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Case Report

Therapeutic Possibilities Approach of a Patient with RA Associated with Lymphangioleiomyomatosis, Lung Form: Case Report and Literature Review

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Abstract

Lymphangioleiomyomatosis (LAM) is a rare disease with cystic lung damage that destroys the lungs. It is accompanied by chronic respiratory failure and frequent respiratory infections, which occur almost exclusively in young, fertile women. Rheumatoid arthritis (RA) is the most common form of inflammatory rheumatism; affects about 1% of the general population, predominantly women. And this disease can affect the lungs in various ways. The combination of these two diseases has a major negative impact on the body and lungs, while raising important issues for the therapeutic approach, as it is known that specific therapy in RA increases the risk of infections and secondary lung damage. The purpose of this article is to provide new information on the incidence of the combination of the two pathologies, the possibilities of diagnosis and treatment, the evolution, complications and prognosis of LAM associated with RA.

Methods: We selected studies that follow the incidence, the therapeutic principles recommended in RA, LAM and prognosis.

Results: The therapeutic possibilities in the case of lung damage caused by RA associated with LAM are limited; modest results obtained by administration of bronchodilators, corticosteroids and sirolimus or everolimus, therapy of modulating immunity by inhibiting the mammalian target of rapamycin (mTOR) complex are presented. More recent studies estimate survival to be nearer to 10 years and there are even reports of apparent spontaneous resolution. In the resulting section we presented the evolution of a patient diagnosed with RA who associated LAM with lung form.

Conclusions: At this time, there is insufficient data to inform specific guidelines for lung transplantation for patients with rheumatic diseases. The association of RA with LAM has worsened the vital prognosis and was a relative contraindication for lung transplantation.

Keywords: Rheumatoid arthritis; Lymphangioleiomyomatosis; Sirolimus; Lung transplant

Abbreviations

LAM: Lymphangioleiomyomatosis; RA: Rheumatoid Arthritis

Introduction

RA is a chronic autoimmune disease, which is progressive, destructive and deforming for the joints, and is usually accompanied by multiple systemic manifestations. It is the most common inflammatory rheumatic disease, with a prevalence of about 1% in the general population [1]. The annual incidence is 0.5 new cases/1000 inhabitants for women and 0.2 new cases/1000 inhabitants for men [2]. RA involves a condition of the connective tissue, of unknown etiology, characterized by symmetrical erosive synovitis that causes severe damage to the joints and systemic damage to various organs and systems [3]. Most patients have a chronic course of the disease, with periods of exacerbation alternating with periods of calm. Left untreated, the disease leads to progressive, irreversible joint destruction, with permanent joint deformities, accompanied by functional deficit, impaired quality of life and reduced life expectancy [4]. The occurrence of visceral lesions is responsible for shortening the average lifespan by 5 to 10 years [5].

An important consequence of the disease is that more than 50% of patients stop their professional activity in the first 5 years of the disease, and 10% of cases show severe disability in the first 2 years of evolution. Given the potential severity and risk of complications, the diagnosis of RA should be confirmed according to the The European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria at an early stage and treatment initiated as soon as possible.

Pulmonary disease in RA is, usually, of the infiltrative type. The pleura are frequently histologically interested, but clinically less often. Production of pneumothorax can be a consequence of the rupture in the pleural cavity of a rheumatoid nodule located sub-pleurally. The localization of rheumatoid nodules in the lung parenchyma can lead to the appearance of circumscribed infiltrates with a diameter of 0.5-3

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cm. Also, still as a consequence of immunological changes specific to RA, patients may exhibit diffuse pulmonary fibrosis and obstructive airway disease, frequently bronchiolitis disease. These manifestations are also seen in other rheumatic conditions such as Sjogren's disease, systemic lupus erythematosus or mixed connective tissue disease [6].

Pulmonary suffering from LAM, a rare lung disease, involves the proliferation of abnormal smooth muscle cells (LAM cells) in pulmonary tissue and along the axial lymphatics of the thorax and abdomen, thin-walled pulmonary cysts, and a high incidence of angiomyolipoma's [7,8].

Etiopathogenesis of this rare disease is still incompletely elucidated, but there are studies that show a link between the fertile period and the onset of this disease; hence specialists have issued some theories in which estrogen would play an important role. This hormone may be involved in the abnormal growth of muscle cells that characterize the disease, similar to its involvement in the growth of smooth muscle in the uterus during a woman's fertile years.

This paper will review the literature to identify the incidence of the association of RA with LAM and the therapeutic interventions in patients diagnosed with rheumatoid arthritis associated with lymphangioleiomyomatosis. It will also be a case study of a rare clinical case of rheumatoid arthritis associated with lymphangioleiomyomatosis.

