sciendo
Internal Medicine 2018 vol. XV No. 5 - www.srmi.ro
10.2478/inmed-2018-0040

PULMONARY ARTERIAL HYPERTENSION IN A FEMALE PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Cristiana Drăgănescu[1], Tudor Constantinescu[2], Oana Enache[1], Marina Speriatu[1], Raida Oneață[1], Alexandra Radu[1], Mihai Bojincă[1], Carina Mihai[1], Ana Maria Gheorghiu[1]
[1]University of Medicine and Pharmacy Carol Davila, Cantacuzino Hospital, Department of Internal Medicine and Rheumatology, Bucharest
[2]Marius Nasta" National Institute of Pneumology, Bucharest
Corresponding author:
Ana Maria Gheorghiu
Internal Medicine and Rheumatology Department, Cantacuzino Hospital
Ion Movila 5-7, 020475 Bucharest, Romania
tel +40 21 210 7113; fax +40 21 210 3410
Email: ana.gherghe@gmail.com

Abstract

Introduction. *Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown origin, characterized by multisystemic involvement and a potentially severe evolution. Pulmonary arterial hypertension (PAH) is a rare complication of SLE, with low 5-year survival.*

Case presentation. *We are presenting the case of a female patient, aged 56 years old, diagnosed in 1992 with SLE with cutaneous manifestations (butterfly-shaped erythematous rash), joint manifestations (polyarthritis), serositis manifestations (massive pleuropericarditis), and immunological manifestations (positive anti-dsDNA antibodies, decreased C3), ignored therapeutically for a long time. In 2010 she complained of dyspnea on medium exertion and leg edemas, with marked increase of PAPs by echocardiography. She was diagnosed with severe PAH (confirmed by right heart catheterization) and in the "Marius Nasta" National Institute of Pneumology she started a treatment with an endothelin receptor antagonist (Bosentan) in combination with a prostacyclin receptor agonist (Selexipag). Since 2013 the patient is on oral anticoagulant treatment for permanent atrial fibrillation.*

In 2015 she was referred back to out clinic as she complained of recurrent episodes of massive ascites with evacuatory paracenteses in amounts of about 6-9L per paracentesis. After excluding other causes, ascites was considered to be secondary to the SLE, and a treatment was initiated with Hydroxychloroquine (HCQ) and pulse therapy with Methylprednisolone, on which the remission of the ascites was achieved during the following months. Currently, the SLE is well controlled without recurrence of ascites on treatment with HCQ and gradual decrease until stopping of cortisone doses, and the PAH is stable.

Internal Medicine

Clinical cases

Conclusion. *PAH is a rare complication of the SLE, with a complex pathophysiological immune mechanism, for which - together with the specific vasodilator treatment - the increase of immune suppression is recommended.*

Key words: *systemic lupus erythematosus, pulmonary arterial hypertension, ascites, atrial fibrillation, serositis.*

Rezumat

Introducere. *Lupusul eritematos sistemic (LES) este o boală autoimună cronică de etiologie necunoscută, caracterizată prin afectare multisistemică si evoluție potențial severă. Hipertensiunea arterială pulmonară (HTAP) este o complicație rară a LES, cu supraviețuire la 5 ani scăzută.*

Prezentarea cazului.

Se prezintă cazul unei paciente în vârstă de 56 ani, diagnosticată în 1992 cu LES cu manifestări cutanate (eritem în vespertilio), articulare (poliartrită), serozitice (pleuro-pericardită masivă) și imunologice (Ac anti-ADNdc pozitivi, C3 scăzut), ignorată terapeutic o perioadă îndelungată.

În 2010 acuză dispnee la eforturi medii și edeme gambiere, cu creșterea marcată a PAPs la ecocord. Este diagnosticată cu HTAP severă (confirmată prin cateterism cardiac drept) și se începe la Institutul Nasta tratament cu un blocant de receptor de endotelină (Bosentan) în combinație cu un agonist de prostaciclină (Selexipag). Din 2013, pacienta urmează tratament anticoagulant oral pentru fibrilație atrială permanentă. În 2015 este reîndrumată către clinica noastră, acuzând episoade recurente de ascită masivă cu puncții evacuatorii în cantități de cca. 6-9 l per puncție. După excluderea altor cauze de ascită, s-a considerat ca fiind secundară LES și s-a inițiat tratament cu Hidroxicloroquina (HHQ) și pulsterapie cu Metilprednisolon, sub care s-a obținut în următoarele luni remiterea ascitei. În prezent, control bun al LES fără recurența ascitei sub tratament cu HHQ și scăderea treptată până la oprire a dozelor de cortizon, iar HTAP este staționară.

