Hemoptysis Associated with Sexual Activity in Lymphangioleiomyomatosis

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To the Editor:

Lymphangioleiomyomatosis (LAM) is a rare disorder caused by mutations in the Tuberous Sclerosis Complex genes leading to activation of the mechanistic target of rapamycin (mTOR) pathway resulting in progressive cystic lung destruction.[1,2] In our practice, we have encountered several LAM patients who have experienced hemoptysis associated with sexual activity (HASA), but there is little literature that provides insight into this manifestation. Our objectives were to determine the frequency of HASA in LAM patients, assess its effect on quality of life, and identify disease characteristics and factors associated with HASA.

Methods

Following approval by the Institutional Review Boards at the University of Cincinnati (UC, IRB Number: 2022-0412) and the University of Sao Paulo (IRB Number: 55598222.2.0000.0068), a web-based survey was administered to LAM patients registered with The LAM Foundation (U.S) in October 2021 and Alambra, the Brazilian Association for LAM, in March 2022. Written informed consent was obtained along with permission to be re-contacted for additional details. Participants were instructed to skip any questions that they were uncomfortable answering. A follow-up survey was administered to those that reported HASA on the initial survey in October 2022 (U.S) and December 2022 (Brazil). Data collection and analysis was performed by utilizing the Research Electronic Data Capture tools hosted at UC. Respondent characteristics and data are reported using frequencies, percentages, central tendency (mean) and range. Fisher's exact test was used to perform comparative assessments. Analyses were performed using GraphPad Prism version 10.2.1; p-value ≤0.05 was considered significant.

Results

Cohort Characteristics

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The initial survey yielded 550 responses: 410 from the U.S. and 140 from Brazil. The email soliciting survey response was accessed by 181 patients in Brazil, 140 of whom (77%) completed the questionnaire. Due to a software change at The LAM Foundation, the data for the number of people who received, opened or accessed the link is no longer retrievable. Key baseline characteristics of both cohorts are presented in **Table 1**.

HASA Frequency

Hemoptysis was reported by approximately 20% of the patients in each cohort, and approximately half of these patients also reported HASA. The frequency of HASA in our cohorts was approximately 10% (U.S.: 41/387, 10.6% and Brazil: 12/134, 9.0%) (**Table 1).**

HASA Associations

There was no significant association between HASA and underlying LAM type (sporadic LAM: 44/408, 11% vs. TSC-LAM: 9/59, 15%, p=0.38). HASA was reported more often by premenopausal women compared with postmenopausal women (28/199, 14% vs. 19/242, 8%, p=0.04). A higher proportion of patients with HASA had a history of pulmonary embolism (PE) compared to the non-HASA group (6/52, 11.5% vs. 14/457, 3.1%, p=0.01) Those reporting HASA were more likely to be on mTOR inhibitor therapy (31/52, 59.6% vs 94/288, 32.6%, p<0.001) (**Table 2**).

HASA Characteristics

Of those reporting HASA, 25 subjects from the U.S. and 8 from Brazil responded to the follow-up survey amounting to a response rate of 62%. Most participants, 75.8% (25/33), stated that they experienced HASA before being diagnosed with LAM, and 36% (9/25) reported that HASA was the major symptom that led to the diagnosis of LAM. HASA was most commonly quantified as minimal (less than 1 teaspoon) (60.6%, 20/33), characterized as bright red blood (46.9%,

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15/32), and cited as a solitary event following sexual activity (66.7%, 22/33)**.** HASA most frequently occurred within one hour after intercourse (60.6%, 20/33) or with orgasm (27.3%, 9/33). Improvement in HASA following initiation of mTOR inhibitors was reported by 41.9% (13/31) of patients.

HASA Impact

HASA led to avoidance of sexual activity in approximately half of patients (50.9%, 27/53) in our initial survey. Approximately half of the patients (54.7%, 29/53) discussed HASA with a physician and a minority of patients (5.7%, 3/53) reported unsolicited physician inquiry regarding HASA**.** On the follow-up survey, we found that HASA led to a significant reduction in sexual desire; 12.5% (4/32) of patients noted reduced sexual drive prior to HASA in contrast to 33% (11/33) after HASA (p=0.046).

Discussion

The major findings from our analysis are: 1) HASA is reported by about 10% of patients with LAM and can be the presenting manifestation leading to the diagnosis of LAM, 2) HASA is more common in premenopausal women with LAM compared with postmenopausal women, 3) HASA is not routinely addressed by clinicians when evaluating patients with LAM, and 4) The presence of HASA has a significant detrimental effect on the patients' sexual health.

To our knowledge, this is the largest study evaluating HASA.[3,4] While the pathophysiology of HASA is not known, it is plausible that sympathetic activation during sexual activity results in pulmonary venous occlusion, elevated pulmonary capillary pressure and pulmonary vascular bed rupture, similar to the proposed mechanism behind exertional hemoptysis.[5-7] Furthermore, infiltration of the pulmonary vasculature by LAM cells[8] may lead to vascular insufficiency that becomes apparent during sexual activity. Female sexual hormones may also play a role in the

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development of HASA. For instance, circulating prolactin levels increase following sexual activity.[9] Activation of prolactin signaling pathways has been documented in LAM lung lesions,[10] suggesting a possible mechanistic link between HASA and LAM. Further investigations are needed to ascertain the pathophysiology of HASA in women with LAM.

While there was no association between HASA and other common comorbid conditions, those with a history of PE were more likely to report HASA. Despite the correlation between history of PE and HASA, the use of anticoagulants was not associated with an increased risk of HASA. HASA was also noted to be more common in LAM patients on mTOR inhibitors compared with untreated patients. This association likely reflects confounding by indication in that patients with more severe disease (or perhaps even patients with HASA) are more likely to be treated with mTOR inhibitors. Improvement in HASA following mTOR inhibitor therapy in a substantial proportion of patients further corroborates this inference, although treatment effect cannot be definitively established from this analysis.

