

BIŃCZYK, Wiktoria, SIUDEK, Bartosz, DRÓZDŹ, Olgierd, BRZOZOWSKA, Patrycja, NOWIŃSKA, Bianka, LISSAK, Karina and SOKOLIK, Renata. A Severe case of antiphospholipid syndrome coexisting with systemic lupus erythematosus with major cardiovascular complications: a case report. Quality in Sport. 2024;18:52945. eISSN 2450-3118.

<https://dx.doi.org/10.12775/QS.2024.18.52945>

<https://apcz.umk.pl/QS/article/view/52945>

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

© The Authors 2024;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.07.2024. Revised: 22.07.2024. Accepted: 17.07.2024. Published: 25.07.2024.

TITLE: A severe case of antiphospholipid syndrome coexisting with systemic lupus erythematosus with major cardiovascular complications: a case report.

AUTHORS:

Wiktoria Bińczyk, Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

wiktoria.binczyk98@gmail.com

<https://orcid.org/0009-0004-6600-9259>

Bartosz Siudek, A. Falkiewicz Specialist Hospital, Wrocław, Warszawska 2, 52-114 Wrocław, Poland

bartosz.siudek98@gmail.com

<https://orcid.org/0009-0002-4053-9724>

Olgierd Drózdź, Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

olgierd.drozdz@gmail.com

<https://orcid.org/0009-0006-6134-9101>

Patrycja Brzozowska, Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

patrycja.brzozowska@hotmail.com

<https://orcid.org/0000-0002-6630-4539>

Bianka Nowińska, 4th Military Clinical Hospital, Weigla 5, 53-114 Wrocław, Poland

bianovinska@gmail.com

<https://orcid.org/0000-0003-2335-3207>

Karina Lissak, Lower Silesian Oncology Center, Hirszfelda Square 12 53-413 Wrocław, Poland

karina.lis2323@gmail.com

<https://orcid.org/0009-0000-9084-4060>

Renata Sokolik, Jan Mikulicz-Radecki University Clinical Hospital, Borowska 213, 50-556 Wrocław, Poland

renata.sokolik@umw.edu.pl

<https://orcid.org/0000-0002-9866-2066>

ABSTRACT

Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are autoimmune diseases that frequently coexist, complicating clinical management due to the compounded risks of systemic inflammation and thromboembolism. We present a case of a 52-year-old female with SLE and APS, initially diagnosed after a pulmonary embolism in 2015. Her medical history includes recurrent anemia, hyperlipidemia, hypertension, and two myocardial infarctions treated with angioplasty and stenting. Despite treatment with hydroxychloroquine, methylprednisolone, methotrexate and apixaban (later switched to warfarin), the patient experienced severe disease flare-ups and cardiovascular complications, prompting consideration for biologic therapy with anifrolumab. This case study illustrates the difficulties associated with the management of concurrent SLE and APS. It is clear that early diagnosis, vigilant monitoring, and aggressive management of both autoimmune and cardiovascular risks are essential to improve patient outcomes.

KEYWORDS: antiphospholipid syndrome, systemic lupus erythematosus, autoimmune disease, cardiovascular events

LEARNING POINTS

- 1) The coexistence of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) presents significant challenges in clinical management due to the overlapping and compounded risks of systemic inflammation and thromboembolism. Early diagnosis, vigilant monitoring, and a comprehensive, multidisciplinary approach are essential for improving patient outcomes.
- 2) Effective anticoagulation is critical in managing APS to prevent thromboembolic events. This case study highlights the preference for warfarin over direct oral anticoagulants (DOACs) in APS patients, as recommended by current guidelines, to achieve optimal anticoagulation and reduce the risk of cardiovascular complications.
- 3) For patients with severe or refractory SLE and APS who do not respond adequately to standard immunosuppressive therapies, biologic treatments such as anifrolumab may offer significant benefits. These therapies can assist in the management of autoimmune symptoms and the reduction of the frequency and severity of disease flare-ups, particularly in complex cases with significant comorbidities.

