

Immunomodulation in antiphospholipid-antibody-associated endocarditis: a case report and review of the literature

Franz Haertel ^{1*}, Daniel Kretzschmar ¹, P. Christian Schulze ¹, and Thomas Neumann^{2,3}

¹Klinik für Innere Medizin I, Universitätsklinikum Jena, Am Klinikum 1, 07747 Jena, Germany; ²Kantonsspital St. Gallen, Klinik für Rheumatologie, Haus 05, Rorschacher Strasse 95, 9007 St. Gallen, Switzerland; and ³Klinik für Innere Medizin III, Universitätsklinikum Jena, Am Klinikum 1, 07747 Jena, Germany

Received 1 May 2021; first decision 8 July 2021; accepted 25 October 2021; online publish-ahead-of-print 10 November 2021

Background

Non-infectious endocarditis is a rare complication in patients with systemic lupus erythematosus or antiphospholipid syndrome (APS). The mitral valve is mainly affected, usually showing vegetations on the ventricular and atrial side of the valve.

Case summary

A 27-year-old female patient with a known APS was referred to our hospital with night sweats, weight loss, reduction in performance, and dizziness. A floating structure associated to the mitral valve was identified in a transoesophageal echocardiogram with typical changes, in accordance with a non-infectious endocarditis (Libman–Sacks). Only a trace of mitral regurgitation was present and a mass on the posterior mitral valve leaflet. Laboratory findings showed antibody and inflammatory marker measurements either negative or within normal range. The patient received therapeutic oral anticoagulation using a vitamin K antagonist and a combined immunosuppression consisting of hydroxychloroquine and prednisolone. The symptoms of the patient resolved within 3 months after starting the initial treatment. The follow-up echocardiogram showed an almost normal mitral valve function with only a slight regional thickening of the posterior mitral leaflet and no stenosis. Following a 7-year period of observation being on a medical regimen of hydroxychloroquine and a vitamin K antagonist, no evidence of clinical and/or echocardiographic recurrence was detected.

Discussion

This case report represents a successful medical management of non-infectious endocarditis using immunosuppressive and anticoagulation therapies without significant residual lesions. Although optimal management of non-bacterial endocarditis remains in the area of uncertainty, this combination therapy deems promising.

Keywords

Case report • Endocarditis • Libman–Sacks • Lupus • Antiphospholipid syndrome • Immunosuppression

ESC Curriculum 4.3 Mitral regurgitation • 2.2 Echocardiography • 4.11 Endocarditis

* Corresponding author. Tel: +49 36419324554, Email: franz.haertel@med.uni-jena.de

Handling Editor: Poonam Velagapudi

Peer-reviewers: Amr Idris; Doralisa Morrone and ; Satish Ramkumar

Compliance Editor: Rahul Mukherjee

Supplementary Material Editor: Ross Thomson

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Learning points

- Heart valve disease can occur in antiphospholipid syndrome (APS) and is part of the spectrum of 'non-criteria' APS manifestations.
- Antiphospholipid syndrome is an autoimmune disease and not only a coagulation disorder.
- Antithrombotic strategies are usually not effective in microvascular and non-thrombotic manifestations of APS.
- Hydroxychloroquine is a therapeutic option for patients with APS-associated heart valve disease, although there are no recommendations for the management of non-criteria APS.
- The 2019 EULAR recommendations for the management of APS in adults formulate an evidence-based, differentiated approach for treating this clinical condition and include antiphospholipid antibody profile, screening for and management of cardiovascular, venous thrombosis risk factors and systemic lupus erythematosus, patient education about treatment adherence, lifestyle counselling, obstetric history, anticoagulatory therapy [LDA, vitamin k antagonist (international normalized ratio 2–3/3–4)], and immunomodulation therapy (hydroxychloroquine/prednisolone).

