Three's company: A woman with rash, uterine mass and cystic lungs

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Abstract

Cystic lung disease encompasses a wide variety of clinical entities, the diagnosis of which is sometimes straightforward and other times obscure. To narrow the list of possibilities, it behooves the physician to consider the context in which the cystic lung disease is uncovered. Clues to the diagnosis might be provided by findings that are not initially obvious and are not located in the thorax. We describe an instructive case of a woman with cystic lungs detected during a search for malignancy prompted by a diagnosis of dermatomyositis. Malignancy was indeed uncovered in the form of endometrial carcinoma, the management of which eventually also established the etiology of cystic lung disease. In the discussion we attempt to connect the patient's autoimmune disease, uterine cancer, and lung cysts. The potential interplay among these three components of her presentation makes for intriguing mechanistic speculation.

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Case Report

A 54-year-old pre-menopausal Caucasian woman presented to the emergency department (ED) of an outlying hospital complaining of worsening rash and weakness of several weeks' duration. The rash had initially appeared in a focal distribution approximately ten months prior to presentation. Outpatient evaluation of the rash led to the eventual diagnosis of systemic lupus erythematosus (SLE) and initiation of hydroxychloroquine and prednisone 10 mg three weeks prior to presentation, subsequent to which she noticed progression of the rash and pronounced weakness. There was also a reported fever of 38.3°C. She was urgently transferred from the outside ED to the ED of our institution due to concern for Stevens-Johnson syndrome from hydroxychloroquine. She did not report weight loss or respiratory symptoms. Her family history was notable for the presence of lung and breast cancer and the absence of pulmonary, cutaneous, and neurological disease. She was a never-smoker and had no significant occupational exposures or travel history. On presentation, she was afebrile with normal vital signs, including resting oxygen saturation. Cardiopulmonary auscultation was normal. Objective weakness was not appreciated. Examination of the skin revealed diffuse scaly erythroderma with a prominent facial component (Figure 1). Routine laboratory evaluation was remarkable only for a creatinine phosphokinase (CPK) level of 2188U/L (normal range 20-168U/L). Her initial portable chest radiograph was normal. Following admission, she underwent skin biopsy, which showed interface dermatitis. Additional connective tissue disease serological testing was negative for ANA, anti-dsDNA, anti-Ro/La, and anti-Sm. Complement levels were normal. On the other hand, there was elevation of serum aldolase to 14.1U/L (normal <7.7U/L). Myositis panel revealed marked positivity for the antibody against TIF1-γ. Muscle biopsy showed no significant abnormalities. The combination of subjective weakness, rash, and abnormal serology led to the clinical diagnosis of anti-TIF1-γ+ dermatomyositis (DM). Treatment with oral glucocorticoids was initiated. As part of an evaluation for underlying malignancy, computed tomography (CT) of the chest was performed, demonstrating diffuse lung cysts without any other associated findings (Figure 2). Pulmonary function testing was normal. CT of the abdomen and pelvis was unremarkable as was magnetic resonance imaging of the brain. Gynecological examination as part of the search for malignancy identified a virginal woman with a soft-tissue mass protruding from the cervical os. Biopsy of this lesion revealed endometrial carcinoma, endometrioid type, FIGO grade I.

Discussion

Lung cysts are defined as round lucencies that have an identi-

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fiable interface (*i.e.*, wall) with the adjacent parenchyma [1]. They are not to be confused with emphysematous changes with or without bullae; in this situation a wall is either imperceptible or extremely thin (*i.e.*, <1 mm) [2]. Another potential mimic is a cavity, which is characterized by a thicker wall than that of a cyst (*i.e.*, >2 mm) [1]. The detection of a single or even multiple isolated lung cysts on chest CT is not necessarily pathological. Diffuse cystic involvement of the lung, however, merits a search for a specific etiology. The differential diagnosis of a pure cystic lung disease without any other accompanying parenchymal abnormalities encompasses several diagnostic categories. In narrowing the possible explanations of our patient's cysts, it is helpful to consider the lung findings through the prism of her demographic characteristics and associated conditions.