INTRODUCTION

Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are autoimmune diseases associated with the presence of antibodies attacking the body's own cells and tissues, predominantly affecting women. In SLE, antibodies target nuclear and cytoplasmic antigens, leading to a systemic inflammatory response and tissue damage. Although the exact etiology of SLE is not yet fully understood, it is believed that the development of autoimmune processes involves genetic predispositions, environmental factors such as UV radiation and infections, and hormones. The pathogenesis of this disease is significantly influenced by a complex dysfunction of the immune system, including loss of tolerance to self-antigens, abnormal activation of B and T lymphocytes, and deposition of immune complexes in various tissues, resulting in an inflammatory response. Complications can affect multiple systems and organs, including the kidneys, lungs, nervous system, and hematopoietic system. Moreover, patients with lupus have an increased risk of infections and cardiovascular diseases [1,2].

In antiphospholipid syndrome, the main role is played by antiphospholipid antibodies directed against phospholipids of cell membranes. Similar to lupus, the etiology involves genetic, environmental, and infectious factors. The pathogenesis of APS includes the binding of antibodies to endothelial cells, platelets, and coagulation proteins, promoting hypercoagulability. This can increase the risk of thromboembolic complications such as pulmonary embolism, deep vein thrombosis, stroke, and recurrent miscarriages [3].

The shared autoimmune component of both diseases promotes their co-occurrence - antiphospholipid antibodies are present in about 40% of patients with SLE, with similar rates observed in the reverse scenario. This can lead to disease exacerbations and an increased incidence of thromboembolic episodes. Additionally, the coexistence of these two conditions can complicate clinical management and prognosis, as patients may experience both the systemic inflammatory effects of SLE and the thrombotic complications of APS. Particularly dangerous is the catastrophic antiphospholipid syndrome, leading to multiorgan failure and death [2,4]

CASE DESCRIPTION

A 52-year-old female patient with a complex medical history, SLE, APS diagnosed in December 2015, and a history of pulmonary embolism in October 2015, was admitted to the Department of Rheumatology and Internal Medicine for routine evaluation and treatment decision making.

Diagnosis of lupus, antiphospholipid syndrome and a pulmonary embolism episode

Prior to 2015, the patient's health was generally stable, except for a miscarriage in her late 20s, periodic anemia, and varicose veins in her legs. In January 2015, she underwent surgery for varicose veins. In August 2015, she experienced shortness of breath and chest pain, which was initially treated with antibiotics for suspected pneumonia. When her symptoms persisted, she went to the emergency room, but was discharged despite a high D-dimer level. Her primary care physician then treated her with enoxaparin injections. A pulmonologist later recommended hospitalization for further evaluation. A CT scan showed no pulmonary embolism, likely due to the enoxaparin treatment. During this hospitalization, laboratory tests revealed elevated lupus-specific antibodies (dsDNA 446) and antiphospholipid antibodies, leading to a diagnosis of APS and SLE and initiation of appropriate treatment, including dabigatran 150 mg twice daily, hydroxychloroquine 200 mg once daily, and

methylprednisolone 4 mg twice daily. Since then, she has been a regular patient in the Department of Rheumatology and Internal Medicine, and her treatment has been adjusted, with hydroxychloroquine dose increased to 200 mg twice daily, methylprednisolone decreased to 4 mg once daily, and atorvastatin 20 mg once daily added.

Other diseases

In addition to SLE and APS, the patient has multiple comorbidities:

- Atherosclerosis and Hyperlipidemia: The patient has carotid atherosclerosis and hyperlipidemia, with cholesterol management playing a critical role in her treatment plan.
- Hypertension: The patient has been diagnosed with hypertension, which is currently well controlled.
- Anemia: Recurrent anemia has been noted for many years (approximately 26), with hemoglobin levels dropping to 8.1 g/dL during her last hospitalization in 2024.

The patient is treated with intravenous iron infusions during most hospitalizations.

