Axillary Hibernoma in woman with Lobular breast cancer and MEN1 syndrome: A case report

Giulia Deguidi a, Sara Mirandola a, Alessia Nottegar b, Vassilena Tsvetkova b, Beatrice Bianchi a, Francesca Pellini a,∗

a Complex Operative Unit of Breast Surgery - Breast Unit AOUI, Verona, Italy
b Department of Pathology and Diagnostics- Breast Unit AOUI, Verona, Italy

ARTICLE INFO

Article history:
Received 12 August 2020
Received in revised form 11 November 2020
Accepted 11 November 2020
Available online 27 November 2020

Keywords:
Hibernoma
Brown fat tumor
MEN-1 syndrome
Breast cancer
FDG CT-PET
Case report

ABSTRACT

INTRODUCTION: The present study reports the case of an axillary hibernoma in a patient with lobular homolateral breast cancer and multiple endocrine neoplasia type 1 (MEN-1).

Hibernoma is a rare benign adipose tissue tumor, and usually manifests as a slowly growing and painless rubbery mass.

These tumors can arise in various sites, but mammary hibernomas remain extraordinarily uncommon. Although hibernomas are metabolically active and therefore “glucose-avid” on fluorodeoxyglucose CT-pet emission tomography (FDG CT-PET), imaging alone is inadequate in providing a reliable diagnosis and definitive differential diagnosis from other malignancy. Only complete surgical excision is diagnostic and, in most cases, curative.

PRESENTATION OF CASE: A 42-years-old woman was followed for MEN-1 syndrome associating with hyperparathyroidism, insulinoma, non-secretory adenoma and thyroid lump. A FDG CT-PET found high glucid hypermetabolism in thickened elongated area on the front axillary line.

Hibernoma was diagnosed after realization of prophylactic left mastectomy, homolateral sentinel lymph node biopsy and exeresis of the known axillary lesion.

DISCUSSION: Clinical importance lies in distinguishing hibernoma from other benign and malignant breast neoplasms, as well as inflammatory conditions that come into the histologic or radiologic differential. Hibernoma is not currently classified as a non-endocrine tumor related to MEN1, but this association could be not fortuitous for the linkage between modification of Menin protein function and pathogenesis of hibernomas.

CONCLUSION: Our case deserves extraordinary attention because, not only it’s a case of MEN1 syndrome associated with hibernoma, but in the context of this lesion there are multiple micro-foci of infiltrating lobular carcinoma.

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1. Introduction

Hibernomas are rare benign soft tissue tumors, slow growing and painless. They may present as an incidental finding or rarely cause symptoms due to compression of adjacent structures.

Our patient, followed for a MEN1 syndrome, was diagnosed with a right infiltrating lobular carcinoma. An FDG CT-PET, 2-years later, found hypermetabolism in an elongated area on the left front axillary line; considering the medical history of the patient, this finding was highly suspicious for lobular invasive breast cancer metastases. The patient undergone left mastectomy, homolateral sentinel lymph node biopsy and complete excision of that area, compatible with hibernoma with micro-foci of infiltrating lobular carcinoma on histological examination. This case report aims to offer details on the management of the rare benign tumor in question and is reported in line with the SCARE criteria [20].

2. Case report

A 42-years-old woman was followed for MEN1 syndrome (missense mutation on the p.Glu26Lys) associating with hyperparathyroidism (treated by one-gland parathyroidectomy); 9 mm benign non-secretory adenoma; thyroid lump of about 1 cm in euthyroidism (with a cytological examination negative for malignant cells). In addition, for severe hypoglycaemias insurgent in 2015, an abdomen ultrasound documented 4 insulinoma on body-tail and another one on cephalo-pancreatic region.

https://doi.org/10.1016/j.ijscr.2020.11.073
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She was familiar with lung cancer (maternal grandmother, maternal aunt, maternal uncle), prostate cancer (paternal grandfather with bones metastases) and pancreatic cancer (father).

In April 2018, the patient underwent a right mastectomy, axillary dissection and placement of sub–pectoral breast expander, for infiltrating lobular carcinoma, solid-alveolar variant (7 cm), G2, neoplastic necrosis and vasculo-lymphatic invasion, intratumorally calcifications.

At immunohistochemical (IHC): Ki 67 20%, Estrogen Receptor (ER) 95%, Progesterone Receptor (PgR) 80%, Hercept test not overexpressed. In summary: pT3 N9/18 M0.

She underwent chemotherapy (4 cycles of Epirubicin + Cyclofos-famide, EC) and hormonal therapy (luteinizing hormone releasing hormone LHRR antagonists) followed by 3 cycles of Taxolo (TXLw) suspended for toxicity (fatigue and headache). She finished the sixth cycle of EC and continued first with Letrozole, crossed to Tamoxifene for intolerance.

