Cardiac tamponade in a patient with moderate hemophilia A and factor VIII inhibitors

Nina Ghosh BSc MD¹, Patrick Teefy MD FRCPC¹, Lori Laudenbach RN¹, Georges-Etienne Rivard MD FRCPC²

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Cardiac tamponade is a rare, life-threatening complication of hemophilia. The management of pericardial bleeding in hemophilia A patients with inhibitors is particularly challenging because antibodies to factor (F) VIII render the use of high-dose FVIII ineffective. Fortunately, the management of uncontrollable bleeding in patients with hemophilia and inhibitors has improved since the introduction of treatments that bypass the need for FVIII and FIX. A case of hemopericardium complicated by cardiac tamponade occurring one month following an upper respiratory tract infection in a patient with hemophilia and FVIII inhibitors is presented. Management of the present case was based on current guidelines on the use of recombinant FVIIa for acute bleeding in patients with hemophilia and inhibitors. The subsequent development of hemothorax in the present case indicates that a more protracted course of recombinant FVIIa is justified following pericardiocentesis for pericardial bleeding in hemophilia with inhibitors. Alternative approaches to the management of this complication are also reviewed.

Key Words: Cardiac tamponade; Coagulation

Pericardial bleeding in hemophilia is extremely rare. There have been only three reported cases of spontaneous cardiac tamponade secondary to a congenital coagulation defect (1-3). Gaston et al (1) reported the case of a patient with hemophilia with presumed pericardial bleeding. In this case, the patient presented with cardiac tamponade and a simultaneous decrease in hematocrit. Anderson (2) reported the case of a patient with hemophilia who presented with hemopericardium, tamponade and clinical stigmata of pericardiotomy syndrome. And Schultz et al (3) presented the case of a patient with congenital factor (F) V deficiency who presented with classic signs of acute cardiac tamponade requiring emergent pericardiocentesis followed by complete pericardiectomy.

We present the case of acute hemopericardium occurring one month following a presumed viral infection in a man with high-titre, high-responding inhibitors to FVIII. The case is of particular interest because it was associated with clinical features of cardiac tamponade and complicated by a postpericardiocentesis hemothorax, suggesting that current guidelines may not adequately address the management of acute pericardial bleed occurring spontaneously or secondary to viral infection in patients with hemophilia and inhibitors.

Une tamponnade cardiaque chez un patient atteint d'hémophilie A modérée avec inhibiteurs du facteur VIII

La tamponnade cardiaque est une complication rare de l'hémophilie mettant en jeu le pronostic vital. La prise en charge du saignement péricardique chez les patients atteints d'hémophilie A avec inhibiteurs pose un défi particulier parce que les anticorps anti-facteur (F) VIII rendent inefficace l'usage de fortes doses de FVIII. Heureusement, la prise en charge de saignements incontrôlables chez les patients hémophiles avec inhibiteurs s'est améliorée depuis l'adoption de traitements qui évitent l'usage de FVIII et de FIX. Est présenté un cas d'hémopéricarde compliqué par une tamponnade cardiaque s'étant manifesté un mois après une infection des voies respiratoires supérieures chez un patient hémophile avec inhibiteurs du FVIII. La prise en charge du présent cas respectait les lignes directrices à jour sur l'usage du FVIIa recombinant en cas de saignement aigu chez des patients atteints d'hémophilie avec inhibiteurs. L'apparition subséquente d'un hémithorax dans le présent cas indique qu'un traitement plus prolongé au FVIIa recombinant est justifié après une ponction péricardique découlant d'un saignement péricardique en cas d'hémophilie avec inhibiteurs. D'autres démarches de prise en charge de cette complication sont également analysées.

CASE PRESENTATION

A 56-year-old man was referred to the cardiology service at Victoria Hospital (London Health Sciences Centre, London, Ontario) for management of a moderately sized pericardial effusion. His past medical history included moderate (3%) hemophilia A with associated recurrent hemarthroses resulting in degenerative arthritis. High-titre FVIII inhibitors developed following intensive exposure to FVIII, which was used for hemostatic protection for bilateral knee arthroplasty performed eight years before his admission. The patient was HIV- and hepatitis C-negative. The patient also had a 25-year, one pack/day history of smoking, which he quit at the time of surgery. He was on medication to treat hypertension and hyperlipidemia. One month before admission, the patient had symptoms of a viral respiratory tract infection, including fever, coryza and shortness of breath on minimal exertion.