- Vitamin D deficiency: significant vitamin D deficiency was found (17.7 ng/mL, with normal levels being 30-100 ng/mL).
- Prediabetes: Elevated fasting glucose levels (8.5 mmol/L) indicate prediabetes.
- Gastroesophageal Reflux Disease (GERD)
- Other conditions: Patient also has uterine fibroids, right ovarian cyst.

Cardiovascular events

The first cardiovascular event correlated with APS and SLE was most likely the pulmonary embolism in 2015. In 2019, the patient experienced an anterior wall STEMI that was treated with angioplasty and stenting. This event marked the beginning of her significant cardiovascular problems related to her underlying autoimmune disease. In 2023, the patient suffered another anterior wall STEMI, which was treated with balloon angioplasty and DES stenting in the LAD, D1 and D2 arteries. She was diagnosed with heart failure with reduced ejection fraction (HFrEF) and severe global left ventricular dysfunction due to ischemic injury. Diagnostic imaging revealed an enlarged left ventricle, severe apical and mid-segment hypokinesia/akinesia, and right ventricular enlargement with reduced systolic function.

Family medical history

The patient's mother and father died of myocardial infarction at the ages of 56 and 69, respectively, after a history of multiple myocardial infarctions. Her sister was diagnosed with Raynaud's disease.

Current condition and planned treatment

At the time of her most recent hospitalization in 2024, the patient remains significantly affected by her cardiovascular and autoimmune conditions. She continues to experience severe joint pain, fatigue, and decreased exercise tolerance. Laboratory studies reveal persistent anemia (Hb 8.1 g/dL), vitamin D deficiency, and low iron levels (serum iron 12.0 µg/dL, ferritin 6.79 ng/mL). Imaging studies show patchy consolidations in multiple lung segments, mild bronchiectasis, and mild pleural effusion. To manage her complex health issues, the patient is on an extensive medication regimen. For her systemic lupus erythematosus (SLE), she takes hydroxychloroquine and methylprednisolone. To further control her autoimmune response, she uses methotrexate and supplements this with folic acid to prevent methotrexate-induced folate deficiency. Her significant vitamin D deficiency is managed with a daily intake of vitamin D supplements. Given her medical history of two anterior wall ST-segment elevation myocardial infarctions (STEMIs), the patient is on clopidogrel for secondary prevention of cardiovascular incidents. Her hypertension and heart failure are treated with bisoprolol and the combination of sacubitril/valsartan, respectively. Furthermore, dapagliflozin is prescribed to manage both heart failure and her prediabetes. Eplerenone is included in her treatment plan for further blood pressure control. Additionally, ranolazine is utilized for the treatment of chronic angina. Due to her antiphospholipid syndrome (APS), which predisposes her to thromboembolic events, she is on anticoagulation therapy with warfarin, ensuring that her international normalized ratio (INR) is maintained within a therapeutic range to prevent further complications. For her gastrointestinal issues, particularly gastroesophageal reflux disease (GERD), she takes pantoprazole.

The patient is currently undergoing qualification for biologic treatment with anifrolumab, a type I interferon monoclonal antibody that has shown promise in the treatment of SLE. This planned treatment aims to better manage her autoimmune symptoms and potentially reduce the frequency and severity of her cardiovascular events.

DISCUSSION

SLE and APS are distinct systemic autoimmune diseases of unknown etiology. They result from complex immune system dysfunction leading to the production of autoantibodies and chronic inflammation [5]. Antiphospholipid antibodies (aPL) are present in approximately 40% of SLE patients, but only about 10% develop clinically evident APS [6]. In cases of co-occurrence, SLE is typically diagnosed first, followed by APS as a secondary condition due to more obvious clinical symptoms such as malar rash, arthritis, and renal involvement, prompting early medical evaluation and diagnosis [7]. In the patient discussed, the course of these diseases was quite unusual. The initial symptoms, miscarriage and subsequent pulmonary embolism, were typical of APS without any prior symptoms suggestive of SLE. In addition, the most common first symptom of APS is deep vein thrombosis in the lower limbs [5], whereas this patient developed pulmonary thrombosis directly.

