Myocardial Infarction in a Young Man Receiving Chemotherapy for Acute Lymphoblastic Leukemia

Wei Yang, MD[1]
Jason C. Kovacic, MD, PhD[2]
Caroline Cromwell, MD[3]
Celia Grosskreutz, MD[3]
John Mascarenhas, MD[3]

[1]Mount Sinai School of Medicine; [2]Department of Cardiology, Mount Sinai School of Medicine; [3]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, New York

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by rapid proliferation of immature lymphocytes in the bone marrow, blood, and other organs.[1] An estimated 5330 new cases of ALL were diagnosed in 2010 in the United States.[2,3] In adults, ALL has a 5-year overall survival rate of only 30% to 40%.[4,5] Patients with ALL can be risk stratified based on adverse prognostic features, which include age, leukocyte count, immunophenotype, genotype, and early treatment response.[6] Analyses of multiple pediatric and adult study group trials show complete induction remission rates of approximately 98% in children and 85% in adults following multidrug induction chemotherapy.[6]

Combination chemotherapy is the primary treatment for patients with newly diagnosed ALL, and induction remission treatment for this condition commonly includes the administration of vincristine and a glucocorticoid, usually with the addition of L-asparaginase, an anthracycline, or both.[6,7] The overall risk of symptomatic thrombosis in children with ALL is estimated to be 5.2%. Approximately half of these thromboses occur in the central nervous system; the remaining ones comprise deep vein thrombosis, pulmonary embolism, right atrial thrombosis, and superficial thrombosis.[8] The thrombotic risk may be up to 8-fold higher in ALL patients with a genetic hypercoagulable defect.[8] Agents used in induction therapy for ALL also have been associated with thrombotic complications.[8-15] We present a case of sequential myocardial infarctions (MIs) in a young man without significant cardiovascular risk factors while receiving induction remission chemotherapy for newly diagnosed B-cell ALL, and review the literature on this topic.

Address correspondence to:
John Mascarenhas, MD, Tisch Cancer Institute, Division of Hematology/Oncology, Mount Sinai School of Medicine, One Gustave L Levy Place, Box 1079, New York, NY 10029; Phone: 212-241-3417; E-mail: john.mascarenhas@mssm.edu.

Case Presentation

The patient was a 36-year-old nonobese Hispanic man without a significant medical history. He initially presented with a rectal abscess, and was found to have a white blood cell count of 15,000/μL with the presence of myeloblasts in the peripheral blood. He was subsequently diagnosed with Philadelphia chromosome negative (Ph–) B-cell ALL on bone marrow biopsy. Additional laboratory findings included a hemoglobin level of 9.3 g/dL, platelet count of 74 × 10^3/μL, fibrinogen level of 369 mg/dL, and D-dimer level of 2.21 μg/mL. There was no history of hypertension, diabetes, hyperlipidemia, hypercholesterolemia, smoking, illicit drug use, prior thrombotic events, cardiovascular disease in first-degree family members, or prior angina symptoms.

He was initiated on combination chemotherapy as per the CALGB 10403 (Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia) protocol; the schedule of administered agents is shown in the Table. The patient received pegylated asparaginase (pegasparaginase) as scheduled on day 4. On day 9, he experienced lightheadedness, dyspnea, and nonradiating retrosternal chest pain. An electrocardiogram (ECG) demonstrated borderline ST-segment elevation of 1 mm or less in leads II, III, and aVF. However, his pain completely resolved over approximately 60 minutes, and given his concurrent pancytopenia, a conservative strategy was adopted. Transthoracic echocardiography performed on day 10 showed a left ventricular ejection fraction (LVEF) of 50% (baseline, 55%), with focal hypocontractility and dyskinesis of the inferolateral wall. Computed tomographic coronary angiography (CTCA) performed on day 11 did not reveal any vascular occlusion, plaque, calcification, or dissection (Figure A). Creatine kinase (CK)-MB peaked at 49.6 ng/mL, and troponin I peaked at 34.1 ng/mL. Additional findings included a fibrinogen level of 35 mg/dL, D-dimer level of 13 μg/mL, prothrombin time of 16.4 seconds,

partial thromboplastin time of 30.8 seconds, white blood cell count of 0.6 × 10^3/μL, hemoglobin level of 9.3 g/dL, and platelet count of 51 × 10^3/μL.

