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Reversible cardiac valvular disease in catastrophic antiphospholipid syndrome

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ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) is a severe form of antiphospholipid syndrome (APS). It frequently leads to multiorgan failure with an approximate mortality rate of 50%. The heart is involved in about 50% of the patients with CAPS. We report two cases with CAPS and severe heart manifestations, documented by echocardiography. Both women show regression of the valvular regurgitation under treatment. Valve replacement therapy was no longer necessary.

In earlier studies and case reports, cardiac valve involvement had been characterised by valve thickening and vegetations. We suppose that (sometimes reversible) microvascular disturbances lead to valvular regurgitation via papillary muscle dysfunction and myocardial stunning.

KEYWORDS

Antiphospholipid syndrome, catastrophic antiphospholipid syndrome, echocardiography, heart valve diseases, therapeutics, valve regurgitation

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease, in which the presence of antiphospholipid antibodies (aPL) is associated with recurrent arterial and venous thrombosis and/or recurrent obstetric morbidity.[1] The clinical manifestations are heterogeneous and mortality is extremely high (~50%) when the disease accelerates to a 'catastrophic' course. Less than 1% of all patients with APS present with this catastrophic form.[2,3]

Catastrophic APS (CAPS) develops by definition within a week and is characterised by: a) clinical evidence of multiple organ involvement (three or more), b) histopathological evidence of multiple small vessel occlusion (a minority also have large vessel thrombosis), and c) persistent presence of aPL, usually in a high titre; only one of the three types of antibodies (lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) and anti-β2 glycoprotein-I antibodies (anti-β2 GPI)), is enough for diagnosis.[2,3]

In approximately 50% of the patients with CAPS the heart is involved.[4] The major cardiac manifestations in APS are heart failure due to cardiac myopathy, macrovascular and microvascular disease, and valvular involvement. Valvular abnormalities are deemed to be due to thickening or vegetations (Libman-Sacks or noninfective endocarditis).[5] The latter is the most common cardiac manifestation in CAPS. The mitral valve is most frequently involved, followed by the aortic valve.[6]

CASE REPORTS

We present two patients with heart valve regurgitation during the acute phase of CAPS, who show regression of the valve lesions under therapy.

Patient A

A 38-year-old woman of 60.4 kilograms presented to the cardiology unit with a two-week history of dyspnoea, orthopnoea and general malaise with 6 kg weight loss, preceded by arthralgias. There was no significant medical history, apart from two early spontaneous abortions, both before the tenth week of gestation. She did not use any medication, smoked approximately 30 cigarettes per day and denied alcohol and drug abuse.

On physical examination, the patient appeared ill and dyspnoeic. Her temperature was 37°C, blood pressure 190/140 mmHg, heart rate 115 beats/min and peripheral oxygen saturation 98% while breathing ambient air. Auscultation of the heart revealed a loud (grade III/VI)

holosystolic murmur on the apex without thrill or S3. Examination of the skin showed purplish discoloration in a patchy distribution over the lower extremities, characteristic of livedo reticularis. Findings on other organ systems were non-contributory; endocarditis stigmata were absent. Laboratory test results are shown in *table 1* and *2*.

A presumptive diagnosis of bacterial endocarditis was made, and a work-up for valve replacement was started.

According to the American Society of Echocardiography (ASE) the severity of a mitral valve regurgitation is quantified by specific and supportive signs. The specific signs include the regurgitation index or RJA/LAA index, i.e. ratio of the regurgitant jet area (RJA) to the left atrial area (LAA), both obtained in the same plane as the maximum regurgitant flow (<20% is mild, 20 to 40% is moderate, >40% is severe). The vena contracta is also an important parameter. This is defined as the narrowest central flow region of a jet that occurs at, or just downstream to, the orifice of a regurgitant valve (<0.3 cm is mild, 0.3 to 0.7 cm is moderate, >0.7 cm is severe). Two other important specific signs of a severe mitral regurgitation are the systolic reversal of flow in the pulmonary veins or a prominent flail of one of the mitral valve leaflets or a ruptured papillary muscle.