The BRCA 1–2 gene loci mutation showed no pathogenic variants.

Since the patient had a breast expander, she did not perform a pre-operative MRI but a FDG CT-PET, which documented high glucid hypermetabolism in thickened elongated area, adjacent externally to the average arc of the IV, V and VI left rib, on the front axillary line (size ApxLxC about 25 × 12 × 50 mm; SUV max 14.6). It also documented high glucid hypermetabolism at both adrenals, enlarged (at right metabolic size maximum about 2 cm with SUV max 8.9; at left metabolic size maximum about 4 cm of bilobate appearance with SUV max 9.3).

She underwent bilateral ultrasound and mammography, which did not detect any focal lesions.

The chest CT confirmed the presence of 30 mm hyperdense areola which made contact with the pectoral, without lymph adenomegalgy characteristics nor unique appearance compatible with local recurrence.

The patient was completely asymptomatic and painless.

Total body CT, performed at diagnostic–stage supplementation, was negative for metastases.

In May 2020 the patient underwent a left prophylactic mastectomy (in light of the risk of developing a lobular breast carcinoma typical of patients with MEN1 mutation), homolateral SLNB with indocyanine green and resection of the known axillary lesion (Fig. 1). Moreover, left breast reconstruction with prosthesis and replaced the right breast expander with prosthesis.

On histological examination: left breast with submillimetre micro–foci of lobular carcinoma in situs of classic type, G1, and isolated aspects of usual ductal hyperplasia. Cute, nipple and surgical resection margins unscathed. Neof ormation consists mainly of a cell population with large eosinophilic cytoplasm, microvacuolate mixed with mature adipocytes, without cytocarcinological atypies, compatible with typical hibernoma. In the context of the lesion there are multiple submillimetre micro–foci of infiltrating lobular carcinoma, G2 sec. Elston-Ellis. At ICH: CD45: Negative; CHERAT. 8/18/19: Positive; E-caderin: Negative; Ki67 AG PROLIF.: 7–8%; HERCEP Test: negative; ER: 90%; PgR: Negative; GATA-3: Positive.

The patient was discharged from the hospital on postoperative day 2. Her post-operative course was uneventful except for a non-infected seroma in the axillary region, resolved with percutaneous drainage (CLAVIEN-Dindo Grade 1).

3. Discussion

3.1. Definition

Hibernoma is a very rare benign tumor that arises from the remnants of fetal brown adipose cells.

3.2. Epidemiology

Hibernomas are seen mainly in adults, with a peak incidence during the third decade of life, with a slight female predominance [9].

3.3. Anatomical sites

Hibernoma predominates in areas in which small amount of brown fat persists: the scapular and interscapular regions, mediastinum and upper thorax. However, it can also occur in the shoulder, arm, abdomen or retroperitoneum. Although these tumors can arise in various sites, mammary hibernomas remain extraordinarily uncommon [9,17].

Hibernomas are usually 5–10 cm in size, at diagnosis, although they have been reported to range from 1 to 27 cm.

3.4. Clinical features

Most Hibernoma cases usually present as an asymptomatic, painless, slowly growing mass. They may present as an incidental finding on screening mammography or other radiologic imaging, or rarely cause symptoms due to compression of adjacent structures.

3.5. Diagnosis and differential diagnosis

Hibernomas arising in extramammary sites are usually radiolucent in contrast to the adjacent muscle; however, in fatty breast tissue, this mass is relatively radiodense [17]. Mammary hibernoma appears as a well-defined, uniformly echogenic mass on breast ultrasonography and the radiologic differential includes other fatty lesions such as lipoma, interlobular stromal fibrous tissue, fibrolipoma, fibroadenolipoma, and early fat necrosis [1].

Computed tomography (CT) scan usually demonstrates a solid, hyper vascularized mass.

On magnetic resonance imaging (MRI), hibernomas demonstrate signal intensity intermediate between that of skeletal muscle and subcutaneous fat on both T1–T2 weighted images, and because of their hypervascularity show contrast enhancement. However, similar imaging features can be seen in other benign or malignant soft tissue neoplasms, such as liposarcoma, so specific imaging characteristics on MRI have yet to be delineated to differentiate them. MRI, however, is also useful to determine relationships with adjacent structures, which can assist in preoperative planning [13,14,19].

Unlike conventional lipomas, given the abundant mitochondria, hibernomas are metabolically active and therefore “hot” or “glucose-avid” on fluordeoxyglucose CT–positron emission tomography (FDG CT–PET). For this reason, the PET–CT findings of hibernoma are indistinguishable from malignancy, often leading to a false-positive radiologic interpretation and requiring a biopsy to exclude a malignant etiology [10,14,18]. Insignificant SUV alone may not accurately reflect the malignant potential of soft tissue tumors but might rather implicate cellular components in the lesions [11,12,16].