The patient was started on a heparin infusion, metoprolol, and rosuvastatin. Aspirin 325 mg was administered on day 10 only, and then discontinued in the setting of thrombocytopenia. The patient received a total of 30 U of cryoprecipitate to correct the fibrinogen to 165 mg/dL by day 14. The cardiac biomarkers progressively normalized and the patient remained stable. Given the normal CTCA, a decision was made to continue chemotherapy with concurrent continuous heparin infusion.

The patient received vincristine and daunorubicin on day 15. The following afternoon, he developed burning chest pain that persisted overnight while on therapeutic intravenous heparin. His ECG evolved to show 1- to 2-mm ST-segment elevation in leads II, III, and aVL, consistent with an acute inferior MI. Coronary angiography revealed total occlusion of the mid-distal right coronary artery (RCA) with extensive thrombus burden (Figure B). The patient received aspirin 325 mg, clopidogrel 600 mg, and bivalirudin bolus and infusion, and underwent percutaneous coronary intervention. Uncharacteristically, the use of mechanical aspiration with a thrombectomy catheter had minimal impact on reducing the thrombus burden (Figure C). A bolus of the platelet glycoprotein IIb/IIIa inhibitor eptifibatide was also administered, and a total of 3 bare metal stents were placed in the right coronary artery, the right posterior descending artery, and the atrioventricular continuation branch. Repeat transthoracic echocardiography the following day (day 18) revealed an LVEF of 30%, with noncontractility of the inferior and inferolateral walls. Troponin I peaked at 22.9 ng/mL. Antiplatelet therapy was switched from clopidogrel to ticagrelor 90 mg twice a day, and a continuous intravenous argatroban infusion was initiated on day 20.

An evaluation of hypercoagulability was conducted that included testing for the presence of prothrombin gene mutation, factor V Leiden, heparin-induced thrombocytopenia antibodies, antiphospholipid syndrome antibodies, and tests for antithrombin III (ATIII), protein C, and protein S activity. The results were only remarkable for a moderately depressed ATIII function of 47% and protein S activity of 32%. Owing to concerns about adverse cardiac healing, prednisone was discontinued, and administration of vincristine and daunorubicin was postponed until day 28. Bone marrow biopsy on day 30 showed a normocellular marrow (60%) with trilineage hematopoiesis without evidence of residual leukemia.

At discharge, the patient was continued on metoprolol, rosuvastatin, ticagrelor, and fondaparinux 7.5 mg daily. Consolidation chemotherapy continued without further cardiac complications. Three months after discharge, the patient's LVEF had improved to 44%.

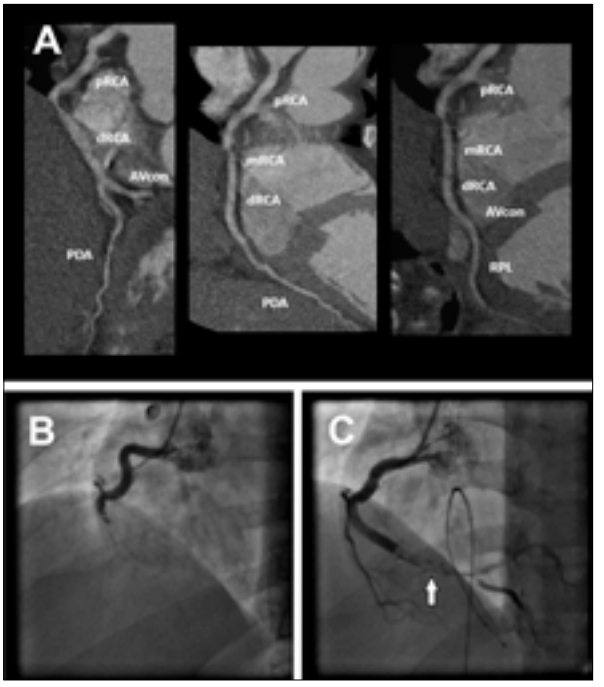

Figure. Computed tomographic coronary angiography (CTCA) and angiographic images of the right coronary artery (RCA). A, Panels showing CTCA reconstruction of RCA and its branches acquired on day 11 after initial myocardial infarction. Three panels are presented, showing differing reconstructions and views. A reconstruction artifact is present in all panels owing to cardiac motion (panels appear to be cut diagonally near the middle and slightly misaligned). Even retrospectively, there is no evidence of calcified or noncalcified atherosclerosis, dissection, luminal defect, or other abnormality.

