CASE REPORT

Rapidly progressive aortic aneurysmal dilation in a child with systemic lupus erythematosus: too early too severe

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SUMMARY

About 10–20% of systemic lupus erythematosus cases occur in children, often with more severe features at onset and more active disease over time compared with adults. Cardiovascular complications are common in this population but thoracic aortic aneurysms rarely occur. Although the pathophysiology of this complication remains unclear, vasculitis seems to play an important role, leading to degeneration and fibrosis of the media and formation of the aneurysm. We report the case of a 9-year-old systemic lupus erythematosus patient with important renal involvement, who underwent aortic replacement surgery for the treatment of an aortic aneurysm. This case highlights the importance of monitoring the thoracic aorta in children with systemic lupus erythematosus and the need for the development of appropriate early management strategies for this serious complication.

BACKGROUND

Systemic lupus erythematosus is a multisystemic autoimmune disease associated with high morbidity and mortality. Cardiovascular complications are common in systemic lupus erythematosus but aortic aneurysm is a rare entity especially in the paediatric population. The pathophysiology of aortic aneurysms in systemic lupus erythematosus patients is still not fully understood. Furthermore, there are no reports of aortic aneurysm in young children with systemic lupus erythematosus. The youngest reported case of thoracic aortic aneurysm in the setting of systemic lupus erythematosus is a 17-year-old boy.¹ We present the case of a 9-year-old boy with rapidly progressive aneurysm involving the aortic root and ascending aorta in the setting of systemic lupus erythematosus that required surgical replacement of the aorta.

CASE PRESENTATION

A 9-year-old boy was admitted to our institution for severe hypertensive crisis. He had a personal history of Henoch-Schönlein purpura. The patient had never undergone surgery, had no family history of aortic aneurysm and did not show any clinical evidence of Marfan syndrome. Two years earlier, he had been diagnosed with systemic lupus erythematosus after initially presenting with fatigue, low-grade fever and arthritis. Subsequent investigations revealed the presence of severe hypertension, nephrotic syndrome and haemolytic anaemia. Antinuclear antibodies were positive (1/5120), as

were anti-DNA antibodies (1149 UI/mL). The patient also had low levels of C3 and C4 proteins at 0.34 g/L and less than 0.02 g/L, respectively. Antiphospholipid antibodies were negative. The 12-lead electrocardiogram was normal, as was a transthoracic echocardiogram that showed a competent aortic valve and absence of aortic dilation. A renal biopsy revealed lupic proliferative glomerulonephritis (WHO class IV-G). The patient was initially treated with three methylprednisolone pulses, followed by prednisone 50 mg daily (1.75 mg/kg) progressively weaned to 20 mg daily over the first 6 months, combined with mycophenolate mofetil 750–1000 mg twice daily (900 mg/m²) throughout his first year. He was also treated for hypertension with daily hydrochlorothiazide 12.5 mg and losartan 50 mg combined with clonidine 0.1 mg three times daily. A year after the diagnosis, he suffered from cystic lymphangioma of the colon with ulcerations and acute inflammatory changes that required sequential resection of the colon. A month later, in order to control the still active lupic proliferative glomerulonephritis, he was given three pulses of methylprednisolone 400 mg and six monthly doses of intravenous cyclophosphamide 0.75 g/m² followed by four intravenous rituximab 0.375 g/m² doses.

The severe hypertensive crisis which led to the hospitalisation described in this report occurred after the first dose of rituximab, 2 years after the initial systemic lupus erythematosus diagnosis. On admission, the patient complained of intermittent non-radiating chest pain that diminished when he leaned forward and increased when he was in the supine position. The patient did not report palpitation nor dyspnoea. On physical examination, his weight was 42.6 kg, his height 138.5 cm and his blood pressure 190/127 mm Hg with regular heart rate at 75 bpm. Heart sounds were normal, without any murmur or pericardial rub, but the patient had a hyperdynamic apex. His lungs were clear and his jugular venous pressure was normal.

