CASE REPORT

Macrophages and cytotoxic T cells infiltrate the destructed mitral tissue in Kawasaki disease

Yuichiro Sugitani,^{1,2} Kenji Furuno,^{1,3} Katsuo Sueishi,⁴ Toshiro Hara¹¹Kawasaki Disease Center, Fukuoka Children's Hospital, Fukuoka, Japan²Department of Cardiology, Fukuoka Children's Hospital, Fukuoka, Japan³General Pediatrics and Interdisciplinary Medicine, Fukuoka Children's Hospital, Fukuoka, Japan⁴Department of Pathology, Fukuoka Tokushukai Byoin, Kasuga, Japan**Correspondence to**
Dr Kenji Furuno,
furuno.k@fcho.jp

Accepted 13 January 2018

SUMMARY

Kawasaki disease (KD) is an acute febrile systemic vasculitic syndrome especially affecting medium-sized arteries, including the coronary artery. Inflammation may involve all organs, and valvulitis is one of the cardiovascular complications that occurs in the acute phase of KD. However, details regarding the mechanism are unclear. An infant developed KD and severe mitral regurgitation with deformity and prolapse of the mitral tissue and underwent mitral valvotomy 1 year later. Histopathological study was conducted, and infiltrating cells consisted of mainly macrophages and cytotoxic T cells were found in resected mitral valve tissue. In addition, inflammation remained a long time after KD had developed.

BACKGROUND

Mitral regurgitation (MR) is a relatively rare cardiovascular complication of Kawasaki disease (KD).^{1–3} The main causes of MR with KD are valvulitis and ischaemia from the stenosis of coronary artery after the formation of aneurysm. MR with valvulitis mostly recovers and disappears. In valvulitis of KD, the infiltration of chronic inflammatory cells to the mitral valve and elongation of the chordal tendineae have been reported in resected mitral tissue and autopsy cases.^{3,4} However, the immunological details of valvulitis complicated KD in vivo are unclear. There have been few reports that the inflammation of mitral valve persisted for long term after the cure of KD. We report a case with severe MR underwent mitral valvotomy at 1 year after being diagnosed with KD, which showed the pathological findings of valvulitis on the resected specimen.

CASE PRESENTATION

A 6-month-old boy had a fever on the first day of his illness and was admitted on the fourth day of his illness. He was born at full term by normal vaginal delivery and had no abnormal history prior to the illness. He had received all scheduled vaccination. At admission, he had mild bulbar conjunctival redness and a rash on the surface of his abdomen. Cardiac murmur was not heard. The chest roentgenogram showed a cardiothoracic ratio of 48%. He was diagnosed with a bacterial infection of unknown origin and treated with ceftriaxone. He was discharged after the fever subsided. However, for relapsing fever, he was readmitted. Antibiotic therapy was restarted because his white cell count

(WCC) and C-reactive protein (CRP) were elevated (WCC $13.1 \times 10^9/L$, CRP 5.87 mg/dL). The fever remained high despite treatment. On the 18th day of his illness, he looked pale and tachycardia, tachypnoea, a systolic murmur at the cardiac apex were recognised. Echocardiography revealed MR with serum brain natriuretic peptide levels elevated to 283 pg/mL (normal range <18.4). He was thought to have suffered from myocarditis and was transferred to our hospital for intensive care.

On admission to our hospital, physical examination showed mild erythema of the lips, a rash on his back and redness around his BCG scar, which are specific findings of KD. Distinct facial features and spider fingers suggesting Huler syndrome and Marfan syndrome were unnoticed. Pansystolic heart murmur of Levine III/VI and mid-diastolic murmur were heard at the cardiac apex. He had a slightly elevated temperature, sinus tachycardia and mild tachypnoea (body temperature 37.6°C, pulse rate 197 beats/min, respiratory rate 48 times/min).

INVESTIGATIONS

Blood examination showed WCC 26 120/μL and CRP 5.2 mg/dL. Repetitive blood cultures were negative at admission. Mild congestion of his lung was recognised on chest X-ray. No ischaemic findings such as the elevation of ST segment or abnormal Q wave were found on ECG. On echocardiography, severe MR, mitral valve prolapse and the dilatation of the right coronary artery (RCA) (4 mm in diameter) were observed (figure 1). There was no definite elongation of the chordae tendineae. The left atrium and left ventricle were also dilated due to MR in echocardiography; the end-diastolic dimension of left ventricle was 28 mm (112% of normal dimension) and the left atrial-to-aortic root ratio was 1.7. There were no abnormal findings for the tricuspid, aortic or pulmonary valves. We diagnosed him with KD based on the presence of four of the six specific symptoms and the dilatation of the RCA, in accordance with the guideline for KD published by the Japanese Society of Kawasaki Disease in 2002. We administered intravenous immunoglobulin (2 g/kg) and aspirin (30 mg/kg/day) and performed plasma exchange for 3 days. We then performed a second round of immunoglobulin therapy until the 23rd day of his illness, at which point his fever began to resolve. Heart failure was treated using diuretics, furosemide and spironolactone, and stabilisation of haemodynamics was achieved. He was discharged on the 37th day of his illness. However, MR and mild dilatation of the RCA remained unresolved.