The presence of the pericardial effusion was detected incidentally when he presented to his local hospital complaining of hip pain. Computed tomography showed hemarthrosis of the right hip. Superior images obtained to exclude a psoas bleed incidentally revealed a pericardial effusion of moderate size, for which he was referred to Victoria Hospital. He was

¹Division of Cardiology, University of Western Ontario, London, Ontario; ²Division of Hematology and Oncology, Hôpital Sainte-Justine, Université de Montréal, Montreal, Quebec

Correspondence: Dr Patrick Teefy, London Health Sciences Centre, University Hospital, 339 Windermere Road, London, Ontario N6A 5A5.

Telephone 519-663-3075, fax 519-663-3516, e-mail patrick.teefy@lhsc.on.ca

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Figure 1) Two-dimensional echocardiogram (subcostal projection) to confirm a diagnosis of pericardial tamponade demonstrating a pericardial effusion of approximately 2.5 cm to 3 cm of fluid separation (denoted by asterisk). The arrow points to the collapsed right ventricle in early diastole. Subsequent pericardiocentesis yielded 1 L of bloody fluid in this patient with hemophilia and inhibitors to factor VIII

moderately dyspneic on arrival, but a chest x-ray performed at this time did not show any pulmonary or pleural abnormalities. Echocardiography (Figure 1) and clinical examination were consistent with cardiac tamponade, including elevated jugular venous pressure, tachycardia (108 beats/min) and a pulsus paradoxus of 20 mmHg. No pericardial rub was auscultated. A decision was made to proceed with pericardiocentesis based on clinical status. Following consultation with the hematology service, recombinant FVIIa (rFVIIa) 90 µg/kg was administered intravenously 30 min before pericardiocentesis and was continued every 2 h thereafter. Pericardiocentesis was achieved with echo-guided percutaneous drainage of the effusion through the left apical approach using a 12-gauge needle. One litre of hemorrhagic fluid was drained and resulted in relief of the tamponade, significant reduction of the effusion and improvement in dyspnea. There was resolution of right-sided chamber collapse seen on follow-up echocardiography. A flexible 8 Fr catheter was left within the pericardial space connected through tubing to a vacuum container.

Before pericardial drain removal, the patient developed shortness of breath, pleuritic chest pain and fever. Broad-spectrum antibiotics (cefotaxime) were initiated due to suspicion of left lower lobe pneumonia. Repeat echocardiography showed minimal pericardial effusion and a moderate left pleural effusion. The pericardial drain was removed, after which rFVIIa was continued for two doses (total of 4 h). Over the course of the following week, chest x-ray demonstrated that the left pericardial effusion had enlarged, occupying approximately 50% of the left pleural space (Figure 2). Computed tomography scan confirmed the presence of an effusion that was deemed large enough to warrant chest tube drainage. The chest tube was left in for four days and yielded more than 3 L of bloody fluid. rFVIIa 90 µg/kg was administered once, at 15 min before chest tube placement, and was continued every 2 h thereafter. When the interval of rFVIIa bolus infusion was decreased from every 2 h to every 6 h, the patient started to ooze bloody fluid around the chest tube, prompting reestablishment of the 2 h intervals. After chest tube removal, the frequency of FVIIa administration was gradually decreased to 3 h and 4 h intervals

Figure 2) Chest x-ray (posteroanterior projection) performed to assess the cause of dyspnea and pleuritic chest pain several days after pericardiocentesis. The arrow points to a left pleural effusion. Subsequent tube thoracostomy yielded 3 L of bloody fluid from the left pleural space in this patient with hemophilia and inhibitors to factor VIII

and continued every 4 h for another four days. There was no further fluid accumulation in the left pleural space as revealed by chest x-ray, and the residual pericardial effusion remained minor. At the time of discharge, the patient's dyspnea had improved markedly from the time of his admission.

The etiology of the pericardial effusion remains elusive. The fluid was sterile for bacteria, fungus and acid-fast bacilli and there was no evidence of malignancy on cytological analysis. Furthermore, antinuclear antibody, rheumatoid factor and thyroid-stimulating hormone levels were not elevated. C3 and C4 complement levels were not decreased. Hence, it is likely that the pericardial effusion was either spontaneous or secondary to the preceding viral illness. Three-month follow-up after initial presentation revealed no further dyspnea, no clinical features of cardiac constriction, and normal chest x-ray and echocardiogram results.