INVESTIGATIONS

Laboratory studies revealed a haemoglobin level of 102 g/L, white cell count of 3.84×10^9 /L, an erythrocyte sedimentation rate of 56 mm/h and a C reactive protein level of 4.6 mg/L. Serum creatinine was measured at 91 µmol/L and blood urea nitrogen 8.4 mmol/L. The antinuclear antibodies were at 1/160, anti-DNA antibodies at 173 UI/mL and C3/C4 concentrations were 0.43 and 0.08 g/L,

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respectively. The 24 h urine collection showed a proteinuria of 6.5 g/day and a protein/creatinine ratio of 0.68. A transthoracic echocardiogram showed mild pericardial effusion, left ventricular hypertrophy, aortic root and ascending aorta dilation (39 mm, $Z=5.08$ and 26.4 mm, $Z=2.81$, respectively) and mild central aortic insufficiency with a normal left ventricular ejection fraction of 77%. The patient was discharged 12 days post-admission with optimised antihypertensive therapy including amlodipine 5 mg twice daily, clonidine 0.1 mg three times daily, hydrochlorothiazide 25 mg daily, losartan 100 mg daily, metolazone 7.5 mg twice daily and etacrynic acid 25 mg twice daily.

On outpatient follow-up 3 months later, laboratory work-up showed an erythrocyte sedimentation rate of 34 mm/h, C3 level of 0.83 g/L, C4 level of 0.13 g/L, antinuclear antibodies of 1/160 and anti-DNA antibodies of 30 U/mL. The blood pressure was normal at 117/60 mm Hg. Physical examination revealed a left parasternal systolic ejection murmur III/VI and a right parasternal diastolic murmur II/VI. The echocardiogram showed a small residual pericardial effusion, left ventricular hypertrophy and left ventricular dilation of 55 mm with normal systolic function. More importantly, the aortic root and ascending aorta dilation had progressed to 47.1 mm ($Z=7.16$) and 39.6 mm ($Z=7.49$), respectively. The aortic insufficiency had also progressed and had become severe with a retrograde holo-diastolic flow in the abdominal aorta. Three weeks later, a 4×4 mm nodule was identified on echocardiography, at the extremity of the non-coronary and left coronary commissure of the aortic valve in addition to a moderate pericardial effusion, a significant left ventricular dilation with a diameter of 64 mm ($Z=6.9$), an indexed systolic left ventricular volume of 45.9 mL/m² and severe aortic insufficiency. Systolic function was preserved with an ejection fraction of 63%. The aortic root and ascending aorta dilation were unchanged at 46.9 mm ($Z=7.67$) and 36.8 mm ($Z=6.70$), respectively. An MRI confirmed the presence of an important dilation of the aortic root (48.7 mm) and ascending aorta (44.6 mm) (figure 1). The MRI also showed dilation of the sinotubular junction and aortic annulus, which was associated with significant aortic insufficiency. Furthermore, the MR showed a mild nodularity of the right coronary sinus at its junction with the left coronary sinus. In the setting of significant dilation of the ascending aorta and progression of aortic insufficiency despite optimal control of blood pressure, the patient underwent surgical replacement of the aortic valve and ascending aorta using a mechanical Carbomedics Carbo-Seal Ascending Aorta Prosthesis (Sorin, Milano, Italy). The procedure was successfully performed with no complication. The postoperative course was uneventful. The patient was discharged on postoperative day 12 with oral anticoagulation therapy. He is regularly seen in the outpatient clinic and continues to be asymptomatic.

OUTCOME AND FOLLOW-UP

Histological analysis of the specimens collected during surgery yielded no sign of active inflammatory reaction. Instead, there was a slight increase of mucoid alcianophilic substance in the adjacent non-dilated portion of the aorta (figure 2, top panel) and thinning, degeneration and fibrosis of the aortic media with important loss of elastic fibres in the dilated portion (figure 2, lower panel), leading to the pathological diagnosis of cystic medial degeneration. No histological lesion of either the pericardium or the aortic valve leaflets was apparent, except for a nodular accumulation of mucoid substance in one leaflet.