Transoesophageal cardiac ultrasound revealed a severe mitral regurgitation (RJA/LAA index >50%, vena contracta 0.74 cm and systolic reversal in the pulmonary vein) and diffuse hypokinesis of the left ventricle. The mitral valve leaflets showed signs of thickening, without vegetations (*figure 1*). Since repetitive blood cultures remained negative, an autoimmune pathogenesis was considered and tested for (*table 3*). A renal biopsy showed severe acellular vasculitis with thrombotic microangiopathy (TMA) and extensive fibrous intimal hyperplasia (FIH) (*figures 3* and *4*). A coronary angiogram showed no signs of macroscopic coronary artery disease.

The patient only met two out of the necessary four ARA criteria for the diagnosis of systemic lupus erythematosus (SLE), namely proteinuria and thrombocytopenia. Her anti-double-stranded DNA antibody (anti-dsDNA) titres were only marginally elevated.

CAPS, however, was a reasonable diagnosis: presence of aPL, thrombocytopenia, renal TMA, cardiac involvement, livedo reticularis and her obstetric history all fitted very well with this diagnosis. Moreover, these manifestations developed within one week, apart from her abortions. Therefore this patient received the diagnosis of CAPS.

She was initially treated with therapeutic dosages of low-molecular-weight heparin (LMWH), intravenous pulses of methylprednisolone of 1000 mg for three days, intensive plasma exchange (consisting of four litres on five consecutive days) and oral cyclophosphamide (2 mg/kg/day).

Table 2. *Results of urinalysis*

Variable	Patient A	Patient B	Reference range
pH	6.0	6.0	5.5-6.5
Screening dipstick			
- Nitrites	Negative	Negative	Negative
- Albumin	Positive	Positive	Negative
- Glucose	(4+)	(2+)	Negative
- Ketones	Negative	Negative	Negative
- Leucocytes	Negative	Positive	Negative
- Erythrocytes	Negative	(3+)	Negative
	Positive	Positive	
	(1+)	(3+)	
		Positive	
		(1+)	
Creatinine clearance (ml/min)	41.5		70-130
Total protein (g/24 hour)	1.76		0-0.15
Sediment (no. per high-power field)	2-5		0-2
- Erythrocyte count	10-20	5-10	0-4
- Leucocyte count	0		0
- Casts			

Table 1. *Results of laboratory tests*

Variable	Patient A	Patient B	Reference range
Erythrocyte sedimentation rate (mm/hr)	117	>120	0-20
Haemoglobin (mmol/l)	7.2	6.3	7.5-10
Mean corpuscular volume (fl)	82	85	80-100
Leucocyte count (x10^9/l)	5.3	18.3	4-10
- Neutrophils	4.0	14.3	1.5-9
- Lymphocytes	1.0	0.7	1.0-4.0
- Monocytes	2.0	0.2	0.2-0.8
- Eosinophils	<0.1	<0.1	<0.4
- Basophils	<0.1	<0.1	<0.2
- Schistocytes		0	0
Thrombocyte count (x10^9/l)	137	70	150-400
C-reactive protein (mg/l)	36	525	<5
Creatinine (µmol/l)*	121	112	50-90
Lactate dehydrogenase (U/l)	262	289	<250
Alkaline phosphatase (U/l)	68	225	0-120
Gamma-glutamyltransferase (U/l)	15	25	<40
Aspartate aminotransferase (U/l)	18	23	0-40
Alanine aminotransferase (U/l)	9	48	0-45
Amylase (U/l)	58	21	0-100
Creatine kinase (U/l)	43	27	<170
Creatine kinase MB isoenzymes (U/l)	9	9	<24
Troponin T (ng/ml) §	<0.05	<0.05	<0.05
NT-pro-BNP (pg/ml)	11451		<125
Activated partial thromboplastin time (sec)	48	41	20-35
Prothrombin time (INR)	1.1	1.0	0.9-1.1
Antithrombin III activity (%)		75	80-120
D-dimer (µg/ml)		7.16	<0.5
Fibrinogen (g/l)		4.9	2.0-4.0

*After 1 week the creatinine concentration rose to 188 and 117 for patient A and B, respectively. After six months there was a gradual decline in creatinine concentration to 135 and 70, respectively. §There was no follow-up of the cardiac enzymes.

