

Non-ST Segment Elevation Myocardial Infarction Associated with IV Infusion of Immunoglobulin

Tamar Koleba, Farzana A. Sayani, and Margaret L. Ackman

INTRODUCTION

Immunoglobulin (IVIG) is used in the treatment of a variety of disorders, including primary and secondary immunodeficiency diseases, Kawasaki disease, and idiopathic thrombocytopenia purpura.¹ Although serious adverse cardiovascular reactions are rare, a recent article reviewed 28 published cases of thrombotic complications occurring in association with IVIG administration between 1986 and 2003.² An additional 36 cases reported recently³⁻⁹ were not included in the review. This article describes 2 patients treated in the same month at the authors' institution for non-ST segment elevation myocardial infarction possibly associated with IVIG administration. To the authors' knowledge, case 1 represents the first reported case of a patient experiencing non-ST segment elevation myocardial infarction after each of 2 consecutive doses of IVIG.

CASE REPORTS

Case 1

A 76-year-old man with a history of hypogammaglobulinemia, chronic obstructive pulmonary disease, and previous bilateral lower lobe pneumonectomy was admitted to the coronary care unit for treatment of non-ST segment elevation myocardial infarction. The patient had received IVIG monthly for the previous 4 years for treatment of the hypogammaglobulinemia.

Two months before this presentation, the patient experienced acute right-sided chest and arm pain 4 h after initiation of an infusion of 5% IVIG (500 mg/kg) at infusion rates up to 3 mL/kg per hour in an outpatient medical clinic. The pain resolved upon discontinuation of the infusion. At the time, the pain was attributed to

muscle spasm associated with costochondritis. The patient was treated with salbutamol by nebulizer and supplemental oxygen. The IVIG infusion was reinitiated and completed without further incident. The patient had no known cardiovascular disease and no apparent cardiac risk factors, other than advancing age and male sex.

One month later, the patient experienced acute right-sided chest and arm pain and shortness of breath 3 h after initiation of an infusion of 5% IVIG (500 mg/kg) at rates up to 3.2 mL/kg per hour. At the patient's request, the infusion rate was decreased to 2.7 mL/kg per hour; the infusion was subsequently discontinued when the symptoms did not resolve. Electrocardiography revealed first-degree atrioventricular block and ST segment depression in leads V₄ and V₅. The serum creatine kinase concentration was 359 U/L, and the serum troponin I concentration was 2.60 µg/L. Acute myocardial infarction was diagnosed, and treatment with acetylsalicylic acid, enoxaparin, clopidogrel, ramipril, and bisoprolol was initiated. Planned angiography was not performed because melena and hypotension developed, and the patient experienced a substantial decline in serum hemoglobin concentration. The patient was managed medically. The non-ST segment elevation myocardial infarction was attributed to cardiac stress due to fluid overload.

The next month, the patient was admitted to the authors' institution with a 3-day history of malaise and chest pain radiating to the right shoulder and ribs. Questioning revealed that his symptoms had begun insidiously within hours after he was discharged from an outpatient medical clinic where he had received a 500 mg/kg dose of IVIG administered as a 5% solution at infusion rates up to 2.5 mL/kg per hour along with furosemide 20 mg, also administered intravenously. Electrocardiography showed T-wave inversion in lead aVL. The peak serum

creatinine kinase concentration was 202 U/L, and the serum troponin I concentration was 9.74 µg/L. Non-ST segment elevation myocardial infarction was diagnosed, and the patient was managed medically with unfractionated heparin, acetylsalicylic acid, clopidogrel, ramipril, bisoprolol, and transdermal nitroglycerin.

Angiography revealed severe coronary atherosclerosis at the bifurcation of the left main coronary artery, with 70% stenosis of the left main coronary artery, 90% stenosis of the proximal left anterior descending coronary artery, and 99% stenosis of the proximal left circumflex coronary artery. A dipyridamole sestamibi scan showed partially reversible chronic ischemia of the left anterior wall at the mid-cavity; the left ventricular ejection fraction was 60%. Because of severe pulmonary disease, the patient was a poor candidate for coronary artery bypass grafting, and he subsequently underwent percutaneous transluminal coronary angioplasty. Plans were made to reduce the dose and infusion rate for future administration of IVIG.

Case 2

An 88-year-old man with a history of hypertension and chronic kidney disease and no history of ischemic heart disease was admitted with the diagnosis of immune thrombocytopenic purpura. IVIG 1 g/kg was administered as a 10% solution at an infusion rate of 1.5 mL/kg per hour; therapy with oral prednisone 1 mg/kg daily was also initiated.

After completion of the IVIG infusion, the patient experienced mild central retrosternal chest pain. At that time, the pain was not attributed to the IVIG administration. Approximately 1 to 2 h after a second infusion of IVIG, the patient experienced more intense recurrent retrosternal chest pain, lasting approximately 2 h, without radiation, dyspnea, or diaphoresis. Electrocardiography revealed normal sinus rhythm with left ventricular hypertrophy and ST segment depression in the inferolateral leads (II, III, aVF, V₅, V₆). The serum troponin I concentration was elevated at 20.99 µg/L. The peak serum creatine kinase concentration was 783 U/L. Non-ST segment elevation myocardial infarction was diagnosed, and standard medical management was initiated, including acetylsalicylic acid, metoprolol, and unfractionated heparin. Coronary angiography revealed 100% occlusion of the mid right coronary artery and 50% occlusion of the left main ostium. Echocardiography revealed mild left ventricular systolic dysfunction, with a left ventricular ejection fraction of 45% to 50%, inferior wall akinesis, and mild mitral regurgitation. The patient was offered coronary artery bypass grafting but refused, opting instead for aggressive medical management of

his coronary artery disease. He received a total of 2 doses of IVIG for the immune thrombocytopenic purpura; the prednisone therapy was continued with no plan for further administration of IVIG.