Pre-menopausal female

When lung cysts are found in this patient demographic, attention reflexively turns to pulmonary lymphangioleiomyomatosis (LAM), an incompletely understood, quasi-neoplastic, cystic lung disease affecting predominantly females of reproductive age. LAM is a frequent (35-50%) pulmonary manifestation of tuberous sclerosis complex (TSC), itself a rare autosomal dominant genetic disorder in the United States, and can occur in males in this context [3,4]. The diagnosis of TSC is typically established in childhood, and neither historical nor clinical features of our patient's case supported the presence of this genetic syndrome. It should be noted, however, that TSC is known to have variable clinical penetrance [5]. The other category is sporadic pulmonary LAM (S-LAM), confined exclusively to females and very rare though usually more severe than TSC-LAM. S-LAM is associated with pleural complications such as chylothorax and pneumothorax, neither of which was present in our case. A common (30-60%) extrathoracic feature of S-LAM is renal angiomyolipoma, also not observed in our patient [6,7]. The absence of these classic manifestations does not preclude the diagnosis of S-LAM, so this possibility received serious consideration.

Dermatomyositis

Of the connective tissue diseases, Sjogren's syndrome is most closely linked to cystic lung disease, whether as a primary lung manifestation or as part of concomitant lymphocytic interstitial

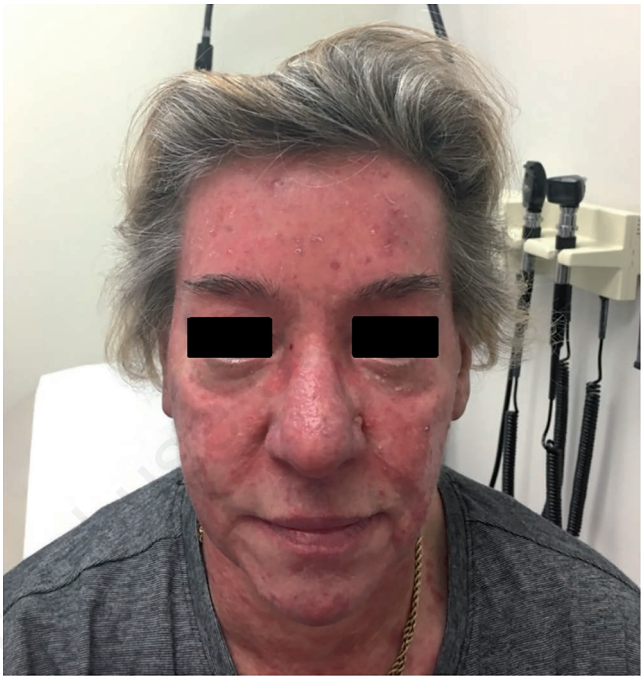

Figure 1. Representative image of our patient's erythematous, scaly rash acquired during a subsequent outpatient encounter for illustration purposes (patient's informed consent obtained). Although only facial involvement is depicted on the image, these cutaneous findings were diffusely distributed.