Figure 1 MRI of the aneurismal thoracic aorta. The short axis view (A) demonstrates the magnitude of the dimensions of the dilation of the aortic root. The long axis (B) illustrates the tortuous aorta in addition to the aortic root dilation.

DISCUSSION

Systemic lupus erythematosus typically occurs during adulthood. Nevertheless, childhood onset occurs in 10–20% of cases.² Paediatric systemic lupus erythematosus has an incidence rate of 0.4–2.5/100 000 and a prevalence of 1.9–25.7/100 000.³ Paediatric systemic lupus erythematosus is increasingly being recognised as a distinct entity from adult-onset systemic lupus erythematosus. It often presents with more severe features at onset and is more active over time.² Libman-Sacks endocarditis is a recognised complication of systemic lupus erythematosus. It is believed to be secondary to deposition of fibrin-platelet thrombi on the affected valve, forming a sterile valvular vegetation. In the present case, the diagnosis of Libman-Sacks endocarditis was first suspected due to the presence of an aortic valve vegetation on the successive transthoracic echocardiograms. However, upon histopathological analysis, the diagnosis could not be confirmed, and was hence excluded.

The pathophysiology of thoracic aortic aneurysms in systemic lupus erythematosus patients is still not fully understood. A recently published meta-analysis sought to identify the mechanisms contributing to aneurysm formation in systemic lupus erythematosus by reviewing the 35 published cases between 1969 and 2008.⁴ The authors concluded that there was a positive correlation between thoracic aneurysms and aortic

Figure 2 Top panel: histology of the non-dilated portion of the aortic wall shows (A) preserved elastic laminae, occasionally separated by small clear areas (haematoxylin–phloxin–safran, $\times 100$). There are (B) multiple small areas containing alcianophilic mucoid substance (alcian blue-PAS, $\times 100$) and (C) regular and well-preserved elastic laminae (Verhoeff-Van Gieson, $\times 100$). Lower panel: histology of the aneurismal portion of the aorta illustrates (D) the thinning and fibrosis of aortic wall with absence of elastic laminae except for a small layer in the deeper media (HSP, $\times 100$). Important fibrosis (E) with mucoid substance (alcian blue-PAS, $\times 100$) and (F) absence of normal elastic laminae are replaced with only small irregular elastic fibres (Verhoeff-Van Gieson, $\times 100$).

dissection as well as cystic medial degeneration. Additionally, a positive correlation between cystic medial degeneration and vasculitis was demonstrated. Implication of cystic medial degeneration in the pathophysiology of aortitis leading to aortic aneurysm has also been described.⁵ These conclusions are consistent with the results of other studies.⁶ Surgical pathology analysis in the present case revealed histological changes of the media that fit the definition of cystic medial degeneration. Thus, the patient's aortic aneurysm was likely the result of a weakening of the aortic wall secondary to the inflammatory process of a systemic lupus erythematosus-associated aortitis. Intense immunosuppressive therapy preceding the surgery could have contributed to the absence of active inflammation on the pathology specimen. Based on a meta-analysis, long-term corticosteroid therapy, as well as hypertension, which is a known risk factor for thoracic aorta aneurysm development in the adult, do not seem to be associated with an increased risk of rupture in systemic lupus erythematosus patients.⁴

