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EPIDEMIOLOGY

Study of breast cancer incidence in patients of lymphangioleiomyomatosis

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Abstract Molecular evidence has linked the pathophysiology of lymphangioleiomyomatosis (LAM) to that of metastatic breast cancer. Following on this observation, we assessed the association between LAM and subsequent breast cancer. An epidemiological study was carried out using three LAM country cohorts, from Japan, Spain, and the United Kingdom. The number of incident breast cancer cases observed in these cohorts was compared with the number expected on the basis of the country-specific incidence rates for the period 2000–2014. Immunohistochemical studies and exome sequence analysis were performed in two and one tumors, respectively. All cohorts revealed breast cancer standardized incidence ratios (SIRs) ≥ 2.25. The combined analysis of all cases or restricted to pre-menopausal age groups revealed significantly higher incidence of breast cancer: SIR = 2.81, 95 % confidence interval (CI) = 1.32–5.57, $P = 0.009$; and SIR = 4.88, 95 % CI = 2.29–9.99, $P = 0.0007$,

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respectively. Immunohistochemical analyses showed positivity for known markers of lung metastatic potential. This study suggests the existence of increased breast cancer risk among LAM patients. Prospective studies may be warranted to corroborate this result, which may be particularly relevant for pre-menopausal women with LAM.

Keywords Breast cancer · Incidence · Lymphangioleiomyomatosis · mTOR · TSC1 · TSC2

Introduction

LAM is a rare neoplastic disease that appears predominantly in women of childbearing age and is characterized by cystic lung destruction [1, 2]. LAM lesions are heterogeneous at the cellular phenotypic level but are typically characterized by the proliferation of estrogen receptor α (ERα)- and progesterone receptor (PR)-positive smooth muscle-like cells with lung metastatic potential whose tissue origin remains unclear [3]. LAM cells commonly carry loss-of-function mutations in the tumor suppressor genes *TSC1* or *TSC2,* and consequently, exhibit abnormal activation of the mechanistic target of rapamycin complex 1 (mTORC1) [4]. Thus, LAM can occur as an isolated disease (termed sporadic LAM) or in association with another rare disorder, tuberous sclerosis complex.

mTORC1 regulates a cancer metastasis transcriptional program [5]. In breast cancer, low expression of *TSC1* or *TSC2* is associated with poor clinical outcome [6], and depletion of *TSC2* expression promotes lung metastasis [7]. These observations led us to the test whether the mediators of breast cancer metastasis to lung could also play a role in LAM. Thus, we identified molecular positivity in LAM lesions for known metastasis mediators [8]. Low *TSC1/2* expression in primary breast tumors was found to be associated with enhanced mTORC1 signaling and lung (but not bone) metastasis. Collectively, the clinical, pathological, and molecular similarities between LAM and breast cancer prompted us to hypothesize a higher incidence of breast cancer in LAM patients. To assess this hypothesis, we compiled the largest epidemiological LAM study to date.

Methods

LAM cohorts

The cohorts comprised LAM patients from three countries (Japan, Spain, and the United Kingdom). Patients were diagnosed by computed tomography scan. In most cases (>80 % of patients in any cohort), diagnosis was complemented by the presence of at least one of the following findings: lymphatic complication, lung biopsy, renal angiomyolipoma, and/or TSC [2, 9, 10]. Collectively, the number of diagnoses per population was consistent with the reported prevalence of the disease in developed countries (1–9 in 10^6 individuals) [10]: 108, 175, and 175 in Japan, Spain, and the United Kingdom, respectively. The ethics committee of the Hospital de Henares approved the international epidemiological study (approval number PI-753). The data from the Japan and United Kingdom cohorts (irreversibly encoded) were provided for combined analysis at the Spanish study center. Informed consent was not required for the epidemiological study (PI-753), as it was based on irreversibly encoded retrospective records; however, approved informed consent was obtained from those patients that provided tumor samples for genetic and immunohistochemical analyses. These studies were approved by the ethics committees of the Bellvitge Institute for Biomedical Research (IDIBELL; PR082/13), the Instituto de Investigación Sanitaria La Princesa (SEPAR-2012), and the Hospital de Henares (PI-753). In addition, all LAM patients in the Japanese cohort provided informed consent for the comprehensive analysis of their clinical data (National Hospital Organization Kinki-Chuo Chest Medical Center, approval number 365).