DISCUSSION

This article reports 2 cases of non-ST segment elevation myocardial infarction associated with the administration of IVIG. According to the adverse effects probability scale developed by Naranjo and others,¹⁰ there was a probable association between IVIG administration and the occurrence of the non-ST segment elevation myocardial infarction in both patients.

The first report of serious thrombotic events occurring during treatment with IVIG was published in 1986.¹¹ In spring 2002, on the basis of 28 published studies and internal medication safety monitoring data, Health Canada,¹² the US Food and Drug Administration,¹³ Baxter (manufacturer of Gammagard, an immunoglobulin product), and the American Red Cross (manufacturer of Polygama, another immunoglobulin product) issued safety warnings regarding the possible association of IVIG with serious thrombotic events.

A recent review summarized published cases of serious thromboembolic events, including 12 that were fatal, occurring during or after IVIG infusion.² Thromboembolic complications were more common in association with higher IVIG doses (greater than 400 mg/kg daily) or more rapid infusion rates, and included myocardial infarction (11 cases), cerebral infarction (10 cases), pulmonary emboli (3 cases), and systemic vascular occlusion (7 cases). Most patients had additional risk factors for thrombosis. An additional 36 reports of thrombosis associated with IVIG (1 case of myocardial infarction, 25 cases of cerebral infarction, 1 case of pulmonary emboli, and 9 cases of systemic vascular occlusion) have been published.³⁻⁹

Several mechanisms have been proposed to explain the possible relation between IVIG and thromboembolic events. It has been suggested that IVIG possesses platelet agonist properties, enhancing adenosine triphosphatase release and consequent platelet aggregation.¹¹ In addition, increases in plasma and blood viscosity and erythrocyte aggregation have been demonstrated following IVIG administration.¹⁴ In one study of 13 patients receiving IVIG, the upper limit of normal viscosity was exceeded in 11 of the patients.¹⁵ Other proposed mechanisms include rapid elevation in platelet count,¹⁴ direct effects on the vascular endothelium,¹⁶ and expansion of plasma volume leading to cardiac decompensation.¹⁷ Product contamination has also been investigated.¹⁸ A total of 29 samples of IVIG from 8



manufacturers were analyzed, of which 26 appeared to be contaminated with coagulation factor XI, a procoagulant substance.

Reductions in IVIG doses and administration at lower infusion rates may be advisable for patients with underlying cardiovascular disease or those who experience anginal symptoms during or after IVIG infusion. Manufacturer guidelines strongly recommend that when there is a potential risk of a thrombotic event, the concentration of IVIG should not exceed 5%, the infusion should be initiated at a rate of 0.5 mL/kg per hour, and the infusion rate should be increased slowly to a maximum of 4 mL/kg per hour as tolerated.^{12,13,19} In patients with known cardiovascular disease or thrombotic risk factors, IVIG should be administered in a setting in which monitoring by 12-lead electrocardiography can be performed. Patients should be monitored for symptoms characteristic of cardiac events, such as chest pain or shortness of breath. Continuous telemetry monitoring may be ideal for high-risk patients but probably precludes IVIG administration in many outpatient settings. Complaints of angina around the time of infusion should trigger prompt discontinuation of IVIG therapy, and the symptoms should be investigated for cardiac events in light of the published cases. Patients experiencing IVIG-associated myocardial infarction should be treated according to the current standard of care and treatment guidelines. IVIG should not be administered during myocardial infarction or the subsequent recovery period. Clinicians should consider decreasing future IVIG doses and/or infusion rates if cardiac events appear to be related to immunoglobulin administration. Preventive treatment with antiplatelet or anticoagulant agents has been suggested,² but there are no clear data to support this recommendation.

The authors have described 2 patients who experienced serious cardiac events after administration of IVIG, one of whom experienced cardiac ischemia in association with 3 successive IVIG infusions. IVIG may precipitate myocardial infarction in patients with underlying coronary artery disease. Although thrombotic complications of IVIG are relatively rare, the potential seriousness of these events necessitates caution and vigilance on the part of the clinician.

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Tamar Koleba, BScPharm, was, at the time of writing, with Regional Pharmacy Services, Capital Health, Edmonton, Alberta.

Farzana A. Sayani, MD, was, at the time of writing, with the Faculty of Medicine, University of Alberta, Edmonton, Alberta.

Margaret L. Ackman, BSc(Pharm), PharmD, is with Regional Pharmacy Services, Capital Health, Edmonton, Alberta.

Address correspondence to:

Tamar Koleba
1797 Mallard Drive
Courtenay BC
V9N 8L9

e-mail: tkoleba@ualberta.net

