

# Acquired hemophilia a in a patient undergoing aortic valve replacement with warfarin anticoagulation therapy

**Keywords:** aortic valve replacement, hemophilia A, heparin sodium, prednisolone, warfarin, anti-coagulant

**Abbreviations:** INR, international normalized ratio; aPTT, activated partial thromboplastin time; F VIII, factor VIII; BU, bethesda units; FFP, fresh frozen plasma; RCC, red cell concentrate

## Introduction

Spontaneous development of acquired hemophilia A is a rare phenomenon and its origin is usually idiopathic.<sup>1</sup> However, acquired hemophilia A has been known to occur after surgery<sup>2</sup> and in underlying diseases such as malignancies and autoimmune diseases.<sup>1,3</sup> Theodossiadis et al.<sup>2</sup> reported 7 patients with surgery-associated acquired hemophilia<sup>2</sup> occurring 1-18 days after surgery. The surgeries were mainly abdominal surgeries such as cholecystectomy, enteric section and abdominal wall hernia repair.<sup>2</sup> In contrast, acquired hemophilia A rarely occurs in patients undergoing cardiovascular surgery<sup>2</sup> or those using the anti-coagulant agent, warfarin.<sup>4-5</sup> One case of a patient undergoing coronary artery bypass grafting was noted among 7 cases of surgery-associated acquired hemophilia.<sup>2</sup> A 66-year-old man underwent aortic valve replacement for severe aortic valve stenosis. After surgery, he was administered warfarin (2mg/day) for anticoagulation and the international normalized ratio (INR) was controlled between 1.8 and 2.0. Approximately 5 months later, he suddenly presented with severe subcutaneous hematoma in the extremities without trauma. Clotting activities worsened (INR, 2.81; activated partial thromboplastin time [aPTT], 103 seconds; normal range, 24-39 seconds). Although warfarin was stopped and the INR normalized (INR 1.07), the aPTT remained prolonged (aPTT, 88.9 seconds). Other anticoagulants such as heparin sodium and dabigatran were not used. Lupus anticoagulant test (dilute Russell viper venom time) was negative. Therefore, we measured the factor VIII (F VIII) clotting activity and its inhibitor's activity; based on this, the patient was diagnosed with acquired hemophilia A for bleeding tendency (F VIII activity, 1.2%; F VIII inhibitor, 152 Bethesda units [BU]). From the definite diagnosis, prednisolone (1mg/kg) was started. However, active bleeding from the upper gastrointestinal tract suddenly occurred. Massive blood transfusion was given until use of recombinant factor VII therapy. Prior to recombinant factor VII infusion, we administered red cell concentrate (RCC) (26 units) and fresh frozen plasma (FFP) (12 units). Two units of RCC (280ml) or 2 units of FFP (120ml) were derived from 400ml of donated whole blood in Japan. After recombinant factor VII infusion, RCC (6 units) alone was transfused. Factor VIII inhibitor activity lowered (<0.5BU) and bleeding tendency resolved. Prednisolone was tapered gradually

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Matsunaga H,<sup>1</sup> Mishima H,<sup>1</sup> Katayama Y,<sup>1</sup> Ishikawa S,<sup>1</sup> Hiroshi Fujita<sup>2</sup>

<sup>1</sup>Department of Cardiovascular Surgery, Tokyo Metropolitan Bokutoh Hospital, Japan

<sup>2</sup>Department of Transfusion Medicine, Tokyo Metropolitan Bokutoh Hospital, Japan

**Correspondence:** Hiroshi Fujita, Department of Transfusion Medicine, 4-23-15 Koutoubashi, Sumida-ku, Tokyo 130-8575, Japan, Fax 81-3-3633-6173, Tel 81-3-3633-6151, Email [hiroshi\\_fujita@tmhp.jp](mailto:hiroshi_fujita@tmhp.jp)

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and then completely discontinued. Fortunately, relapse of acquired hemophilia A was not noted even without prednisolone (aPTT, 26.7-36.0s). Re-administration of warfarin induced good control of the patient's anticoagulation (INR, 1.8-2.0) and no relapse of acquired hemophilia A has been seen.

Three reports have presented 5 patients with acquired hemophilia A associated with anticoagulation with warfarin;<sup>4-6</sup> the 3 case reports are shown in Table 1. The 5 patients were elderly women (mean age, 68 years), while in the present case, the patient was a 66-year-old man. Two among the 5 patients were undergoing long-term warfarin therapy for mechanical valve replacement.<sup>4-5</sup> We speculate that acquired hemophilia may be masked by warfarin therapy among patients undergoing valve replacement. Therefore, prolonged aPTT during warfarin therapy should be noted and checked if it leads to a diagnosis of complicated acquired hemophilia. The 5 patients described previously demonstrated a potential delayed diagnosis of acquired hemophilia during anticoagulation with warfarin. The patient in the present case was also administered warfarin for aortic valve replacement, 5 months prior to the onset of hemophilia. He had no history of other diseases, such as malignancy or autoimmune diseases.<sup>1</sup> Fortunately, he achieved complete remission on prednisolone and no relapse has been noted after discontinuation of prednisolone. Furthermore, re-administration of warfarin did not induce relapse, while in previous reports, no data was shown on relapse in 2 patients who took warfarin again.<sup>4-6</sup> In the present case, because onset of acquired hemophilia occurred approximately 5 months after surgery, it is not thought to be surgery-associated.<sup>2</sup>

**Table 1** Clinical features of warfarin-masked acquired hemophilia A

Age/ Gender	Underlining Diseases	Bleeding Symptom	Clotting Tests	Hemostatic Control	Immunosuppressive Treatment	Outcome	Reference
	Reason of Warfarin Use		aPTT (s) FVIII Inhibitor (Bethesda units)				
72 /F	Mitral valve replacement (10 years ago) Chronic Obstructive lung disease Diabetes mellitus Chronic renal failure Surgery and radiation for Breast cancer (4 years ago)	Limb hematoma Hematuria Pulmonary hemorrhage	133 s 4	Vitamin K Intravenous Immunoglobulin RCC	Prednisolone	Remission	4
64/F	SLE (38 years ago) Aortic valve replacement (3 years ago)	Retroperitoneal hematoma	82 s 1	Vitamin K RCC, FFP Desmopresin Intravenous Immunoglobulin Prothrombin complex concentrate	Prednisolone Cyclophosphamide	Remission	5
60/F	SLE (20 years ago) Deep vein thrombosis	Back hematoma	72 s 12	Vitamin K RCC, PCC	Cyclosporin	Remission No relapse after reused warfarin	5
72/F	Atrial fibrillation Deep vein thrombosis	Retroperitoneal and inguinal hematoma	95 s 2	Vitamin K RCC, FFP Factor VII infusion Prothrombin complex concentrate	Prednisolone Cyclophosphamide	Remission	6
71/F	Systemic sclerosis Pulmonary hypertension	Bleeding from leg ulcer	81 s 2.2	Warfarin discontinuation	None	Remission	6
Our case 66/M	Aortic valve replacement (5 months ago)	Limb hematoma	103 s 152	RCC, FFP Factor VII infusion	Prednisolone	Remission	

## Conclusion

Acquired hemophilia A can be complicated in a warfarin-masked patient undergoing cardiovascular surgery. Immediate and accurate diagnosis of acquired hemophilia A may reduce the usage of transfusion product for bleeding episodes.

## Acknowledgements

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## Conflict of interest

The author declares no conflict of interest.

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