CASE REPORT

Coronary artery bypass grafting in a patient with active idiopathic cryoglobulinemia: revisiting the issue

Hafiz Abdul Moiz Fakih, MD1*, Emmanuel Elueze, MD, PhD1 and Rajiv Vij, MD1,2

1Department of Graduate Medical Education, Good Shepherd Medical Center, Longview, TX, USA; 2East Texas Kidney Specialists, Longview, TX, USA

Background: Cryoglobulinemia is a cold-reactive autoimmune disease. It is of distinctive importance in cardiac surgery because of the use of hypothermic cardiopulmonary bypass (CPB). Cryoglobulins, which activate at variable levels of hypothermia, can cause precipitation during surgery leading to possibly severe leukocytoclastic or necrotizing vasculitis, clinically manifested as ischemic events, such as cutaneous ulcerations, glomerulonephritis, arthritis, or peripheral neuropathies among the most reported associated comorbidities. Management of CPB and systemic protection in this rare but unique scenario requires individualized planning. We report the case of a patient with active cryoglobulinemia who was preoperatively managed with plasmapheresis. He underwent hypothermic coronary bypass with no precipitation and flare during and after surgery.

Case presentation: We describe the case of a 59-year-old Caucasian male with clinically significant idiopathic cryoglobulinemia and history of recurrent skin lesions and toe amputations secondary to cold exposure. He presented with 2-h duration of chest pain and new onset atrial fibrillation. After cardiac catheterization, a diagnosis of three-vessel coronary artery disease was established and coronary artery bypass grafting (CABG) was scheduled. Because of a high risk of flare-up during surgery, the patient was preemptively treated with two sessions of plasmapheresis before bypass. He then underwent hypothermic CABG. The pre- and perioperative course was unremarkable without any clinical evidence of precipitation. The patient was discharged on day 6 postoperatively without any complications.

Conclusion: Preoperative plasmapheresis before hypothermic coronary bypass can prevent fatal cryoglobulinemia-related complications in patients with active disease.

Keywords: cardiopulmonary bypass; cryoglobulinemia; cryoglobulins; plasmapheresis

*Correspondence to: Hafiz Abdul Moiz Fakih, 205 SE 16th Ave, Apt 12 G, Gainesville, FL 32601, USA, Email: hafizfakih@gmail.com

Received: 10 November 2015; Accepted: 5 January 2016; Published: 17 February 2016

Cryoglobulinemia is characterized by serum proteins or protein complexes that undergo reversible precipitation at low temperatures (1). It has been associated with viral infections (hepatitis A, B, C, and cytomegalovirus), connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, scleroderma, polyarteritis nodosa, polymyositis, cold agglutinin disease), and lymphoid disorders (chronic lymphoid leukemia macroglobulinemia, lymphoma) (2). Cutaneous symptoms resulting from altered blood flow from cryoprecipitation within capillaries include Raynaud’s phenomenon; acrocyanosis; necrosis of fingers, toes, the tip of nose, ears, or legs; vascular purpura; supramalleolar leg ulcers; and livedo reticularis. Renal manifestations result from either endomembranous deposits of cryoglobulins or diffuse glomerulonephritis. Peripheral neuropathies, joint manifestations, and major vascular thrombosis have also been reported (1). In patients undergoing surgery, particularly cardiovascular surgery, presence of these factors should alert the clinician about underlying cryoglobulinemia.

Cardiopulmonary bypass (CPB) with systemic hypothermia (core temperature ≤ 34°C) (3), blood or cold crystalloid cardioplegia, and topical myocardial cooling are techniques commonly used during cardiothoracic surgery. Only rare experiences have been reported in literature regarding management of cryoglobulinemia during CPB, and there are no standardized guidelines. Multiple approaches have been used, including double filtration plasmapheresis (DFPP) pre- and postoperatively as well as during CPB (4), normothermic CPB with continuous warm blood cardioplegia (5), or preoperative plasmapheresis and steroid therapy (6, 7).