Introduction

Antiphospholipid syndrome (APS) is an immune coagulopathy and can be classified according to clinical and laboratory criteria.¹ Those criteria only include the most common features such as venous, arterial, or microvascular thrombosis and/or pregnancy complications. As a rare occurrence, non-infectious valvular heart disease can be diagnosed as Libman–Sacks (LS) endocarditis in the presence of antiphospholipid antibodies and must not be overlooked.

Case presentation

A 27-year-old female presented to the emergency department with the chief complaint of night sweats, weight loss, reduction in performance, and dizziness. Her past medical history showed an APS, acquired 5 years earlier in connection with a miscarriage within the 29th week [cardiolipin antibodies, Immunoglobulin G (IgG) 16.4 IgG Phospholipid units (GPL)—U/ml, normal < 10 GPL—U/ml, β 2—glycoprotein antibodies, IgG 14.5 U/ml, normal < 8 U/ml and positive lupus anticoagulant]. Other findings such as recurring thrombosis/

embolisms or signs of connective tissue disease (photosensitivity, Raynaud's phenomenon, or arthralgia) were denied. She gave birth to two healthy children. One before and one after the diagnosis of APS. Prior to her presentation, the patient took no permanent medication. Her vital signs were stable, and the physical and neurological examination remained non-remarkable. As part of our diagnostics work-up for possible cardiac causes of the symptoms, first a non-invasive transthoracic and then a transoesophageal echocardiogram were performed showing typical changes, in accordance with a non-infectious endocarditis (LS), with a thrombotic deposit measuring 16×9 mm on the mitral valve between the posterior mitral valve leaflet (PML) (P2 and P3) as well as on the tip of the anterior mitral leaflet (A1) with increased left ventricular inflow and involvement of the posteromedial papillary muscle (*Figure 1*, *Videos 1* and *2*). Only a trace of mitral regurgitation was present (*Video 3*). A 12-lead electrocardiogram (*Figure 2*) and 24 h Holter monitor showed no abnormalities. Irregular left/right ventricular function, segmental wall-motion abnormalities, or other valve malfunctions were not present. Corresponding to that, a normal B-type natriuretic peptide could be measured (21 pg/mL). To rule out a potential further cardiac involvement, a cardiac magnetic resonance imaging (MRI) was performed in

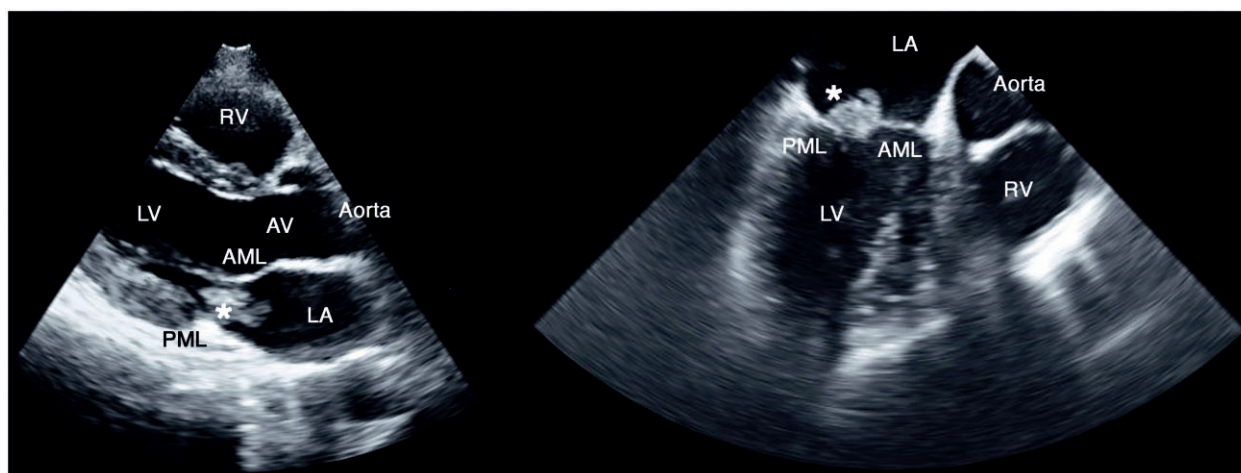
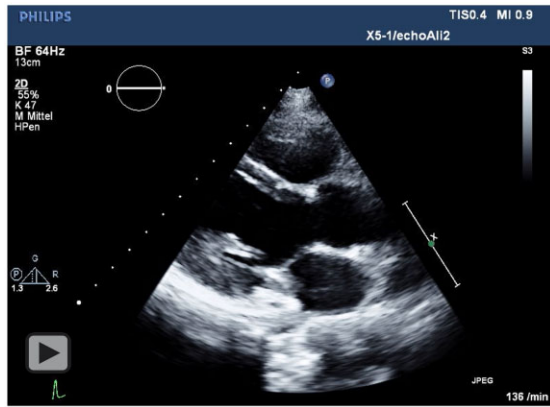
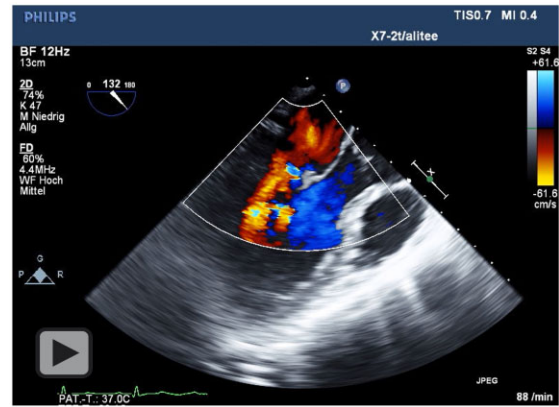