Methods

We selected incidence studies, recommended therapeutic principles in RA, LAM, and prognosis. No age or sex restrictions will be imposed. We have included all studies related to the proposed objectives. We did not restrict studies to any type of framework; we used Books and Documents, Clinical Trial, Meta-analysis, Randomized Controlled Trial, Review, Systematic Review. I did not use language restrictions. For data collection, we used the PubMed platform. We excluded duplicates and studies referring to other extra thoracic sites in LAM. In the case of studies with RA, we selected studies that refer to the specific treatment for lung damage in RA. For the following keywords: "Lymphangioleiomyomatosis/etiology" [Mesh] OR "Lymphangioleiomyomatosis/genetics" [Mesh] OR "Lymphangioleiomyomatosis/immunology" [Mesh] OR "Lymphangioleiomyomatosis/mortality" [Mesh] OR "Lymphangioleiomyomatosis/therapy)" "Immune System Diseases" [Mesh]) AND "Arthritis, Rheumatoid" [Mesh] No study has been identified. We reduced the keywords used in RA and Lymphangioleiomyomatosis; thus, 12 publications were identified. To assess the incidence, treatment and mortality of Lymphangioleiomyomatosis we used the following keywords: "Lymphangioleiomyomatosis" [Mesh] AND "Lymphangioleiomyomatosis/epidemiology" [Mesh] OR "Lymphangioleiomyomatosis/mortality" [Mesh] AND therapy [Mesh]). We have identified 48 results. 21 review, 2 meta-analyses (Figure 1).

In order to support the information related to the problem of LAM treatment associated with RA, we will present the case of a young patient who presented these two diseases. We will highlight the symptomatology, the paraclinical investigations, the evolution of the patient under treatment, the therapeutic measures performed.

Results

The results obtained by accessing the national database in Great Britain show the presence of respiratory failure grade 3 in 55% of patients with LAM after 10 years of onset and 10% have grade 4. The 5-year survival rate is 85.1% and 71.1% 10 years after lung biopsy. There are also results that show the benefits of hormonal and bronchodilator treatment. The therapeutic benefit of sirolimus treatment on lung function has been shown. Lung transplantation is an accepted therapy for end-stage LAM, with superior results to other indications for transplantation [14]. Sirolimus and everolimus have been recommended for the treatment of LAM to stabilize lung function and decrease the prevalence of renal LAM. The efficacy and safety of combination therapy (sirolimus/everolimus with doxycycline and triptorelin) remain to be explored [15]. Lung transplantation is a therapeutic option in patients with LAM [16]. A prospective study of a cohort of 152 patients at the National Hospital Organization Kinki-Chuo Chest Medical Center showed that all patients with LAM were female and described one incidence of 1 in 152 cases with RA [17]. In total, there were only 12 studies, of which 10 studies were excluded because they did not refer to our topic. No study provided an overall estimate of either the incidence or prevalence of LAM in the general population. However, two studies have estimated the prevalence of LAM in patients with TSC (Tuberous sclerosis complex). Castro et al. [18] undertook a retrospective study over 43 years (1948-1991) of patients attending the Mayo clinic; 388 patients had TSC and nine of these had LAM diagnosed, giving a prevalence of 2-3%. Dwyer et al. [19] gave an estimated prevalence of less than 1%, but they did not say how they reached this conclusion [20].

Case Presentation

The case we present (with the approval of the ethics commission 1030/28.04.2021) is that of a 30-year-old woman who came to the Rheumatology Department from Pelican Hospital (Oradea, Bihor, Romania) in December 2019 with joint pain and symmetrical inflammation at the level of her hands (bilaterally, metacarpophalangeal joints II and III; and bilaterally, interphalangeal joints II, III and IV); of her knees (bilaterally); and with muscular pain, severe neurasthenia, fatigue, morning stiffness over 90 minutes, decrease in the force of the fingers grip. The symptoms started in the first trimester of pregnancy. We should mention that the patient was a non-smoker, with no personal or family pathological history. Paraclinical investigations identified a significant biological inflammatory syndrome with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increased more than 3 times the normal value (normal value: CRP 0.5-1 mg/L, ESR 2-15 mm/h), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP antibodies) values increased more than 5 times the normal value (normal value: RF 0-14 IU/mL, anti-CCP antibodies <7U/mL). Musculoskeletal ultrasound identified active synovitis in the small joints of the hands bilaterally. A diagnosis of seropositive RA was established at the onset, according to the 2010 ACR/EULAR classification criteria for RA [10]. Given that the patient was in her third month of pregnancy, she refused the initiation of disease-modifying anti-rheumatic drugs (DMARDs) and anti-inflammatory treatment. After 10 months from first reporting to the Rheumatology Department, the patient exhibits an altered functional status, Health Assessment Questionnaire (HAQ) over 1.5,