In conclusion imaging alone is typically inadequate in providing a reliable, definitive differential diagnosis. Well-differentiated liposarcomas have been described as often demonstrating decreased vascularity and typically with irregular thickened, linear and/or nodular septations. This is in contrast to hibernomas, which tends to be smoother with a capsule, like a rubbery mass, and with increased vascularity. Incisional biopsy is not recommended secondary to hypervascularity and potential for bleeding complications.
Fig. 1. Hibernoma, gross appearance: axillary rubbery mass with well-defined margins, encapsulated and non-adherent during surgical dissection.

Fig. 2. H&E stain 20x: Hematoxylin-eosin staining revealed the presence of a cluster of small neoplastic cells in a fibrous septum of the axillary hibernoma (original magnification: ×20). E-Cadherin 20x: Neoplastic cells resulted totally negative for the immunostaining for E-cadherin (original magnification: ×20).

GATA-3 20x: Epithelial neoplastic cells stained positively for GATA-3, indicative of their mammary origin (original magnification: ×20).

3.6. Anatomo-pathology features

Benign lipomatous lesions are grouped into 5 major categories: lipoma, variants of lipoma, lipomatous tumor, infiltrating lipoma and hibernoma.

The most common type of hibernoma is the typical variant, such in our case, followed by the pale cell subtype, the mixed cell and the eosinophilic cell subtype. No atypia was identified in any case and all variants followed a benign course, even though some clinicopathologic differences [4,5].

Grossly, the mass was well-defined, soft with a yellow cut surface and 4.8 cm in diameter.

Histologically, the tumor was composed of a uniform population of large adipose cells with pale
and eosinophilic multivacuolated cytoplasm, without significant cytological atypia, consistent with
the diagnosis of hibernoma [14]. Among the brown adipose tissue, multiple sub-millimetric clusters of small round epithelial cells, arranged in a linear or single file pattern, were present. The latter cells showed minimal pleomorphism, evenly dispersed chromatin and no nucleoli.

Taking into consideration the medical history of the patient, these findings were morphologically highly suspicious for lobular invasive breast cancer metastases.
The immunohistochemical analysis demonstrated strong and diffuse positivity for CK8–18 and GATA3 and absence of expression of E-cadherin on the small clusters of cells, confirming the initial hypothesis of metastases from lobular invasive breast cancer. Most hibernomas show positivity for S100 and negative for CD34; however, rarely it’s necessary to resort to ICH stains or molecular testing to distinguish hibernoma from other lesions [5] (Fig. 2).

3.7. Treatment, outcome and follow up

Treatment is complete surgical resection and assurance of benign behaviour could allow providers to avoid large surgical resections. In most cases, the smooth, well-encapsuled mass is non-adherent during surgical dissection and full excision is achieved.

While surgical excision remains the gold standard of treatment and diagnosis. Local recurrence is possibly thought uncommon; metastases however have never been documented.

3.8. Hibernoma and MEN 1 syndrome

Non-endocrine tumors have been observed in MEN1 patients, but hibernoma is not currently classified as a non-endocrine tumor related to MEN-1. Only three observations describing an association between hibernoma and MEN1 have already been published [2,3,8].

Peroxisome proliferator-activated receptor γ (PPAR-γ) is a nuclear receptor regulating genes associated with growth and differentiation of adipose tissue; it was shown that Menin, the product of the MEN1 gene, was involved in the PPAR-γ-mediated adipogenesis. So, a modification of Menin protein function, which leads to modifications of PPAR-γ gene expression, could be as well an important element of the pathogenesis of lipomas and hibernomas [7,15,16]. This case report aims to offer details on the management of the rare benign tumor in question and is reported in line with the SCARE criteria [20].

4. Conclusion

In conclusion, the association between MEN1 syndrome and hibernoma must be evoked in front of a fatty hypermetabolic lesion in these patients.

Our case deserves extraordinary attention because of the linkage between MEN1 syndrome and an axillary hibernoma and because in this area there were multiple micro-foci of infiltrating lobular carcinoma [6]. However, there have been few studies regarding the association between breast cancer and MEN1 syndrome and between hibernoma and MEN1 syndrome; further studies and additional case reports are required to clarify this connection.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

No research ethics approval was necessary for this case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

DEGUIDI GIULIA: study conception, acquisition of data, writing, reviewing and editing

MIRANDOLA SARA: writing, reviewing and editing

NOTTEGAR ALESSIA: writing, reviewing and editing

TSVETIKOVA VASSILENA: writing, reviewing and editing

BIANCHI BEATRICE: writing, reviewing and editing

PELLINI FRANCESCA: study conception, acquisition of data, writing, reviewing and editing

All authors read and approved the final manuscript.

Registration of research studies

N/A.

Guarantor

Dr’s Francesca Pellini and Giulia Deguidi are to be considered the co-guarantor’s for this manuscript.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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