Herein, we describe the case of a patient with active cryoglobulinemia who underwent two sessions of plasmapheresis before undergoing CPB.
Case
A 59-year-old Caucasian male presented with complaints of chest pain for 2 h and racing heart. The pain started at rest, substernal, crushing in nature, constant, 7/10 in severity, non-exertional, not relieved by rest or nitroglycerin. With the pain not getting any better, he decided to come to the emergency room. There he was found to be in atrial fibrillation with rapid ventricular response. He has an established diagnosis of idiopathic cryoglobulinemia for the last 14 years for which he has been treated with plasmapheresis and rituximab in the past, and is currently on oral prednisone. He has history of multiple leukocytoclastic vasculitic skin lesions involving his trunk and extremities, gangrene of right first and second toe, and left index finger requiring amputations. His last flare was 6 months ago (Fig. 1), and he has not had any further skin lesions. He also has history of acute renal failure with nephrotic syndrome 12 months back that was treated with plasmapheresis and steroids. Other past history includes hypertension, coronary artery disease status post two stents – the last one placed 7 years ago – gout, degenerative joint disease, and left eye surgery for retinal detachment. He has no history of smoking, drinking, or illicit drug use. His home medications included allopurinol, prednisone, sotalol, and lisinopril. Vital signs at presentation to the emergency room were blood pressure 141/91, pulse 150/min irregularly irregular, and respiratory rate 22/min, and pulse oximetry showed 97% saturation on room air. Skin examination revealed areas of palpable purpura with no discharge or bleeding bilaterally on the knees and abdomen. The abdominal lesions appeared more chronic as compared to the more recent lesions on the knee. His complete blood count showed white count of 11.1 × 10^3/mm^3, hemoglobin 15.9 g/dL, hematocrit 48%, and platelet count 123 × 10^9/mm^3. INR was 0.89, while chemistry showed sodium 136 mEq/L, potassium 4.1 mEq/L, chloride 103 mEq/L, bicarbonate of 21.1 mEq/L, creatinine 1.03 mg/dL, BUN of 15 mg/dL, and albumin of 2.9 g/dL. His 6-h serial of cardiac enzymes was 0.04, 1.27, and 1.56 (normal ranges <0.4 ng/mL). He was found to have a significant three-vessel disease by cardiac catheterization and was planned to have coronary artery bypass grafting (CABG).

Given the high risk for end organ damage during hypothermia for CABG, close association was established between nephrology, cardiac surgery, and hematology/oncology services. It was very clear that the patient needed an intervention to prevent peri- and postoperative complications. At admission, his qualitative cryoglobulin was positive. We performed two sessions of plasmapheresis with 4-L plasma volume with 5% albumin exchange. On the third day, the cryoglobulins by qualitative analysis were negative.

After median sternotomy and heparinization, the patient was put on CPB using aortic venous antegrade cannulas. Once adequate flow had been achieved, cross-clamp was applied and the heart was arrested using blood cardioplegia at 31°C, which was given every 20 min throughout the case. No topical cooling was used. The distal anastomoses of a left internal mammary artery graft and three saphenous vein-aortocoronary grafts were placed on the arrested heart. Three proximal aortic anastomoses were completed with systemic hypothermia, a spontaneously beating heart, and partial CPB. Total aortic cross-clamp time was 1 h and 42 min. CPB was discontinued after 2 h and the patient made an uneventful recovery. There was no electrocardiographic or enzyme evidence of perioperative myocardial infarction. The minimal nasopharyngeal and bladder temperature during the procedure was 32.4°C.

Postoperatively, patient did not have any complications associated with cryoglobulinemia such as renal failure or skin rash. At discharge, the patient was again restarted on his home dose of prednisone. His total postoperative stay in the hospital was 6 days.

Discussion
Our case exemplifies the importance of distinguishing potentially fatal complications that can occur in cryoglobulinemic patients undergoing CPB and that individualized preoperative management may prevent these complications. The frequency of clinically important cryoglobulinemia has been estimated at approximately 1 in 100,000, even though detectable levels of circulating cryoglobulins have been seen in a substantial proportion of patients with chronic infections and/or inflammation (8, 9). Surgery, in particular cardiac surgery, is a challenge in these patients given the fact that case reports have described adverse outcomes in patients with cryoglobulinemia. Carlsson and Tavassoli (10) described a 60-year-old woman with lymphoma and cryoglobulins in whom acute renal failure

Fig. 1. Picture taken during flare of cryoglobulinemia-induced leukocytoclastic vasculitis, ulcerations, and gangrene affecting the lower extremities. This was 6 months prior to the current presentation.
developed after gastrectomy in a cold operating room. Takeishi et al. (11) reported a 63-year-old man with 13-year history of asymptomatic proteinuria who had hypothermal atrial myxoma resection. He developed fever, renal failure, and skin rash. The diagnosis of cryoglobulinemia was made. Testing revealed an IgM lambda clone and high titer of rheumatoid factor activity and polyclonal IgG. Treatment with high doses of steroids and plasmapheresis was initiated. The treatment was ineffective and the patient died of colon necrosis due to thrombotic occlusion in the supra-mesenteric arteries. Keeping these in mind, we knew that hypothermic CPB in our patient, with clinically active leukocytoclastic vasculitis, was going to be a high-risk surgery. Given his significant three-vessel coronary artery disease and the benefit that he would achieve with a revascularization surgery, a close association between the different subspecialties was established.