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Follow-up and breast cancer ascertainment

In all clinical settings, LAM patients underwent regular follow-up evaluations with a periodicity of 3–12 months, depending on the country and each patient's condition. In addition, follow-up was updated via telephone, and patient conditions, including death, were recorded in each database. Given that LAM has only been monitored for a short time [9], and since breast cancer screening programs were not fully implemented in some countries until relatively recently, only patients diagnosed from 2000 were considered in this study, which corresponded to >80 % of the cases in each cohort (Supplementary Table 1). In all cases, follow-up started with LAM diagnosis and finished with the first occurrence of one of the following events: death, breast cancer diagnosis, date of last contact, or end of the study (December 31st, 2014). Breast cancer diagnosis required pathological confirmation. Since national breast cancer rates do not include in situ tumors, only invasive cases were considered.

Statistical analysis

The incidence of breast cancer in the LAM cohorts was compared with the incidence observed in the general population, using standardized incidence ratios (SIRs) [11]. This ratio corresponds to the observed versus expected number of cases, where the expected number is obtained considering age (5-year groups) and period- (2000–2004, 2005–2009, and 2010–2014) specific incidence breast cancer rates in each country. The same analysis was repeated considering pre-menopausal age groups (women younger than 50). Person-years in each stratum were calculated using the *survival* package (version 2.38, R software), and SIR confidence intervals were computed under the Poisson assumption and using the exact method [12].

Antibodies

The antibodies used in this study were anti-ERα (#IR151, Dako), anti-FSCN1 (#SC-56531, Santa Cruz Biotechnology), anti-HMB-45 (#SC-59305, Santa Cruz Biotechnology), anti ID1 (#SC-488, Santa Cruz Biotechnology), anti-PR (#IR168, Dako), anti-phospho-Ser235-236 S6 ribosomal protein (anti-pS6; clone 91B2, Cell Signaling Technology), anti-SMA (#A2547, Sigma-Aldrich), and anti-SOX9 (#AB5535, Millipore).

Immunohistochemistry

Immunohistochemical assays were performed using standard protocols with the EnVision (Dako) method. Each tissue and biomarker was evaluated in at least two independent assays and no substantial differences were observed. Equivalent sections were processed to include incubation with immunoglobulin controls (Sigma-Aldrich), which did not reveal staining in any case. The immunohistochemistry results were evaluated independently by at least two expert pathologists.

Exome sequencing

Breast cancer (>50 % tumor cells) DNA was extracted from a surgical sample following standard protocols and the exome sequence analyzed by GATC Biotech. The coverage was of >10× for at least 90 % of the genome and some *TSC1/2* exonic regions were targeted by Sanger sequencing to obtain full annotation. Variant mapping, alignment, calling, annotation, and filtration were performed using the genome reference hg19 (GRCh37) and the GATK modules [13].

Results

Analysis of standardized incidence ratios

The three LAM cohorts revealed breast cancer SIRs ≥ 2.25 (Table 1, which also includes the observed and expected numbers per cohort and for the combined analysis). In fact, the United Kingdom cohort revealed a significant SIR of 3.16; 95 % confidence interval (CI) = 1.08–8.15, $P = 0.039$. Thus, the global estimation of an excess of breast cancer cases was found to be significant: SIR = 2.81, 95 % CI = 1.32–5.57, $P = 0.009$ (Table 1).

Since LAM is generally diagnosed in women of fertile age and an increased risk of breast cancer may be associated with earlier age of onset [14], an analysis restricted to pre-menopausal age groups (women younger than 50) was performed. A significantly higher incidence of breast cancer in the cohorts of Spain and the United Kingdom was observed, with SIRs = 4.98 and 7.09; P values = 0.023 and 0.003, respectively. Moreover, the global analysis was also found to be significant: SIR = 4.88, 95 % CI = 2.29–9.99, $P = 0.0007$ (Table 1).

Immunohistochemical features of breast tumors from LAM patients

Approximately, two-thirds of the breast tumors that develop in pre-menopausal women in the general population are hormone receptor-positive [15]. In our study, all tumors with available pathological information ($n = 8$) were recorded as ERα- and PR-positive. While none presented family history of the disease, relatively uncommon

Table 1 Number of breast cancer cases observed and expected, and SIRs in the three LAM cohorts