Six days later, the patient suffered an inferior ST-segment elevation myocardial infarction and was taken immediately to the catheterization laboratory. B, RCA angiography demonstrates total occlusion in the segment that was shown in Figure A to be normal by CTCA. C, Percutaneous coronary intervention was performed with right ventricular pacing wire now in situ and flow restored to the distal vessel. This image demonstrates the large thrombus burden in the distal RCA prior to stent implantation, seen as an extensive luminal filling defect (arrow).

AVcon, atrioventricular continuation branch; d, distal; m, mid; PDA, posterior descending artery; p, proximal; RPL, right posterolateral artery.

Discussion

The patient in this case experienced 2 acute coronary events within a 1-week period during induction chemotherapy for ALL. He had normal coronary arteries by CTCA, and no evidence of atherosclerosis. The second and most dramatic of these events occurred while the patient was receiving a therapeutic heparin infusion.

Table. Acute Lymphoblastic Leukemia Induction Remission Chemotherapy Schedule

Agent	Day	Dose	Route
Allopurinol	1-28	300 mg	Oral
Cytarabine	1	70 mg	Intrathecal
Vincristine	1, 8, 15, 22*	2 mg	Intravenous
Daunorubicin	1, 8, 15, 22*	52 mg	Intravenous
Prednisone	1-28†	120 mg	Oral
Pegylated asparaginase	4	5225 IU	Intravenous
Methotrexate	8, 29	15 mg	Intrathecal

*Day 22 was postponed to day 28.
†Ceased on day 18 following second myocardial infarction owing to concerns about adverse cardiac healing and ventricular rupture.

Together, these features suggest the possibility of chemotherapy-induced hypercoagulability leading to MI. Decreased fibrinogen and elevated D-dimer levels, along with the resistant nature of the coronary thrombus to disruption, further support a coagulopathic process as the likely mechanism.

Among the agents our patient received prior to his thrombotic events, asparaginase is most commonly associated with thrombotic complications in 4% to 10% of patients, ranging from day 5 to 15 after administration.[9,16] A prospective study of children with ALL showed a venous thromboembolism frequency of 10.4% when asparaginase is administered with prednisone as part of induction therapy.[17] Additionally, brand, total dose, and duration of asparaginase therapy have been shown to influence thrombotic risk in the setting of ALL.[8] Depressed levels/activity of ATIII, fibrinogen, and protein C/S implicate a mechanism of activated coagulation and impairment of fibrinolysis.[10,16,18] Studies have described a correlation between depressed levels of ATIII and increased risk of thrombotic events in patients receiving asparaginase, and ATIII repletion appears be effective in lowering the rate of thrombosis in ALL patients receiving asparaginase.[16,19,20]

Our patient received pegasparaginase, which has been shown to have antileukemic activity comparable to that of asparaginase, and has been introduced into current chemotherapeutic regimens owing to its longer half-life (6-9 days) and improved hypersensitivity profile.[21-23] According to a randomized trial comparing pegasparaginase with asparaginase in children with ALL, the incidence of thrombosis was similar between groups receiving pegylated vs native formulations.[23] However, whether pegasparaginase holds the same thrombotic risk as asparaginase in adults has not been thoroughly investigated.

Although thrombosis is a well-established adverse event in asparaginase recipients, thrombotic events described are predominantly of venous rather than arterial origin (80% vs 20%), including upper- and lower-extremity deep vein thrombosis, subclavian vein thrombosis, and sagittal sinus thrombosis.[9] To our knowledge, there have been only 2 reported cases of MI in adult ALL patients treated with asparaginase.[11,12] In both instances, asparaginase was the most recent chemotherapeutic agent administered before occurrence of the MI (regimens included vincristine, daunorubicin, and prednisone). Our case is unique in that it is the only occasion in which the culprit site of coronary occlusion was known to be entirely normal and free of atherosclerosis (Figure A). Furthermore, our case occurred during therapeutic intravenous heparin administration.