Figure 1. *Echocardiography, apical four chamber view. A: Thickening of the mitral leaflets. B: Severe mitral regurgitation.*

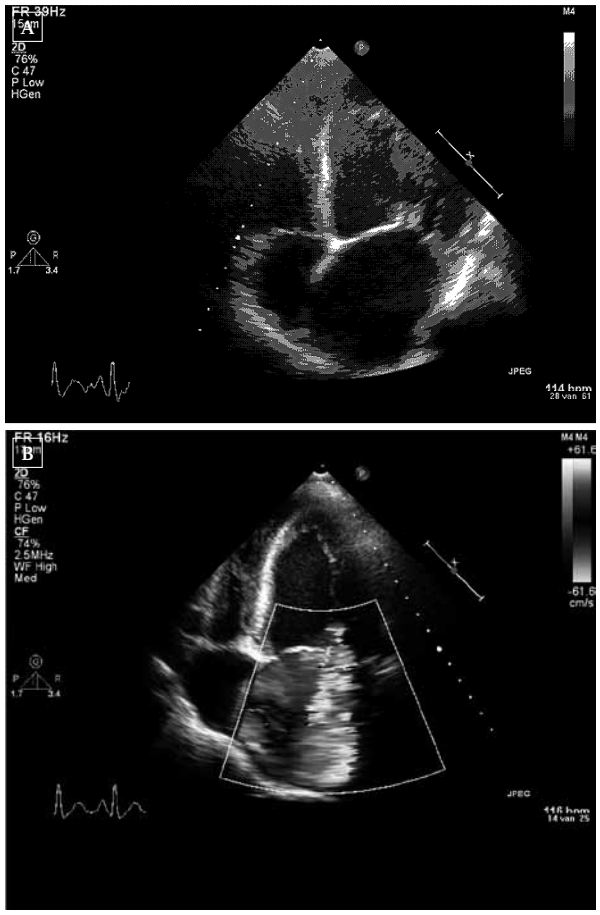
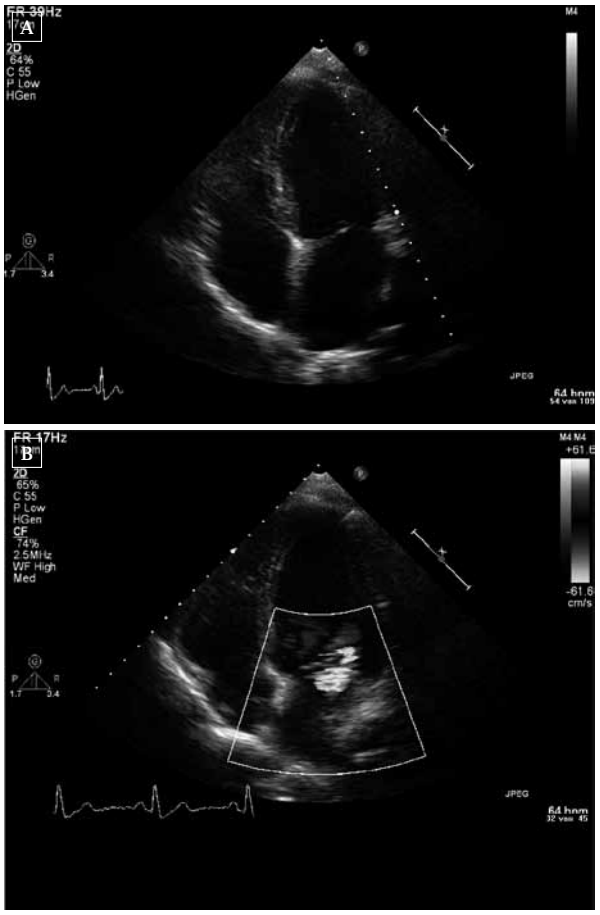


Figure 2. *Echocardiography, apical four chamber view. A: Minimal mitral valve thickening. B: Moderate mitral regurgitation.*



During follow-up, LAC could not be detected due to oral anticoagulation. IgG-aCL were still present, 11 months after the acute phase.