All cases						
Country	Person-years	Observed cases (*n*)	Expected cases (*n*)	SIR	95 % CI	*P* value
Japan	605.02	1	0.44	2.25	0.12–12.96	0.36
Spain	899.01	3	1.13	2.64	0.72–7.77	0.11
United Kingdom	809.22	4	1.26	3.16	1.08–8.15	0.039
Combined	2313.26	8	2.84	2.81	1.32–5.57	0.009
Pre-menopausal (<50 years old)						
Country	Person-years	Breast cancer cases/cohort (*n*)	Expected cases (*n*)	SIR	95 % CI	*P* value
Japan	453.32	0	0.27	–	–	–
Spain	620.00	3	0.60	4.98	1.36–14.63	0.023
United Kingdom	568.36	4	0.56	7.09	2.42–18.28	0.003
Combined	1641.68	7	1.43	4.88	2.29–9.99	0.0007

clinical and histopathological features were noted. Three Spanish cases were diagnosed with multifocal breast cancer, one of them was diagnosed at age 37 with rapid progression following 8 months of rapamycin treatment for LAM [10]. Whole exome sequencing did not identify *TSC1/2* mutations in a fresh tumor sample for this case; importantly, exonic *TSC1/2* mutations are common but not seen in all sporadic LAM patients [16]. The tumor exome analysis did uncover a known oncogenic mutation in *PIK3CA* (c.3140A > G, H1047R), which was confirmed by Sanger sequencing (Supplementary Fig. 1); however, mutations in this gene are found relatively frequent in ERα-positive breast cancer [17].

Immunohistochemical analyses of the above depicted tumor and of an additional case showed positivity for both ERα and PR in cells with apparently different phenotypes (Fig. 1). Both cases were also positive for a canonical marker of mTORC1 activity and for the lung metastatic mediators revealed in our original study (FSCN1, ID1, and SOX9; Fig. 2). Heterogeneity was also apparent and positive cells were linked to either an epithelial or a spindle phenotype (Fig. 2). Together, the observations of multifocal ERα-positive tumors in pre-menopausal LAM patients without family history of the disease would further suggest a link to a specific breast cancer subtype.

Discussion

In previous analyses, we tested the hypothesis that the metastatic properties of LAM cells could be further depicted using knowledge of breast cancer tropism to lung, and thus identified the expression of metastatic mediators and cancer cell stemness molecular determinants in LAM lesions [8]. Following on from this evidence, and given that the tissue of origin of LAM cells remains a subject of debate [3, 18, 19], we aimed to assess breast cancer incidence in LAM patients. The results of our study of three cohorts in different countries suggest that LAM patients, particularly those in the pre-menopausal age range, are at higher risk of developing invasive breast cancer than women from the general population. This might therefore indicate a shared cell origin and/or shared genetic risk factors between the two diseases. However, we cannot rule out that the retrospective nature of the survey and/or the regular clinical monitoring of LAM patients may have led to an over-estimation of breast cancer incidence.

Apart from brain and kidney malignancies [20], there is no previous evidence of other cancer susceptibilities in patients with tuberous sclerosis complex; indeed, among the LAM patients with breast cancer in our study, only one (1/15; 6, 7 %) was diagnosed with this disease (i.e., carrier of a germline *TSC2* mutation), so the others were sporadic LAM cases. Intriguingly, however, a recent study of 1,000 breast cancer patients incidentally identified a pathogenic germline *TSC2* mutation [21]; therefore, further germline studies of *TSC1/2* may be warranted to assess the potential link with breast cancer risk. In our study, exome analysis of a breast tumor sample did not reveal mutations in these genes, but exonic mutations are not detected in all sporadic LAM patients [16], which further suggests heterogeneity in the biology of LAM.

Hypothetically, multiple tissue or organ origins can co-exist if it is considered that enhanced mTORC1 activity mediates metastatic behavior in different cancer types [5]. Nevertheless, the link between LAM and women at childbearing age [2, 10] suggests tissue and/or cell type specificity. Dependence on hormone signaling is a hallmark of several cell types in breast tissue [22]. In this scenario, the repeated cycles of vast cell proliferation that