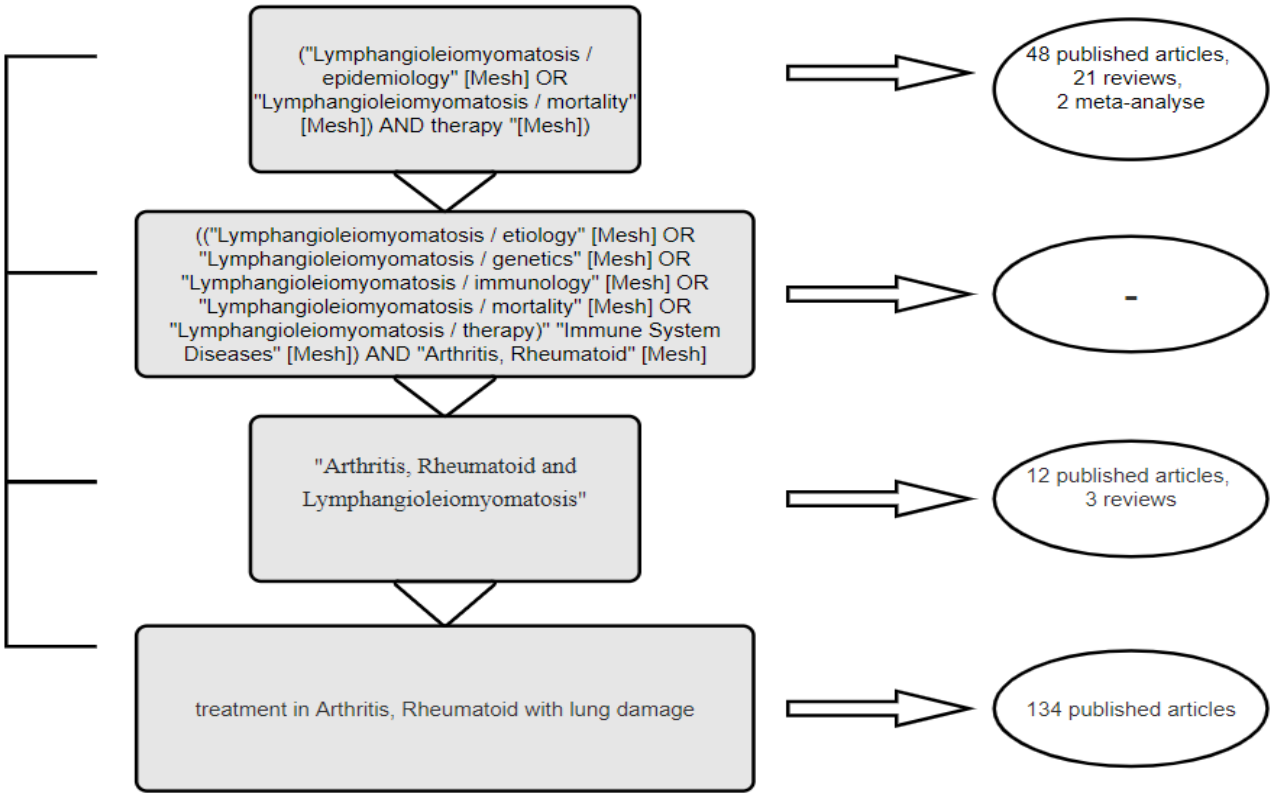

Figure 1: Search strategy for PubMed from 1995-februarie 2022.

Table 1: The patient's symptoms.

S. No	Symptomatology	No. painful / swollen joints	DAS	VAS
I	Symmetrical joint pain and inflammation, stiffness over 90 minutes and bilateral functional hand deficit, neurasthenia	12/12	5.57	70
II	Symmetrical joint pain and inflammation, stiffness over 90 minutes and bilateral functional hand deficit, neurasthenia	11/15	5.1	90
III	Nausea, vomiting, loss of appetite, malaise after methotrexate administration, dyspnea on exertion	6/9	5.9	70
IV	Persistent dyspnea, haemoptysis, hair loss, severe neurasthenia, decreased muscle strength, depression	10/15	5.88	90
V	Severe dyspnoea and respiratory infections	3/2	2.1	20
VI	Repeated hemorrhagic cystitis secondary to cyclophosphamide treatment, weight loss of approximately 5kg in 4 weeks, hair loss, marked polyarthralgia with inflammation. character, swelling of the small joints bilaterally in the hands, knees, elbows	14/12	6.1	80

VAS: Visual Analogue Scale; DAS: Disease Activity Score Calculator for Rheumatoid Arthritis

