A 34-Year-Old Woman from Brazil with Pulmonary Lymphangioleiomyomatosis Diagnosed by Raised Serum Vascular Endothelial Growth Factor-D (VEGF-D) Levels and Lung Cysts on Computed Tomography Imaging Presenting with COVID-19 Pneumonia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient:	**Female, 34-year-old**
Final Diagnosis:	**COVID-19 • lymphangioleiomyomatosis**
Symptoms:	**Dyspnea • fever • hypoxemia • myalgia**
Medication:	**Sirolimus**
Clinical Procedure:	**—**
Specialty:	**Pulmonology**

Objective: Unusual clinical course

Background: There is growing concern about the clinical course of certain diseases in patients who are simultaneously infected by SARS-CoV-2. This report is of a 34-year-old woman from Brazil with a recent diagnosis of pulmonary lymphangioleiomyomatosis (LAM) diagnosed by raised serum VEGF-D levels and the finding of lung cysts on computed tomography (CT) imaging, who presented with COVID-19 pneumonia.

Case Report: Five months after the diagnosis of pulmonary LAM, which was based on the presence of diffuse and bilateral cystic lesions on CT scan associated with high serum VEGF-D levels, the patient presented with worsening dyspnea, drop in peripheral oxygen oxygenation, fever, and diffuse myalgia. She was using Sirolimus because it inhibits the development of LAM cells. A worsening of lung abnormalities was demonstrated in a chest CT examination, with the appearance of areas of consolidation and ground-glass abnormalities. A nasal swab sample tested positive for SARS-CoV-2 infection using reverse-transcription polymerase chain reaction. Thus, Sirolimus was suspended because of concern about its immunosuppressive action. She received hospital support following the institutional protocol in force at the time, without the need for invasive mechanical ventilation. After 2 weeks, she was discharged from the hospital, with supplemental oxygen at home and return of Sirolimus.

Conclusions: This report has described the presentation of COVID-19 pneumonia due to SARS-CoV-2 infection in a 34-year-old woman with a recent diagnosis of LAM involving the lungs.

Keywords: Sirolimus • Lymphangioleiomyomatosis • COVID-19 • Severe Acute Respiratory Syndrome Coronavirus 2
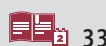
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Background

Lymphangioleiomyomatosis (LAM) is an unusual condition where there is disordered cell growth, occurring especially in females [1,2]. Although changes in the lymphatic vessels and the presence of abdominal tumors (such as angiomyolipomas and lymphangioleiomyomas) can occur, pulmonary involvement is prominent in most cases [1]. In the respiratory system, the most common finding is the presence of multiple pulmonary cysts, although recurrent pneumothorax and chylothorax may appear in the course of the disease [3]. Clinically, patients with pulmonary involvement by LAM manifest with dyspnea on exertion, cough, hemoptysis, chest pain, and problems related to chylous reflux in the airways and pleura [2]. In general, patients evolve with continuous deterioration of pulmonary function, with predominance of an obstructive ventilatory disorder resulting from the proliferation of immature smooth muscle cells in the airway wall and the formation of retention cysts [2,3]. Over time, many of these patients may evolve with impaired gas exchange and respiratory failure, with the terminal stage being reached in a period ranging from a few years to about 3 decades [2-4].

In the lungs, the diagnosis of LAM is highly suggestive when rounded, bilateral, and cystic (usually thin-walled) lesions of different dimensions on chest computed tomography (CT) scan are observed in adult women [3-5]. In the absence of additional confirmatory findings of LAM (including tuberous sclerosis complex, renal angiomyolipomas, lymphangioleiomyomas and chylous pleural effusion), the measurement of serum vascular endothelial growth factor-D (VEGF-D) should be requested for non-invasive diagnostic confirmation of LAM [6,7]. Transbronchial biopsy or video-assisted thoracoscopic surgery can provide a definitive diagnosis, although these invasive procedures should be considered in cases without extrapulmonary lesions of LAM and after the measurement of serum VEGF-D levels [5-8]. Regarding treatment of LAM, the American Thoracic Society and the Japanese Respiratory Society (ATS/JRS) recommend therapeutic management with Sirolimus (high evidence) [6]. This is a mammalian target of rapamycin (mTOR) inhibitor that also demonstrated in vitro the reduction of the inflammatory activity triggered by Middle-East respiratory syndrome coronavirus (MERS-CoV) [9].