Nevertheless her clinical condition improved. We saw complete resolution of the haematological abnormalities and improvement of GFR and proteinuria. Moreover, the dyspnoea disappeared. The patient was dismissed with a maintenance dosage of cyclophosphamide (2 mg/kg/day) and prednisolone (20mg/day), acenocoumarol, cotrimoxazole (480 mg/day) and lisinopril. A second cardiac ultrasound – eight weeks later – showed significant regression of the mitral valve regurgitation, with an RJA/LAA index of less than 40%, a smaller vena contracta (0.59 cm) and no longer any signs of a systolic reversal of flow in the pulmonary veins (*figure 2*). Her serum creatinine peaked on day 3 of admission to 188 µmol/l [this was before start of cotrimoxazole], and stabilised at 94 µmol/l (14 months after admission with a MDRD[4] clearance of 58 ml/min/1.73 m^2, and a completely normal urinalysis). At follow-up three months after presentation the patient had a greatly improved renal function and a stable cardiac condition. Unfortunately her renal function did not recover to normal due to the chronic ischaemic nephropathy also seen in the renal biopsy. After three months therapy, cyclophosphamide was switched to azathioprine (1.5 mg/kg/day), and she was weaned from prednisolone. The scheduled valve replacement surgery could be cancelled.

Patient B

A 39-year-old woman, of Indonesian descent, presented at the emergency department with progressive abdominal pain in the right upper quadrant and nausea. Five days earlier her general practitioner had prescribed nitrofurantoin for an alleged cystitis. Further questioning revealed progressive exercise intolerance for a few months. Her medical history revealed four spontaneous births, and three missed abortions. Her regular medication consisted of alprazolam, diclophenac, omeprazole and tramadol for five days. She denied smoking, alcohol or drug abuse.

On physical examination, the patient appeared ill and apathic. The temperature was 35.9°C, blood pressure was 128/83 mmHg, and heart rate 105 beats/min. Neurological examination showed normal consciousness (Glasgow Coma Score E4-M6-V5), without signs of meningism or localising

Table 3. *Results of immunological tests*

Variable	Patient A	Patient B	Reference range
Direct antiglobulin (Coombs) test	Positive		Negative
Complement (g/l)			
- C3	1.0	0.6	0.9-1.8
- C4	0.2	0.3	0.1-0.4
Cryoglobulins	Negative	Negative	Negative
Autoantibodies			
- Antinuclear antibodies	Negative	Negative	Negative
- Anti-dou ble-stranded DNA antibody (U/ml)	Dubious	Negative	Negative
- Anti-smooth muscle antibody	Negative	Negative	Negative
- Anti-extractable nuclear antigens	Negative	Negative	Negative
- Anti-neutrophil cytoplasmic antibody	Atypical	Negative	No fluo-rescence
- Anti-PR3 and anti-MPO	Negative	Negative	Negative
- Lupus anticoagulant*	Positive*	Positive*	Negative
- IgG anticardiolipin antibody§	Positive	Negative	Negative
- IgM anticardiolipin antibody§	Dubious	Negative	Negative
- IgG anti-β2 glycoprotein-I antibody	Not tested	Negative	Negative
- IgM anti-β2 glycoprotein-I antibody	Not tested	Negative	Negative

***In patient A, tests for lupus anticoagulant could not be repeated while under anticoagulant therapy. * In patient B, lupus anticoagulant remained detectable two weeks after the acute phase; afterwards the test could not be repeated while under anticoagulant therapy. §In patient A, IgG anticardiolipin antibodies remained detectable for more than 11 months; IgM anticardiolipin antibodies became undetectable.**

Figure 4. *Renal biopsy, glomerulus with extensive fibrin deposition and stasis of red blood cells.*