Visual Analogue Scale (VAS) 90, Disease Activity Score (DAS 28) 5.1. Biological investigations showed high values of the RF and anti-CCP antibodies (more than 10 times the normal value, normal value: RF 0-14 IU/mL, anti-CCP antibodies <7U/mL), high values of acute phase reactants: CRP > 5 times the upper limit of normal (0.5-1 mg/L) and ESR > 80mm/h (2-15 mm/h). Clinical examination of the patient revealed a large number of swollen (no.11) and painful joints (no.15), as well as the presence of extra-articular manifestations (rheumatoid nodules in the elbow), morning stiffness over 120 minutes, severe functional impotence. Radiologically, marginal erosion at the right metacarpophalangeal II level is obvious. Treatment with methotrexate (MTX) 20mg/week, corticosteroid 0.5mg/kg body, folic acid, with slight improvement of joint inflammatory symptoms. The administration of vitamin D is recommended in patients with RA, and the discussion remains open between the correlations of the level of serum 25 (OH) D with the severity of the disease [21]. At the 3-month reassessment, the patient complains of nausea, vomiting, loss of appetite, malaise after taking methotrexate. Methotrexate is discontinued and leflunomide 20mg/day, non-steroidal anti-inflammatory drug (NSAID) is administered. Also, the patient suffers from dyspnea on exertion, and investigations reveal the persistence of a severe biological inflammatory syndrome, the disease being active under treatment (VAS: 70, DAS 28: 5.9, SJC: 6, TJC: 4) (number of swollen joints - SJC and number of tender joints - TJC), elevated immunological marker values (RF 356 IU/mL (0-14 IU/mL), anti-CCP 1245 IU/ml (<7U/mL)), mild normochromic normocytic anemia, and chest computed tomography (CT) scan shows diffuse pulmonary fibrosis with *honeycombing* appearance, CT scans show numerous thin-walled cysts throughout the lungs. Sulfasalazine 3gr/day, corticosteroids (prednisone 5 to 10 mg daily), bronchodilators (ventolin-salbutamol) are added to the treatment. After another 3 months, at evaluation, the patient still shows increased disease

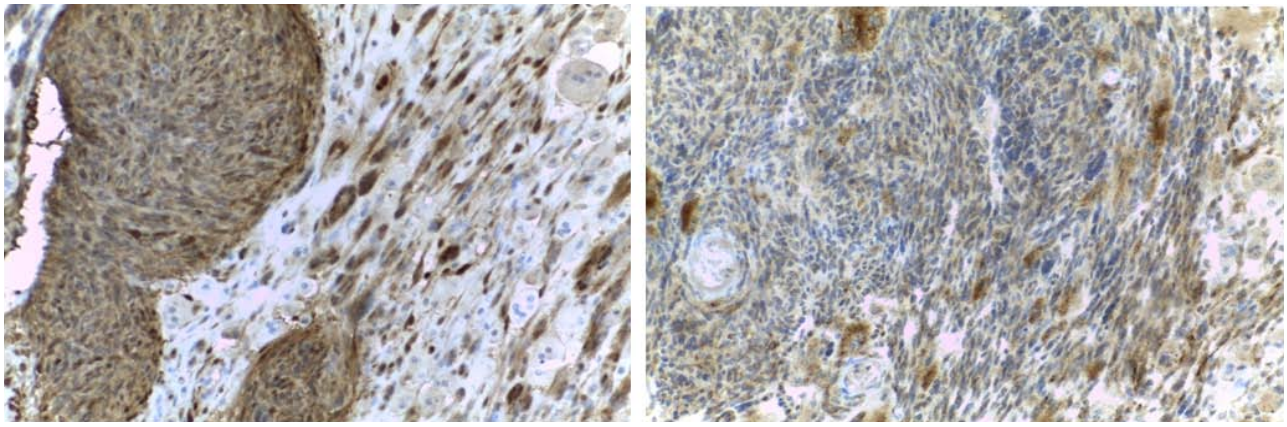

Figure 2: Histopathological changes obtained in the patient with pulmonary lymphangioleiomyomatosis and RA (own archive).

Table 2: Therapeutic management according to clinical and paraclinical examination.

Assessment	ESR mm/h, CRP mg/l	RF UI	Ac-ACCP U/L/ VEGF-D pg/mL	Treatment
I	45/25	70	40	refuse
II	80/ 25	140	100/It is not determined	Methotrexate (MTX) 20mg/week, corticosteroids 0.5mg/kg body weight, folic acid, vitamin D
III	80/25	356	1,245/It is not determined	Leflunomide, sulfasalazine, corticosteroids, bronchodilators
IV	75/30	It is not determined	It is not determined	Biological therapy against TNF-alpha, adalimumab 40mg 1f/2 weeks, leflunomide 20mg/week, NSAIDs
V	29/ 6,8	It is not determined	It is not determined	Cyclophosphamide 50mg 4tb/day, plaquenil (hydroxychloroquine) 2x1 tb/day, medrol 16mg/day, colchicine 1mg 1tb/day
VI	85/20	It is not determined	It is not determined	Rituximab, hydroxychloroquine
VII	90/30	It is not determined	It is not determined/≥800	Sirolimus

activity, is non-responding to 2 DMARDs in maximum doses over 3 months of administration of each, which is why she is evaluated to initiate anti - tumor necrosis factor (TNF) - alpha targeted biological therapy according to the protocol for treating RA [6].

In addition to joint pain and swelling, the patient suffers from persistent dyspnea, hemoptysis, hair loss, severe neurasthenia, decreased muscle strength, depression. Screenings for hepatitis B, hepatitis C, and pulmonary tuberculosis were all negative, and treatment with adalimumab 40mg 1f/2 weeks was initiated, continuing the treatment with leflunomide 20mg/day and oral NSAID (naproxen), inhaled corticosteroids (salbutamol). Three months after the start of biological therapy, the biological and clinical joint inflammatory syndrome improves, the joint pain and swelling (DAS 28-2.1, VAS-22, CRP-6.8, ESR-29, TJC-3, SJC-2) partially subside, but severe dyspnea and respiratory infections occur, repeated shortly afterwards and are put back on antibiotic treatment (levofloxacin, 750mg IV daily) and local corticosteroids, albuterol nebulizer treatment [22].