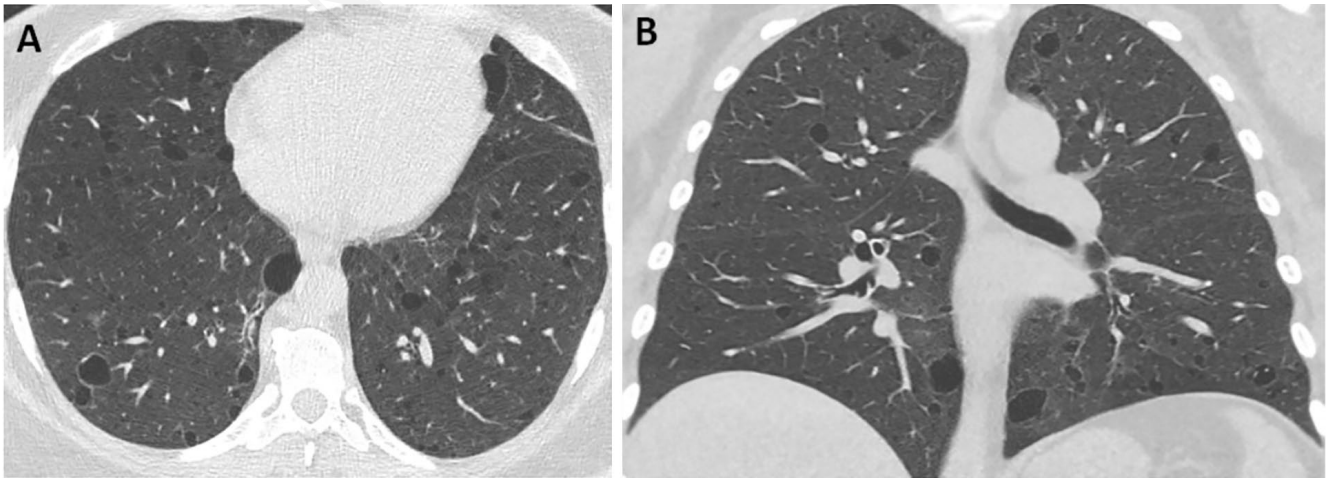

Figure 2. Computed tomography of the chest without administration of intravenous contrast showing multiple simple cysts scattered throughout the lung parenchyma on a representative axial image (A) and on an image from coronal reconstruction (B).

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pneumonia [8,9]. The latter usually presents with the combination of cysts and nodules and has not been described in association with DM [10]. Unlike the cystic component of honeycombing, primary cystic lung disease has likewise never been reported as a feature of DM. Thus, a direct connection between the patient's DM and her cystic lung disease was felt to be unlikely.

Malignancy

Cystic lung metastases are an important diagnostic consideration in the patient with numerous randomly distributed lung cysts. Many different primary tumor types have been reported to produce cystic metastases to the lung, notably sarcomas and adenocarcinomas of the genitourinary tract. Our patient's underlying endometrial tumor, albeit low-grade on biopsy, reasonably raised this possibility. Arguing against metastatic endometrial carcinoma was the absence of extrauterine involvement on CT of the pelvis as well as on transvaginal pelvic ultrasound.

Infection

Multiple lung pathogens, most classically *Pneumocystis jiroveci*, *Staphylococcus aureus*, *Coccidioides immitis,* and *Paragonimus westermani*, are capable of presenting with cystic lung lesions. Although our patient reported a fever at home, elevated temperatures were not documented in the ED or ward, nor did she exhibit leukocytosis. She was non-toxic and was not manifesting symptoms of pneumonia as would be typical of *S. aureus* lung infection. Presentation of *P. jiroveci* pneumonia (PJP) can be subtler. Although the combination of DM and recent low-dose prednisone intake rendered our patient relatively immunosuppressed, her clinical course and host factors made PJP an unlikely etiology of lung cysts [11]. As a resident of the northeastern United States without domestic or foreign travel, she would not be expected to contract coccidioidomycosis or paragonimiasis.

The next step in the evaluation of this patient's cystic lung disease was bronchoscopy with transbronchial biopsy performed in search of histopathological features of LAM and evidence of metastatic uterine carcinoma. Neither process was detected by tissue sampling. In the meantime, her serum vascular endothelial growth factor-D (VEGF-D) level returned at 412 pg/ml. To address her apparently localized uterine malignancy, for which surgery is standard management, she proceeded to hysterectomy with bilateral salpingo-oophorectomy. Surgical pathology confirmed the preoperative diagnosis of endometrial adenocarcinoma, endometrioid type, without myometrial invasion. In the dissection specimen of two right pelvic lymph nodes, an incidental discovery was made of near-complete replacement of normal nodal architecture with spindle-shaped cells arranged in fascicles (Figure 3 A,B). Also observed were cleft-like lymphatic spaces (Figure 3A). This process exhibited immunohistochemical positivity for smooth-muscle actin and desmin (Figure 3 C,D). HMB-45 staining was weakly positive. Positive D2-40 and CD34 stains identified the presence of lymphatic and vascular endothelium, respectively. The lesion also stained positively for estrogen (2+) and progesterone (3+) receptors. Collectively these features established the diagnosis of nodal LAM.