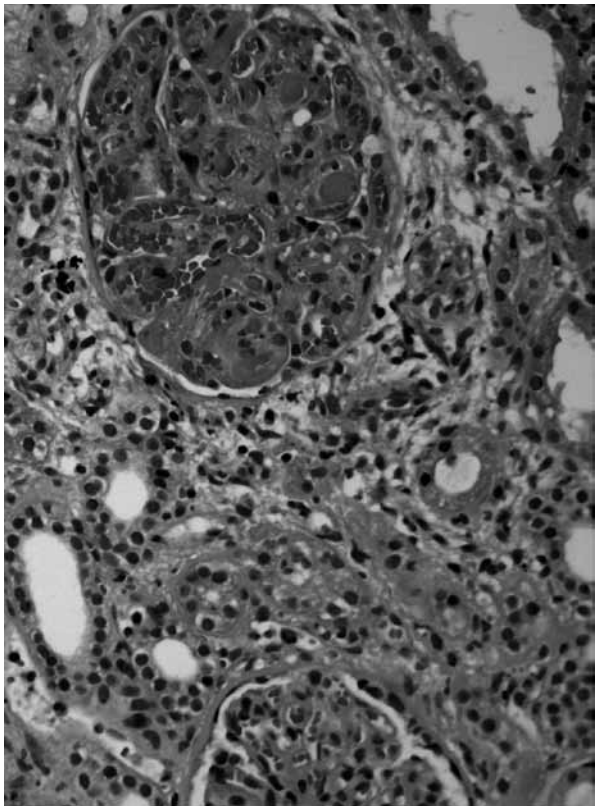
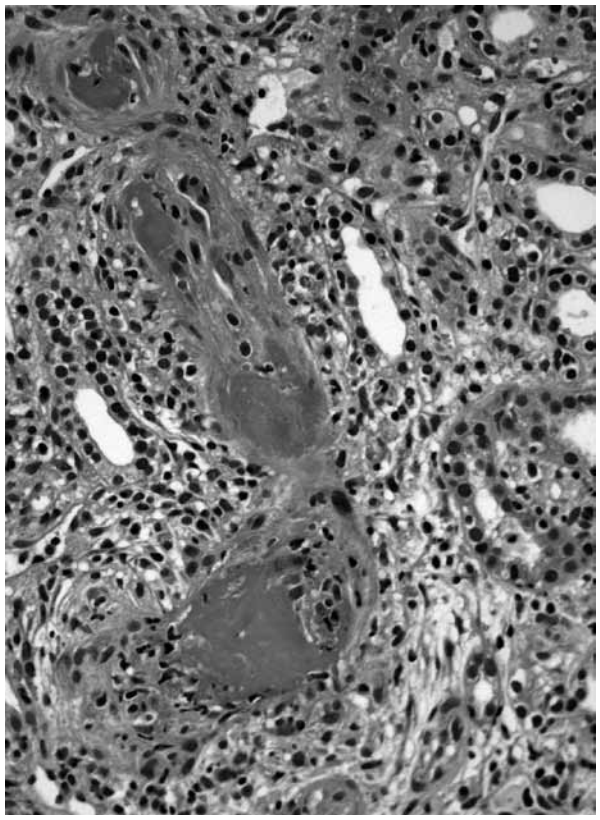


Figure 3. *Renal biopsy, arteriole with fibrinoid necrosis (original magnification: 40x).*



signs. Abdominal examination revealed normal peristalsis and diffuse tenderness with guarding on palpation of the right hypochondrion, and pain in the right costo-phrenic region. Vaginal and rectal examination were normal.

Laboratory test results are shown in *tables 1* and *2*. Ultrasonography of the abdomen did not show any abnormalities; chest radiography showed interstitial lung disease. A presumptive diagnosis of urosepsis with impending respiratory insufficiency due to ARDS was made and the patient was admitted to the intensive care unit. Antibiotic therapy with amoxicillin/clavulanic acid was started, which was later changed into ciprofloxacin when blood and urine cultures showed *Escherichia coli*. Major cerebrovascular disease was excluded with an MRI. Although quick resolution of fever followed after starting antibiotic therapy, stupor, abdominal pain, respiratory insufficiency, and thrombocytopenia persisted. CT angiography of the abdomen and thorax was performed, showing a triangular-shaped perfusion defect in the upper pole of the left kidney (renal infarction) and bilateral pleural effusions, without signs of pulmonary embolism or mesenterial thrombosis. Transthoracic cardiac ultrasound revealed a severe tricuspid regurgitation (vena contracta 0.74 cm, no signs of flow reversal in the liver veins, but a dense triangular jet density with an early peaking), a dilated right ventricle and atrium, a moderate mitral valve

regurgitation (RJA/LAA 20 to 40%, vena contracta 0.54 cm, no signs of systolic flow reversal in the pulmonary veins) with thickened valve leaflets and a diffuse left ventricular hypokinesis.

The increase of her APTT could not be corrected by addition of normal plasma, suggesting an inhibitor; this inhibitor turned out to be LAC.

This finding in combination with persistent thrombocytopenia, increased level of D-dimers, unremitting organic psychosyndrome, respiratory insufficiency and renal infarction, led to the diagnosis of CAPS (*table 3*). LAC was persistently present two weeks after the acute phase; later tests for LAC could not be repeated because of anticoagulant therapy. Anti-CL and anti-β2 GPI were negative and have remained negative for up to three months after the acute phase.