The patient is re-evaluated in the lungs and it is found (CT, respiratory functional explorations) that, 6 months after the initiation of biological therapy, she shows a progressive deterioration of respiratory function, initially considered as extra-articular rheumatoid lung disease. It is decided to discontinue adalimumab and leflunomide because patients using tumor necrosis factor (TNF) antagonists are at increased risk of severe infections. Altered lung function increases the risk of infections. Continue treatment with cyclophosphamide 50mg 4tb/day, plaquenil (hydroxychloroquine) 2x1 tb/day, medrol 16mg/day, colchicine 1mg 1tb/day. In the meantime, the general condition of the patient, from the point of view of rheumatic disease, is deteriorating: she presents repeated hemorrhagic cystitis secondary to cyclophosphamide treatment, weight loss of about 5kg in 4 weeks, hair loss, marked polyarthralgia's with inflammatory character, swellings of small joints bilaterally in her hands, her knees, her elbows (TJC: 12, SJC: 14, ESR: 85, DAS 28: 6.1). The patient's quality of life decreased dramatically. Under these circumstances it is decided to continue the patient's biological treatment with rituximab (chimeric monoclonal antibody targeted against B-lymphocyte antigen CD20) which, in combination with hydroxychloroquine, is indicated for the treatment of adult patients with active, severe RA who have had an inadequate response or intolerance to other DMARDs including one or more tumor necrosis factor (TNF) inhibitor treatments. The dose of rituximab was 1000mg given as an intravenous infusion followed by a second intravenous infusion of 1000mg after two weeks. At 24 weeks after the previous treatment series, the need for subsequent series should be assessed. The patient was also biologically investigated: ESR, CRP values greatly elevated, antinuclear antibodies (ANA) negative, human leukocyte antigen (HLA B27) negative, antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin antibodies (to exclude associated micro thrombotic processes and autoimmune vasculitis), myositis profile (to exclude myositis/antisynthetase syndrome), all negative, and serum vascular endothelial growth factor D (VEGF-D) was >800pg/mL. Under these conditions, corroborating the current

imaging appearance of the chest CT scan-pulmonary fibrosis with *matte glass* appearance-, the result of the histopathology examination, the respiratory symptoms, the patient's age, it is concluded that the degradation of the respiratory function is due to LAM and not to rheumatoid lung disease. Treatment with sirolimus 2mg/day is initiated, with monitoring of its blood level [23]. The patient's general condition is deteriorating, with multiple swellings and joint pain (TJC: 14, SJC: 10), and her respiratory function is further deteriorating. Acute respiratory failure, moderate pulmonary hypertension, 1st degree mitral insufficiency, and 1st degree tricuspid insufficiency, occur. The patient shows severe mixed dysfunction throughout the bronchial tree, more pronounced in the periphery, forced vital capacity (FEV1) <1l, reduction of maximal ventilation by 80%, continuous oxygen therapy, ESR, CRP values greatly increased (CRP: 5.88 (normal value: CRP 0.5-1 mg/L), ESR: 110 (normal value: ESR 2-15 mm/h)). Due to severe oxygen-dependent respiratory failure, the patient is evaluated, proposed for lung transplantation and put on the waiting list. The patient dies 3 years after the onset of RA symptoms and about 10 months after the onset of respiratory symptoms, awaiting lung transplantation. Table 1 summarizes the present symptoms, the number of affected joints, the evaluation of the disease activity (DAS 28) and the joint pain perceived by the patient (VAS).

Histopathological images confirm the diagnosis (Figure 2). Table 2 includes the therapeutic management adopted according to the clinical and paraclinical response.

Discussion

In patients with RA, interstitial lung damage occurs in approximately 20-60% of individuals, and imaging progression of the disease occurs in approximately 35-45% of them. Lung damage in arthritis affects the morbidity and mortality of patients, especially since there is a lack of treatment to influence lung changes. The biological therapy administered influences to a certain extent. Treatment directions target cellular immune dysfunction [9,10]. Treatment of high-dose corticosteroids in combination with specific antibiotic therapy should be initiated promptly [11]. Resveratrol treatment significantly improved lung disease and prevented the production of proinflammatory cytokines [12].

Differences in the respiratory system between women and men begin in the uterus. Biological sex plays a key role in the development of the fetus, the different anatomy of the airways, thus leading to differences in disease risk, as well as clinical manifestations, morbidity and mortality [13].