Ever since its first description over 80 years ago, LAM has remained an enigmatic disease with myriad thoracic and extrathoracic manifestations. It is worth recalling that in 2015 the World Health Organization reiterated pulmonary LAM's nature as not that of an interstitial lung disease but rather as that of a perivascular epithelioid cell tumor, landing it in the company of several rare tumors composed of perivascular epithelioid cells with immunophenotypic features of smooth muscle (*e.g.*, desmin) and melanocytic (HMB-45) differentiation [12]. The grouping of LAM with more conventional neoplastic entities is intriguing because it has been proposed that LAM cells fitting the above description bud off in clusters from their tissue of origin and travel through lymphatic channels to various destinations, including lymph nodes and lung, where they implant: a process that mimics metastasis [13]. Their embolization into pulmonary lymphatics is thought to result in disruption of lymphangiogenesis and eventual cystic degeneration of the lung parenchyma [14]. An important related theory is the pathogenetic role of VEGF, specifically VEGF-D, in facilitating the migration and tissue destruction of LAM cells [14]. Elaborated by LAM cells and often elevated in the serum of patients with clinical LAM, VEGF-D measurement has become a recommended part of the non-invasive evaluation of cystic lung disease [15,16]. At a threshold value of 800 pg/ml, serum VEGF-D is 100% specific for LAM, though only 71% sensitive, in a woman with diffuse lung cysts [17]. Of relevance, VEGF has also been implicated in the tumorigenesis of endometrial carcinoma [18] and in the pathogenesis of DM [19], both concurrent conditions discovered in our patient alongside LAM. It is tempting to hypothesize about VEGF's role as a possible common mediator in her complex presentation.

Besides the well-established nature of DM as a paraneoplastic phenomenon, whether or not VEGF plays a role, it is intriguing to explore a potential separate connection between endometrial carcinoma and LAM. In this context, it is important to consider evidence that the organ of origin of LAM cells could be the uterus, at least in sporadic cases essentially restricted to females. Hayashi et al found uterine LAM cells in 9 out of 10 patients with pulmonary LAM [20]. Eight of these 9 had lymph nodes examined, and LAM cells were found in nodal tissue of all 8, supporting the notion that pulmonary LAM arises due to dissemination to the lung from the uterus via lymphatics. The sub-diaphragmatic origin of pulmonary LAM cells is further suggested by the near-universal association of pulmonary disease with abdominopelvic lymph node involvement in the largest available series of extrapulmonary pathology in LAM [21]. Progression from nodal to pulmonary LAM is not invariable, however, as illustrated by a series of 19 patients with positive lymph nodes none of whom developed lung disease during a mean follow up period of nearly 3 years [22]. Other similar series [23-26] have likewise not reported lung involvement in their patients with pelvic and para-aortic lymph node LAM: a total of 59 cases. What does feature prominently among these cases is endometrioid adenocarcinoma of the uterus, present in 26 of the 59 described cases (44%). Whether this represents coincidence, given the high prevalence of this type of uterine malignancy, or a correlation is yet to be determined. It is interesting to consider, nevertheless, that estrogen receptors are structural components of both endometrial and LAM cells, raising the possibility that estrogenic stimulation could be a shared pathogenetic mechanism. In fact, nulliparity - applicable to our patient's case - is a risk factor for endometrial carcinoma presumably through greater estrogen exposure and is also more common in those with pulmonary LAM than in comparable controls [27]. The possibility that proliferation of LAM cells is promoted by a hyperestrogenic milieu is a question that warrants further investigation. Whereas the role of hormonal influence in LAM remains obscure, groundbreaking work has helped elucidate