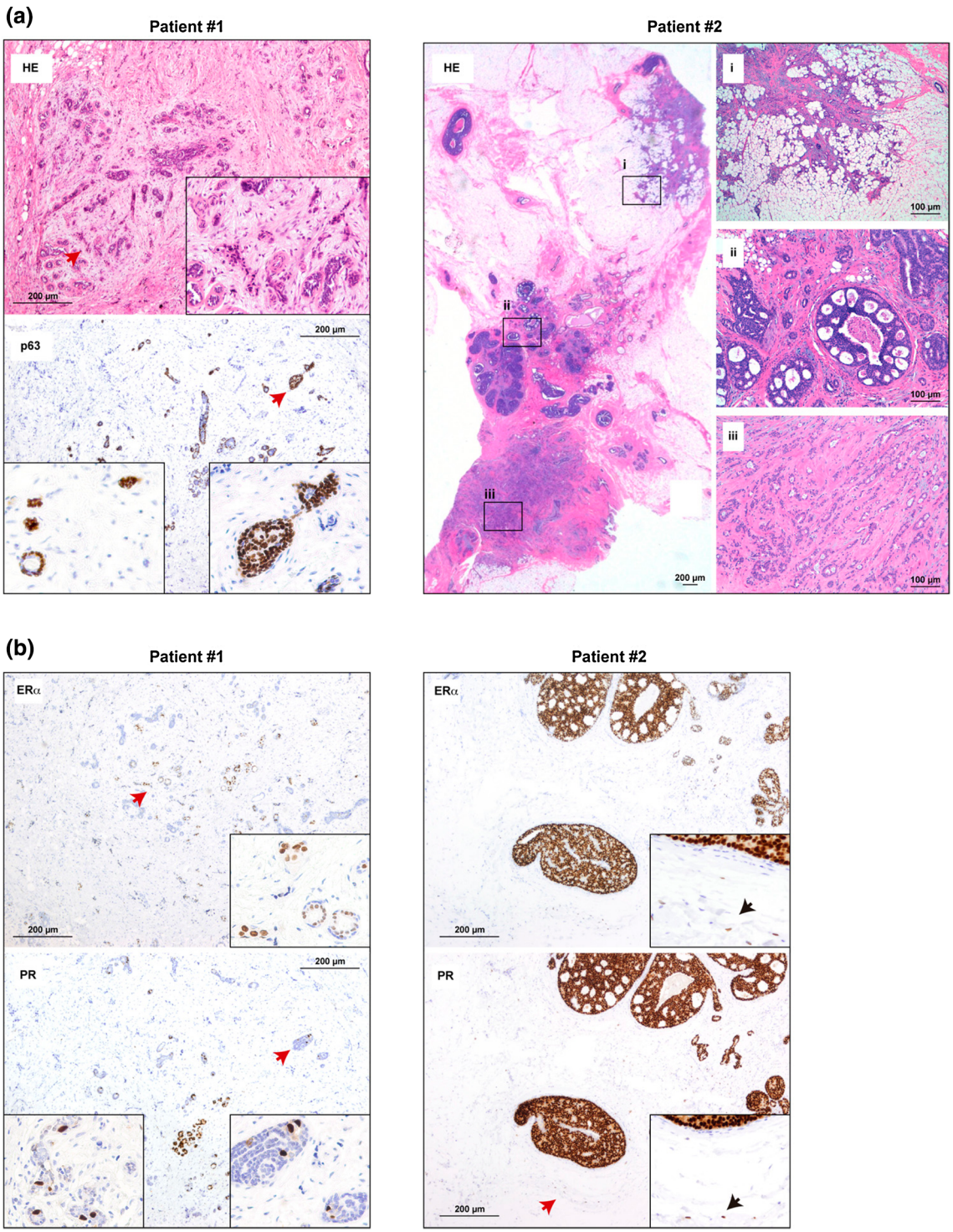

Fig. 1 Histopathological and immunohistochemical characterization of breast tumors in two LAM patients. **a** Hematoxylin-eosin (HE) and p63 (patient #1 only) staining results from the corresponding tumors in LAM patients. *Arrows* mark magnified fields shown in the insets. *Three panels* are shown for patient #2, which correspond to (i) invasive, (ii) in situ, and (iii) desmoplastic histologies. The p63 marker was used as evidence of a metaplastic carcinoma. **b** Immunostaining results for ERα and PR in the corresponding breast tumors. *Red arrows* mark magnified fields shown in the *insets* and *black arrows* mark positive cells with a spindle-like phenotype

occur in normal breast tissue at reproductive age provide the time window for acquiring somatic genetic mutations by chance. Thus, if a mutation is acquired in a specific population of ERα/PR-positive cell progenitors [22] leading to an increase in mTORC1 activity, the corresponding cells would possess metastatic behavior with lung tropism.

