Massive, Fatal, Intracardiac Thrombosis Associated With Prothrombin Complex Concentrate

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Prothrombin complex concentrates are frequently used to rapidly reverse anticoagulation with vitamin K antagonists associated with life-threatening bleeding. We report a patient receiving warfarin who presented to the emergency department with an international normalization ratio greater than 12.8 in cardiac tamponade and received prothrombin complex concentrate for rapid reversal of anticoagulation. On correction of the tamponade, the patient developed a massive and fatal right-sided ventricular thrombus. Thrombogenic complications of treatment with prothrombin complex concentrate have been reported before. Caution should be used when using prothrombin complex concentrates for reversal of anticoagulation. [Ann Emerg Med. 2009;53:758-761.]

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INTRODUCTION

Initially indicated for the treatment of hemophilia B, the use of prothrombin complex concentrates has been advocated for the rapid correction of warfarin-associated anticoagulation in patients with life-threatening bleeding,[1,2] and in particular intracranial hemorrhage.[3,4] Prothrombin complex concentrates are plasma-derived, concentrated, vitamin K–dependent coagulation factors, with the predominant in vitro activity coming from factor IX. There are more than 5 prothrombin complex concentrates available for use, each with differing concentrations of coagulation factors. Prothrombin complex concentrates are convenient in that they provide faster correction of the international normalization ratio compared with vitamin K and fresh frozen plasma and are not associated with significant volume infusion.[1] In addition, potentially time-consuming blood type matching is not required for prothrombin complex concentrate, as it is with fresh frozen plasma.

Given these favorable characteristics, prothrombin complex concentrates are recommended by consensus guidelines for reversal of life-threatening bleeding associated with warfarin.[5-7] The Food and Drug Administration has not approved prothrombin complex concentrates for this indication, and only 1 prothrombin complex concentrate is licensed as such in the United Kingdom. Despite these recommendations, the body of literature to support the effectiveness of prothrombin complex concentrates for this indication is in its infancy and to date consists of case series and retrospective data only.[2,3,8] Although the literature and expert opinion suggest that prothrombin complex concentrates are effective, the safety of prothrombin complex concentrates and in particular accurate rates of thrombotic complications remain unknown, largely because of a lack of data. In these case series, thrombotic complications were reported in patients receiving prothrombin complex concentrates. They include deep venous thrombosis, myocardial infarction, and bilateral renal infarcts.[2,3] In addition, multiple case reports have associated the use of prothrombin complex concentrate with thrombotic complications. They include myocardial infarction, limb ischemia, thrombotic stroke, and myocardial necrosis.[9,10] Further complicating this issue is the heterogeneous nature of prothrombin complex concentrates as a drug class. Subsequently, the already small body of literature on this topic is additionally hindered by a lack of generalizability. Here we report a patient presenting to the emergency department (ED) with a hemorrhagic pericardial effusion who developed a massive, fatal, intracardiac thrombus after use of prothrombin complex concentrate and drainage of the pericardial effusion.

CASE REPORT

A 72-year-old man presented to the ED for altered level of consciousness. The patient had experienced 3 to 4 days of fatigue, diarrhea, and decreased appetite and continued to receive his normal insulin dose. The patient was found to have critically low blood glucose level in the field and was given intravenous dextrose, with improvement in mental status. In the ED, the patient had no specific complaints except for being fatigued. The patient had a medical history of diabetes mellitus, hypertension, recent ischemic stroke, chronic renal disease (creatinine level 2.0 mg/dl), and deep venous thrombosis. The patient was taking warfarin (started 2 months before), gabapentin, pravastatin, dipyridamole-ASA, omeprazole, metoprolol, nifedipine, and insulin. The initial vital signs were a blood pressure ranging from 103/68 to 90/40 mm Hg, with a

pulsus paradoxus of 28 mm Hg, a pulse rate of 50 to 68 beats/min, a respiratory rate of 18 breaths/min, a temperature of 33.7 °C (92.6°F), and a pulse oximetry of 95% on 2 L/minute of oxygen by nasal cannula. The patient's physical examination was notable for distended neck veins, decreased heart and lung sounds, and distended abdomen with brown stool that was negative for occult blood on rectal examination. The patient had a normal mental status, and the remainder of the physical examination was unremarkable.

An ECG showed sinus bradycardia with a QRS interval of 84 ms, left-sided ventricular hypertrophy, normal ST segments, and no signs of peaked T waves. A chest radiograph revealed an enlarged cardiac silhouette with a "globular" shape and otherwise clear lung fields. A point-of-care electrolyte panel revealed a potassium level of 8 mmol/L and a blood glucose level of 280 mg/dL.