the genetic basis of this disease. Germline mutation of the tuberous sclerosis complex gene 1 or 2 (TSC1 or TSC2), more commonly the latter, gives rise to LAM in the setting of TSC [14]. S-LAM, in contrast, is the product of acquired inactivating mutations of both alleles of the TSC2 gene only [9]. Disabling of TSC genes allows upregulation of the mTORC1 signaling system, one component of which is the more familiar protein called mammalian target of rapamycin (mTOR). When this happens, control over protein synthesis, autophagy, and other functions related to cell fate is lost, resulting in autonomous cell proliferation and cancerous behavior [9]. Another common thread in our patient's presentation is the prominent oncogenic part played by the mTOR pathway not only in LAM, for which mTOR inhibition is the only available pharmacotherapy, but also in endometrial carcinoma [28]. Likewise of note is a small experimental study indicating that mTOR is expressed in polymyositis, thereby raising the possibility of a unifying role for mTOR in all three components of her case [29]. In this regard it is worth mentioning that a single published report exists of a 47-year-old nulliparous Japanese woman who was diagnosed with the constellation of connective tissue disease (systemic lupus erythematosus), endometrial carcinoma, and LAM of the retroperitoneal lymph nodes [30]. In contrast with our patient, lung involvement was not detected. Figure 4 depicts the putative pathophysiological connections among LAM, DM, and endometrial carcinoma proposed in this discussion.

Conclusions

This case is a reminder that pulmonary LAM could occur as one aspect of a complicated multipartite presentation that includes concurrent extrathoracic and systemic disorders. The link between lung cysts and the other pathology may not be obvious, yet evaluation of the accompanying conditions could establish LAM as the etiology of cystic lung disease, as it did in our patient. Interestingly, more than a year after her initial presentation, she returned for a routine follow up visit and was found to have a spontaneous pneumothorax, which is the most common thoracic complication of LAM [31].

