CASE REPORT

Reoperation after mitral valve repair in viewpoints of kidney injury as well as hemolytic anemia

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Abstract A 70-year-old woman developed anemia and kidney injury 10 months after mitral valve (MV) repair. Serological findings and Doppler echocardiography suggested hemolytic anemia due to mitral regurgitation jet collision with an annuloplasty ring (MRCR). Since kidney injury persisted even without exacerbation of anemia over 10 months, we performed an MV replacement. The anemia improved rapidly after the surgery; however, the renal function remained chronic kidney disease (CKD) after reoperation. Kidney injury was thought to be due to iron deposition and decreased renal perfusion that caused tubular injury. A comprehensive literature review shows that hemolysis due to MRCR in the early postoperative phase (within 3 postoperative months) can be often ameliorated with endothelialization without the need for reoperation; however, hemolysis in the late postoperative phase can persist even for a long period without reoperation. Chronic hemolysis can lead to kidney injury and progress to CKD even without clinical evidence of exacerbation of anemia. Therefore, in cases of late postoperative phase hemolysis, reoperation should be considered for better management of kidney injury and hemolytic anemia.

Keywords Mitral valve repair · Hemolytic anemia · Kidney injury · Chronic kidney disease

Introduction

Hemolysis following mitral valve (MV) repair can be caused by annuloplasty dehiscence, protruding suture material, or whiplash motion of a ruptured tendon. In addition, mitral regurgitant (MR) jet collision with a pledget, the atrial wall, or the annuloplasty ring can cause hemolysis [1–6].

MR jet collision with the annuloplasty ring (MRCR) inhibits endothelialization at the collision site, which further exacerbates hemolysis that is dependent on the shear stress caused by collision with an unendothelialized rough surface and red blood cells [7, 8]. Two treatment options are available for such cases: reoperation for MV repair and replacement, and observation for amelioration of the shear stress and endothelialization.

The indications for reoperation are recurrent severe MR, or progression to severe MR, the presence of mitral stenosis, severe hemolytic anemia, and symptoms of fatigue, dyspnea, shortness of breath at rest, or angina [9, 10]. However, it is difficult to determine the appropriate time for reoperation. In addition, although hemolysis and subsequent hemoglobinuria are thought to result in kidney injury [11], kidney injury is not considered an indication for surgery, and there have been no reports on kidney injury as an indication for reoperation.

In this study, we report on a case of hemolysis due to MRCR resulting in kidney injury after MV repair and discuss the indications for reoperation in cases of kidney injury.

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Case report

A 70-year-old woman who presented to our hospital with severe MR due to MV prolapse underwent MV repair via a quadrangular resection of the posterior leaflet and ring annuloplasty with a 29-mm Tailor™ Flexible Ring (St. Jude Medical, Inc., St. Paul, MN, USA).

Ten months postoperatively, she complained of shortness of breath and brown urine (Fig. 1), prompting admission to our hospital. Table 1 outlines laboratory data on admission. Remarkable findings included the following: red blood cell, $211 \times 10^4/\mu\text{L}$; hemoglobin (Hb), 6.8 g/dL; serum aspartate aminotransferase (AST), 98 IU/L; serum lactate dehydrogenase, 2168 IU/L; total bilirubin, 2.23 mg/dL; direct bilirubin, 0.53 mg/dL; and serum creatinine (Cr), 1.48 mg/dL. Urinary findings showed 3+ occult blood and negative cast formation. *N*-acetyl- β -D-glucosaminidase (NAG) and β 2-microglobulin (β 2m) increased to 36.5 U/gCr and 45435 $\mu\text{g/gCr}$, respectively. Comparison with the data before MV repair (Hb, 12.1 g/dL; AST, 23 IU/L; Cr, 0.4 mg/dL; no occult blood), the data at admission showed progression to hemolytic anemia and kidney injury. International normalized ratio of prothrombin time was prolonged (2.09) due to warfarin therapy administered post-MV repair for the management of paroxysmal atrial fibrillation. Other parameters considered in the differential diagnosis of hemolysis (Table 2) were fragmented red blood cells, haptoglobin level <10 mg/dL, negative direct Coombs' test results, no paroxysmal nocturnal hemoglobinuria including CD55- or CD59-, and no glycosylphosphatidylinositol anchor-negative cells according to flow

cytometry. Transesophageal Doppler echocardiography revealed MRCR (Fig. 2). Therefore, the patient was diagnosed with hemolysis caused by MRCR following MV repair. Although anemia was not exacerbated later, kidney injury remained persistent over 10 months; computed tomography (CT) revealed an increase in renal cortex, liver, and spleen hyperdensity compared with that seen 2 years previously (Fig. 3).

Thus, MV replacement was performed. Intraoperative observation showed insufficient endothelialization of the annuloplasty ring at the MRCR site. Postoperatively, hemolytic anemia improved and urine findings were ameliorated. One month postoperatively, Hb level improved to 12.2 g/dL, and NAG and β 2m levels decreased to 6 U/gCr and 347 $\mu\text{g/gCr}$, respectively. However, Cr level did not recover sufficiently to 0.9 mg/dL at the 1-year follow-up (Fig. 1).

Discussion

There have been many reports of hemolysis following MV repair in the literature. To date, to the best of our knowledge, 18 case reports and five case series of hemolysis following MV repair have been reported in English (Table 3). Of these, the reports we chose fulfilled the following three conditions: a clear degree of MR jet as seen on Doppler echocardiography; a clear interval from initial operation to the appearance of hemolysis, and a clear one-to-one relation between the MR grade and the interval in the case series; and an absence of causes other than MR jet

Fig. 1 Clinical course. *BUN* blood urea nitrogen, *Cr* serum creatinine, *Hb* hemoglobin, *IVC* inferior vena cava, *NAG* *N*-acetyl- β -D-glucosaminidase

Table 1 Laboratory data on admission

Peripheral blood	
WBC	6900/ μ l
RBC	211×10^4 / μ l
Hb	6.8 g/dl
Ht	20.9 %
Plt	26.9×10^4 / μ l
Blood chemistry	
LDH	2168 IU/l
AST	98 IU/l
ALT	18 IU/l
T-bil	2.23 mg/dl
D-bil	0.53 mg/dl
BUN	26.2 mg/dl
Cr	1.48 mg/dl
Na	141 mEq/l
K	4.4 mEq/l
Cl	101 mEq/l
Fe	65 μ g/dl
TIBC	152 μ g/dl
Ferritin	253 μ g/dl
Coagulation study	
PT-INR	2.09
Urinalysis	
Gravity	1.013
pH	6.0
Protein	2+
Occult blood	3+
Bilirubin	+
Sediments	
RBC	-/HPF
WBC	-/HPF
Cast	10–20/HPF
Urinary chemistry	
Protein	1.38 g/gCr
NAG	36.5 U/lgCr
β 2-microglobulin	45435 μ g/gCr

NAG *N*-acetyl- β -D-glucosaminidase, PT-INR international normalized ratio of prothrombin time, TIBC total iron binding capacity

collision, including partial annuloplasty dehiscence, protruding paravalvular suture material, the whiplash motion of tendinous chords, or regurgitant jet collision with the pledget or atrial wall. We evaluated nine case reports and two case series of hemolysis caused by unendothelialization of the annuloplasty ring with or without MR jet collision as measured by echocardiography or reoperation (Table 3) [4, 12–21]. The cases of reoperation include seven reports and two series. Among them, renal information is described in only five cases. Additionally, there

are no reports describing indication for reoperation when considering kidney injury.

We show the correlation between the degree of MR and the interval from the initial operation to appearance of hemolysis is shown in cases of MRCR (Fig. 4a). Some patients have only MR 1+ (without collision) in the early postoperative phase (within 3 months), whereas this is not seen in the late postoperative phase. In addition, all of five cases of hemolysis, which have been reported on amelioration under observation without reoperation, were occurred in the early postoperative phase, not in the late postoperative phase (Fig. 4b). Shear stress between the annuloplasty ring and the MR jet is severe just after surgery and then gradually decreases as endothelialization progresses in the early postoperative phase. In animal models of valve or nonvalvular device implantation, the process of endothelialization begins as early as 1 month after surgery and is completed within 3–6 months after surgery [22–25]. Therefore, in the early postoperative phase, hemolysis can be sometimes caused by mild MR, and is often ameliorated with endothelialization without reoperation. However, hemolysis in the late postoperative phase, which occurs with MR jet collision, can remain unameliorated for a long period without reoperation, because the shear stress is strong enough to destroy any endothelialization, thereby inhibiting tissue repair. In our case, hemolysis occurred in the late postoperative phase, and did not ameliorate for 10 months; hence, we performed reoperation.