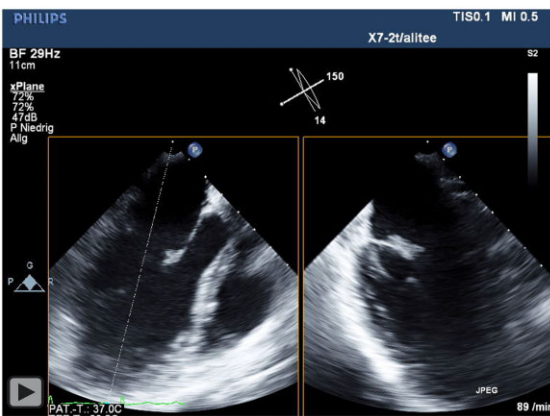
Figure 1 Transthoracic and transoesophageal echocardiograms before treatment showing the affected posterior mitral leaflet of the mitral valve (*). AML, anterior mitral leaflet; AV, aortic valve; LA, left atrium; LV, left ventricle; PML, posterior mitral leaflet; RV, right ventricle.



Video 1 Transthoracic, parasternal long-axis view performed at hospital admission before treatment showing a mobile mass on the posterior mitral leaflet.



Video 3 Transoesophageal three-chamber view and colour Doppler disclosing a mobile mass on the posterior mitral leaflet and mild mitral regurgitation (performed at hospital admission before treatment).



Video 2 Transoesophageal X-plane view (three-chamber view combined with long-axis view) performed at hospital admission before treatment showing a mobile mass on the posterior mitral leaflet.

addition. Here, late enhancement (cine imaging) and myocardial oedema (T2*-weighted imaging) as well as thrombus formation in the left/right ventricle and atrial appendage were not present. Important laboratory findings included negative anti-nuclear antibodies as well as anti-double stranded DNA antibodies, anti-SSA/anti-SSB antibodies, anti-neutrophil cytoplasmic antibodies (p-ANCA, c-ANCA), and anti-cardiolipin antibodies (IgG, Immunoglobulin M) within normal range. C-reactive protein and blood count were normal. Multiple blood cultures remained sterile. A chest X-ray showed a normal lung status. The patient was started on oral anticoagulation using a vitamin K antagonist (phenprocoumon) with a target international normalized ratio (INR) of 2–3 and a combined immunomodulation with hydroxychloroquine (200 mg/400 mg on alternating days) and prednisolone (initial dose of 15 mg once daily with weekly reduction by 2.5 mg until 5 mg once daily for a month and final reduction to 2.5 mg