Blood pressure control in hypertensive patients is part of the general medical management of thoracic aortic aneurysm as it is a risk factor for dissection as well as for cardiovascular morbidity and mortality. Owing to the rarity of thoracic aortic aneurysm in the paediatric population, few efforts have been devoted to the development of paediatric specifications except in the case of Marfan syndrome patients.⁷ Initiation of treatment and blood pressure targets for hypertension in children and adolescents are based on the severity of systemic hypertension as defined in percentiles.⁸ Paediatric clinical trials evaluating the effectiveness of specific antihypertensive drugs have used reduction in blood pressure as their primary endpoint. However, the effects of these drugs on long-term clinical outcomes have not been studied.⁹ Therefore, unlike in the adult population, the choice of a first-line agent is largely dictated by physician preference, except in the setting of underlying or concomitant conditions that warrant the use of specific agents (eg, ACE inhibitors or angiotensin-receptor blockers in chronic kidney disease). In the present case, initial therapy with losartan was aimed, in

addition to treating elevated blood pressure, at reducing the persistent proteinuria and to slow the progression of the chronic renal involvement. These effects are suggested by paediatric studies on hypertension on one hand¹⁰ and for systemic lupus erythematosus on the other hand.¹¹

Finally, β -blockers could be considered in cases with significant dilation of the ascending aorta as suggested by the American Heart Association for Marfan syndrome patients with aortic aneurysm. Nevertheless, a non-randomised study published in 2005 suggested superior haemodynamic and clinical results with the use of enalapril compared with β -blockers despite significant reduction of heart rate with the later.¹² In this perspective, the comparative effectiveness of β -blockers versus antiangiotensin drugs, in Marfan syndrome, has yet to be disclosed following the ongoing randomised clinical trials.

Aortic aneurysms rarely occur in the paediatric population. Nonetheless, the potential complications associated with this condition in children are similar to those in adults, namely rupture, dissection and valvular incompetence when the aortic root is involved.¹³ There are insufficient data to guide the timing of prophylactic surgery in thoracic root aneurysm in children.¹³ Indications for surgery in Marfan syndrome associated ascending aortic aneurysm are the most well established in the paediatric population.⁷ Giving the lack of clear guidelines for systemic lupus erythematosus patients, our multidisciplinary team decided to perform prophylactic surgery based on Marfan syndrome guidelines because of the rapid progression of the aortic root dilation (10 mm in 4 months) and also its size (46.9 mm, Z score=7.67).

While aortic aneurysm is a rare complication of systemic lupus erythematosus, its consequences are often catastrophic.¹⁴ Younger systemic lupus erythematosus patients are at a higher risk of presenting thoracic aortic involvement.⁴ This raises the question of whether or not specific management strategies should be adopted for this population of patients to allow for early detection of aortic disease and timely intervention. Until 2004, no paediatric guidelines about the management of

systemic lupus erythematosus had been published. In 2004, they were the first proposed recommendations for the required investigations at diagnosis and during follow-up of childhood-onset systemic lupus erythematosus.¹⁵ The authors suggest that serial chest X-rays and echocardiography be performed every 3 years to detect cardiac involvement. Routine echocardiography screening for silent cardiac abnormalities has also been proposed.^{16 17}

In summary, we report the case of a 9-year-old patient with systemic lupus erythematosus who underwent aortic replacement surgery for the treatment of an aortic aneurysm. This is, to our knowledge, the youngest reported case of aortic aneurysm in this context. This report highlights the importance of a close monitoring of these young patients to promote early detection of this rare but potentially fatal complication.

Learning points

This is, to our knowledge, the youngest reported case of aortic aneurysm in a patient suffering from systemic lupus erythematosus which highlights the following points:

- ▶ Severe aneurismal dilation of the aorta, a known entity in the adult with systemic lupus erythematosus, can also occur in young children.
- ▶ The aortic aneurysm is likely the result of a weakening of the aortic wall secondary to the in situ inflammatory process.
- ▶ Serial monitoring of the thoracic aorta with echocardiographic studies and early referral to a surgical team is important in these patients.

Contributors SR-d'A abstracted the case history, reviewed the literature and drafted the initial manuscript. ND is the managing cardiologist who supervised the preparation of the review and the writing of the manuscript. PB performed, reviewed and provided the histological analysis and discussion. CS-C is the managing rheumatologist who reviewed the literature and the manuscript. All authors approved the final manuscript as submitted.

Competing interests None.

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