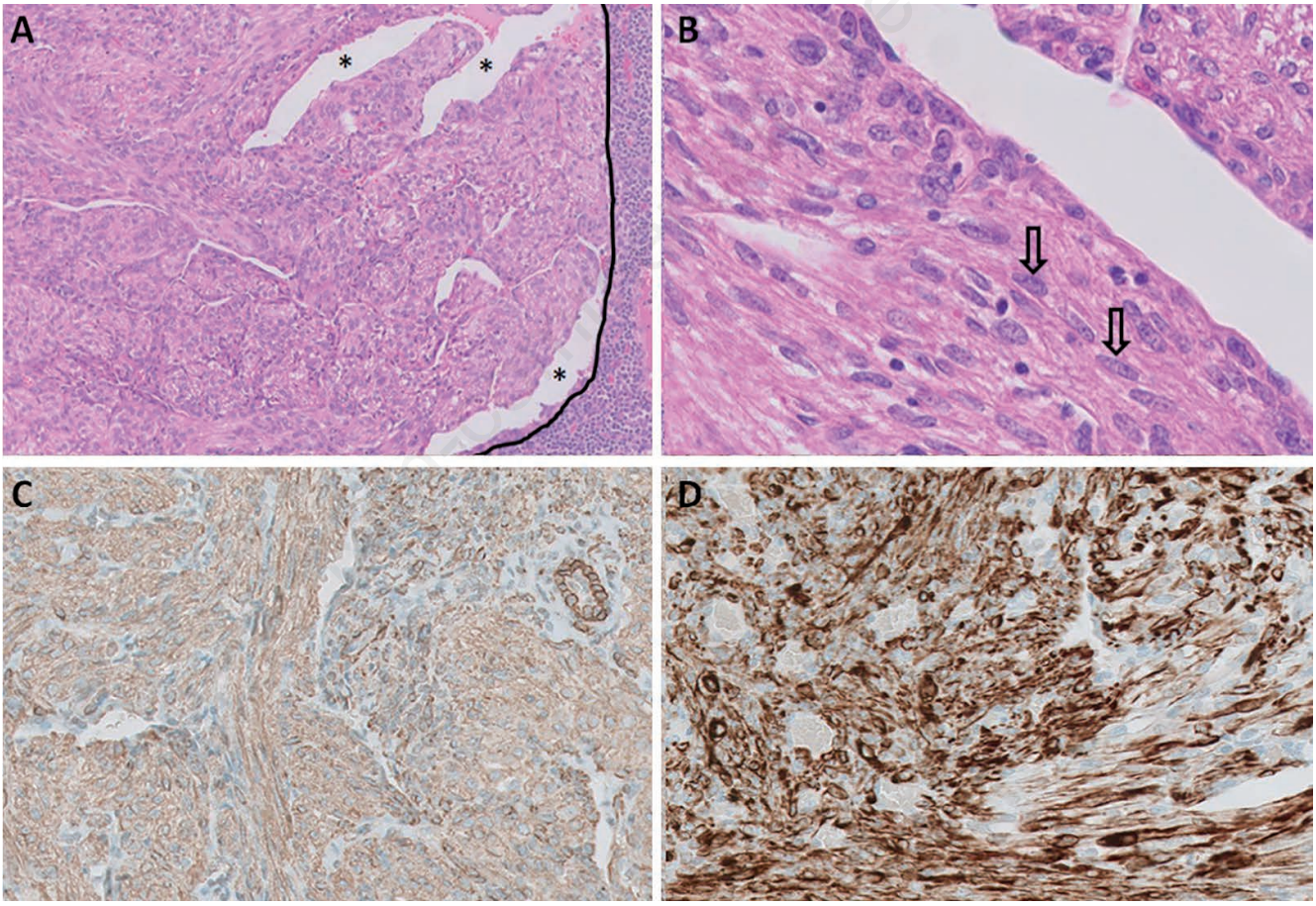

Figure 3. A) Microscopic section of pelvic lymph node under low power showing infiltration by a population of spindle-shaped cells arranged in fascicles; the vertical black line separates this infiltrative process to the left from remaining normal nodal architecture to the right; cleft-like lymphatic spaces are seen and marked with asterisks; Hematoxylin & Eosin, original magnification x 100. B) Higher magnification (400x) of the infiltrating cells from (A) highlights their eosinophilic cytoplasm and spindle-shaped nuclei (arrows) and illustrates an absence of atypia and mitosis. Immunohistochemical positivity for smooth muscle actin (C, 200x) and desmin (D, 200x) points to smooth muscle differentiation of these cells, supporting their identification as LAM cells. Please see text for results of additional immunostains not depicted in this figure.