Considering the age of onset, the high values of acute phase reactants, and RF, respectively, anti CCP antibodies, the presence of erosion, since the diagnosis of the disease it was considered that the patient has a potentially unfavorable evolution of the disease [24]. The appearance of respiratory symptoms, at the beginning, has been attributed to the extra-articular, systemic involvement of RA. RA treatment was adapted to the respiratory fibrosis disease by discontinuing methotrexate treatment and starting biological therapy with adalimumab and cortisone [25]. Favorable joint and unfavorable respiratory evolution (fever, hypoxia and respiratory distress, frequent respiratory infections, fatigue and weight loss over the past year) raised suspicion of another cause of pulmonary distress [22].

In 2016, the American Thoracic Society and the Japanese Respiratory Society published clinical practice guidelines that state a definitive diagnosis of LAM can be established if the patient has a compatible clinical history: young to middle-aged, female, with worsening dyspnea and/or pneumothorax/chylothorax in the absence of features suggestive of other cystic lung diseases, has a characteristic high-resolution CT (HRCT) of the chest, has one or more of the following features: tuberous sclerosis, renal angiomyolipoma, elevated serum vascular endothelial growth factor D (VEGF-D) of >800pg/mL, thoracic or abdominal chylous effusion, lymphatic malformations, demonstration of LAM cells or LAM cell clusters on cytological examination of effusions or lymph nodes, or histopathological confirmation of LAM by lung biopsy or biopsy of retro peritoneal or pelvic masses [8].

The patient presents the elements of a positive diagnosis for LAM [23]. Lymphangioleiomyomatosis causes damage to lung tissue that results in such problems as the inability to fully oxygenate blood, the fluid in the lungs, and the collapsed lung. Although there is no cure, treatment includes drugs that can improve lung function, oxygen therapy and lung transplantation for those with severe disease [7].

The prevalence of lymphangioleiomyomatosis is probably underestimated based on its clinical latency and the absence of specific laboratory tests. With the utilization of international LAM data registries, the "classical" picture of the disorder appears to be evolving as a larger number of patients are evaluated. An increased awareness of LAM and its common clinical presentation may advance the development of new therapeutic strategies and reduce the number of mistakenly diagnosed patients [26]. In Japan, the prevalence rate of LAM is approximately 1.2-2.5 per million individuals [27].

Sporadically, LAM is due to somatic mutations associated with the tuberous sclerosis-causing genes, tuberous sclerosis proteins (TSC) 1 and 2, also known as hamartin (TSC1) and tuberin (TSC2), form a protein-complex, which encode the key signaling proteins hamartin and tuberin. The mutations result in excessive proliferation of LAM cells. In TSC, germ-line mutations are found. Considerable progress for comprehension of the disease has been made when mutations of the tuberous sclerosis genes TSC1 and TSC2 were discovered in LAM cells. Therapeutic consequences of these studies are important, leading to clinical trials with sirolimus for LAM [27].

Bronchodilators are part of the supportive measures in LAM patients with dyspnea and sometimes are the only treatment LAM patients require. Depending on the disease severity, some patients are started on sirolimus or everolimus, immune-modulating therapies that target the mammalian rapamycin (mTOR) signaling pathway by inhibiting the mTOR complex, which provides a median transplant-free survival of approximately 29 years from the onset of symptoms and 10-year transplant-free survival of 86% [28,29]. It should be noted that these therapeutic options are only stabilizing and not curative, and lung transplantation remains the last treatment option for patients with advanced LAM for improvement in their quality of life [29]. Rapamune (sirolimus) was designated as an orphan medicinal product on 14 July 2016 (EU/3/16/1704) and received marketing authorization on 27 November 2015. Sirolimus inhibits T-cell

activation induced by most stimuli, blocking both calcium-dependent and calcium-independent intracellular signal transduction. Studies show that its effects are mediated by a different mechanism than cyclosporine, tacrolimus and other immunosuppressive agents [30]. Experimental studies suggest that sirolimus binds to the cytosolic-specific protein, the binding protein for the immunosuppressive drug (FKPB-12), and the FKPB 12-sirolimus complex inhibits activation of mammalian target factor of rapamycin (mTOR), a critical kinase for cell cycle progression. Inhibition of mTOR leads to blockade of specific signal transduction pathways. The end result is inhibition of lymphocyte activation, leading to immunosuppression. LAM involves infiltration of lung tissue with smooth muscle-like cells harbouring inactivating mutations of the tuberous sclerosis complex (TSC) gene (LAM cells) [25]. Loss of TSC gene function activates the mTOR signaling pathway, leading to cell proliferation and release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and thus LAM cell proliferation [26].

A randomized, double-blind, multi-center trial has confirmed the efficacy of sirolimus in stabilizing lung function, improving functional performance and quality of life, and reducing lymphatic manifestations in patients with LAM [26]. Accordingly, recent guidelines issued by the American Thoracic Society and the Japanese Respiratory Society recommend sirolimus treatment for patients with LAM and reduced lung function. Sirolimus represents an important drug for LAM that should be proposed to patients with a rapid alteration of lung function or with a significant clinical impairment, after individual evaluation of the risk/benefit ratio [14]. Tolerance and safety concerns are serious limits to the long-term treatment of patients with sirolimus [22].