Treatment with LMWH was started and later replaced by acenocoumarol. Thrombocytopenia, which had been progressive in spite of resolution of sepsis, only improved after full anticoagulation with LMWH. The same was true for the organic psychosyndrome, which we attributed to cerebral microvascular disease. The interstitial lung disease and elevated pulmonary artery pressure could have been due either to adult respiratory distress syndrome (ARDS) due to sepsis or to CAPS. Cardiac ultrasound – eight weeks later – was normal besides a mild mitral valve regurgitation (RJA/LAA <20%, vena contracta 0.23 cm).

We omitted immunosuppression in this patient because of quick resolution of the symptoms under anticoagulation. While under treatment with full-dose acenocoumarol and without immunosuppression, patient remained in good condition during her follow-up of more than 24 months.

DISCUSSION

Both our patients had CAPS with hypokinesis of the left ventricle and valvular regurgitation as cardiac manifestations. An underlying mechanism of the formation of valvular vegetations is circulating aPL, which stimulates thrombin formation on endothelium.[6] Complement and aCL immunoglobulin deposits are also found in the subendothelial connective tissue of the deformed valves. This results in valve thickening, fusion, and rigidity causing dysfunction.[6]

We speculate that microvascular thrombosis in the myocardium and the papillary muscles could be an alternative explanation for the reversible regurgitation and hypokinesis in our patients. Unfortunately, there was no follow-up of the cardiac enzymes in our patients, as a marker for cardiac ischaemia.

Heart failure in patients with secondary APS (i.e. due to SLE) is thought to be the result of myocarditis due to immune complex formation and complement activation. Granular deposits of complement and immunoglobulin are found in myocardial blood vessels and muscle bundles.[7]

Septic myocardial depression in humans is characterised by reversible biventricular dilation and decreased systolic contractile function.[8] Cytokines, especially TNFα and IL-1β, are implicated as potent myocardium depressant factors in sepsis. Recently it has become clear that a multitude of cytokines may contribute to the multiorgan damage during the thrombotic storm in CAPS.[9] And thus could also have caused part of the cardiac manifestations in our patients.

Likewise, reversible pulmonary hypertension, which can be ascribed to either CAPS[10] or sepsis,[8] may have aggravated regurgitation of the tricuspid valve in patient B.

Echocardiography, especially transoesophageal, has shown to be an important technique that allows diagnosis of cardiac manifestations.[11] However, we expect that cardiac MRI will become a very important noninvasive modality, which can provide useful information regarding the presence of viable myocytes in patients with ischaemic or nonischaemic cardiac diseases.[12] In this setting, cardiac MRI may be an escape for myocardial biopsy.

Some recent guidelines for the management of patients with (C)APS are given in *table 4*.

Table 4. *Recommendations for the management of patients with (C)APS*

1. Treat the precipitating factor: infection, malignancy, autoimmune disorders
2. The mainstay of therapy for APS is anticoagulation; immunosuppression alone is not enough[13,14]
3. High-dose anticoumarin therapy does not seem to be necessary in view of recent information: INR 2.5 to 3.0 will do[15,16]
4. Do not forget to do enough blood cultures to exclude bacterial endocarditis
5. Because of its high mortality, catastrophic APS should be treated aggressively. Consider intensive immunosuppression with plasma exchange and/or intravenous immunoglobulins, pulses with methylprednisolone and cyclophosphamide in life-threatening CAPS (although there are no randomised controlled trials to support this policy)[15,17]
6. In case of operations, do not interrupt anticoagulation for longer than strictly necessary: operations are well-known precipitating factors for (a new bout of) CAPS[14,15,16]
7. Do not rush for cardiac surgery (see this paper!)

CONCLUSION

In our case reports we describe regression of valve regurgitation and left ventricular hypokinesis under intensive treatment for CAPS. Partial and complete regression of the cardiac manifestations have been described earlier, but reports are conflicting. We hypothesise that reversal of the valvular disease in our patients is (partially) due to the effect of anticoagulant (and

possibly immunosuppressive) therapy on microvascular disease.

We expect that an MRI is an important noninvasive way of providing more information about microvascular cardiac disease.

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