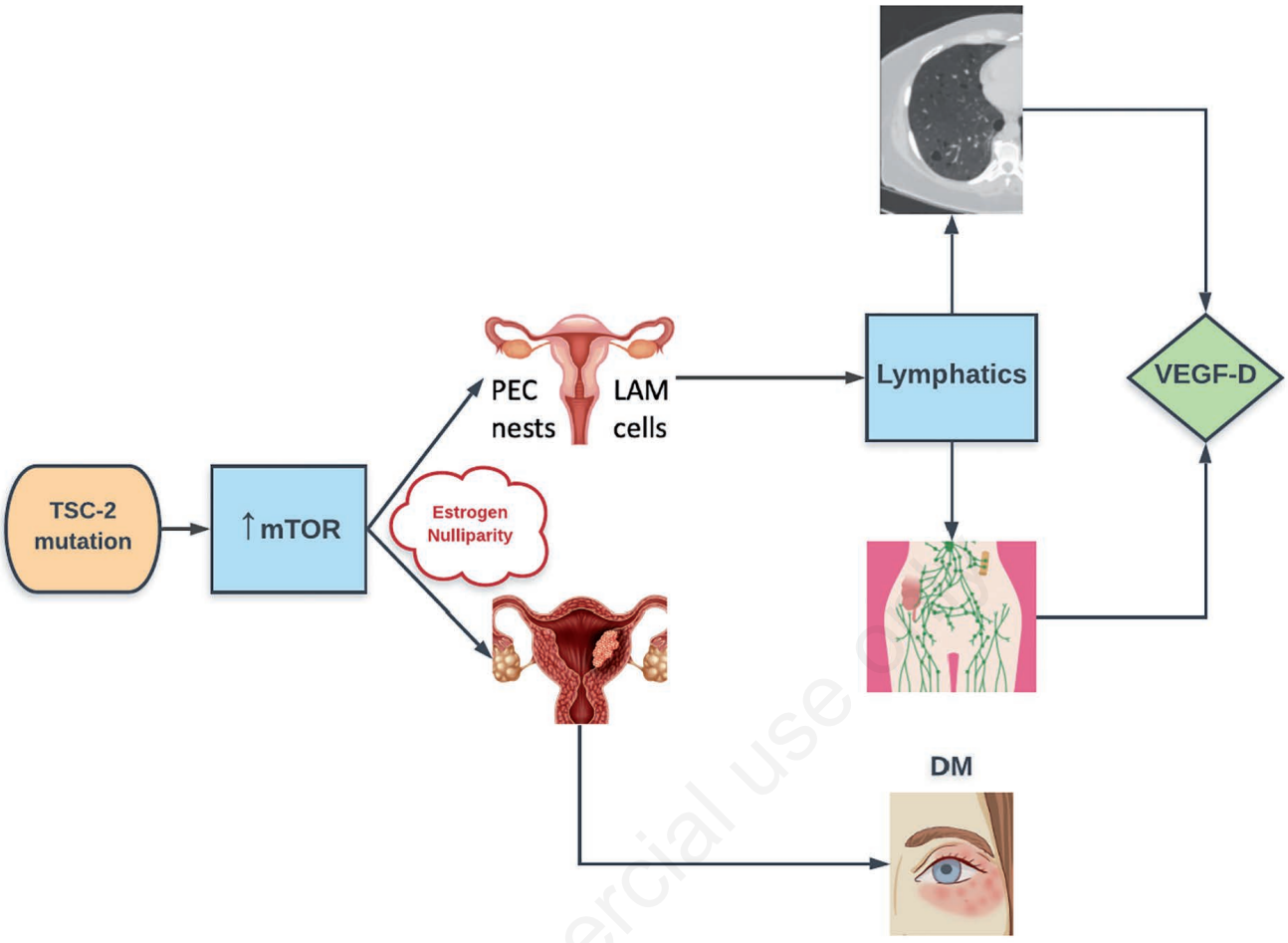

Figure 4. Graphical depiction of a putative mechanistic link among the features of the presentation of the patient described in this case (left to right). Somatic mutation of the Tuberous Sclerosis Complex-2 (TSC-2) gene leads to abnormal activation of the mammalian Target of Rapamycin (mTOR) signaling network, resulting in diminished cell fate regulation. This derangement, aided by factors such as nulliparity that increase estrogen exposure, may promote the genesis of uterine perivascular epithelioid cells (PECs), including those responsible for lymphangioleiomyomatosis (LAM). Increased estrogen exposure is also a risk factor for endometrial carcinoma, out of which dermatomyositis can then arise as a paraneoplastic syndrome. Uterine LAM cells have been proposed to migrate via lymphatics to locoregional lymph nodes and the lung, producing the changes of LAM at those sites. LAM cells secrete Vascular Endothelial Growth Factor-D (VEGF-D) that is integral to both pulmonary LAM pathogenesis and diagnosis.

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