DISCUSSION

Spontaneous and postinfectious hemorrhagic pericardial effusions in patients with hemophilia are rare. The present case illustrates the complexities of management and complications associated with pericardiocentesis in a patient with cardiac tamponade and FVIII inhibitors. In these patients, the presence of antibodies to FVIII renders the prophylactic use of FVIII ineffective (4). Furthermore, the current evidence of clinical effectiveness in the treatment of acute bleeding in hemophilia A with inhibitors is clinically and methodologically heterogeneous (4). Most guidelines pertain to the management of bleeding complications common to patients with hemophilia, namely, hemarthroses or central nervous system hemorrhage, and do not address the optimal management of intrapericardial bleeding (4). Because bleeding diathesis is a relative contraindication to pericardiocentesis, it is debatable whether the current approaches to treating acute bleeds in hemophilia with inhibitors render the risks associated with pericardiocentesis acceptable in the face of acute cardiac tamponade (5).

rFVIIa has been shown to restore hemostasis in hemophilia A patients with high-titre inhibitors in various

acute bleeding situations (6). The rFVIIa molecule is thought to facilitate hemostasis by binding or complexing with tissue factor to the cell surface of activated platelets either directly or indirectly (7). Recommended doses of 40 µg/kg to 120 µg/kg repeated two to four times at 2 h intervals is considered to stop 80% to 90% of spontaneous hemorrhages, such as hemarthroses (7).

Because no other case of spontaneous cardiac tamponade and its management in patients with hemophilia and inhibitors has been reported in the literature, the above recommendation was used in an attempt to prevent continued pericardial bleeding in our patient. Although pericardial bleeding and symptoms of cardiac tamponade resolved with this regimen, a hemothorax developed over the course of a week following pericardiocentesis. Whether this was the result of the entry site of the pericardial drain with secondary leaking into the pleural cavity or a parapneumonic phenomenon remains conjectural, although the timing was more consistent with an iatrogenic cause. Indeed, a subxiphoid approach that is extrapleural and avoids coronary, pericardial and internal mammary arteries, rather than a left apical approach, may have circumvented this complication (8). On the other hand, continued administration of rFVIIa for a longer period of time following removal of the pericardial drain may have prevented a hemothorax regardless of the method of pericardiocentesis. Shapiro (9) has also advocated the use of high-dose regimens of rFVIIa to overcome the significant variability of its effectiveness from individual to individual. These so-called 'megadoses' of 300 µg/kg to 320 µg/kg have been shown to be more effective without an increased risk of adverse effects (9,10). The unpredictable efficacy of rFVIIa in the treatment of acute bleeding in our patient was also demonstrated by the degree to which its

dosage and frequency had to be fine-tuned to stop oozing from the pleural bleed.

Currently, both rFVIIa and activated prothrombin complex concentrates are acceptable treatment options for patients with hemophilia and high-titre, high-responding inhibitors (6). However, the thrombogenicity associated with activated prothrombin complex concentrates makes myocardial infarction a particularly undesirable complication in the face of threatened cardiovascular function from cardiac tamponade.

Uncorrected coagulopathy is a relative contraindication to pericardiocentesis (8). Gaston et al (1) successfully managed hemopericardium presenting as cardiac tamponade without pericardial tap. With the use of hemostatic methods available at the time, the size of their patient's heart shadow progressively decreased and symptoms of cardiac tamponade resolved. Their case demonstrates that in some cases, treating the coagulopathy rather than risking further bleeding using invasive methods may be sufficient to relieve hemodynamic compromise in cardiac tamponade. Given our patient's hemodynamic deterioration, the benefits of pericardiocentesis seemed to offset the potential risks.

Acute hemopericardium occurring spontaneously or postvirally in patients with hemophilia is such a rare event that no consensus exists as to its optimal management. The present case is the first report of acute postviral/spontaneous cardiac tamponade in a patient with hemophilia and inhibitors, and gives some insight into this complication of hemophilia. Our case demonstrates that the current recommendation of 90 µg/kg given every 2 h and continued for only 4 h after removal of a pericardial drain may not be sufficient to prevent continued bleeding in patients presenting with spontaneous cardiac tamponade. Indeed, an initial longer course of rFVIIa or the use of higher doses may have circumvented the development of hemothorax.

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