The patient was initially treated with calcium gluconate, albuterol, insulin, glucose, and sodium polystyrene sulfonate. The CBC count showed a WBC count of 14,600 per μL, a hemoglobin concentration of 6 g/dL, and a platelet count of 377,000/μL. Blood chemistry was remarkable for a sodium concentration of 136 mmol/L, a potassium concentration of 7.9 mmol/L, a bicarbonate concentration of 8 mmol/L, a creatinine concentration of 5.2 mg/dL, a blood urea nitrogen of 164 mg/dL, an alanine aminotransferase of 771 U/L, and an aspartate aminotransferase of 1,451. Coagulation studies showed a prothrombin time of greater than 100 seconds, an international normalization ratio of greater than 12.8, a partial thromboplastin time of 59.8 seconds, and a fibrinogen level of 414 mg/dL.

An echocardiogram showed a large pericardial effusion, with collapse of the right ventricle, consistent with cardiac tamponade (Figure, A). The decision was made to rapidly reverse the anticoagulation with prothrombin complex concentrate and drain the pericardial effusion. The patient was given Profilnine (factor IX complex; Grifols Biologicals Inc, Los Angeles, CA) 50 U/kg intravenously during 1 minute, vitamin K 10 mg intravenously, and desmopressin acetate 24 μg intravenously. Fifty minutes later, a pericardiocentesis was performed by using the subxyphoid approach. Four hundred milliliters of frank blood was withdrawn and a pericardial drain was placed. Immediately after the pericardiocentesis, the patient developed pulseless electrical activity with a narrow complex bradycardia at a rate of 20. Given the concern for complications from the pericardiocentesis, a repeated bedside echocardiogram was performed immediately after the patient's decompensation. This showed interval resolution of the pericardial effusion and new echogenic material occupying the entirety of the right ventricle. This was consistent with the "formal" echocardiogram obtained after resuscitation in the Figure (B). A prolonged resuscitation then ensued that included endotracheal intubation; multiple doses of calcium chloride, epinephrine, sodium bicarbonate, and atropine; and electrical cardioversion for an episode of ventricular fibrillation. Return of spontaneous circulation was achieved after 22 minutes, with a pulse of 30 beats/min, and the patient began receiving a high-dose epinephrine infusion.

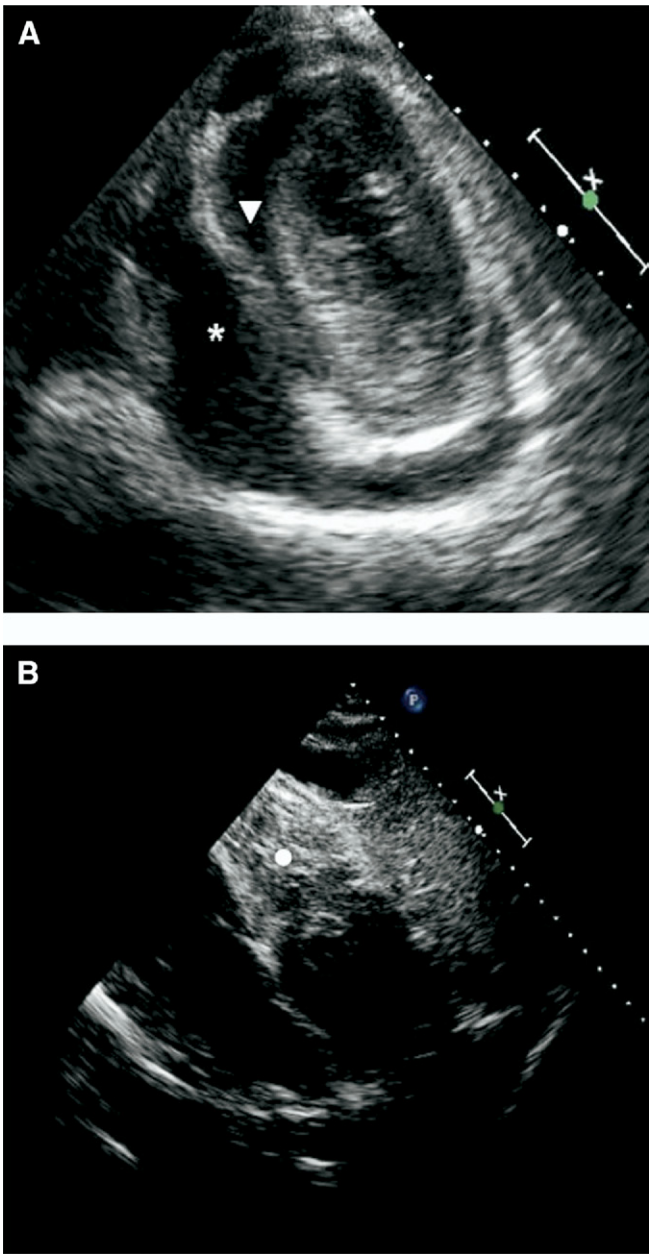

Figure. *A,* Echocardiogram of patient on presentation. The asterick indicates pericardial effusion. The inverted arrow indicates right ventricle. *B,* Echocardiogram of patient after pericardicentesis. The circle indicates thrombus in right ventricle.