once daily followed by termination after 4 months). She was discharged with an INR of 2.9. The symptoms of the patient resolved completely. The patient was followed up shortly after and from that point on once a year. Within 3 months after starting the initial treatment, the patients echo showed, apart from unaltered good ventricular function, an almost normal mitral valve function (trace of regurgitation) with a slight regional thickening of the PML measuring 3 × 3 mm without additional malfunctions/abnormalities of the other valves (Figure 3, Supplementary material online, Videos S1 and S2). In the last 7 years, she remained clinically stable and asymptomatic on hydroxychloroquine (200 mg once daily) and a vitamin K antagonist (target INR 2–3).

She became pregnant again with her third child. Her medication was continued until the 5th week of the pregnancy (gestational age) and then interrupted. Anticoagulation remained but was changed to 20 000 IE fragmin s.c. daily. Her post-pregnancy medication was prescribed in the same form and dosage after giving birth as it was before the pregnancy.

Discussion

Libman–Sacks endocarditis is a type of non-bacterial thrombotic endocarditis (NBTE) describing sterile vegetations on the cardiac valves.² Malignancies are the most common causes of LS endocarditis.² Antiphospholipid syndrome, which had been diagnosed previously, was the most convincing cause of valve abnormality.

Thromboembolic phenomena or transient ischaemic attacks are the most common clinical manifestations and are a relevant concern with LS.^{2,3} In our patient, we did not find any clinical signs of embolism.

Usually, the basal and mid portion of the mitral and aortic valves are affected, diffuse, or focal leaflet thickening exhibiting regurgitation as well as pericardial effusion can occur.² Valve lesions are defined by: (i) valve thickness >3 mm; (ii) localized thickening involving the