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, it has been observed that the lungs are among the organs most frequently affected in infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [10]. Pulmonary involvement can be asymptomatic, although it can vary between mild and moderate conditions and severe forms requiring intensive care support [10,11]. The most common forms of lung injury caused by SARS-CoV-2 are pneumonia, pulmonary edema, interstitial fibrosis, and acute respiratory distress syndrome [11].

This report is of a 34-year-old woman from Brazil with a recent diagnosis of pulmonary LAM diagnosed by raised serum VEGF-D levels and the finding of lung cysts on lung CT imaging, who presented with COVID-19 pneumonia.

Case Report

A 34-year-old non-smoker woman presented 2 years ago with dyspnea initially due to great efforts progressing to small efforts. One year later, she developed spontaneous pneumothorax. A chest CT scan revealed, in addition to pneumothorax, diffuse and bilateral cystic lesions (Figure 1) and the VEGF-D levels were high (1700 pg/mL). The cranial CT scan did not show images suggestive of tuberous sclerosis complex (TSC), while the abdominal CT scan did not show images of renal angiomyolipomas. At the same time, an obstructive ventilatory disorder was evidenced in the pulmonary function tests (PFTs), with normal total lung capacity (TLC), increased residual volume (RV) and RV/TLC, and diffusion capacity of the lungs for carbon monoxide (DLco) markedly reduced (24% of the predicted value). By clinical-radiological correlation, the diagnosis of pulmonary LAM was made without association with the TSC. The patient then started treatment with Sirolimus (1 mg per day), bronchodilators, and home oxygen therapy (2 L/min) since she had hypoxemia at rest.

