CASE REPORT

Primary antiphospholipid syndrome, hypertrophic non-obstructive cardiomyopathy and hypotelorism

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Accepted 22 March 2016

SUMMARY

Antiphospholipid syndrome (APS) is an autoimmune disorder associated with arterial/venous thrombosis. Cardiac manifestations of APS include valve stenosis/insufficiency, coronary artery disease and myocardial dysfunction presenting as dilated cardiomyopathy. In the following report, we present the case of a man with primary APS, hypertrophic non-obstructive cardiomyopathy and hypotelorism—a combination that has not yet been reported in the literature.

BACKGROUND

We believe that our unique case informs the reader about a novel disease combination that has not been described before. Cardiac manifestations of antiphospholipid syndrome (APS) are frequently misinterpreted and underdiagnosed, thus, extensive knowledge is needed to make the correct diagnosis.

CASE PRESENTATION

A 27-year-old Caucasian man was referred to our emergency department because of dyspnoea and visual impairment of the left eye for 2 days. On physical examination, the patient, who had an abnormal facies characterised by remarkable hypotelorism, was tachypnoeic and had a diastolic heart murmur. His peripheral blood oxygen saturation was 93% and 12-lead ECG showed sinus tachycardia with unspecific repolarisation abnormalities. The patient's medical history was significant for an unprovoked acute pulmonary embolism a few years prior. At that time, thrombophilia genetic screening had revealed heterozygous factor V Leiden mutation. The patient was not on anticoagulation therapy at the time of hospital admission.

Initial laboratory results showed elevated cardiac biomarkers (hs-troponin T: 0.129 ng/mL, N-terminal pro b-type natriuretic peptide: 11 996 pg/mL). Assessment of electrolytes was within normal ranges, however, unspecific renal impairment characterised by reduced glomerular filtration rate (calculated using Cockcroft Gault equation; 48.4 mL/min) and microalbuminuria (23 mg/dL) was detectable.

CT angiography showed normal coronary and pulmonary arteries, however, the patient had typical signs of pulmonary oedema. The pulmonary fluid overload was due to heart failure with reduced ejection fraction (EF: 40%, as assessed by echocardiographic biplane Simpson's method). An irregularly thickened, functional bicuspid aortic valve (due to commissural fusion of the right and left coronary cusp) with moderate insufficiency and

characteristics of non-obstructive hypertrophic cardiomyopathy (HCM) with asymmetric septal hypertrophy were additional echocardiographic findings. Cardiac MRI (CMR) showed pathognomonic late gadolinium enhancement pattern with hyper-enhancement at the inferior right ventricular insertion points (figure 1A, B). Biopsy of the subcutaneous fatty tissue did not show histological signs of systemic amyloidosis and subsequent genetic testing for Morbus Fabry and common sarcomeric protein gene mutations (MYH7, MYBPC3) was negative. The patient was normotensive and there was no obvious condition of abnormal ventricular overload (ie, coarctation of the aorta or aortic valve stenosis) that could have explained septal hypertrophy, thus, the HCM was classified as idiopathic.

Ophthalmic examination was performed because of the visual impairment. Funduscopy revealed a branch retinal artery occlusion (BRAO) with retinal vessel dilation, haemorrhage and tortuosity (figure 1D).

Because of the recurrent thromboembolic complication, we tested for APS, a thrombophilic disorder known to manifest as arterial/venous thrombosis. Laboratory results were in accordance with definite APS (based on the Sydney Criteria) showing a triple positive high-titre antiphospholipid pattern (anti-cardiolipin IgG 1892 U/mL, anti-β-2 glycoprotein-1 IgG 6670 U/mL, positive lupus anticoagulant). As a consequence, indefinite oral anticoagulation was initiated.

Noteworthy, the patient showed neither dermatological symptoms, arthralgia/arthritis nor neurological disorders to indicate presence of systemic lupus erythematosus or lupus-like disease. Antinuclear antibodies, anticytoplasmic antibodies and complement components C3/C4 were within normal ranges, hence, the APS was classified as primary.

Renal sonography was normal and MR angiography did not show signs of renal artery stenosis—an entity that has been associated with impaired renal function in APS. Consequently, a diagnosis of APS-associated nephropathy was made.