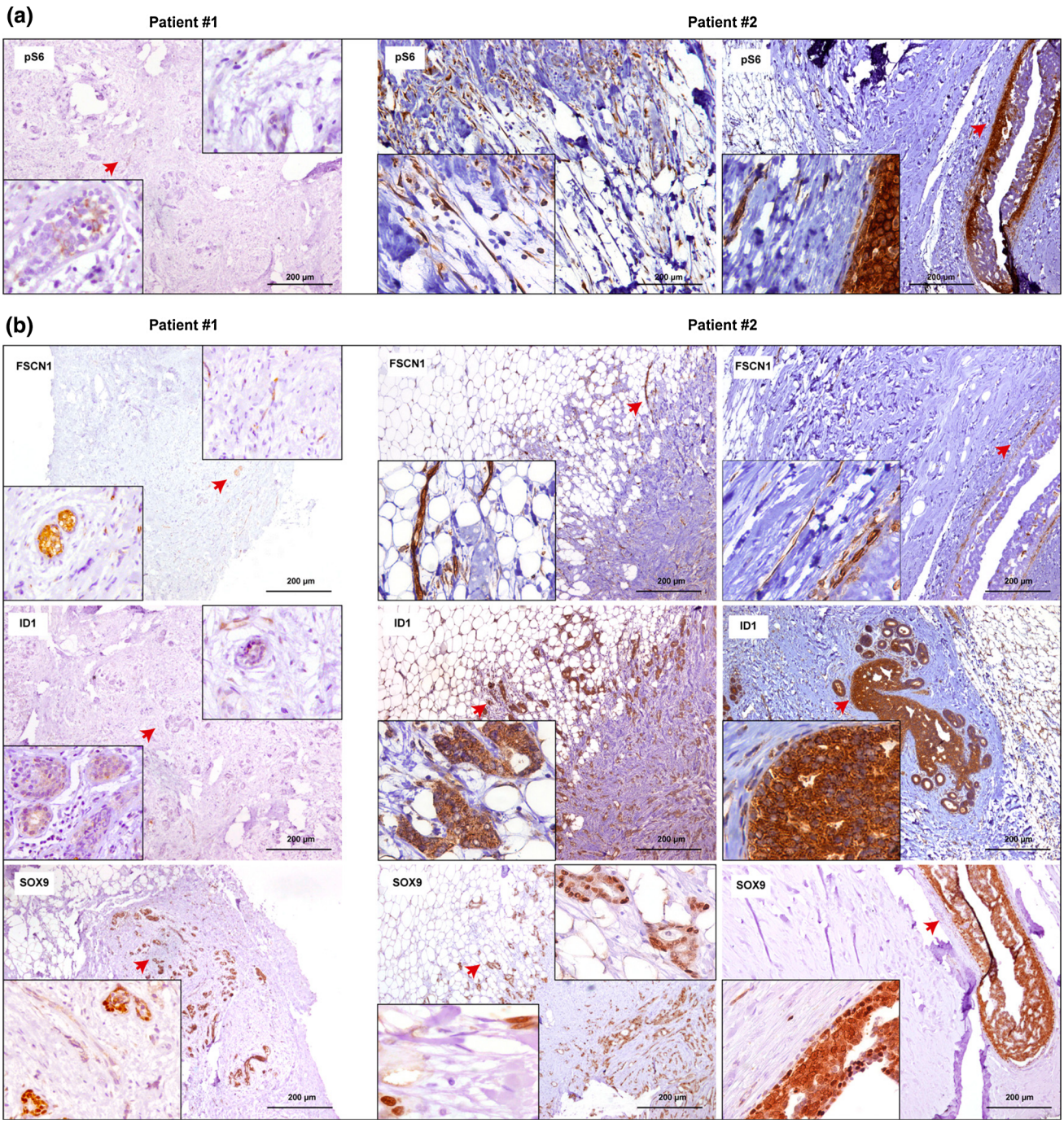

Fig. 2 Positivity for mTORC1 signaling and metastatic markers in breast tumors of LAM patients. **a** Results of phospho-Ser235/236-ribosomal protein S6 (pS6) staining in two available breast tumors. Heterogeneity (i.e., positive and negative tumor cells in case #1) and positive cells with a spindle phenotype (case #2, *right panels*, depicted in *insets*) can be observed (*arrows* mark magnified regions). **b** Results of the analysis of the metastatic markers (FSCN1, ID1, and SOX9) in both cases. Heterogeneity (particularly in case #1) and spindle-like phenotypes (particularly in case #2) can be observed (*arrows* mark magnified regions)

Abnormal activation of mTORC1 would not produce invasive tumors unless additional mutations are acquired, which we speculate might have occurred in the identified cases of LAM and breast cancer. Overall, prospective studies may be warranted to corroborate our findings, which may be particularly relevant for pre-menopausal women with LAM.

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Authors' contributions OM, MP, and MAP conceived of the study and participated in its design. GRG, CH, GM-B, JP, FM, AP, FC, TS, AV, JIL, and NG conducted analysis of pathology specimens. GRG, JVS-M, and ME conducted genetic analyses. AR, SRJ, YI, MH, AC, AG, RO, MJP, MC, EA, MM-M, CV, JA, AX, PU, and RL collected the clinical data. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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