Patients with concurrent SLE and APS experience a variety of complications, with thrombotic events being the most common, affecting up to 50% of cases. These include myocardial infarction, stroke, and venous thromboembolism. Studies suggest that the presence of both SLE and APS compounds this risk due to the additive effects of disease-related factors from both conditions. The prevalence of cardiovascular events in SLE patients ranges from 6-10%, while cardiovascular events may occur in up to 50% of APS patients alone. When these conditions coexist, the cardiovascular risk is further increased [8]. In the case described, the patient's pulmonary embolism and recurrent myocardial infarctions illustrate the serious impact of the combined autoimmune diseases.

Several mechanisms contribute to the increased cardiovascular risk in patients with SLE and APS. Upon binding to their targets, antiphospholipid antibodies activate endothelial cells, platelets, and monocytes, leading to the expression of procoagulant molecules such as tissue factor and adhesion molecules. Binding of aPLs to endothelial cells disrupts normal endothelial function, leading to increased permeability and expression of pro-inflammatory cytokines. This activation increases cell adhesion and aggregation, promoting a prothrombotic state and the development of atherosclerosis. In addition, the pro-inflammatory state in SLE further accelerates atherosclerosis [9,10]. These mechanisms indicate why anti-inflammatory and anticoagulant therapy is critical in these patients.

Although direct oral anticoagulants (DOACs) are generally safer and more effective than vitamin K antagonists (VKAs) in many indications, warfarin remains the drug of choice for secondary prophylaxis of thromboembolic events in APS patients, according to EULAR recommendations. Warfarin should be administered under INR control, with a recommended

range of 2-3, and even 3-4 considered if ineffective [11,12]. The reason for the initial prescription of apixaban to the patient in this case remains unclear. Recent studies, including systematic reviews and meta-analyses, indicate that DOACs (both rivaroxaban and apixaban) have significantly lower efficacy in preventing thromboembolic events in APS patients [12]. Appropriate prophylaxis with warfarin could have prevented or at least mitigated the cardiac complications such as myocardial infarctions in the patient discussed here, but it is nevertheless beneficial that the apixaban was later replaced by warfarin. Furthermore, low-dose aspirin (75-100 mg daily) is recommended for primary prevention in patients with a high-risk aPL profile, which is supported by the pathomechanism of cardiovascular complications in these diseases [11]. Therefore, this approach should have been considered for the patient prior to her first myocardial infarction.

Management of active lupus in these patients is challenging because long-term use of glucocorticoids, the basis of anti-inflammatory treatment in SLE, can exacerbate traditional cardiovascular risk factors such as hypertension and dyslipidemia [14]. Therefore, when glucocorticoid therapy is necessary, the lowest possible dose should be used to minimize potential cardiovascular harm [15]. This explains the initial reduction in the patient's methylprednisolone dose, which was later increased from 4 mg to 8 mg daily due to high disease activity. Concurrent therapy with cholesterol-lowering and antihypertensive drugs allowed control of these risk factors.

Despite standard therapy with hydroxychloroquine and glucocorticoids, the patient experienced severe flare-ups resulting in two anterior wall STEMIs. Biological treatment should be considered in such patients when standard therapy is ineffective. Currently recommended biological drugs for patients with both SLE and APS include rituximab, which targets B cells; belimumab, which targets B-cell activating factor; and anifrolumab, which targets the type I interferon receptor. Anifrolumab has shown promise in the treatment of SLE and is being considered for the patient in this case. Other major indications for initiating biological treatment in patients with co-existing SLE and APS, in addition to refractory disease despite standard treatment, include frequent flares and severe organ involvement [11,16].