After an extensive literature search, we found many case reports regarding management of CPB and cold agglutinin disease. But there are only six described cases of CPB in patients with cryoglobulinemia (4–7, 12, 13). Among them, Fontana et al. (12) described a 44-year-old woman with chronic hepatitis C and type III cryoglobulinemia who underwent a temperature-dependent differential serum cryoprecipitation profile in vitro prior to surgery. This helped define a range of temperatures (22–24°C) and surgery was performed above those temperatures. But this was different from our case in the sense that their patient never had any complications from cryoglobulinemic vasculitis before surgery. Muehrcke and Torchiana (13) reported CABC with normothermic CPB and warm-blooded cardioplegia in a 69-year-old man with primary cryoglobulinemia presenting with cutaneous vasculitis after cardiac catheterization. The cryoglobulinemia crisis was thought to have been brought on by the cardiac catheterization, which used room temperature contrast. Murata et al. (5) described the case of a 70-year-old woman with cryoglobulinemia who underwent emergent surgery for unstable angina and mitral regurgitation under normothermic CPB with continuous warm blood cardioplegia. In contrast to these cases, our surgery was non-emergent and provided more time for planning and deciding the best course for our patient.

Plasmapheresis transiently removes the circulating cryoglobulins and has been identified (in combination with immunosuppressive therapy) to be effective in decreasing morbidities related to cryoglobulinemia (14). The objectives of plasmapheresis are to remove plasma cryoglobulins and pathogen component, thus altering the antigen–antibody ratio, to eliminate cytokines and to increase immune complex clearance (15, 16). Only three case reports have been reported previously which used plasmapheresis for managing patients with cryoglobulinemia undergoing CPB. But all three used different techniques and combinations. Kotsuka et al. (4) reported a case of 58-year-old woman with past history of Sjogren’s syndrome and lymphoid interstitial pneumonitis with no active vasculitic disease. Her preoperative examinations revealed cryoglobulinemia (cryocrit 5.8%) and macroglobulinemia. They also demonstrated that macroscopic precipitation of her cryoglobulins started at 18°C. The patient underwent four sessions of DFPP for four consecutive days decreasing the cryocrit to 0.1%. The patient underwent CPB at 27°C. The peri- and postoperative course was uneventful. During the postoperative period, her IgM gradually increased. With the concern for blood hyperviscosity due to macroglobulinemia, DFPP was carried out three times and discontinued when her serum relative viscosity was 1.6. In our case, we had initially planned for both pre- and postoperative plasmapheresis, but given that the patient had uneventful surgery, we did not perform postoperative plasmapheresis.

Osada et al. (6) reported the case of a 57-year-old woman with thoracic aneurysm, with mixed cryoglobulinemia related to rheumatoid arthritis with a cryocrit level of 29%. Steroid therapy and preoperative plasmapheresis were performed until cryocrit levels decreased to 0% before operating. Interestingly, systemic hypothermia (25°C) and cold cardioplegia were successfully used, and no clinical evidence of microcirculation damage was evident postoperatively. Because of delayed reporting of send-out labs, we did not quantify cryocrit levels pre- and post-plasmapheresis, but our qualitative analysis did demonstrate that no cryoglobulins were present after the second session of plasmapheresis. The latest published case report was in 1998 by Yatsu et al. (7). They described a 57-year-old man with cryoglobulinemia who had aortic valve replacement for aortic regurgitation. They used preoperative steroid therapy with prednisolone for 6 months and plasmapheresis on the day before the surgery to attenuate the degree of cryoglobulinemia. The patient had hypothermic CPB and showed an uneventful intraoperative course, and there was no postoperative complication associated with cryoglobulinemia.