About 5 months after the diagnosis of LAM, the patient contacted the assistant team by phone with concerns of diffuse myalgia and fever. The patient received remote care because of the pandemic due to SARS-CoV-2, and was advised that she should use azithromycin (500 mg per day for 5 days). However, 5 days after the onset of symptoms, the patient presented worsening of dyspnea and it was necessary to increase the oxygen flow from 2 L/min to 4 L/min. Nasal swab collection was performed, with a positive result for SARS-CoV-2 using reverse-transcription polymerase chain reaction (RT-PCR). The test was performed using the XGEN MASTER COVID-19 (Mobius Life Science, Inc., Pinhais, Paraná, Brazil) kit, where the RT-PCR in which reverse transcription and subsequent amplification of the specific target sequence takes place in the same reaction well; this RT-PCR method has a specificity of 100% for SARS-CoV-2, a sensitivity (limit of detection) SARS-CoV-2 (ORF1ab gene) 10 copies/reaction with probability ≥95%, and a sensitivity (limit of detection) SARS-CoV-19 (gene N) 50 copies/reaction with probability ≥95% [12]. In addition, she had fever, non-secretive cough, and diarrhea. Ten days after the onset of symptoms, there was worsening of the cough with the presence of frequent hemoptoics. On that occasion, she contacted the medical team that opted for hospitalization in an isolation bed. On examination, the patient was in regular general condition, afebrile, tachypneic with peripheral oxygen saturation (SpO$_2$) equal to 97% using 4 L/min of oxygen; on respiratory auscultation, she had diffuse breath sounds, with no adventitious sounds.
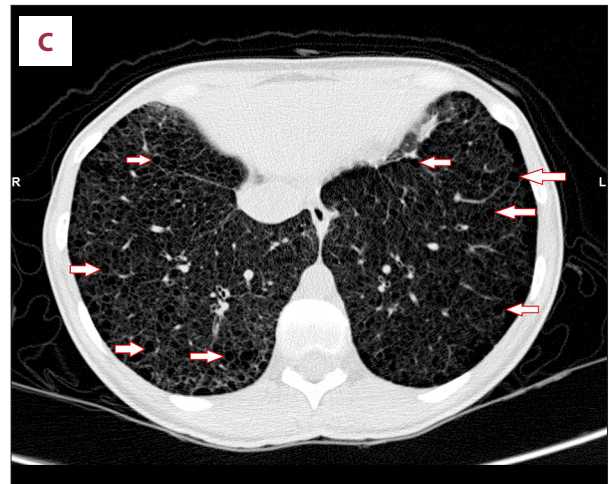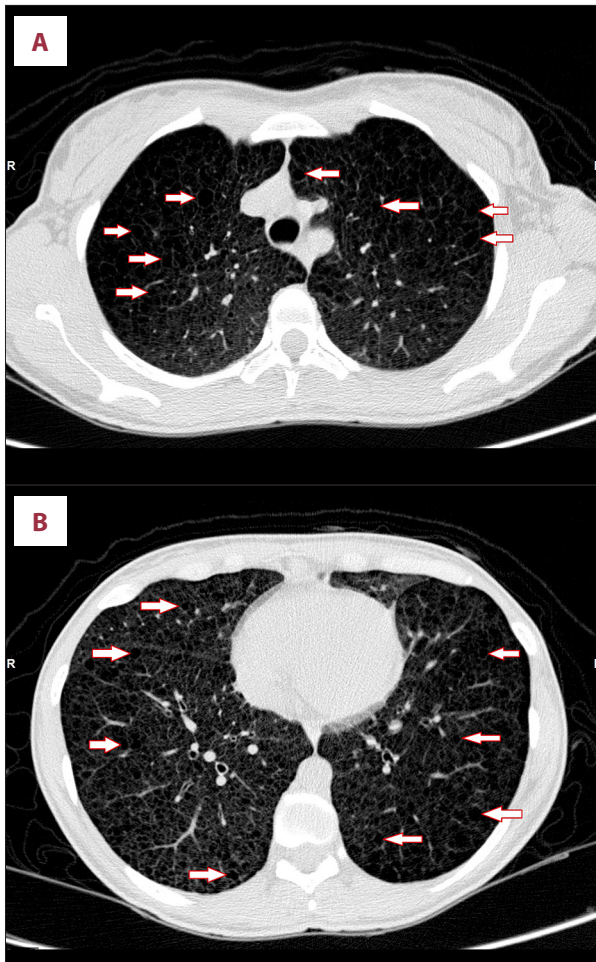
Figure 1. Chest computed tomography images of the patient when the diagnosis of pulmonary lymphangioleiomyomatosis was made. (**A**) The superior lobes show diffuse, rounded, bilateral, and thin-walled cysts of varying sizes (arrows). (**B**) The average portion of the lungs shows diffuse, rounded, bilateral, and thin-walled cysts (arrows). (**C**) The lower lobes show diffuse, rounded, bilateral and thin-walled cysts (arrows).

(1 mg/day). The patient is under remote monitoring by our team and has no further complications.