To cite: Sugitani Y, Furuno K, Sueishi K, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223584

Figure 1 Echocardiography findings at admission. (A) Prolapse of posterior leaflet of mitral valve (white arrow). (B) Severe mitral regurgitation (arrow heads). (C) Dilatation in RCA (white arrow). Ao, aorta; LA, left atrium; LCA, left coronary artery; LV, left ventricle; RCA, right coronary artery.

TREATMENT

Treatment was continued with aspirin (3 mg/kg/day), furosemide and captopril. However, he failed to thrive, and the degree of MR remained unchanged. At 1 year of age, MR was assessed using cardiac catheterisation procedure. On left ventriculography, the degree of MR was Sellers classification III, and there were no coronary arterial lesions. At 1 year and 6 months of age, he underwent mitral valvotomy. The intraoperative findings showed that the P2 segment of the posterior leaflet was deformed, elongated and prolapsed. There were no findings of ischaemia, such as rupture of the papillary muscle. After the affected mitral valve was resected by the quadrangular method, the adjacent valve tissues were sutured. Mitral annuloplasty was performed by Kay-Reed method.

OUTCOME AND FOLLOW-UP

The resected tissue was evaluated histopathologically. The tissue was irregularly thickened and had an increased amount of myxoid stroma. (H&E and immunohistochemical stainings were performed. H&E staining showed that mononuclear inflammatory cells were scattered throughout the valve tissue, particularly in the superficial stroma. These inflammatory cells were immunohistochemically positive mainly for CD8 and CD68, with few CD4 and CD20 positive cells also recognised (figure 2).

Figure 2 Mitral valve tissue affected by valvulitis with KD. (A) Inflammatory cells are scattered (H&E staining, ×100). (B) Leucocyte antigen (LCA) (immunohistochemical staining, ×100). (C) CD68 positive macrophage and (D) CD8 positive lymphocyte are scattered in the superficial layer (immunohistochemical staining, ×100).

DISCUSSION

We reported a patient with severe MR as a complication of KD without severe coronary arterial lesions. Deformation and elongation of the posterior leaflet caused irreversible severe MR. The patient underwent mitral valvotomy 1 year after the diagnosis of KD. We described the histopathological details of the valvular changes. The immunohistopathological findings show that the infiltrated cells in the inflamed mitral tissue were macrophages and cytotoxic T cells.

The aetiology of MR in children consisted of congenital defects and acquired abnormality. Acquired abnormalities due to other diseases including rheumatic fever, infectious endocarditis, cardiomyopathy, metabolic diseases, as well as KD. Other diseases causing MR could be ruled out owing to the absence of specific clinical findings. The myxoid change of the resected mitral valve was found. In infant, this change is uncommon and implies the existence of inflammatory disease such as KD, while the lesion is a relatively common pathological change seen in adult patients with mitral valve prolapse.^{5,6} The causes of MR as a complication of KD are well recognised, and ischaemia, papillary muscle dysfunction from pancarditis and valvulitis are thought to be the major causative factors.^{3,7-9} Shiraishi *et al* showed that 95 patients were diagnosed as acute rupture of mitral chordae tendineae in the last two decades in Japan with 80 patients underwent surgical operation. Among them, KD was diagnosed in 10 patients before the onset of rupture.⁵

Ischaemia was caused by the stenosis of the coronary artery after an aneurysm formed and developed from a period of several months over several years after the initial diagnosis of KD. The dilatation of the coronary artery gradually progresses to stenosis.¹⁰ Therefore, MR developed slowly in these cases. Findings of ischaemia on ECG, such as the rising of the ST segment or chest pain, may be observed at the onset of MR in older patients. Although our case had transient dilatation of the RCA, there was no stenosis of the RCA, and rupture of the papillary muscle and histopathological ischaemic changes were not observed. These suggest that ischaemia was unlikely the underlying cause of MR in our case.

Valvulitis may be included in pancarditis and develop in the acute phase of KD. Nagata *et al* proved the existence of valvulitis as well as vasculitis, myocarditis and pericarditis by high echogenicity of the mitral valve in patients with KD.¹¹ MR caused by pancarditis disappeared spontaneously, while the other conditions caused by dysfunction of the valve and papillary muscle persisted.⁷ Imakita *et al* reported a female case with MR affected by valvulitis who died suddenly.⁴ The mitral valve was deformed and elongated at autopsy. The histological findings showed infiltration of inflammatory cells, an increase in the amount of fibrous connective tissue and the proliferation of small capillaries on the valvular lesion.