Conclusion
In conclusion, there are no guidelines for the management of patients with cryoglobulins during CPB and only rare experiences are reported in this field. One of the reasons for this case report is to review this rare yet challenging scenario given that this subject has not been visited for a long time. The fundamental questions that still remain unanswered include how many plasmapheresis sessions should be used and when should these sessions be performed. Given our literature review, we came to the conclusion that the management should be individualized depending on the severity of the clinical disease preoperatively, and there should be a balance between risk and benefit. A close association between
nephrology, hematology/oncology, and cardiovascular surgical services is of utmost importance.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editor of this journal.

Authors’ contributions

HAMF performed literature review, collected data, and prepared the manuscript. EE and RV provided input during manuscript preparation and literature survey. EE critically appraised the manuscript and edited the scientific data. RV was the consultant nephrologist in the treatment of this patient and conceived the idea. All authors participated in discussions about the manuscript and approved the final version.

Conflict of interest and funding

None of the authors have a conflict of interest and funding. All authors had access to the data and a role in writing the manuscript.

References

1. Foerster J. Cryoglobulins and cryoglobulinemia. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, eds. Wintrobe’s clinical hematology. Volume 2. 10th ed. Philadelphia, PA: Lea & Febiger; 1999, pp. 2725–37.
2. Russo GE, Caramiello MS, Vitaliano E, De Marco CM, Pennachia M, Giusti S, et al. Haemorheological changes in mixed cryoglobulinaemia during apheresis treatment. Transfus Sci 1996; 17(Suppl 4): 499–503.
3. Ho KM, Tan JA. Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: A systematic review. Cardiovasc Ther 2011; 29(Suppl 4): 260–79.
4. Kotsuka Y, Nakajima J, Miyari T, Nakahara H, Suzuki M, Kanda J, et al. Coronary artery bypass grafting in a patient with cryoglobulinemia. J Cardiovasc Surg (Torino) 1991; 32(1): 53–5.
5. Murata S, Tabayashi K, Schinozaki S, Shimizu M, Ito T, Konnai T. Successful cardiac surgery using normothermic cardiopulmonary bypass in an elderly patient with cryoglobulinemia. Nihon Kyobu Geka Gakkai Zasshi 1995; 43: 65–8.
6. Osada T, Kawachi K, Uchino T, Hirayama T, Ishimaru S, Furukawa K. A successful case of thoracic aortic aneurysm with mixed cryoglobulinemia. Nihon Kyobu Geka Gakkai Zasshi 1992; 40(Suppl 7): 1100–4.
7. Yatsu Y, Kimura F, Muraoka M, Tsubo T, Ishihara H, Matsuki A. Perioperative management of a patient with cryoglobulinemia for open heart surgery. Masui 1998; 47: 53–6.
8. Bonnet F, Pineau JJ, Taupin JL, Feyler A, Bonarek M, de Witte S, et al. Prevalence of cryoglobulinemia and serological markers of autoimmunity in human immunodeficiency virus infected individuals: A cross-sectional study of 97 patients. J Rheumatol 2003; 30: 2005.
9. García-Carrasco M, Ramos-Casals M, Cervera R, Trejo O, Yagüe J, Sísó A, et al. Cryoglobulinemia in systemic lupus erythematosus: Prevalence and clinical characteristics in a series of 122 patients. Semin Arthritis Rheum 2001; 30: 366.
10. Carloss HW, Tavassoli M. Acute renal failure from precipitation of cryoglobulins in a cold operating room. JAMA 1980; 244: 1472–3.
11. Takeishi M, Mimori A, Adachi D, Arai E, Suzuki T. Case of fulminant mixed cryoglobulinemia developing after atrial myxoma resection. Nihon Rinsho Meneki Gakkai Kaishi 2001; 24(Suppl 4): 168–74.
12. Fontana M, Ruchat P, Horisberger J, Aubert V, Mayor C, Spertini F. Prevention of cryoprecipitation during cardiopulmonary bypass in a patient with HIV-HCV co-infections. Perfusion 2006; 21: 263–5.
13. Muehrcke DD, Torchiana DF. Warm heart surgery in patients with cold autoimmune disorder. Ann Thorac Surg 1993; 55: 532–3.
14. Scarpato S, Tirri E, Naclero C, Moscato P, Salvati G. Plasmapheresis in cryoglobulinemic neuropathy: A clinical study. Dig Liver Dis 2007; 39(Suppl 1): S136–7.
15. Siami GA, Siami FS. Cryofiltration apheresis in the United States. Ther Apher 1998; 2(Suppl 3): 228–35.
16. Rocks MA, Clark WF. Plasma exchange for treating cryoglobulinemia: A descriptive analysis. Transfus Apher Sci 2010; 42: 247–51.