Upon hospital admission, laboratory tests showed the following results: polycythemia (hemoglobin=16.7 g/dL and hematocrit=51.6%); normal leukometry (white blood cell=3.42×10^3/μL with 1.07×10^3/μL of lymphocytes); platelets=170×10^3/μL; D-dimer=757 ng/mL; troponin <0.1 ng/mL; lactic dehydrogenase=745 IU/L; aspartate aminotransferase=284 IU/L; alanine aminotransferase=353 IU/L; and ferritin=1894 ng/mL. A chest CT scan showed worsening of the underlying disease, in addition to foci of consolidation and ground-glass opacities (**Figure 2**). On the same day of hospital admission, Sirolimus was suspended and treatment was started for possible bacterial pneumonia associated with cefepime (2 g every 8 h for 10 days), in addition to ivermectin (single dose) and chloroquine (450 mg/day) following the institutional protocol used at that time. After 72 h of hospitalization, the patient showed improvement in diffuse myalgia and dyspnea with reduced oxygen flow, returning to baseline at 2 L/min and maintaining SpO$_2$ equal to 97%. She remained afebrile throughout the hospitalization without hemoptoics, with inflammatory markers and transaminases in decline until normalization. After 2 weeks of hospitalization, she was discharged from the hospital, with supplemental oxygen at home and return of Sirolimus

Discussion

LAM is an uncommon condition with disordered cell growth that occurs most often in women of childbearing age [1]. In addition to lesions of lymphatic vessels and neoplasms in the abdomen (angiomyolipomas and lymphangioleiomyomas), patients with LAM present with multiple cysts in the lung tissue [1,2]. In addition to occurring sporadically, LAM can also be associated with a hereditary neurocutaneous syndrome, which is the TSC; the latter often presents with hamartomas, brain tissue calcifications, mental retardation, and epilepsies [13,14]. The pathophysiological mechanism of LAM includes genetic changes in the TSC; these genetic changes cause functional loss in hamartin and tuberin proteins that have the role of inhibiting the mTOR, a protein molecule that regulates cell growth and multiplication [15]. In LAM, the inactivation of TSC1 and TSC2 genes results in constant activation of the mTOR pathway [16-18]. The neoplastic cells that cause LAM represent a clonal proliferation of smooth muscle cells around the airways, blood, and lymph vessels [19]. They express VEGF-D, which facilitates access to the lymphatic channels and metastatic spread [20,21]. If VEGF-D is >800 pg/mL, LAM can be identified with a sensitivity of 73% and specificity of 100% [22]. ATS/JRS recommends the measurement of VEGF-D as a non-invasive confirmatory diagnosis of
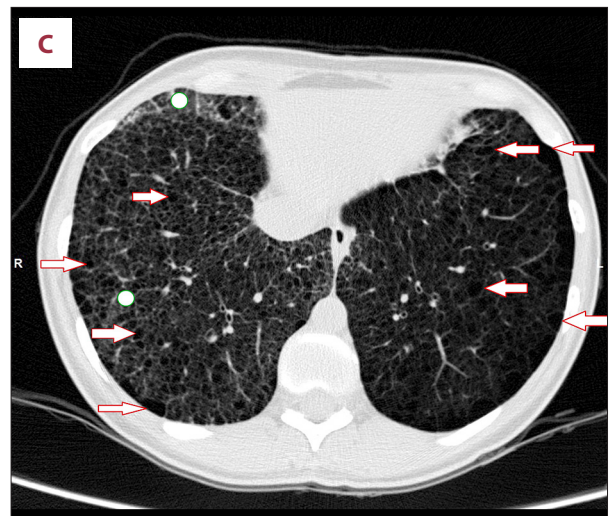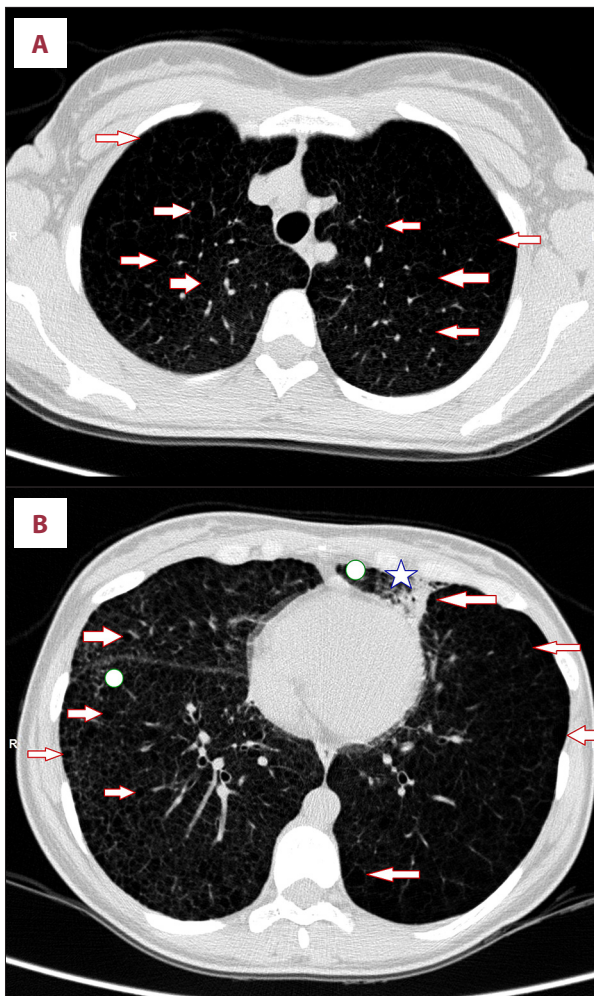
Figure 2. Chest computed tomography images of the patient when she had COVID-19 pneumonia 5 months after the diagnosis of pulmonary lymphangioleiomyomatosis (**A**) The superior lobes show diffuse, rounded, bilateral and thin-walled cysts of varying sizes (arrows). (**B**) The average portion of the lungs shows diffuse, rounded, bilateral cysts (arrows), foci of consolidation in lingular segment (star), and ground-glass opacities (circles). (**C**) The inferior lobes show diffuse, rounded, bilateral cysts (arrows) and ground-glass opacities (circles).

LAM associated with a compatible chest CT scan [6]. VEGF-D is an indicator of little improvement in drug intervention and is related to lymphatic involvement [23].

Dyspnea on exertion, recurrent pneumothorax, chylothorax, and abdominal tumors (including renal angiomyolipomas and lymphangioleiomyoma) are the most common findings in LAM [2,3]. Less commonly, fatigue, cough, hemoptysis, chest pain, and manifestations related to chylous reflux in the pleura, pericardium, airways, and genitourinary tract can also be seen [2]. Exacerbations of LAM have already been associated with the use of oral contraceptives and pregnancy [24]. In the presence of these lesions, LAM confirmation is done mainly when chest CT shows cysts diffusely distributed through the lungs; these cysts are usually round, of multiple sizes (1-45 mm in diameter) and have thin walls [3]. For diagnostic completion, an abdominal CT scan can also be performed to assess abdominal tumors. Transbronchial biopsy or video-assisted thoracoscopic surgery can provide a definitive diagnosis [4]. PFTs in patients with LAM most commonly demonstrate obstructive disorder [25]. As LAM becomes more severe, there

is a pronounced drop in both DLco and forced expiratory volume in 1 second (FEV$_1$) [26].

Therapeutic management with Sirolimus in patients with LAM and FEV$_1$ <70% (value in percentage of predicted) is suggested by the ATS/JRS [6]. Because Sirolimus is a potent mTOR regulator, it inhibits the development of LAM cells [6,23]. The Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) Trial showed maintenance of baseline FEV$_1$ values with this drug [23]. It is interesting to note that mTOR inhibitors have also demonstrated in vitro a reduction in the inflammatory activity triggered by MERS-CoV, suggesting new drug targets for therapeutic intervention strategies [9].

