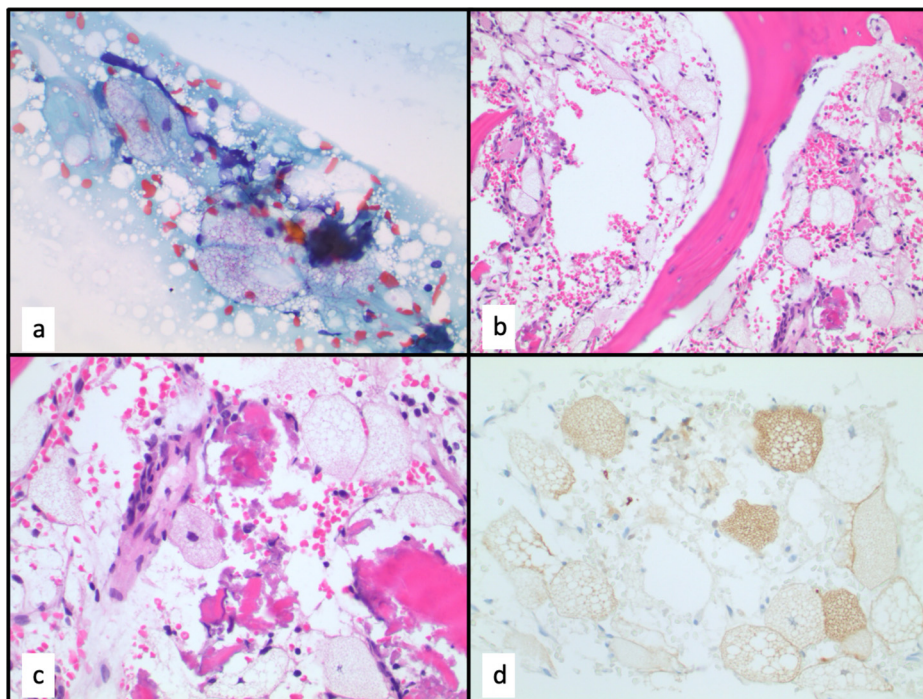
Recently, a third class of adipocyte has been recognized in the literature as “beige” adipose tissue. Essentially, white adipocytes may be chemically induced to express increased levels of UCP1, as well as morph their single, large lipid droplet

into multiple smaller lipid droplets, thereby functionally converting to a brown adipocyte through the white adipocyte pathway [41].

Historically, only white adipocytes were thought to reside in the bone marrow. It wasn’t until 2006 that brown adipose tissue was first identified within the bone marrow [7]. However, it is possible that brown adipocytes physiologically exist within the marrow space at all stages of life [42]. Within the last few decades, bone morphogenetic protein 7 (BMP7) has been identified as being integral in brown adipogenesis [43]. BMP7 is also well-known for its ability to induce osteoblasts and bone growth, thus its historical use in treating fracture nonunion [44]. Therefore, the presence of BMP7 during primary bone development may simultaneously promote brown adipocyte differentiation within the bone marrow, providing a nidus for intraosseous hibernoma development over time.

Intraosseous hibernomas follow predictable, albeit non-specific, clinical, radiographic, and histopathologic patterns. Following a comprehensive literature review, there appears to be a 3:1 female:male predominance with an average age at presentation of 58.9 years (range 36-85 years). No common features of past medical history were identified among the case reports. Half of all reported intraosseous hibernomas were incidental findings, while the remaining half were discovered on imaging studies performed secondary to chronic pain. Importantly, many of the reports indicate concomitant disc herniation and spinal stenosis consistent with the pattern of pain. Therefore, the consensus among the literature is that intraosseous hibernomas are painless lesions that may otherwise not be identified if not for concomitant pain work-ups secondary to unrelated conditions [23].





**Fig. 6 – (A) Cytology specimen smear Papanicolaou stain (40x) demonstrating round to polygonal brown adipocytes with multivacuolated cytoplasm pushing nuclei to the side. (B) Hematoxylin and eosin (20x) microscopy demonstrating clusters of round to polygonal brown adipocytes with multivacuolated cytoplasm pushing nuclei to the side or indenting the nuclei, sitting next to the eosinophilic lamellar bony trabeculae. (C) Hematoxylin and eosin (40x) microscopy demonstrating clusters of round to polygonal brown adipocytes with multivacuolated cytoplasm pushing nuclei to the side or indenting the nuclei, sitting next to the eosinophilic lamellar bony trabeculae. (D) Immunohistochemical stain (40x) shows the lesional brown adipocytes are positive for S100, which also highlights the multivacuolated cytoplasm. Additional slides (not shown) demonstrated cells to be negative for AE1/AE3 and CD68.**

After careful review of current literature, most lesions were localized to either the pelvis (57%) or the spine (27%), with femoral (8%), sternal (5%), and thoracic rib cage (3%) lesions accounting for the remaining cases. Regarding radiographic assessment, plain films were not reliable at detecting the lesion (45%), while those that did identify the intraosseous hibernoma demonstrated sclerosis (55%). On CT scan, the majority (81%) of lesions were sclerotic. A smaller subset (19%) of studies demonstrated lytic lesions with or without sclerotic rims. Magnetic Resonance (MR) imaging characteristics typically demonstrate central T1 hypointense and heterogeneous hyperintense T2 signal. Two reports (8%) differed in MR assessment in that the T1-weighted imaging demonstrated isointense signal to subcutaneous fat. Post-contrast MRI enhancement varied considerably among reports with the mild to moderate enhancement being most often observed. Seven total patients underwent FDG-PET imaging (19%), which demonstrated variable metabolism ranging from no hypermetabolism to mild/moderate hypermetabolism (SUV 2.5–4.6). Similarly, bone scans varied in results with some lesions demonstrating no uptake and others demonstrating intense uptake. One report included Gallium-68 Dotatate imaging, which yielded three times the uptake of that of the most intensely hypermetabolic FDG-PET scan (SUV 12.4).

From a histopathologic perspective, gross visualization of the sample will demonstrate tan/brown coloring secondary to both the vascularity of the tumor, as well as the numerous iron-laden mitochondria present within each cell [45]. Microscopic evaluation of hibernomas demonstrate large, multivacuolated adipocytes with a “foamy” appearance and paracentrally placed nuclei [46]. Immunohistochemically, hibernoma cells are known to characteristically stain positive for S-100, while staining negative for cytokeratin and brachyury [47]. Given the wide differential based on radiographic assessment alone, including lipoma, atypical lipomatous tumor, liposarcoma, angioliipoma, notochordal rest, and clear cell sarcoma [48], this immunohistochemical pattern is essential for accurately diagnosing an intraosseous hibernoma.

Given the benign nature of an intraosseous hibernoma, no treatment is necessary once the condition is confirmed via histopathology. Our review of the literature identified only two patients who underwent surgical resection [20, 22] and 2 patients who received radiofrequency ablation [13,27]. Consistent with the current body of literature, neither of our 2 patients required further intervention following definitive diagnosis. A common theme amongst published cases is concurrent pain emanating from a separate condition that ultimately led to the incidental discovery and subsequent work-up of the intraosseous hibernoma. As such, careful diagnostic acumen

aimed at identifying the true source of pain is of paramount importance given that intraosseous hibernomas are generally considered to be a painless lesion of bone.

In conclusion, intraosseous hibernomas are rare primary tumors of bone. It is essential that all clinicians, spanning orthopedic surgeons, radiologists, and pathologists, be aware of the possibility of a hibernoma occurring within the bone so to limit the potential for misdiagnosis of this benign condition.

### Patient consent statement

Informed consent for publication has been obtained from all patients.

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