In our case, the posterior leaflet of the mitral valve was similarly grossly deformed, and chronic valvulitis was noted on a histopathological examination. We speculated that the mitral leaflet tissue was damaged by active endocardial inflammation in the acute phase of KD following sustained valvulitis. Although there were two autopsy cases with the findings of valvulitis at several months after the onset of KD, they provided the report of mild inflammation of mitral valve.¹²

The histopathological findings of the coronary artery at the acute phase of KD are inflammation in all layers of the arterial wall, intima, media and adventitia. Inflammatory cells, particularly CD68+ macrophages, infiltrate all layers and neutrophils mainly in the media early after KD.¹³ Motomura *et al* recently reported that cardiac CD11C+ macrophages play a pivotal role in the development of acute coronary arteritis in FK565-treated mice.¹⁴ Although the existence of inflammatory cells in mitral valve tissue of KD has been reported in both surgical and autopsy findings, the immunological details of these inflammatory cells have been unclear. In the present case, we found that the affected mitral valve was infiltrated by inflammatory cells that mainly consisted of CD68+ and CD8+ leucocytes. Although these findings might have been non-specific, to our knowledge, this is the first report that the *in vivo* existence of macrophages in the mitral tissue in KD-related valvulitis was histopathologically proven to be the same as those found in vasculitis in KD. As Kusuda *et al* reported, we speculate that the molecules derived from microbes mimicking FK565 stimulate the innate immunity and induce valvulitis by macrophage and cytotoxic T cell.¹⁵

The results of this case suggest that the recruitment of immune cells, mainly macrophages and cytotoxic T cells, plays an important role in the destruction of valvular structures, leading to the development of MR in patients with KD, and the inflammation process persists even after the acute phase.

Learning points

- Valvulitis with Kawasaki disease (KD) is the main cause of mitral regurgitation.
- In our case, it was proven that inflammatory cells, mainly macrophages and cytotoxic T cells, infiltrate the mitral tissue and play an important role in the destruction of valvular structures in the acute phase and that the inflammation process persists until the chronic phase of KD.

Contributors YS and KF contributed to the diagnosis, workup and writing the manuscript. KS performed the pathological examination and reviewed the manuscript. TH contributed to the interpretation of pathology findings and manuscript review.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Tomita H, Sawada Y, Higashidate Y, *et al*. Mitral regurgitation with gross deformity of a mitral leaflet due to Kawasaki disease. *Pediatr Cardiol* 1990;11:153–5.
- 2 Mishima A, Asano M, Saito T, *et al*. Mitral regurgitation caused by ruptured chordae tendineae in Kawasaki disease. *J Thorac Cardiovasc Surg* 1996;111:895–6.
- 3 Gidding SS, Shulman ST, Ilbawi M, *et al*. Mucocutaneous lymph node syndrome (Kawasaki disease): delayed aortic and mitral insufficiency secondary to active valvulitis. *J Am Coll Cardiol* 1986;7:894–7.
- 4 Imakita M, Sasaki Y, Misugi K, *et al*. Kawasaki disease complicated with mitral insufficiency. Autopsy findings with special reference to valvular lesion. *Acta Pathol Jpn* 1984;34:605–16.
- 5 Shiraishi I, Nishimura K, Sakaguchi H, *et al*. Acute rupture of chordae tendineae of the mitral valve in infants: clinical perspective. *Circulation* 2014;130:1053–61.
- 6 Wilcken DE, Hickey AJ. Lifetime risk for patients with mitral valve prolapse of developing severe valve regurgitation requiring surgery. *Circulation* 1988;78:10–14.
- 7 Akagi T, Kato H, Inoue O, *et al*. Valvular heart disease in Kawasaki Syndrome. *Am Heart J* 1990;120:366–72.
- 8 Takao A, Niwa K, Kondo C, *et al*. Mitral regurgitation in Kawasaki disease. *Prog Clin Biol Res* 1987;250:311–23.
- 9 Takahashi T, Kadoba K, Taniguchi K, *et al*. Long-term results of surgical treatment for mitral regurgitation with severe left ventricular dysfunction after myocardial infarction caused by Kawasaki disease. *J Thorac Cardiovasc Surg* 1996;111:893–4.
- 10 Fukushige J, Takahashi N, Ueda K, *et al*. Long-term outcome of coronary abnormalities in patients after Kawasaki disease. *Pediatr Cardiol* 1996;17:71–6.
- 11 Nagata H, Yamamura K, Uike K, *et al*. Evaluation of echogenicity of the heart in Kawasaki disease. *Eur J Pediatr* 2014;173:1089–93.
- 12 Orenstein JM, Shulman ST, Fox LM, *et al*. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. *PLoS One* 2012;7:e38998–398.
- 13 Takahashi K, Oharaseki T, Naoe S, *et al*. Neutrophilic involvement in the damage to coronary arteries in acute stage of Kawasaki disease. *Pediatr Int* 2005;47:305–10.
- 14 Motomura Y, Kanno S, Asano K, *et al*. Identification of pathogenic cardiac CD11c+ macrophages in Nod1-mediated acute coronary arteritis. *Arterioscler Thromb Vasc Biol* 2015;35:1423–33.
- 15 Kusuda T, Nakashima Y, Murata K, *et al*. Kawasaki disease-specific molecules in the sera are linked to microbe-associated molecular patterns in the biofilms. *PLoS One* 2014;9:e113054.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow