

Recurrent mitral regurgitation with haemolytic anaemia after MitraClip procedure: an autopsy case report

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Background

Transcatheter edge-to-edge mitral valve repair (TMVr) has been developed as an alternative therapeutic approach to patients with severe mitral regurgitation (MR) at high-surgical risks. Single leaflet device attachment (SLDA) is a well-known complication after the TMVr procedure, while an autopsy case experiencing haemolytic anaemia has been scarcely reported.

Case summary

A 79-year-old woman presented with New York Heart Association Class 3 congestive heart failure due to severe MR. The Heart Team planned TMVr using the MitraClip considering a high-surgical risk due to the history of open-chest surgery. The procedure was successful with two clips and a significant reduction of MR was confirmed. On the 12th day after the procedure, congestive heart failure was worsened and a transthoracic echocardiogram revealed severe MR suggestive of SLDA. Blood test showed normocytic anaemia with serum lactate dehydrogenase level elevation and renal function deterioration. We diagnosed as mechanical haemolysis induced by recurrent MR because of a decrease in serum haptoglobin level and the presence of schizocyte in the blood smear. Despite our intensive medical treatment, she died on the 119th day after the procedure. The pathological autopsy demonstrated that the ruptured leaflet was thickened with layered structure and severe fibrosis, while there were no findings of calcification, vegetations, or abscesses.

Discussion

Single leaflet device attachment and subsequent mechanical haemolysis are rare but fatal complications after TMVr with the MitraClip. Not only degenerative MR but also functional MR may be associated with valve leaflet degeneration. A possibility of mechanical haemolysis should be considered when recurrent MR is observed after TMVr.

Keywords

Transcatheter mitral valve repair • MitraClip • Haemolytic anaemia • Single leaflet device attachment • Autopsy • Case report

ESC Curriculum

4.3 Mitral regurgitation • 7.1 Haemodynamic instability • 7.4 Percutaneous cardiovascular post-procedure • 6.3 Heart failure with preserved ejection fraction • 2.2 Echocardiography

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Learning points

- Our autopsy findings suggested that not only primary mitral regurgitation (MR) but also secondary atrial functional MR may be associated with valve leaflet degeneration.
- Atrial functional MR lacks coaptation of valve leaflets due to mitral annular dilatation that may cause excessive stretching stress on the leaflets when grasping by the clips.
- A possibility of mechanical haemolysis should be considered when recurrent MR was observed after transcatheter mitral valve repair.

Introduction

Mitral regurgitation (MR) is the most common valvular disease. Echocardiography is a gold standard to assess the severity, aetiology, and leaflet morphology for MR in order to determine appropriate therapeutic strategies.¹ Transcatheter edge-to-edge mitral valve repair (TMVr) was developed as an alternative to surgery for inoperable or high-risk MR patients.² Herein, we report a case of recurrent MR and concomitant haemolytic anaemia after the TMVr procedure. We also discuss the complications in the light of echocardiogram and autopsy findings.

Timeline

20 years prior to transcatheter edge-to-edge mitral valve repair (TMVr)	Ascending aortic replacement for acute aortic dissection
11 years prior to TMVr	Moderate mitral regurgitation (MR) and chronic atrial fibrillation detected
7 years prior to TMVr	Descending aortic replacement for second acute aortic dissection
3 years prior to TMVr	Hospitalizations due to congestive heart failure had repeated thereafter.
Day 0	TMVr with MitraClip NT (G2) was performed, resulting in mild residual MR.
Day 5	MR progressed to moderate.
Day 12	MR progressed to severe. Transesophageal echocardiogram revealed single leaflet device attachment. Blood test showed haemolytic anaemia. The Heart Team decided conservative medical therapy instead of repeat MitraClip procedure.
Day 119	The patient died. Autopsy was performed.

Case presentation

A 79-year-old Japanese woman presented with dyspnoea due to congestive heart failure (New York Heart Association Class III). She had

been diagnosed with moderate MR for the past 11 years and repeatedly hospitalized for congestive heart failure for the past 3 years. During the follow-up, her MR had progressed to severe. She received oral medications including bisoprolol (1.25 mg o.d.), furosemide (40 mg o.d.), spironolactone (25 mg o.d.), tolvaptan (15 mg o.d.), and warfarin (2.5 mg o.d.). On admission, her blood pressure was 130/66 mmHg with a heart rate of 70 beats/min, and oxygen saturation was 98% in room air. On physical examination, pan-systolic murmur was evident at the apex and bilateral lower legs were mildly oedematous, but jugular venous distension and lung murmur were not evident. Transthoracic echocardiography showed left atrium enlargement and severe MR deviating from the A2P2 coaptation to the posterior wall of the left atrium (Figure 1A). Transesophageal echocardiography (TEE) showed functional shortening and limited motion of the posterior mitral leaflet retracted to the posterior wall (Figure 1B–D; Video 1). The A2 leaflet was slightly thickened and prolonged, suggesting pseudo-prolapse. The coaptation length, coaptation depth, and P2 length were 2, 4, and 11 mm, respectively. The mitral valve area was 4.6 cm² and the mitral annular diameter was 36 mm. There was no evidence of valve perforation, tendon rupture, or vegetations. Society of Thoracic Surgeons (STS) risk score for isolated mitral valve replacement was estimated as 11.8%. The blood tests and echocardiographic parameters are summarized in Table 1.

Based on these findings, we established a diagnosis of atrial functional MR (AFMR) plus mild anterior mitral valve degeneration. In addition to the history of ascending and descending aortic replacement for aortic dissection, her comorbidities such as atrial fibrillation, chronic kidney disease, and advanced frailty precluded repeat open-chest surgery for severe MR. Therefore, the Heart Team planned TMVr using the MitraClip NT (G2) (Abbott Vascular, Santa Clara, CA, USA).

During the procedure, the first clip was placed slightly medial to the A2P2, after which the MR decreased to mild to moderate. After placing the second clip slightly lateral to the A2P2, the MR became milder (Figure 2A). The mean mitral valve pressure gradient was 1 mmHg post-procedure (Figure 2B). Although there were two small regurgitant orifices bilateral to the second clip (Figure 2C and D; Video 2), the procedure was uneventfully completed with mean left atrial pressure dropping from 20 mmHg to 15 mmHg. However, MR was progressed to moderate on the 5th day and to severe on the 12th day after the procedure (Figure 3A–C), thereby worsening congestive heart failure with significant systemic fluid retention. Notably, she had a low-grade fever and dark-coloured urine but jaundice was not evident. The blood test showed normocytic anaemia concomitant with serum haptoglobin below the limit of measurement. Schizocytes were evident in the blood smear (Figure 3D). Based on these findings, we established a diagnosis of mechanical haemolysis induced by

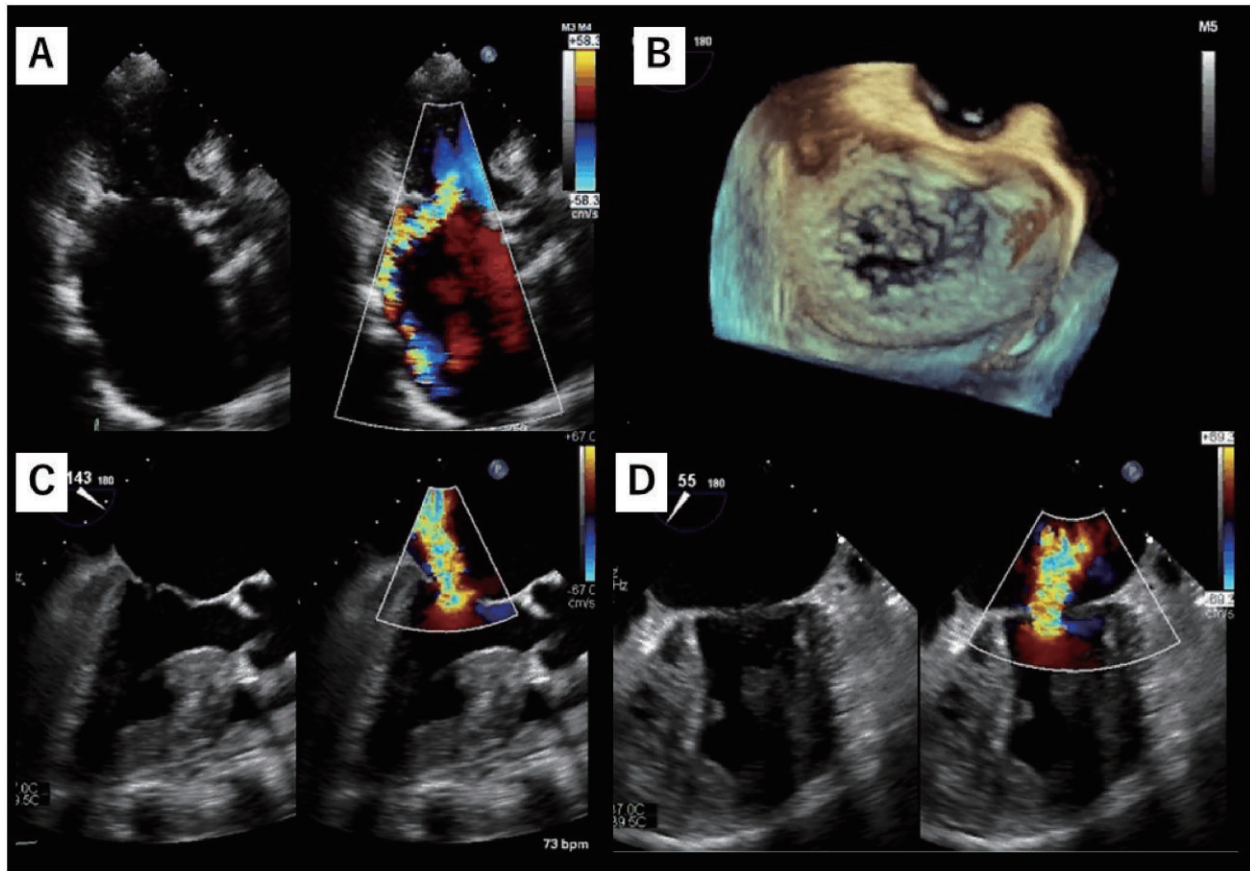
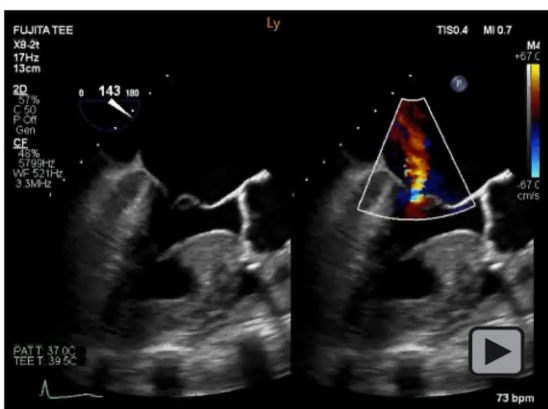


Figure 1 Pre-procedural echocardiography findings. (A) Transthoracic three-chamber view; (B) Transesophageal (3D) surgeon's view; (C) Transesophageal long-axis view; and (D) Transesophageal bi-commissure view.



Video 1 Transesophageal echocardiography pre-procedure.

recurrent MR. Transesophageal echocardiography detected protrusion of the clip on the lateral side into the left atrium with a high degree of MR (Figure 3E–G; Video 3). The Heart Team finally made an agonizing decision for conservative medical therapies because repeat

MitraClip procedure was considered to be extremely challenging to control severe regurgitation. Fluid retention and haemolytic anaemia were stabilized after our intensive treatment including β -blocker, haemodialysis, and haptoglobin replenishment. However, the patient had a significant progression of disuse syndrome and eventually died of aspiration pneumonia.

An autopsy revealed that the lateral side of A2 was dehiscd and the clip on the lateral side was deviated to the left atrium, concluding as a single leaflet device attachment (SLDA) (Figure 4A–C). Microscopic findings revealed that the A2 leaflet was thicker with a layered structure obscured with severe fibrosis, but there were no findings of calcification or vegetations or abscesses (Figure 4D–G).

Discussion

Mechanical haemolysis is a well-known complication after surgical mitral valve repair,³ whereas little is known about haemolysis after the TMVr. In the present case, severe regurgitation occurring in the proximity of the prosthesis—due to SLDA confirmed by an autopsy—was associated with haemolysis. Subsequent anaemia and renal dysfunction might contribute to the worsening of haemodynamic conditions.

Table 1 Transitions of laboratory and echocardiographic parameters during the hospitalization

	Pre-procedure	Immediately after the procedure	12 days after the procedure	Normal range
Laboratory parameters				
White blood cells (μL)	4100	6500	5900	4350–5550
Haemoglobin (g/dL)	13.4	13.7	9.4	13.7–16.8
Platelets (μL)	138 000	127000	177 000	158 000–348 000
Albumin (g/dL)	3.6	3.9	3.7	3.9–4.9
Asparate aminotransferase (U/L)	17	20	81	13–30
Aalanine aminotransferase (U/L)	14	10	14	10–42
Lactate dehydrogenase (U/L)	227	200	1687	120–240
Total bilirubin (mg/dL)	2.1	1.0	3.6	0.4–1.5
Creatinine (mg/dL)	2.10	1.87	3.39	0.65–1.07
NT-proBNP (pg/mL)	9327	3478	52 150	<125
Echocardiographic parameters				
Left ventricular end-diastole diameter (cm)	5.4	5.2	5.4	3.7–5.2
Left ventricular end-systole diameter (cm)	2.9	3.1	3.0	2.2–3.4
Left ventricular ejection fraction (%)	64	60	62	54–74
MR grade	Severe	Mild	Severe	None
Regurgitant volume (mL)	49	18	48	N/A
Regurgitant fraction (%)	47	18	48	N/A
Effective regurgitant orifice area (cm^2)	0.29	0.10	0.28	N/A
Pulmonary artery systolic pressure (mmHg)	41	36	58	18–25

NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

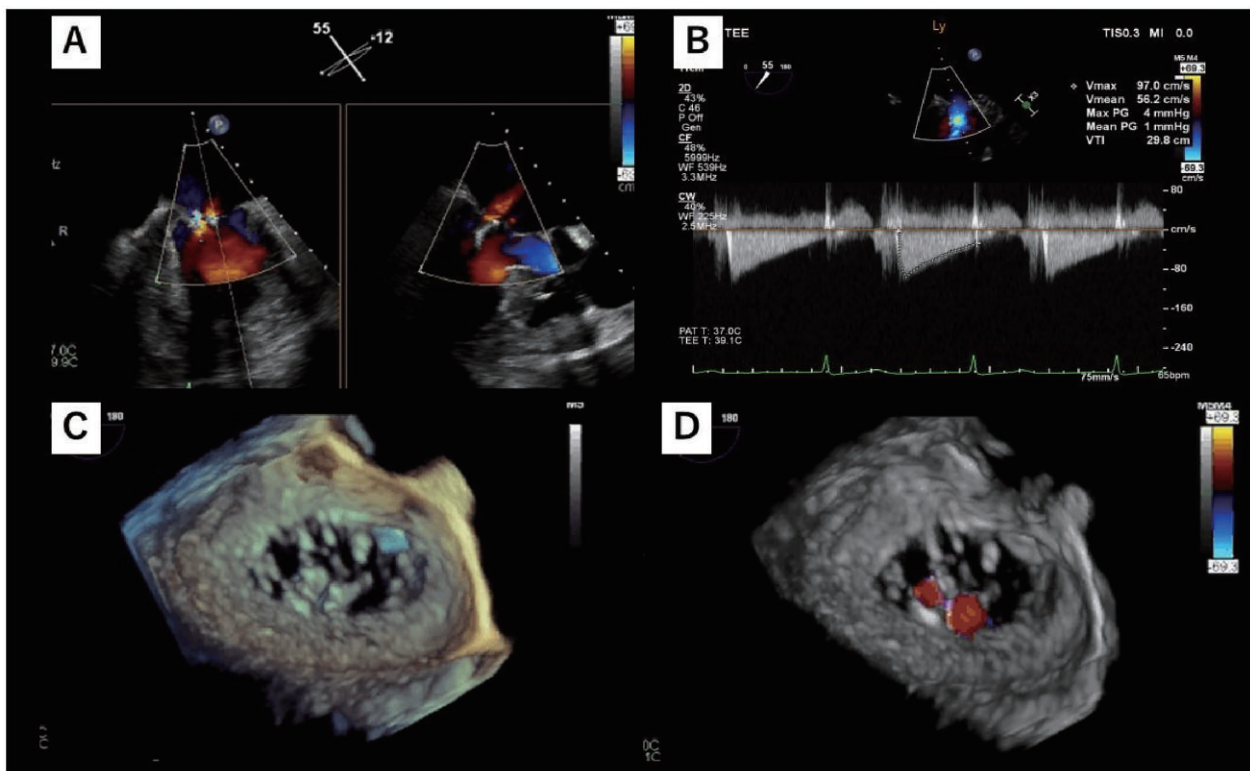
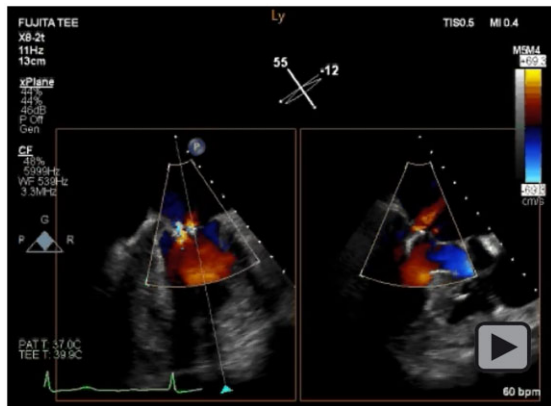


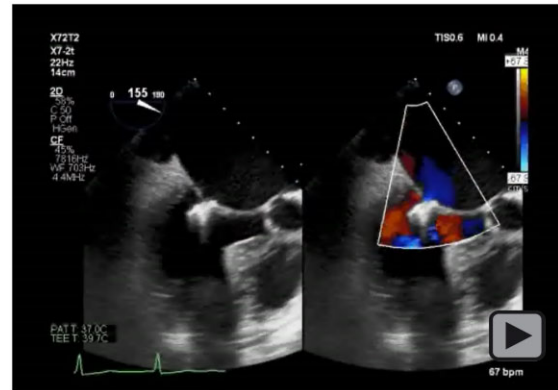
Figure 2 Post-procedural transesophageal echocardiography findings. (A) Mild residual mitral regurgitation; (B) mitral valve pressure gradient was measured; and (C and D) 3D surgeon's view indicated two regurgitant orifices bilateral to the second clips.

Based on the pre-procedural echocardiography, our clinical diagnosis in the context of MR aetiology was primarily due to AFMR caused by left atrial enlargement secondary to atrial fibrillation. We did not see any complexity of anatomy for the MitraClip procedure based on the recent literature.⁴ Stephens *et al.*⁵ reported that exposure to high regurgitant flow could cause histological degeneration of the mitral leaflets. Although leaflet tear is associated with underlying valve disease characterized by fibro-elastic deficiency or diffuse

myxomatous degeneration,⁶ it is generally challenging to detect mitral leaflet degeneration by echocardiography specifically in AFMR.⁷ It is known that patients with chronic kidney disease develop valvular calcification, which may also contribute to the mechanical weakness of the leaflets.⁸ In the present case, however, Kossa staining revealed no evidence of microcalcifications in the mitral valve tissue. Atrial functional MR lacks coaptation of valve leaflets by mitral annular dilation, which may cause excessive stretching stress on the leaflets



Video 2 Transesophageal echocardiography post-procedure.



Video 3 Transesophageal echocardiography at recurrent mitral regurgitation.