Concluzie.

HTAP este o complicație rară a LES, la care se consideră că există un mecanism patofiziologic imun, pentru care se recomandă întărirea imunosupresiei, pe lângă tratamentul vasodilatator specific.

Cuvinte cheie: *lupus eritematos sistemic, hipertensiune arterială pulmonară, ascită, fibrilație atrială, serozită.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, with multisystemic involvement and a potentially severe evolution. Pulmonary arterial hypertension (PAH) is a rare complication of SLE, with a prevalence between 0.5% and 17.5%, and with low 5-year survival.

We are presenting the case of a female patient known to the clinic with SLE since 1992, with cutaneous, joint, serositis, and immune manifestations, clinically and therapeutically ignored for a long time, but with auto-administration of prednisone in medium dose permanently between 1992-2007. The patient gave her consent for publishing the data.

Reasons for hospital admission

In April 2015 the patient was admitted to our clinic referred from the "Marius Nasta" National Institute of Pneumology for the reassessment of the SLE, complaining of important increase in volume of the abdomen and leg edemas with onset in the last months prior to the hospital admission.

History of the disease

The onset of the SLE was in 1992, at the age of 30 years, and in the same year she was diagnosed in our Clinic with SLE with cutaneous manifestations (butterfly-shaped erythematous rash) and joint manifestations (polyarthritis), A treatment was initiated with Hydroxychloroquine 400mg/day (stopped of her own will after a year), in association with Prednisone with gradual decrease of the doses from 50 mg/day to 10 mg/day in 2005. We are mentioning the fact that the patient did not come any more to the medical visits until 2004.

In 2004 she had an episode of hemoptysis, cough, a stabbing pain in the chest on the right, and dyspnea, that raised the suspicion of a pulmonary thromboembolism (PTE), not investigated. During the same hospitalization a right pleurisy was objectified, which worsened progressively, and in 2007 she developed a massive pleuropericarditis. A mini-pulse therapy with Methylprednisolone 250mg/day for 2 days was applied, without any improvement of the symptomatology, and we initiated a treatment with Azathioprine for 6 months, stopped by the patient due to the gastrointestinal adverse reactions (vomiting).

Subsequently she received Methotrexate, but it was also discontinued after a year from the patient's own initiative. As the serositis persisted, a mini-thoracotomy on the left with pleuropericardial window and pericardial biopsy was performed, and it identified an inflammatory infiltrate. 2 month after performing the pleuropericardial window, the serositis reoccurred and after a short while the patient developed a cardiac tamponade with draining of 1.6 L of pleuropericardial fluid.

In 2010 she was admitted to the "Marius Nasta" National Institute of Pneumology with dyspnea on medium exertion and leg edemas (Figure 1, Figure 2), with increased PAPs at echocardiography, that raised the suspicion of pulmonary arterial hypertension (PAH). It was decided to perform a right heart catheterization, and it identified a pulmonary artery pressure (PAP) of 69 mmHg, confirming the suspicion of PAH. The patient was included in the PAH National Program; a treatment with Bosentan 250mg/day was initiated, and the treatment with Hydroxychloroquine 400mg/day was restarted.

Internal Medicine

Clinical cases

One year later, in April 2011, she was included in a study with a prostacyclin receptor agonist (Selexipag), most probably receiving placebo until July 2014, when she entered in the open-label extension of the study, and she received active medication.
In October 2013 she was diagnosed with permanent atrial fibrillation for which she received treatment with Digoxin and oral anticoagulant.
In March 2014, following an episode of melena with mild anemia she was investigated with upper digestive endoscopy and colonoscopy, without evidence of pathologic items; therefore, so a digestive hemorrhage on the small intestine due to Acenocoumarol overdose was suspected (INR=11).
Since April 2014 she started having ascites in high amount, accompanied by leg edemas, for which she was referred to our clinic.