A temporal relationship between the sequential administration of vincristine and daunorubicin and the coronary events raises the possibility these agents also contributed to the arterial thrombotic complication. ALL protocols incorporating anthracyclines are associated with higher rates of thrombosis (6.1% vs 2.7%), independent of the type of anthracycline.[11] Although the incidence of thrombotic events with vincristine administration has not been well described, there are isolated case reports of patients who developed ischemic heart disease while on vincristine alone or in combination with anthracycline therapy.[13-15] Prednisone is also associated with increased thromboembolic risk. A prospective study in children receiving induction therapy for ALL revealed a thrombosis frequency of 10.4% in the group receiving asparaginase with prednisone compared with 1.8% among patients receiving asparaginase with dexamethasone.[17] Potential mechanisms through which prednisone, vincristine, and anthracyclines could exacerbate an already tenuous hemostatic system include contribution to activation of coagulation and direct vascular endothelial damage.[24-29]

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Commentary

Myocardial Infarction in a Young Adult Undergoing Induction Treatment for Acute Lymphocytic Leukemia

Nina Kadan-Lottick, MD,[1] Raymond Russell, MD,[2] and Nikolai Podoltsev, MD, PhD[3]

Section of Pediatric Hematology-Oncology; [2]Department of Internal Medicine, Section of Cardiology; [3]Department of Internal Medicine, Section of Hematology, Yale University School of Medicine, New Haven, Connecticut

Address correspondence to:
Nikolai Podoltsev, MD, PhD, Assistant Professor of Medicine, Department of Internal Medicine, Hematology Section, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520; Phone: 203-737-2572; E-mail: nikolai.podoltsev@yale.edu.

We reviewed with interest the case report by Yang and colleagues, which highlights a rare but important side effect of acute lymphoblastic leukemia (ALL) induction chemotherapy.[1] ALL by itself can cause a hypercoagulable state that may be significantly exacerbated by additional factors, including its treatment (L-asparaginase), heritable thrombophilias (ie, Factor V Leiden, prothrombin gene mutation, antithrombin III, and protein C and S deficiencies), the presence of central line catheters, and acquired hypercoagulable states. Acquired hypercoagulable states include antiphospholipid syndrome (APS) and heparin-induced thrombocytopenia (HIT).

The authors describe a case of a 36-year-old man without a significant medical history or a family history of thrombotic or cardiovascular events who was diagnosed with Philadelphia chromosome negative B-cell ALL and received treatment with induction chemotherapy according to the CALGB 10403 (Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia) protocol, which includes systemic administration of vincristine, daunorubicin, pegylated asparaginase (pegasparaginase), and prednisone. He developed a non-ST segment elevation myocardial

infarction (MI) on day 9 after administration of pegasparaginase on day 4. A computed tomographic coronary angiogram performed on day 11 was described as unremarkable. He received treatment for his MI, which included heparin infusion and administration of cryoprecipitate owing to low levels of fibrinogen. While on heparin infusion, he developed an ST-segment elevation MI on day 15. Cardiac catheterization was performed, and aggressive technical maneuvers had minimal impact on reducing thrombus burden. Eventually, 3 bare metal stents were successfully placed. The patient received aggressive antiplatelet therapy, as well as argatroban infusion, and was discharged on therapeutic fondaparinux.

Development of arterial thrombosis in a young patient usually prompts the hypercoagulability workup, which includes testing for APS and HIT. Testing patients for heritable thrombophilias, which primarily predispose to venous thrombosis, is less likely to be helpful.[2] Arterial thrombosis has been associated with the methylenetetrahydrofolate reductase polymorphism, but more recent studies suggest that hyperhomocysteinemia has uncertain clinical significance.[3] A workup for APS includes testing for lupus anticoagulant, anticardiolipin antibody, and β_2-glycoprotein 1 antibody.[4] The first 2 tests were negative in this patient. Diagnosis of HIT is a clinical-pathologic entity based on the analysis of the clinical scenario (the pretest probability could be high in the presented patient, but his thrombocytopenia can be explained by chemotherapy administration), as well as testing for heparin-platelet factor 4 antibodies (sensitivity >90%), which was negative.[5] Heparin was excluded from the patient's management after his second MI, and he was subsequently managed with argatroban followed by fondaparinux.