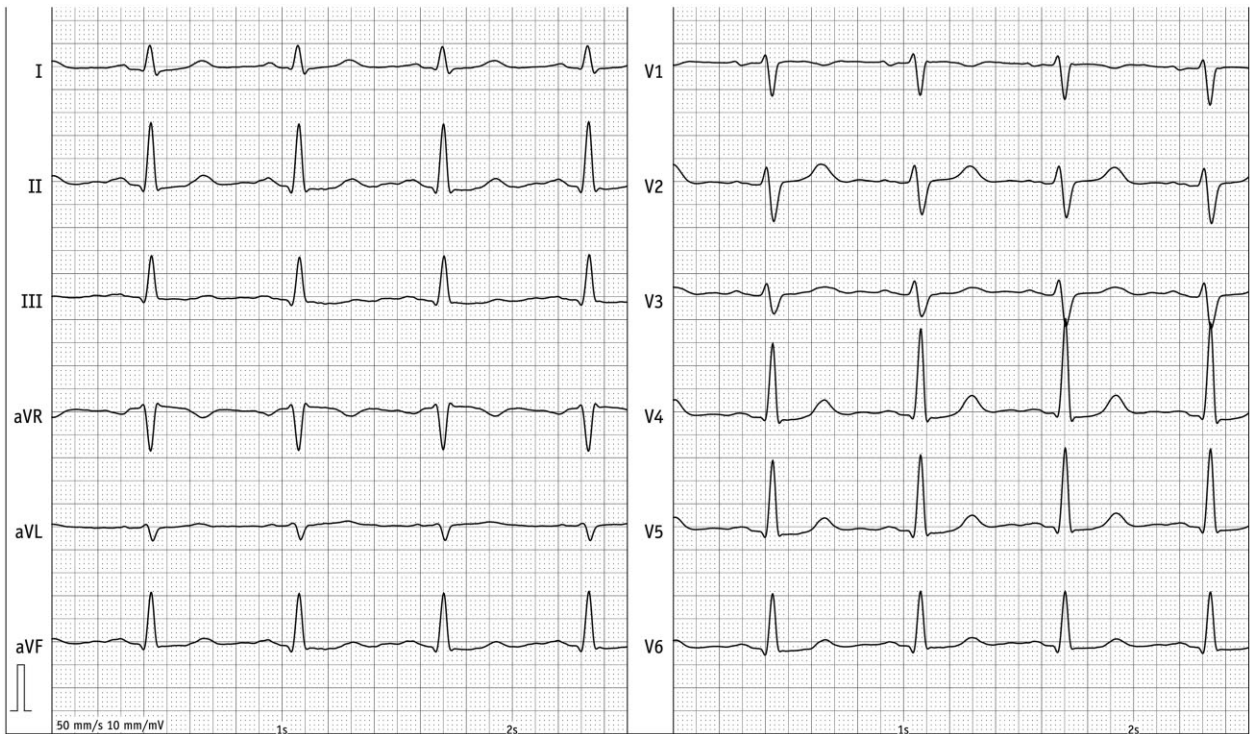


Figure 2 A 12-lead electrocardiogram at admission. Sinus rhythm. Normal QRS axis. Heart rate: 90–100/min. PR-interval: 156 ms; QRS duration: 86 ms in V6. QTc: 411 ms.

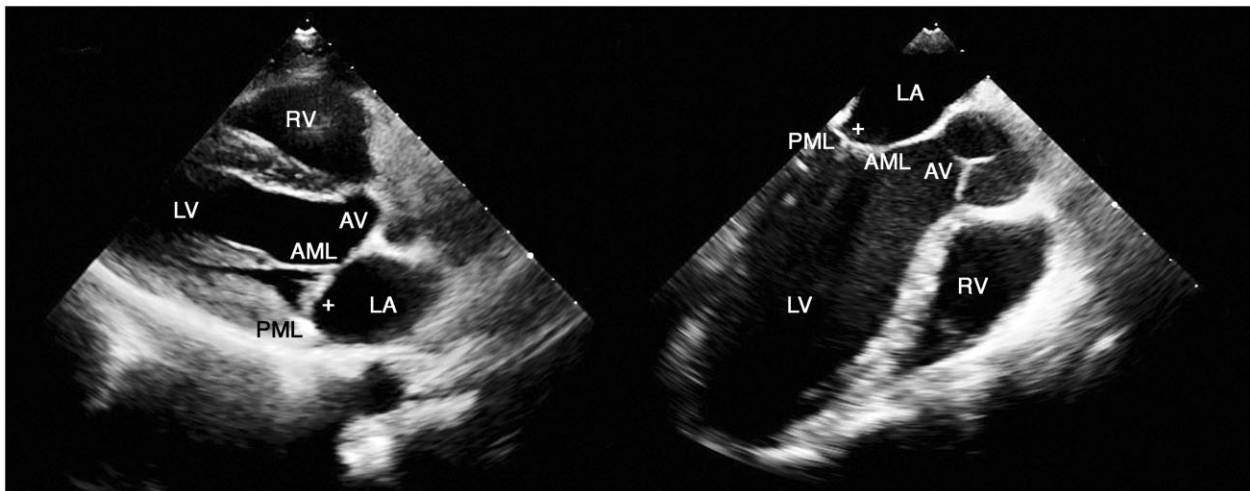


Figure 3 Transthoracic and transoesophageal echocardiograms within 3 months after treatment initiation showing a thickened posterior mitral leaflet of the mitral valve (+). AML, anterior mitral leaflet; AV, aortic valve; LA, left atrium; LV, left ventricle; PML, posterior mitral leaflet; RV, right ventricle.

proximal or middle portion of the leaflets; or (iii) irregular nodules on the atrial face of the mitral valve and/or the vascular face of the aortic valve.^{4,5} In our case, only the mitral valve was affected with residual thickening after treatment.