Hemolysis and subsequent hemoglobinuria involves kidney injury that results from the following three mechanisms [11]: (a) reabsorption and deposition of iron into proximal tubular cell, which leads to generation of reactive oxygen species; (b) obstruction of tubules due to intratubular casts that form by the interaction between hemoglobin and Met-hemoglobin; and (c) a decrease in renal perfusion due to depletion of serum nitric oxide by interaction with plasma-free hemoglobin. In addition, tubular obstruction promotes reabsorption of free hemoglobin into proximal tubular cell, which results in proximal tubular cell injury furthermore. In our case, elevated NAG and β 2m levels indicate proximal tubular cell injury, and CT revealed that the hyperdensity of the renal cortex, liver, and spleen increased more than that before hemolysis. Magnetic resonance imaging (MRI) shows hypointensity of the renal cortex that is consistent with iron deposition due to MV repair compared with the renal medulla on both T1 and T2-weighted images [26], and hypointensity on both T1 and T2-weighted MR images and hyperdensity on CT images of liver are indicative of iron overload [27]. Thus, this finding of CT suggests continuous iron deposition in the renal cortex, liver, and spleen throughout the

Table 2 Additional data on intravascular hemolysis

intravascular hemolysis		Flow cytometry	
Peripheral blood
RBC fragmentation	1.7 %		
Serological study			
Haptoglobin	<5 g/dl		
LDH isozyme			
LDH1	42 %		
LDH2	39 %		
LDH3	14 %		
LDH4	3 %		
LDH5	2 %		
ADAMTS13	77 %		
Direct Coombs test			
Urinary study			
Urinary hemoglobin	1 mg/dl		

GPA
glycosylphosphatidylinositol
anchor

GPA
glycosylphosphatidylinositol
anchor

observation period. The blood urea nitrogen–Cr ratio increased without significant change in body fluid volume, as measured by the diameter of the inferior vena cava (Fig. 1), which indicated decreased renal perfusion. However, it is unclear whether the ratio was affected by the decreased serum nitric oxide level. There was very little urinary cast formation. Therefore, kidney injury in this case is thought to be due to iron deposition and decrease in renal perfusion that caused proximal tubular cell injury. Incidentally, we could not perform renal biopsy because the patient was receiving anticoagulation therapy for atrial fibrillation. In addition, the anticoagulation therapy was needed for the patient because intravascular hemolysis and insufficient endothelialization of the annuloplasty ring were considered to be risk of thrombosis.

Chronic hemolysis and subsequent proximal tubular injury resulting from iron deposition could cause progression to CKD in cases of paroxysmal nocturnal hemoglobinuria (PNH), which is representative of intravascular hemolysis [28]. However, kidney injury in cases of PNH can progress even without clinical evidence of intravascular hemolysis [28]. Therefore, the possibility that chronic hemolysis can result in renal iron deposition and subsequent progression to CKD must be considered, even without clinical evidence of anemia. In this case, kidney injury progressed to CKD without clinical evidence of exacerbation of anemia.

Fig. 2 Transesophageal echocardiography showing the annuloplasty ring in the mid-esophageal four-chamber view (**a**, arrowhead). Color Doppler imaging revealed MRJCR (**b**, arrow). LA left atrial, LV left ventricle

In conclusion, hemolysis due to MRCR in the late postoperative phase can remain unameliorated for long periods if reoperation is not performed. Chronic hemolysis can lead to progression to CKD even in the absence of clinical evidence of anemia. Therefore, reoperation should be considered in case of kidney injury and hemolysis due to MRCR in the late postoperative phase of MV replacement.