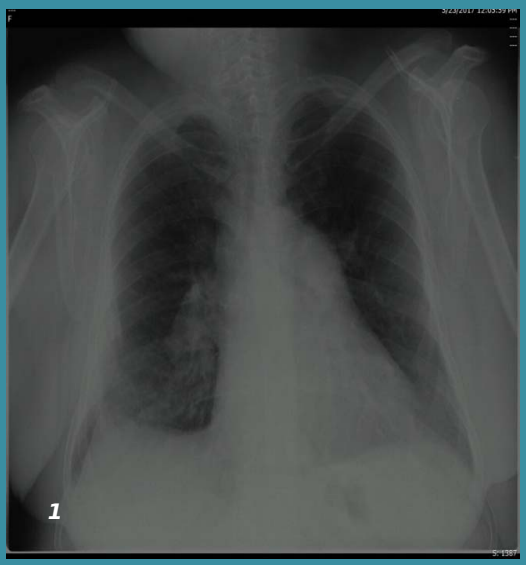
Clinical examination

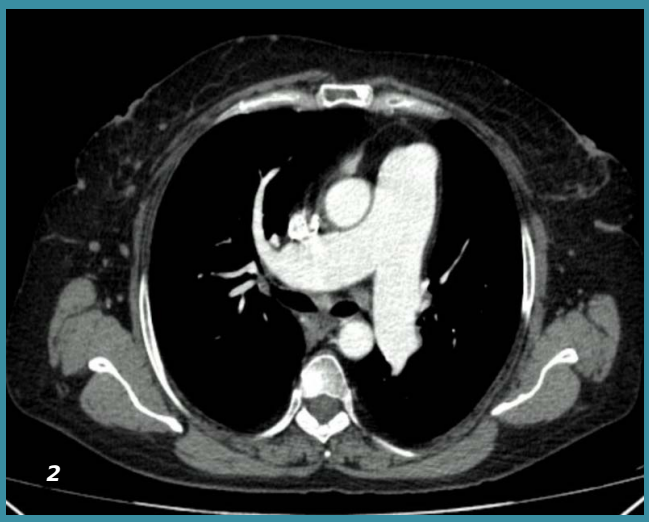
At the time of admission to our Clinic, the patient had no fever, she had skin changes specific to the SLE (butterfly-shaped erythematous rash), the abdomen was markedly increased in volume due to fluid overload, and she had central cyanosis. She was in atrial fibrillation and the respiratory system was well balanced.

Investigations

The laboratory tests showed decreased serum complement (0.75g/L), positive antinuclear antibodies with anti-dsDNA antibodies in high titers, and positive anticardiolipin antibodies, otherwise within normal limits. Abdominal echography and CT of the chest and abdomen confirmed the presence of ascites fluid in high amount; additionally a globally enlarged liver (RL=145mm) was described, without other pathological items (Figure 3). At the first paracentesis 5 liters ascites fluid were evacuated, having the characteristics of an exudate (proteins in the fluid ˃3g/dL), without cell atypias. The echocardiography showed right cavities markedly dilated, severe tricuspid regurgitation, PAPs=110 mmHg, no fluid in the pleural or pericardial cavity. NT-proBNP had a value of 1500 pg/mL.

Differential diagnoses discussed at this time point include: severe right heart failure secondary to PAH, complicated with cardiac cirrhosis, acute episode of SLE, infections (e.g. tuberculosis), neoplasms, liver cirrhosis.
The hypothesis of a lupus nephritis was infirmed by the nephrology assessment by a nonsignificant 24 h proteinuria. The gastroenterology assessment eliminated a liver cirrhosis from the possible etiologies of





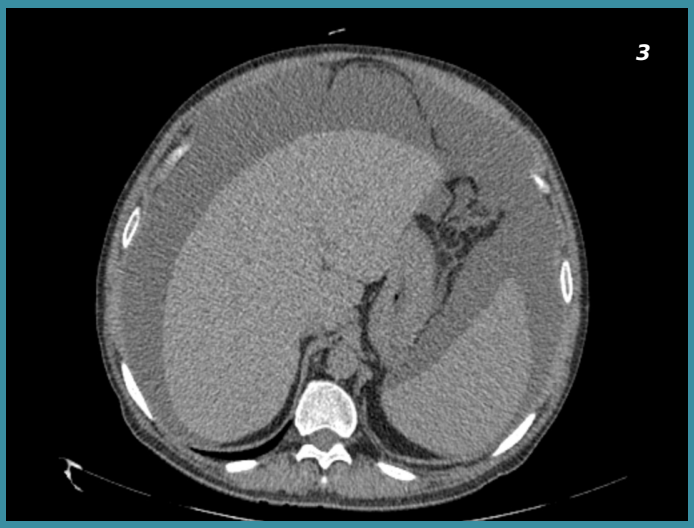


Figure 1. *Chest radiograph: cardiomegaly*

Figure 2. *Computed tomography showing the dilation of the pulmonary artery trunk*

Figure 3. *Computed tomography showing ascites in high amount*

Figure 4. *Butterfly-shaped erythematous rash (2018)*

the ascites, and a TB cause was infirmed in the "Marius Nasta" National Institute of Pneumology.