Major limitations of our study include the possibilities of selection and recall bias. These biases are somewhat mitigated by the inclusion of an independent external (Brazilian) cohort with similar results to the original (U.S.) LAM cohort and the relatively large sample size compared to other survey-based studies in LAM.[11-15] We are not able to correlate the occurrence of HASA with pulmonary function parameters, radiological patterns, histopathological features, or circulating hormone levels, and propose these as future research goals.

Conclusions

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HASA is noted in approximately 10% of women with LAM and has a significant detrimental impact on patients' quality of life and sexual health. Clinicians caring for LAM patients should inquire about HASA during their assessments.

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Table 1. Cohort characteristics*

	United States	Brazil
Race		
American Indian/Alaska Native	1/392 (0.3%)	2/140 (1.4%)
Asian	27/392 (6.9%)	3/140 (2.1%)
Black or African American	12/392 (3.1%)	10/140 (7.1%)
Native Hawaiian or Other Pacific Islander	1/392 (0.3%)	1/140 (0.7%)
White	337/392 (86.0%)	96/140 (68.6%)
Other	17/392 (4.3%)	25/140 (18.6%)
Ethnicity		
Hispanic or Latino	37/374 (9.9%)	82/130 (63.1%)
Not Hispanic or Latino	326/374 (87.2%)	18/130 (13.8%)
LAM Subtype		
Sporadic LAM	310/392(79.1%)	98/138 (71.0%)
TSC-LAM	39/392 (9.9%)	20/138 (14.5%)
Unclear LAM type	43/392 (11.0%)	20/138 (14.5%)
Age at diagnosis, years (Mean (SD))	40.0 (11.26)	39.6 (8.53)
Menopausal Status		
Premenopausal	165/385 (42.9%)	34/127 (26.7%)
Postmenopausal	194/385 (50.4%)	48/127 (37.8%)
Unknown/Unsure	26/385 (6.8%)	45/127 (37.0%)
Supplemental Oxygen Use	78/314 (24.8%)	19/137 (13.9%)
Cigarette Smoking History		
Never smoked	306/394 (77.7%)	119/139 (85.6%)
Previously smoked	82/394 (20.8%)	18/139 (12.9%)
Currently smoking	6/394 (1.5%)	2/139 (1.4%)
Comorbidities		
Hypertension	142/387 (36.7%)	40/134 (29.9%)
Pulmonary Hypertension	19/387 (4.9%)	8/135 (5.9%)
Heart Failure	5/387 (1.3%)	5/134 (3.7%)
Valvular Heart Disease	63/386 (16.3%)	19/134 (14.2%)
History of Pulmonary Embolism	17/387 (4.4%)	7/134 (5.2%)

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Medications		
Therapeutic anticoagulation	40/384 (10.4%)	12/133 (9.0%)
Antiplatelet agents	117/384 (30.5%)	42/132 (31.8%)
mTOR inhibitors	229/386 (59.3%)	75/134 (56.0%)
Hormonal therapy	43/387 (11.1%)	13/133 (9.8%)
Most Common Symptoms		
Dyspnea	285/386 (73.8%)	82/135 (60.7%)
Fatigue	246/386 (63.7%)	95/135 (68.1%)
Cough	158/386 (40.9%)	52/135 (38.5%)
Chest pain	136/386 (35.2%)	42/135 (31.1%)
Hemoptysis		
Hemoptysis	81/387 (20.9%)	27/134 (20.1%)
HASA	41/387 (10.6%)	12/134 (9.0%)

Abbreviations: HASA = Hemoptysis Associated with Sexual Activity, LAM = Lymphangioleiomyomatosis, mTOR = Mechanistic target of rapamycin, TSC = Tuberous Sclerosis Complex, SD = Standard deviation

* Given the variable response rates to each survey question and the use of branching logic questions, the denominators for some questions differ and we have reported the exact denominator for each question in the results. Overall rate of missing responses varies from 4 – 23% in the U.S. cohort and 0 – 9% in the Brazil cohort.

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Table 2. Characteristics of respondents with HASA compared to patients without HASA*

	HASA	Without HASA	p-value
Comorbid Conditions			
Hypertension	16/51 (31.3%)	116/459 (25.2%)	0.40
Pulmonary Hypertension	6/52 (11.5%)	21/426 (4.9%)	0.10
Heart Failure	1/52 (1.9%)	9/454 (2.0%)	1.0
Valvular heart disease	11/52 (21.1%)	71/442 (16.1%)	0.33
Pulmonary Embolism	6/52 (11.3%)	14/457 (3.1%)	0.01
Smoking History			
Previous or Current Tobacco Use	9/53 (17%)	99/480 (20.6%)	0.59
Oxygen Use			
On supplemental oxygen	11/52 (21.2%)	86/477 (18.0%)	0.57
Medications			
Therapeutic anticoagulation	7/51 (13.7%)	45/446 (10.1%)	0.47
Antiplatelet agents	10/48 (20.8%)	149/446 (33.4%)	0.10
mTOR inhibitors	31/52 (59.6%)	94/288 (32.6%)	<0.0001
Hormonal replacement	6/52 (11.5%)	49/459 (10.7%)	0.81

* Given the variable response rates to each survey question and the use of branching logic questions, the denominators for some questions differ and we have reported the exact denominator for each question in the results. Overall rate of missing responses varies from 0 – 2% in the HASA cohort and 3 – 42% in the non-HASA cohort.

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