In conclusion, this case highlights the complexity of managing a patient with coexisting SLE and APS, particularly with regard to the prevention and treatment of cardiovascular complications. Early diagnosis and aggressive management of both autoimmune activity and traditional cardiovascular risk factors are crucial to improve outcomes in these patients.

DISCLOSURE

AUTHOR'S CONTRIBUTION

Conceptualization: WB, BS; Formal analysis: BS; Investigation: WB, BS; Resources: PB; Data curation: BS, OD; Writing - rough preparation: WB, BS, OD; Writing - review and editing: BS, OD, KL, RS; Supervision: RS;

Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

FINANCING STATEMENT

This research received no external funding.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Written informed consent has been obtained from the patient to publish this paper.

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICT OF INTEREST

The authors deny any conflict of interest.

REFERENCES

- [1] Zucchi D, Elefante E, Schilirò D, et al. One year in review 2022: systemic lupus erythematosus. *Clin Exp Rheumatol*. 2022;40(1):4-14. doi:10.55563/clinexprheumatol/nolysy
- [2] Kokosi M, Lams B, Agarwal S. Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome. *Clin Chest Med*. 2019;40(3):519-529. doi:10.1016/j.ccm.2019.06.001
- [3] Sammaritano LR. Antiphospholipid syndrome. *Best Pract Res Clin Rheumatol*. 2020;34(1):101463. doi:10.1016/j.berh.2019.101463

- [4] Meroni PL, Tsokos GC. Editorial: Systemic Lupus Erythematosus and Antiphospholipid Syndrome. *Front Immunol.* 2019;10:199. doi:10.3389/fimmu.2019.00199
- [5] mp.pl [Internet]. Choroby reumatyczne. [cited 2024 Jun 2]. Available from: <https://www.mp.pl/interna/chapter/B16.II.16>.
- [6] Talari K, Anandh U, Patrick A. Lupus Nephritis with Coexistent Antiphospholipid Antibodies Associated Nephropathy: A Case Report and Literature Review. *Indian J Nephrol.* 2018;28(2):164-166. doi:10.4103/ijn.IJN_204_16
- [7] McMahon MA, Keogan M, O'Connell P, Kearns G. The prevalence of antiphospholipid antibody syndrome among systemic lupus erythematosus patients. *Ir Med J.* 2006;99(10):296-298.
- [8] Statkute L, Traynor A, Oyama Y, et al. Antiphospholipid syndrome in patients with systemic lupus erythematosus treated by autologous hematopoietic stem cell transplantation. *Blood.* 2005;106(8):2700-2709. doi:10.1182/blood-2005-01-0330.
- [9] Urowitz MB, Gladman D, Ibañez D, et al. Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2010;62(6):881-887. doi:10.1002/acr.20122
- [10] Tektonidou MG. Cardiovascular disease risk in antiphospholipid syndrome: Thromboinflammation and atherothrombosis. *J Autoimmun.* 2022;128:102813. doi:10.1016/j.jaut.2022.102813
- [11] Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis.* 2019;78(10):1296-1304. doi:10.1136/annrheumdis-2019-215213
- [12] Sawlani A, Masood R, Bai S, Anwar A. Systemic Lupus Erythematosus and Anti Phospholipid Syndrome in a Male Patient: A Case Report. *Clin Case Rep Int.* 2023;7(1):1614. doi:10.25107/2638-4558.1614.
- [13] Al Sulaiman K, Hafiz A, Badreldin HA, et al. Evaluation of Apixaban in Patients With Antiphospholipid Syndrome: A Case Series and Review of Literature. *J Investig Med High Impact Case Rep.* 2022;10:23247096221099893. doi:10.1177/23247096221099893
- [14] Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol.* 2000;16(4):505-511.
- [15] Drosos GC, Vedder D, Houben E, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus

erythematosus and antiphospholipid syndrome. *Ann Rheum Dis.* 2022;81(6):768-779.
doi:10.1136/annrheumdis-2021-221733

[16] Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis.* 2024;83(1):15-27. doi:10.1136/ard-2023-224002.