There are publications about the role of cardiac MRI examinations in patients with APS to detect cardiac manifestations. In this regard, echocardiography and cardiac MRI are superior to computed tomography or nuclear techniques. However, in terms of assessment of

valvular mass motion, echo-imaging has the advantage of a higher frame rate (higher temporal resolution) and is faster and more widely available. But it should be kept in mind that technology advanced to the point where we are able to non-invasively assess myocardial tissue regarding inflammation even further using mapping and strain cardiac MRI.

To confirm the diagnosis, patients suspected of LS-endocarditis should be put under full assessment including complete blood count, inflammatory markers, lupus anticoagulant, antiphospholipid antibodies, and blood cultures to differentiate from other aetiologies such as infective endocarditis.² In the absence of inflammatory or microbiological findings, the evaluation for LS-endocarditis is then based on the demonstration of valvular vegetations by transoesophageal echocardiography.² The diagnostic challenge lies in thoroughly excluding vegetations with a possible infectious association, especially in patients with the background of recurrent infections in the immediate past and risk factors for infection and non-infectious endocarditis. In our case, both forms of imaging allowed the detection and confirmation of LS-endocarditis considering that inflammatory markers and blood cultures remained negative.

Heart valve disease is part of the spectrum of 'non-criteria' APS.⁵ Oral anticoagulant treatment and aspirin have been shown to be ineffective in terms of valvular lesion regression.⁶ Therefore, we decided to treat our patient with immunomodulation as it is recommended for recurrent pregnancy complications.⁷

Anticoagulation is the mainstay of therapy with or without evidence of systemic emboli after ruling out intracranial bleeding³ but especially in patients with a thromboembolic event for secondary prevention.² Our patient received a vitamin K antagonist (phenprocoumon) after an initial treatment phase with heparin. While anticoagulation in APS is recommended lifelong, there is no evidence for a specific duration of hydroxychloroquine treatment.

Even though our patient had no recurrence of LS-endocarditis and remained clinically well and stable with low to no disease activity, patients usually develop recurrent thromboembolic events, cognitive disability, and death.² LS-endocarditis correlates with disease duration and activity.⁸ In cases of significant valvular dysfunction, patients should be closely followed.² Consequences in clinical practice are heart failure, valve replacement or death from heart failure.⁵

Conclusion

In the case of our patient with APS and NBTE, our treatment concept of anticoagulation and immunosuppression seems to be a promising option to guarantee effective and safe management of the underlying disease and its initial symptoms. To this day, this therapy remains successful over 7 years of follow-up.

Lead author biography



Franz Haertel studied medicine at University of Halle, Germany (2007 - 2015) and is now working in the department of cardiology at University of Jena, Germany since 2015.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

References

- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;**4**:295–306.
- Ibrahim AM, Siddique MS. *Libman Sacks Endocarditis*. Treasure Island (FL): StatPearls; 2020.
- Choi JH, Park JE, Kim JY, Kang T. Non-bacterial thrombotic endocarditis in a patient with rheumatoid arthritis. *Korean Circ J* 2016;**46**:425–428.
- Petri MA. Classification criteria for antiphospholipid syndrome: the case for cardiac valvular disease. *J Rheumatol* 2004;**31**:2329–2330.
- Abreu MM, Danowski A, Wahl DG, Amigo MC, Tektonidou M, Pacheco MS et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. *Autoimmun Rev* 2015;**14**:401–414.
- Zavaleta NE, Montes RM, Soto ME, Vanzini NA, Amigo MC. Primary antiphospholipid syndrome: a 5-year transesophageal echocardiographic followup study. *J Rheumatol* 2004;**31**:2402–2407.
- Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019;**78**:1296–1304.
- Moyssakis I, Tektonidou MG, Vasiliou VA, Samarkos M, Votteas V, Moutsopoulos HM. Libman-Sacks endocarditis in systemic lupus erythematosus: prevalence, associations, and evolution. *Am J Med* 2007;**120**:636–642.