Fig. 3 Computed tomography showing the hyperdensity of the renal cortex (**b, c arrowhead**) compared to the medulla 2 years previously (**a, arrowhead**). The liver and spleen show more hyperdensity (**b**) than that seen 2 years previously (**a**)

Table 3 Previous case reports and case series

	Year	Author	MR grade	Interval from initial operation to RCFS appearance	Other causes	Collision with the ring	Reoperation	Renal information	References
<i>Case report</i>									
1	1972	Moisey	–	7 weeks	–	–	Yes	–	
2	1978	Miki	–	10 days	–	–	Yes	–	
			–	2 months	–	–	No	–	
3	1980	Warnes	–	3 days	–	–	Yes	–	
			–	2 months	–	–	Yes	–	
4	1989	Mok	–	6 days	–	–	Yes	Cr1.4	
5	1990	Wilson	1+	2 months	–	–	Yes	–	
			1–2+	5 days	–	–	Yes (re-rep air)	–	[4]
6	1992	Dilip	1+	5.5 weeks	Yes	Yes	Yes	–	
7	1992	Mestres	1–2+	7 days	–	–	Yes	–	[11]
8	1993	Seyr	1+	3 days	–	–	Yes	CCr22	[12]
9	1996	Stoschitzky	–	Few months	Yes	–	Yes	–	
10	1997	Brandon	–	7 days	Yes	–	Yes	–	
		Bravo	–	3 months	–	–	Yes	–	
		Bruinsma	–						
11	2000	Ward	3+	7 weeks	Yes	–	Yes	–	
12	2003	Inoue	2+	2 months	–	Yes	No	–	[13]
			2–3+	3 weeks	–	–	Yes	–	[14]
13	2004	Duono	2–3+	3 months	Yes	–	Yes	–	
14	2005	Shingu	3+	16 days	Yes	Yes	Yes	Cr3.63	
15	2005	Oki	1+	3 days	–	Yes	Yes	–	[15]
16	2010	Abe	1+	4 weeks	–	Yes	Yes	Cr3.33	[16]
17	2010	Gungunes	3+	2 months	–	–	No	–	[17]
18	2013	Acharya	2+	7 months	–	Yes	Yes (re-rep air)	–	[18]
	2013	Our case	3+	10 months	–	Yes	Yes	CM.48	

Table 3 continued

Year	Author	MR grade	Interval from initial operation to RCFS appearance	Other causes	Collision with the ring	Reoperation	Renal information	References
<i>Case series</i>								
1	1997	Cerfolio (10 cases)	1+:2 cases 2+:5 cases 2–3+:2 cases 3+:1 cases 1–2+:5 cases	87 days (40–165 days)	Yes: 1 case	9 cases	Yes: 10 cases (re-repair: 3 cases)	–
2	1998	Yeo (13 cases)	3+:8 case	2.9 months (25 days–6.3 months)	Yes: 2 cases	11 cases	Yes: 12 cases (re-pair: 3 cases) no: 1 case	–
3	2004	Lam (32 cases)	2+:7 cases 3+:6 cases 4+:18 cases	3 months (0.17–54 months)	Yes: 21 cases	4 cases	Yes: 31 cases (re-pair: 3 cases) no: 1 case	–
4	2005	Ishibashi	1+ 2+ 2+ 3+ 2+ 1+ 3+ 2+ 2+	4 weeks 4 weeks 4 weeks 7 months 11 days 3 months 8 months 125 days 54 days	– – – – – Yes – – Yes	Yes Yes Yes Yes Yes Yes Yes Yes –	No No No Yes (re-rep air) Yes (re-rep air) Yes (re-rep air) Yes Yes Yes	– – – – – – – – –
5	2008	Demirsoy	1–2+ 2+ 2–3+	60 days 2 years 1 day	– Yes Yes	Yes – –	Yes Yes Yes	– Cr2.4 –

Among 18 case reports and five case series, the cases unqualified for the conditions are in gray rows. We evaluated nine case reports and two case series

Cr Creatinine, CCr Creatinine clearance

Fig. 4 Correlation between the degree of MR and the interval between initial operation and appearance of hemolysis in (a) patients who underwent reoperation, and (b) patients who were only observed. Filled Circle, Filled Square a case with collision (MRCR), Open circle, Open Square a case without collision

Conflict of interest The authors declare no conflicts of interest.

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