Over the past 20 years, lung transplantation has come to be used worldwide in a large number of eligible patients with severe lung tissue disorders ranging from pulmonary fibrosis to autoimmune connective tissue diseases. Pulmonary involvement is common in connective tissue disease (CTD), and respiratory failure is a major cause of morbidity and mortality in CTD - related interstitial lung disease (CTD - ILD) [31]. Lung transplantation is very important for these patients. A study that evaluated survival, outcomes, and management of these patients after transplantation was made in Korea. The study evaluated the outcomes for CTD - ILD compared to those for idiopathic pulmonary fibrosis (IPF) after lung transplantation. The conclusion was that the patients with CTD - ILD and those with IPF who underwent lung transplantation had similar survival rates [32].

In Romania, lung transplantation is a minor option in the treatment of patients with severe lung disease. In 2019, 3 cardiopulmonary transplants were performed; and in 2018, 4 cardiopulmonary transplants were performed, according to the National Transplant Agency; and in 2015, 2016, and 2017 no cardiopulmonary transplants were performed at all. So, in the last 5 years, in relation to a population of 20 million inhabitants, 7 cardiopulmonary transplants have been performed in Romania, of which 3 patients have died, and 8 patients are currently waiting, as the first successful solid transplant in humans in Romania was performed in February 1980 (kidney from a living donor) [33].

Other issues are also under discussion [34]. Despite the progress made by modern medicine, there are still patients in intensive care units with severe respiratory failure who need a lung transplant to survive. Patients with respiratory failure following active autoimmune disease raise issues not only of therapeutic conduct but also of ethics [31].

If the autoimmune disease, in our case RA, is active, can the patient be eligible for a lung transplant? Provided there is a major issue of availability of a lung, the tolerability of the transplanted organ under optimal conditions (no autoimmune disease), and the high costs of post-transplant patient care and monitoring [35].

To be considered a candidate for transplantation, should the RA patient be in clinical and biological remission? For how long before transplantation? Can she continue DMARDs therapy? What about biological therapy? Who determines the eligibility criteria of a patient with autoimmune disease for transplantation?

The selection process may vary by center, there are no absolute guidelines, and the decision to transplant depends upon the centre's practices, waiting list and other factors [36].

International consensus guidelines on lung transplantation state that systemic disease quiescence should be achieved, including any evidence of active vasculitis, before transplant, but provides no further guidance on timeline or definition of quiescence [29].

Conclusion

At this time, there is insufficient data to inform specific guidelines for lung transplant for the patients with rheumatic diseases. These experiences highlight a critical need for further development of guidelines and research in this area, particularly because the prevalence of autoimmune disease continues to rise. It was previously believed that there was a relentless and severe deterioration after the onset of LAM. The average survival time was reported to be 4-8 years in 1971 [5]. More recent studies estimate that survival is closer to 10 years and there are even reports of apparent spontaneous resolution. The association with RA worsened the vital prognosis and was a relative contraindication for lung transplantation. Adalimumab treatment was effective against joint and biological inflammatory syndrome, induced RA remission, but did not influence pulmonary symptoms. The evolution of lymphangioleiomyomatosis and the destruction of the lung tissue were fulminant, causing severe respiratory and multi-organ failure leading to the death of the patient, soon after she was diagnosed. The patient died about 3 years after being diagnosed with rheumatoid arthritis and about 10 months after the first diagnosis of lung disease.

All authors contributed equally to the first author to this paper.

References

1. Behl T, Kaur I, Sehgal A, Zengin G, Brisc C, Brisc MC, et al. The Lipid Paradox as Metabolic Checkpoint and Its Therapeutic Significance in Ameliorating the Associated Cardiovascular Risks in RA Patients. Int J Mol Sci. 2020; 21.
2. Pascalău N, Cioară F. Aspecte generale si particulare în cele mai frecvente reumatisme inflamatorii. Oradea: Editura Universitatii din Oradea. 2015.
3. Hua C, Buttgereit F, Combe B. Glucocorticoids in RA: current status and future studies. RMD Open. 2020; 6.
4. Teaha D, Pascalau N, Marcu F, Lazar L. Comparative Study on the Extent of Damage to Life Quality in RA Patients with Different Therapeutic Strategies. Revista de Chimie. 2019; 70: 2908-2911.

5. Harari S, Spagnolo P, Cocconcelli E, Luisi F, Cottin V. Recent advances in the pathobiology and clinical management of lymphangioleiomyomatosis. Curr Opin Pulm Med. 2018; 24: 469-476.

6. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 RA classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010; 62: 2569-2581.

7. Lamattina AM, Taveira-Dasilva A, Goldberg HJ, Bagwe S, Cui Y, Rosas IO, et al. Circulating Biomarkers from the Phase 1 Trial of Sirolimus and Autophagy Inhibition for Patients With Lymphangioleiomyomatosis. Chest. 2018; 154: 1070-1082.

8. Taillé C, Borie R, Crestani B. Current management of lymphangioleiomyomatosis. Curr Opin Pulm Med. 2011; 17: 374-378.

9. Yoo H, Hino T, Han J, RFanks TJ, Im Y, Hatabu H, et al. Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality (ILA): Evolving concept of CT findings, pathology and management. Eur J Radiol Open. 2021; 8: 100311.