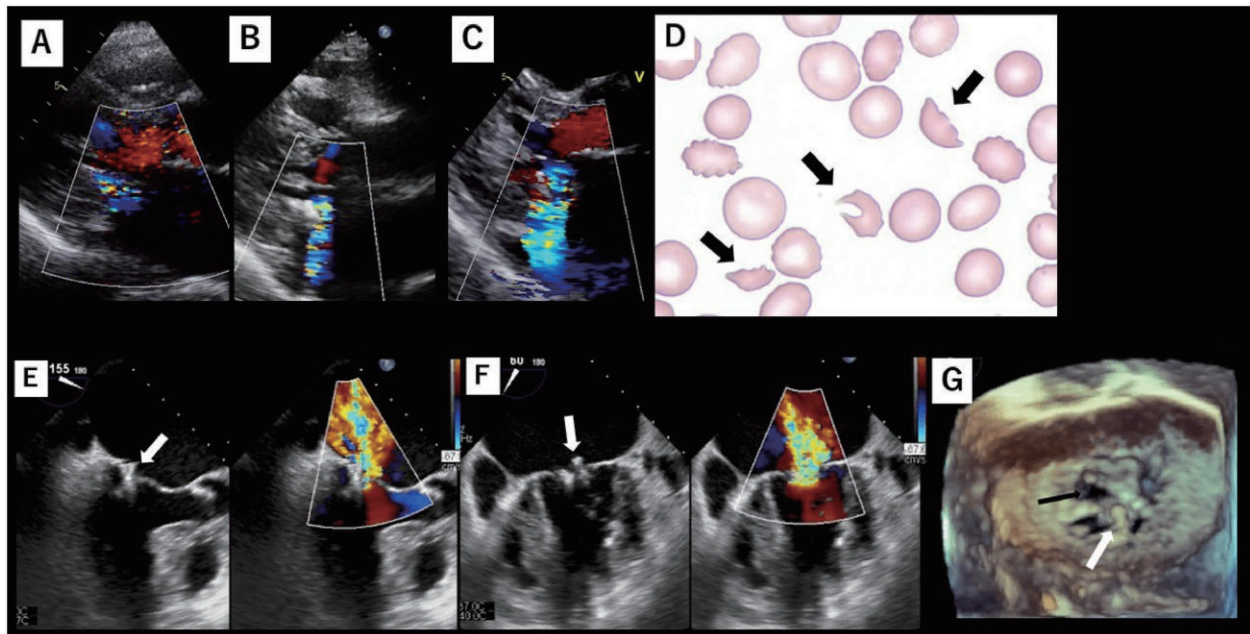


Figure 3 Transition of echocardiographic findings over time. (A) Mild mitral regurgitation immediately after the procedure; (B) Moderate MR on the 5th day and (C) Severe mitral regurgitation on the 12th day after the procedure; (D) Appearance of schizocytes in the blood smear (black arrows); and (E–G) The clip on the lateral side protruded into the left atrium (white arrow) with severe regurgitation on the 12th day after the procedure. Gap on the lateral side of A2 was indicated in black arrow. MR, mitral regurgitation.