A formal echocardiogram obtained after the resuscitation showed interval resolution of the pericardial effusion, reexpansion of the right ventricle, and a large right-sided ventricular thrombus occupying the entire right side of the ventricle (Figure, B). After consultation with cardiology, the thrombus and subsequent hemodynamic compromise were

deemed nonsurvivable processes. This was discussed with the family, and support was withdrawn. The patient died 2 minutes after discontinuation of mechanical ventilation and epinephrine infusion.

On autopsy, a recently formed blood clot, 6×5×3 cm, was found in the right ventricle. The pericardial drain was observed to be in the pericardium without damage to the coronary circulation or ventricle wall. The coronary arteries were patent and free of clot. The pericardial cavity contained a scant amount of red fluid, and the pericardial sac was observed to be hemorrhagic. There was no pulmonary embolism or deep venous thrombosis found on autopsy. The RBC count of the pericardial effusion was 1.6 million/μL, which was similar to the patient's RBC count of 1.8 million/μL. A repeated international normalization ratio tested during the resuscitation was still greater than 12.8. The cause of death was determined to be cardiac failure from the right ventricular thrombus and hyperkalemia.

DISCUSSION

We report a case of intracardiac thrombus associated with the use of prothrombin complex concentrate. We postulate that the thrombus formed from a combination of the hypercoagulable state induced with prothrombin complex concentrate and desmopressin acetate, combined with stasis of blood on reexpansion of the right ventricle. Desmopressin acetate causes release of von Willebrand factor and factor VIII from endothelial cells. This, combined with prothrombin complex concentrate, likely led to a relative hypercoagulable state.

Other less likely causes of the patient's rapid decompensation deserve mention. It is possible that the patient developed cardiovascular collapse from the hyperkalemia. However, the initial hyperkalemia was aggressively and appropriately treated. In addition, multiple doses of calcium chloride and sodium bicarbonate failed to have any effect on the cardiac rhythm, which would be atypical for a hyperkalemic arrest. It is also possible that the patient experienced a myocardial infarction associated with the prothrombin complex concentrate infusion, as has been reported before.[8,9] Autopsy findings suggest that this was not the case because the coronary arteries were free of any significant thrombosis. Death from complications of the pericardiocentesis seem unlikely as well, given the autopsy findings of the pericardial drain observed to be in the correct location without injury to the myocardium or coronary arteries.

Disseminated intravascular coagulation remains a contraindication to the use of prothrombin complex concentrates. Although it is possible that the patient was in disseminated intravascular coagulation when he first presented, the normal fibrinogen level, the normal platelet count, and the relatively normal partial thromboplastin time (compared with the prothrombin time) suggest this was not the case. A D-dimer level was not measured. Unfortunately, the diagnosis of disseminated intravascular coagulation cannot be made on autopsy. There is, however, no single reason why the patient presented with such an increased international normalization ratio. It is possible that the recent diarrheal illness resulted in a change in bacterial flora, leading to malabsorption of vitamin K. Additionally, the patient presented with markedly increased liver function tests, which could represent an acute hepatitis and a reduction in the production of coagulation factors. There was no recent change in warfarin dose, but the patient had not had his international normalization ratio measured in the 2 weeks before presentation.

The failure of prothrombin complex concentrate to correct the international normalization ratio in this case deserves mention. Disseminated intravascular coagulation could explain this but seems unlikely, given the initial laboratory findings mentioned above. The initial international normalization ratio could have been so significantly above the upper limit of the laboratory's testing capacity that after the prothrombin complex concentrate infusion, it was still registering as greater than the laboratory's capability. More likely, though, is that the ventricular thrombus consumed most active factor on dilatation of the previously collapsed right ventricle and the international normalization ratio did not correct because of a consumptive process.

Because prothrombin complex concentrates are being used more frequently in EDs for rapid reversal of warfarin-induced coagulopathy, it is critical to recognize the thrombogenic adverse effects and reserve its use only for life-threatening bleeding. Future studies comparing the safety and efficacy of prothrombin complex concentrates to fresh frozen plasma should shed light on the rates of these potentially lethal adverse effects.

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