Although the right heart failure could not be excluded as an etiology of the ascites, hypothesis also supported by the serum-ascites albumin gradient >1.1, it was considered that there are also undoubtable evidence of SLE activity, such as decreased serum complement or high titer of anti-dsDNA antibodies. Additionally, even PAH is considered to have an immune mechanism of occurrence in SLE.

Treatment

Treatment with Methylprednisolone in pulse therapy was initiated (dose 250mg/pulse, 6 months), with oral corticosteroid therapy in medium dose between the pulses, associated to Hydroxychloroquine 400mg/day, on which she had a slowly favorable evolution. Additionally the chronic treatment was continued with Selexipag (4tbs/day), Macitentan (10mg, 1tb/day), Digoxin (0.25mg 1tb/day), Diurex (50mg, 2tbs/day).

The episodes of massive ascites with evacuatory paracenteses in high amounts (6-9L per paracentesis) decreased gradually until they disappeared in the next year. The serum complement level returned to normal, and NT-proBNP decreased with over 30% vs the time of therapy initiation. The increase of immune suppression was discussed (e.g. treatment with Cyclophosphamide) but due to the favorable clinical and paraclinical evolution it was not considered necessary.

Long-term evolution

At the last assessment in our Clinic in March 2018 the patient was without ascites since over 2 years, and the PAH was stable (Figure 4). The chest CT performed in January 2018 showed cardiomegaly, without pericardial or pleural effusion and without images of thrombosis in the main pulmonary arteries or in their lobar branches.

The corticosteroid therapy was progressively decreased until stopping in April 2016. She had repeated episodes of anemia or melena secondary to Acenocoumarol overdose, therefore Acenocoumarol was replaced with Apixaban as the latter had a lower bleeding risk.

Discussion

SLE is a rare chronic autoimmune disease, with multisystemic manifestations. PAH is a potentially fatal complication of SLE, having various prevalences - between 0.5% and 17.5% - depending on the methods used for the diagnosis (echocardiography - with low accuracy or right heart catheterization - the

golden standard for the diagnosis). The mechanism of the occurrence of PAH in SLE is considered to be immune, subsequently leading to the imbalances of vasoactive mediators[1].

Some manifestations and immunological changes were identified as predictors of PAH in observational studies. In an analysis on a Chinese cohort, pleurisy was an independent predictive factor of PAH in lupus[2]. The antibodies specific to the antiphospholipid syndrome, especially anticardiolipin antibodies and lupus anticoagulant, were associated with a high risk of PAH. In our case both risk factors were present.

An unexpected item for this case was the occurrence of the acute episode pf SLE manifested by PAH and serositis at more than 20 years after the onset of the SLE, as in most cases the disease is more active in premenopausal women.

The therapeutic options cited in literature are represented on one hand by the increase of immune suppression (Cyclophosphamide and corticosteroid therapy), and on the other hand by the vasoactive treatment specific for PAH[3]. The treatment should be promptly initiated in order to increase survival. In our patient, the evolution on cortisone treatment in pulse therapy and Hydroxychloroquine was spectacular, with the disappearance of the massive ascites and the decrease with over 30% of the NT-proBNP, a prognostic marker in PAH[4]. The introduction of Cyclophosphamide was discussed, but due to the favorable evolution it was not considered necessary; additionally the risk of adverse reactions was high due to the age of the patient and the co-morbidities.

Conclusions

A case of SLE with multiple complications, with an acute episode of the disease with massive ascites and severe secondary pulmonary arterial hypertension at more than 20 years after the diagnosis, which required the increase of the immuno-suppressive therapy.

References

1. *Kofi A. Mensah, Rajwardhan Yadav, Terence K. Trow - "Lupus-Associated Pulmonary Arterial Hypertension: Variable Course and Importance of Prompt Recognition," Case Reports in Medicine, vol. 2015, Article ID 328435, 5 pages, 2015*
2. *Tselios K, Gladman DD, Urowitz MB - Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. Open Access Rheumatology : Research and Reviews. 2017;9:1-9. doi:10.2147/OARRR.S123549.*
3. *Atiya Dhala - "Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus: Current Status and Future Direction," Clinical and Developmental Immunology, vol. 2012, Article ID 854941, 12 pages, 2012*
4. *Leuchte HH, El Nounou M, Tuerpe JC, Hartmann B, Baumgartner RA, et al. (2007) N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 131: 402-409*