Renal insufficiency and microalbuminuria remained stable under heart insufficiency treatment during the following months, thus, we did not perform renal biopsy for histological confirmation. Immunosuppressive therapy was not considered because the patient did not fulfil the diagnostic criteria for catastrophic APS or thrombotic storm as described before.¹ The patient was scheduled for frequent follow-up at our outpatient clinic, to

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To cite: Kellermair J, Kammler J, Laubichler P, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214765

Figure 1 Morphological characteristics. Cardiac MRI shows asymmetric septal hypertrophy with a maximum septal diameter of 25 mm (A) and typical late gadolinium enhancement pattern (B). Transoesophageal echocardiography (mid-oesophageal, 127°) reveals significant thickening of the right aortic cusp and the intraventricular septum (C). Retinal-fluorescence-angiography shows tortuosity and vessel dilation without leakage (D).

monitor renal and cardiac function and re-evaluate lupus-associated symptoms and biomarkers.

DISCUSSION

Known cardiac manifestations of APS include valvular disease,^{2,3} coronary artery disease and myocardial dysfunction presenting as dilated cardiomyopathy.⁴ Valvular disease is seen in about two-thirds of all patients. A typical echocardiographic feature in APS is irregular leaflet thickening due to immune-complex deposition resulting in predominantly left-sided valve stenosis/insufficiency, as seen in our patient.

Cardiomyopathy is a less frequently reported manifestation in APS. Case reports⁵ have indicated the association of APS with dilated cardiomyopathy. The most likely underlying pathomechanism is intramyocardial microvascular thrombosis with subsequent myocardial necrosis. HCM, however, has not been associated with APS in the literature. HCM is defined by the presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions.⁶ Approximately 60% of HCM cases are caused by mutations in cardiac sarcomere genes while non-genetic disorders (ie, storage diseases) account for up to 10%.⁶ In our patient we excluded both.

A specific genetic background of APS has not yet been identified. Large sample size genome-wide linkage analysis could contribute to identify the genetic disorder, but related studies have not been published. The fact that our patient had heterozygous factor V Leiden (mutation of gene F5 on chromosome 1q23), idiopathic HCM, primary APS and an abnormal facies, strongly indicates a genetic background. In fact, hypotelorism has been

associated with various genetic disorders, however, to our knowledge, there is no reported genetic syndrome that features the above described phenotype.

Learning points

Primary antiphospholipid syndrome (APS) is associated with various cardiac manifestations ranging from valvular insufficiency/stenosis to dilated cardiomyopathy. The combination of APS and hypertrophic cardiomyopathy is novel and the common pathophysiology is unknown, thus, further research is needed to evaluate a potential genetic background.

Acknowledgements The authors thank Daniel Kiblböck (MD) for preparing the MRIs.

Contributors The manuscript has neither been published nor is it under consideration for publication elsewhere. The text, figure and table have been written/designed by the authors and have not been copied from other material in the literature. All the authors participated in the work, reviewed the text and agree with the content. Noteworthy, the concerned patient reviewed the text and also agreed with the content and with publication. JKa and JKe acquired the data and designed the figures, and PL and CS contributed to data acquisition, and revised and analysed the data.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Aguiar CL, Erkan D. Catastrophic antiphospholipid syndrome: How to diagnose a rare but highly fatal disease. *Ther Adv Musculoskelet Dis* 2013;5:305–14.
- 2 Amigo MC. What do we know about the cardiac valve lesion in the antiphospholipid syndrome (APS)? *Lupus* 2014;23:1259–61.
- 3 Tenedios F, Erkan D, Lockshin MD. Cardiac involvement in the antiphospholipid syndrome. *Lupus* 2005;14:691–6.
- 4 Denas G, Jose SP, Bracco A, *et al.* Antiphospholipid syndrome and the heart: a case series and literature review. *Autoimmun Rev* 2015;14:214–22.
- 5 Vaccaro F, Caccavo D, Roumpedaki E, *et al.* Dilated cardiomyopathy due to thrombotic microangiopathy as the only manifestation of antiphospholipid syndrome: a case report. *Int J Immunopathol Pharmacol* 2008;21: 237–41.
- 6 Elliott PM, Anastakis A, Borger MA, *et al.*, Authors/Task Force members. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2733–79.

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