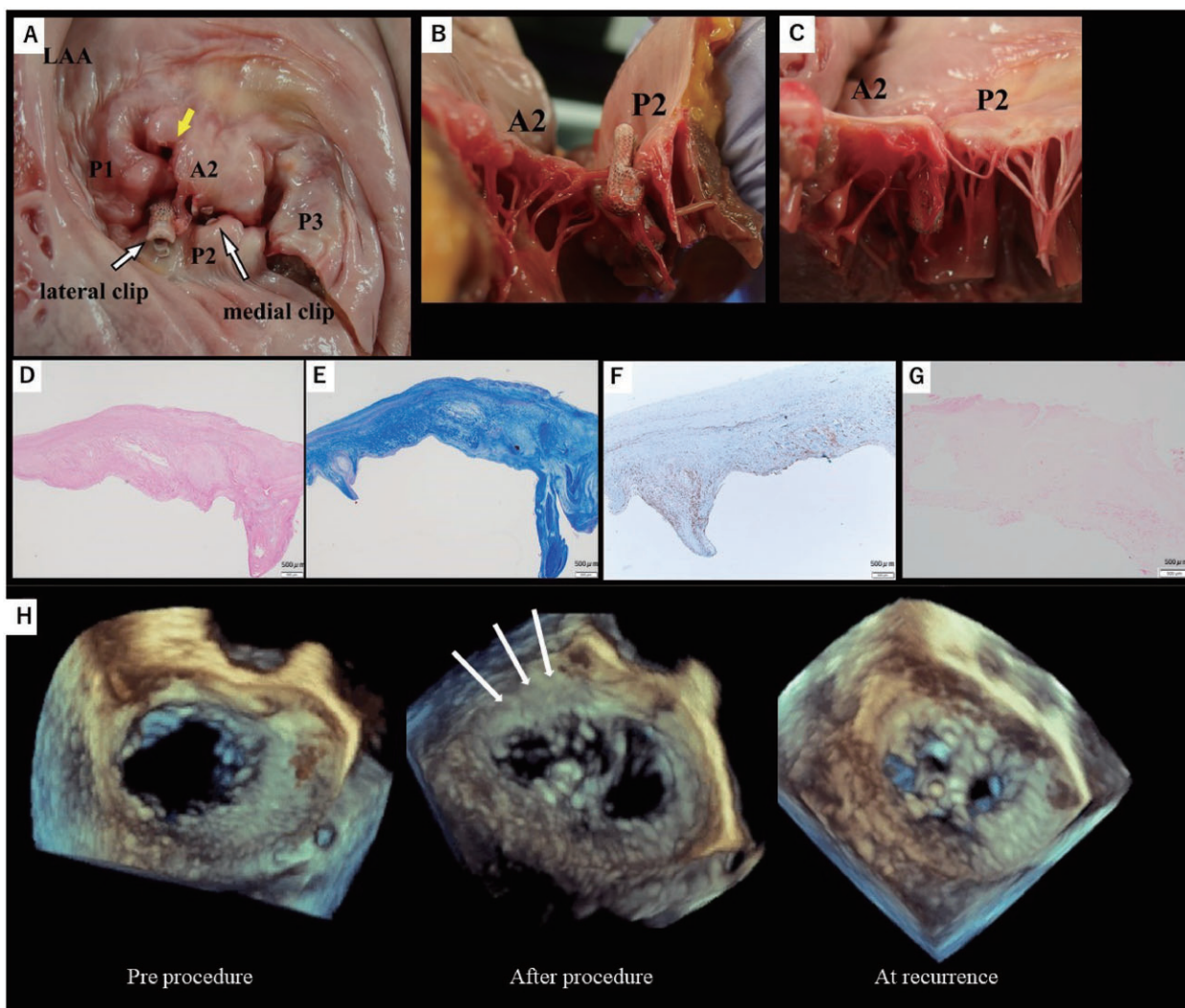


Figure 4 Macroscopic and microscopic findings of the ruptured mitral leaflet. (A) The clip on the lateral side protruded into the left atrium (left white arrow) and the tear on the lateral side of A2 leaflet was indicated (yellow arrow); (B) single leaflet device attachment (SLDA) of the clip on the lateral side was evident; (C) The clip on the medial side appropriately grasped the leaflets; (D) haematoxylin and eosin staining, A2 leaflet was thick and layered structure was obscured; (E) Azan staining, severe fibrosis and (F) CD34 staining, the growth of fibroblasts were evident in the leaflet tissue; (G) Kossa staining, no evidence of microcalcification; and (H) Comparison of transesophageal 3D surgeon's views. Transient annulus deformation after the procedure suggested excessive tension on the lateral side of A2 leaflet (white arrows).

when grasping by the clips.⁹ Our retrospective observation of the TEE findings suggested medial deviation of the mitral annulus and excessive tension on the anterior mitral leaflet immediately after the TMVr procedure, which may have contributed to the SLDA (Figure 4H; Supplementary material online, Video S1).

The incidence rate of MitraClip failure defined as SLDA, loss of leaflet insertion, or clip embolization was 3.5% in the worldwide FILM registry.¹⁰ Of these, 34.7% of patients underwent repeat MitraClip procedure and the success rate was 75%. Conversely, as much as 48.2% of patients were treated with medical therapy alone, and nearly a half of patients died within 2 years after the procedure. The present case was considered too sick to undergo a repeat procedure and mechanical haemolysis concomitant with renal dysfunction might

accelerate the worsening of congestive heart failure. Previous literatures discussed the potential mechanisms of haemolytic anaemia after the TMVr, including shear stress or mechanical trauma to red blood cells caused by regurgitation flow or the device (MitraClip) itself.^{11–14} In our case, haemolysis was most noticeable when MR was worsened, and it was then stabilized after intensive medical and mechanical treatments. This finding may suggest that the haemodynamic severity of MR rather than the MitraClip itself mainly contributed to the mechanical haemolysis in this case.

The newer generation devices, MitraClip NTW and XTW (G4), have a wider grasping area and thereby reducing the risk of SLDA associated with leaflet tear. The PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, CA, USA) is also expected to

reduce the mechanical stress on the valve leaflets by introducing a central spacer within the mitral valve regurgitant orifice.¹⁵ Such new devices may reduce the recurrence rate of MR in AFMR cases.

Conclusions

Our autopsy findings suggested that not only primary MR but also secondary MR (AFMR) may be associated with valve leaflet degeneration. A possibility of mechanical haemolysis should be considered when recurrent MR is observed after the TMVr procedure.

Lead author biography



Naoki Hoshino, MD, is an echo cardiologist at the Fujita Health University Hospital, Toyoake, Japan. He graduated from the Fujita Health University School of Medicine in 2010. His current clinical and academic interests include echocardiography, transcatheter structural heart disease interventions, and comprehensive management of heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated

text has been obtained from the husband of patient in line with COPE guidance.

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Conflict of interest: None declared.

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