Infection with SARS-CoV-2 can present asymptomatically, ranging from mild and moderate to severe forms requiring intensive care support [27,28]. The severe form of COVID-19 coincides with a dramatic increase in inflammatory cytokines and other inflammatory biomarkers [27]. Some researchers point out that the use of mTOR inhibitors can also decrease the inflammatory reaction resulting from the replication of SARS-CoV-2 and thus change the clinical course of COVID-19 [28]. Such effects are due to a reduction in the proliferation of T lymphocytes and maintenance of the population of regulatory T cells, which could, in this way, reduce the cytokine storm [29]. Evaluating 26 patients diagnosed with TSC and/or LAM using mTOR inhibitors (Sirolimus or Everolimus), Peron et al [30] observed that 5

of them with symptoms suggesting COVID-19 (although without laboratory confirmation) showed a benign course. More recently, Baldi et al [31] also described 6 patients with LAM and confirmed COVID-19 (3 of them using mTOR inhibitors); in this case series, only 1 patient required use of supplemental oxygen for 3 days. The use of mTOR inhibitors appears to induce interferon signaling and downregulation of IL-6, causing positive effects in limiting the initial SARS-CoV-2 infection and in the progression of COVID-19-related pneumonia in women with LAM [32]. In addition to acting on the immunostimulatory effects of T cell response, mTOR inhibitors appear to generate a repertoire of antibodies with heterosubtypical protection in various types of viral infections, including that related to influenza virus [33].

In the present case, few alterations compatible with pulmonary SARS-CoV-2 infection were observed between chest CT scans before and after the diagnosis of COVID-19, with the exception of the appearance of foci of consolidation and ground-glass opacities (Figure 1). Two reasons may partially explain this fact: a) a possible less aggressive evolution of the pulmonary SARS-CoV-2 infection in patients using Sirolimus (possible interaction between mTOR inhibitors and SARS-CoV-2 infection); and b) few changes in lung images resulting from SARS-CoV-2 infection due to gross structural changes caused by LAM (as also occurs in patients with extensive emphysema) [6,23].

It is worth mentioning that severe SARS-CoV-2 infection requiring hospitalization occurred in our patient, despite the use of Sirolimus. Although there is a theoretical basis for the anti-COVID-19 inflammatory activity induced by Sirolimus, it should be emphasized that the clinical improvement only occurred after the suspension of Sirolimus. In fact, there is a concern about the immunosuppressive action of Sirolimus, which may increase the risk for COVID-19 in patients with LAM [30]. Therefore, the question remains whether the use of mTOR inhibitors can improve the clinical evolution of COVID-19, and controlled longitudinal trials are needed to clarify this hypothesis.

Conclusions

This report has described the presentation of COVID-19 pneumonia due to SARS-CoV-2 infection in a 34-year-old woman with a recent diagnosis of LAM involving the lungs.

Institution Where Work Was Done

State University of Rio de Janeiro, Rio de Janeiro, Brazil

Conflict of Interests

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Harari S, Torre O, Moss J. Lymphangioleiomyomatosis: What do we know and what are we looking for? Eur Respir Rev. 2011;20(119):34-44

2. Kelly J, Moss J: Lymphangioleiomyomatosis. Am J Med Sci 2001; 321(1):17-25

3. Medeiros Junior P, Carvalho CRR. Linfangioleiomiomatose pulmonary. J Bras Pneumol. 2004;30(1):66-77

4. Hohman DW, Noghrehkar D, Ratnayake S. Lymphangioleiomyomatosis: A review. Eur J Intern Med. 2008;19(5):319-24

5. Tanaka H, Imada A, Morikawa T, et al. Diagnosis of pulmonary lymphangioleiomyomatosis by HMB45 in surgically treated spontaneous pneumothorax. Eur Respir J. 1995;8(11):1879-82

6. McCormack FX, Gupta N, Finlay GR, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis diagnosis and management. Am J Respir Crit Care Med. 2016;194(6):748-61

7. Koba T, Arai T, Kitaichi M, et al. Efficacy and safety of transbronchial lung biopsy for the diagnosis of lymphan-gioleiomyomatosis: A report of 24 consecutive patients. Respirology. 2018;23(3):331-38