The factor in his treatment that most likely explains the development of MI is the use of pegasparaginase. L-asparaginase has been the mainstay of pediatric ALL management since the 1970s; during the last decade, it has also been used more commonly for the management of adult patients with ALL. Depletion of asparagine leads to selective killing of the leukemic blasts[6] but also leads to decreased synthesis of naturally occurring anticoagulants including proteins C and S, plasminogen, and especially AT.[7] The patient had low functional AT and protein S activity, which may have been due to pegasparaginase use or acute thrombus; the low AT may have been due to the use of heparin.[2]

Currently, pegasparaginase is the first-line asparaginase preparation used for the management of ALL in both children and adults. The incidence of thrombosis may be lower with native asparaginase but data are limited.[8] The incidence of thrombosis clearly varies with the patient's age, and is seen in 5% of pediatric patients and 9% of adult patients with ALL.[9,10] Most of the thrombotic complications in children and adults (90%) occur during the induction phase of treatment.[10] Thrombosis occurs most frequently on the venous side of the circulation, but arterial thrombosis—including stroke—occurs in up to 10% of patients.[9] MI is much less frequent, with only a couple of cases reported in the literature.[11,12]

MI caused by coronary thrombosis generally occurs when a vulnerable atherosclerotic plaque ruptures, exposing the components of the plaque to the bloodstream. Rupture of the fibrous cap of a vulnerable plaque is thought to occur because of alterations in hemodynamic forces combined with remodeling of the fibrous cap by matrix metalloproteinases.[13] Therefore, plaque rupture in a prothrombotic environment would increase the risk of complete occlusion of the coronary artery and subsequent MI. Although it is tempting to hypothesize that pegasparaginase therapy could also affect the dynamics of plaque remodeling, causing the plaque to become vulnerable, the exceedingly low incidence of MI noted above would suggest that this mechanism does not contribute to the pathophysiology of coronary artery thrombosis.

Because pegasparaginase is commonly administered with vincristine, anthracycline, and a corticosteroid, these agents are thought to contribute to a hypercoagulable state in patients who undergo induction chemotherapy for ALL, even though there is minimal evidence to support this claim. Use of anthracyclines, but not corticosteroids, was associated with a higher incidence of thrombosis during induction in a meta-analysis of pediatric ALL patients.[9] Prednisone, but not dexamethasone, in the postinduction period resulted in a higher rate of thrombus events. When used in other malignancies, these drugs are not believed to be associated with an increased risk of thrombosis.

Monitoring of coagulation parameters—including partial thromboplastin time, prothrombin time, AT, and fibrinogen level—in asymptomatic patients remains controversial, but at least 1 multisite expert panel recommends this for patients who develop thrombohemorrhagic complications during pegasparaginase use.[8] Actual practice varies among centers and between adult and pediatric clinical trial consortia.

The complicating factor for the management of patients with thrombosis who are treated with pegasparaginase is the risk of bleeding that is thought to be due to depletion of fibrinogen, although thrombosis is the predominant complication. After a diagnosis of thrombosis is established, anticoagulation is started. Cryoprecipitate and platelet transfusions are added if the patient has hypofibrinogenemia (fibrinogen levels <100 mg/dL or <50 mg/dL, depending upon the authors) and significant thrombocytopenia, and AT concentrate may be added if AT levels are low (<60 mg/dL).[8,14]

There is some possibility that the use of AT could have prevented the development of the second coronary event in this patient, so AT use could have been considered. In general, the use of fresh frozen plasma should be avoided

because it repletes asparagine and may negate the antileukemic effect of asparaginase.[8]

Significant progress has been made in the management of children and adults with ALL, even though we continue to treat these patients with the same medications that were available 40 years ago. The success of treatment can be partially attributed to adherence to complicated protocols that include pegasparaginase. The degree to which pegasparaginase can kill a patient's ALL cells in vitro is highly predictive of long-term outcome.[9] It is important to resume pegasparaginase if possible after resolution of a thrombotic event. Reintroduction is recommended when acute toxicity and clinical signs resolve and anticoagulation therapy is stable or completed.[8] The authors adhered to this recommendation, and the patient did not have further cardiac complications. Future pharmacokinetic and genetic association studies are needed to better understand how thrombotic risk from pegasparaginase varies by age and among individuals so that strategies to limit toxicities can be developed.

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