10. Nannini C, Ryu JH, Matteson EL. Lung disease in RA. Curr Opin Rheumatol. 2008; 20: 340-346.

11. Yamakawa H, Ogura T, Kameda H, Kishaba T, Iwasawa T, Takemura T, et al. Decision-Making Strategy for the Treatment of RA-Associated Interstitial Lung Disease (RA-ILD). J Clin Med. 2021; 10.

12. Yang G, Lyu L, Wang X, Bao L, Lyu B, Lin Z. Systemic treatment with resveratrol alleviates adjuvant arthritis-interstitial lung disease in rats via modulation of JAK/STAT/RANKL signaling pathway. Pulm Pharmacol Ther. 2019; 56: 69-74.

13. Criner RN, Al-Abcha A, Lambert AA, Han MK. Lung Diseases Unique to Women. Clin Chest Med. 2021; 42: 507-516.

14. Sathirareuangchai S, Shimizu D, Vierkoetter KR. Pulmonary Lymphangioleiomyomatosis: A Case Report and Literature Review. Hawaii J Health Soc Welf. 2020; 79: 224-229.

15. Wang Q, Luo M, Xiang B, Chen S, Ji Y. The efficacy and safety of pharmacological treatments for lymphangioleiomyomatosis. Respir Res. 2020; 21: 55.

16. Ansótegui Barrera E, Mancheño RFanch N, Peñalver Cuesta JC, Vera-Sempere F, Padilla Alarcón J. Lung transplantation in sporadic lymphangioleiomyomatosis: study of 7 cases. Med Clin (Barc). 2013; 141: 349-352.

17. Futami S, Arai T, Hirose M, Sugimoto C, Ikegami N, Akira M, et al. Comorbid connective tissue diseases and autoantibodies in lymphangioleiomyomatosis: a retrospective cohort study. Orphanet J Rare Dis. 2018; 13: 182.

18. Castro M, Shepherd CW, Gomez MR, Lie JT, Ryu JH. Pulmonary tuberous sclerosis. Chest. 1995; 107: 189-195.

19. Dwyer JM, Hickie JB, Garvan J. Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. Q J Med. 1971; 40: 115-125.

20. Hancock E, Osborne J. Lymphangioleiomyomatosis: a review of the literature. Respir Med. 2002; 96: 1-6.

21. Sirbu E, Buleu F, Tudor A, Dragan S. Vitamin D and disease activity in RA patients: a retrospective study in a Romanian cohort. Acta Biochimica Polonica. 2020; 67.

22. Rhee JA, Adial A, Gumpeni R, Iftikhar A. Lymphangioleiomyomatosis: A Case Report and Review of Literature. Cureus. 2019; 11: e3938.

23. Lymphangioleiomyomatosis (LAM).

24. Teaha D, Pascalau N, Lazar L. Comparative study of the clinical response of patients to different treatment regimens in RA. Farmacia. 2019; 67.

25. Raport de evaluare a tehnologiilor medicale.

26. Hohman DW, Noghrehkar D, Ratnayake S. Lymphangioleiomyomatosis: A review. Eur J Intern Med. 2008; 19: 319-324.

27. Hayashida M, Seyama K, Inoue Y, Fujimoto K, Kubo K, Respiratory Failure Research Group of the Japanese Ministry of Health Lb, and Welfare. The epidemiology of lymphangioleiomyomatosis in Japan: a nationwide cross-sectional study of presenting features and prognostic factors. Respirology. 2007; 12: 523-530.

28. Oprescu N, McCormack FX, Byrnes S, Kinder BW. Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: a population-based registry. Lung. 2013; 191: 35-42.

29. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015; 34: 1-15.

30. McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management. Am J Respir Crit Care Med. 2016; 194: 748-761.

31. Committee on Hospital Care ScoS, and Section on Critical Care. Policy statement--pediatric organ donation and transplantation. Pediatrics. 2010; 125: 822-828.

32. Park JE, Kim SY, Song JH, Kim YS, Chang J, Lee JG, et al. Comparison of short-term outcomes for connective tissue disease-related interstitial lung disease and idiopathic pulmonary fibrosis after lung transplantation. J Thorac Dis. 2018; 10: 1538-1547.

33. Statistical report transplant, transplant - donation. 2018.

34. Pascalau N, Cioara F, Rosca E, et al. Atypical case of Sjogren's syndrome with psychiatric and peripheral neurological disorder. Romanian Journal of Morphology and Embryology. 2016; 57.

35. Lapin B, Rammel J, Ramirez A. Ethics Forum: What to do When Autoimmune Patient Needs a Transplant? 2018.

36. Verleden GM, Dupont L, Yserbyt J, Schaevers V, Van Raemdonck D, Neyrinck A, et al. Recipient selection process and listing for lung transplantation. J Thorac Dis. 2017; 9: 3372-3384.