8. Feemster LC, Lyons PG, Chatterjee RS, et al. Summary for clinicians: Lymphangioleiomyomatosis diagnosis and management clinical practice guideline. Ann Am Thorac Soc. 2017;14(7):1073-75

9. Kindrachuk J, Ork B, Hart BJ, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. Antimicrob Agents Chemother. 2015;59(2):1088-99

10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506

11. Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020;55(6):327-31

12. Brazil. Ministry of Health. Accuracy of diagnostic tests registered with ANVISA for COVID-19. https://portalarquivos2.saude.gov.br/images/pdf/2020/June/02/AcuraciaDiagnostico-COVID19-atualizacaoC.pdf [in Portuguese]

13. Franz DN, Brody A, Meyer C, et al. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med. 2001;164(4):661-66

14. Sparagana SP, Roach ES. Tuberous sclerosis complex. Curr Opin Neurol. 2000;13(2):115-19

15. Napolioni V, Curatolo P. Genetics and molecular biology of tuberous sclerosis complex. Curr Genomics. 2008;9(7):475-87

16. Carsillo T, Astrinidis A, Henske EP. Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. Proc Natl Acad Sci USA. 2000;97(11):6085-90

17. Sato T, Seyama K, Fujii H, et al. Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangioleiomyomatosis. J Hum Genet. 2002;47(1):20-28

18. Schmelzle T, Hall MN. TOR, a central controller of cell growth. Cell. 2000;103:253-62

19. Glassberg MK: Lymphangioleiomyomatosis. Clin Chest Med 2004;25(3):573-82

20. Kumasaka T, Seyama K, Mitani K, et al. Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangioleiomyomatosis. Am J Surg Pathol. 2005;29(10):1356-66

21. Kumasaka T, Seyama K, Mitani K, et al. Lymphangiogenesis in lymphangioleiomyomatosis: its implication in the progression of lymphangioleiomyomatosis. Am J Surg Pathol. 2004;28(8):1007-16

22. Young LR, Vandyke R, Gulleman PM, et al. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. Chest. 2010;138(3):674-81

23. Young L, Lee HS, Inoue Y, et al. Serum VEGF-D a concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: A prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial. Lancet Respir Med. 2013;1(6):445-52

24. Kreisman H, Robitaille Y, Dionne GP, Palayew MJ. Lymphangioleiomyomatosis syndrome with hyperparatyreoidism: A case report. Cancer. 1978:42(1):364-72

25. Chu SC, Horiba K, Usuki J et al: Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999;115(4):1041-5.

26. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al. Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2003;168(12):1427-31

27. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-29

28. Terrazzano G, Rubino V, Palatucci AT, Giovazzino A, et al. An open question: is it rational to inhibit mTor-dependent pathway as COVID-19 therapy? Front Pharmacol. 2020;11:856

29. Strauss L, Whiteside TL, Knights A, et al. Selective survival of naturally occurring human CD4+CD25+Foxp3+regulatory T cells cultured with rapamycin. J Immunol. 2007;178(1):320-29

30. Peron A, Briola FL, Bruschi F, et al. Tuberous sclerosis complex (TSC), lymphangioleiomyomatosis, and COVID-19: The experience of a TSC clinic in Italy. Am J Med Genet A. 2020;182(11):2479-85

31. Baldi BG, Amaral AF, Colares PFB, et al. COVID-19 and lymphangioleiomyomatosis: experience at a reference center and the potential impact of the use of mTOR inhibitors. Am J Med Genet A. 2020;182(12):3068-70

32. Tang Y, Kwiatkowski DJ, Henske EP. mTORC1 hyperactivation in lymphangioleiomyomatosis leads to ACE2 upregulation in type II pneumocytes: implications for COVID-19. Eur Respir J. 2021;57(2):2002737

33. Keating R, Hertz T, Wehenkel M, et al. The kinase mTOR modulates the antibody response to provide cross-protective immunity to lethal infection with influenza virus. Nat Immunol. 2013;14(12):1266-76