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CASE REPORT PEER REVIEWED | OPEN ACCESS

A case study of successful percutaneous coronary intervention in a young adult with chronic graft-versus-host disease with acute coronary syndrome

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ABSTRACT

Introduction: Acute coronary syndrome in pediatric patients with graft-versus-host disease is rare.

Case Report: We present an 18-year-old male with graft-versus-host disease referred for chest pain, electrocardiogram abnormalities, and troponin leak. Additional risk factors for acute coronary syndrome included chronic steroid use, elevated triglyceride/low-density lipoprotein (LDL) levels and cannabis use. A catheterization revealed >90% occlusion of the left coronary artery and he underwent successful percutaneous intervention.

Conclusion: Given the overall rarity of acute coronary syndrome in pediatric patients, it may go unrecognized and underappreciated as a significant cause of morbidity in those with graft-versus-host disease.

Keywords: Acute coronary syndrome, Case report, Graft-versus-host disease, Pediatrics

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INTRODUCTION

Graft-versus-host disease (GVHD) is a well-known and frequent complication of allogenic hematopoietic stem cell transplant (HSCT), leading to significant morbidity and mortality [1]. Intra-cardiac manifestations of GVHD in pediatric patients, however, are rare and not well described in the literature [2]. When cardiac complications do occur in these patients, they are typically secondary to chemotherapy toxicity, direct radiation exposure to the chest, immune-mediated therapies, or infections. Thus far, only three cases of suspected acute coronary syndrome (ACS) secondary to GVHD have been reported in the literature in pediatric patients [3–5]. Only one of these cases resulted in percutaneous coronary intervention (PCI), while the others resulted in mortality. To the best of our knowledge, we present a second case of suspected ACS secondary to cardiac GVHD in a pediatric patient who underwent successful PCI.

*These authors contributed equally to the manuscript.

CASE REPORT

History of presentation

An 18-year-old male with a history of relapsed acute myelogenous leukemia (AML) who underwent matched unrelated donor peripheral blood stem cell transplant, complicated by a three and half year history of chronic GVHD, presented to a routine outpatient oncology visit. During the visit, he reported a recent episode of non-bloody, non-bilious emesis, which was followed shortly by acute onset, non-radiating substernal, squeezing chest pain associated with diaphoresis and mild shortness of breath. The pain resolved within 20 minutes after taking oxycodone. There were no associated palpitations, dizziness, syncope, or musculoskeletal tenderness. He returned to his normal activities without recurrence. Family history was notable only for coronary artery disease (CAD) in his paternal grandfather and paternal uncles in their 50s.

On physical exam, he was afebrile with a blood pressure 120/72 mmHg, heart rate 88 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation of 98% in room air. He was non-toxic in appearance. He had a regular heart rate and rhythm without murmurs and no tenderness to palpation of the chest wall. He was breathing comfortably with clear breath sounds bilaterally. His skin was scaly and hyperpigmented on the neck and forehead, consistent with his known dermatologic GVHD.

Past medical history

The patient was diagnosed with AML at 15 years of age and subsequently developed refractory disease despite multiple chemotherapy regimens. His initial chemotherapy regimen was as per the COG AAML-1031 protocol (high risk arm) and was administered over the first two years after diagnosis. It included treatment with cytarabine (20 mg/m^2 cytarabine, with an additional intrathecal cytarabine ×3), daunorubicin (intravenous, cumulative dose 150 mg/m^2), mitoxantrone (intravenous, 40 mg/m^2), and etoposide (cumulative dose 1250 mg/m^2, by mouth). He was also intermittently on sorafenib (200 mg, twice daily by mouth). At the time of relapse 14 months later, he was started on reinduction chemotherapy with cytarabine (100 mg/m^2 twice daily for 10 days) and daunorubicin (50 mg/m^2 daily for three days) with dexrazoxane as a cardioprotectant and underwent planning for allogenic HSCT.

Allogenic HSCT using peripheral blood stem cells from a human-leukocyte antigen-matched unrelated donor was performed. His pre-transplant echocardiogram showed a structurally normal heart with normal biventricular function. He was treated with a conditioning regimen (busulfan and cyclophosphamide), GVHD prophylaxis post-transplant (cyclosporine, methylprednisolone, and methotrexate), and a GVHD treatment regimen (long-term systemic steroids and mycophenolate mofetil). His post-transplant course was complicated by Grade IIa gastrointestinal and skin GVHD, avascular necrosis of the left shoulder, and bronchiolitis obliterans.

Differential diagnosis

The differential diagnosis of chest pain is broad, and the more common diagnoses include gastroesophageal reflux (GERD) and costochondritis. The nature of this patient's chest pain was inconsistent with GERD. The squeezing nature, associated diaphoresis, and shortness of breath that the patient endorsed, made GERD an unlikely diagnosis. Costochondritis was also considered, but the patient's pain was not reproducible on physical exam.

In high risk patients, such as this case, there are several fatal diagnoses that must be diagnostically explored and ruled out before considering more benign etiologies. These include myocarditis, pericarditis, pulmonary embolism, coronary vasospasm and ACS. In this case, this patient had several risk factors that increased the likelihood of these diagnoses, including prior anthracycline exposure and underlying malignancy. Thus, the initial diagnostic workup was pursued in an effort to rule these out.

Investigations

An electrocardiogram (ECG) revealed normal sinus rhythm with deep Q waves in V1 and V2, 2 mm ST elevations and biphasic T waves in V2, 2–3 mm ST elevations in V3, and 1 mm ST elevation in V4, representing a change from his baseline ECG (Figure 1). Blood work was significant for an elevated troponin T of 0.17 ng/mL (NL <0.01 ng/mL) and brain natriuretic peptide (BNP) 281 pg/mL (NL 0–100 pg/mL). Additional routine laboratory results are included in Table 1 and were noncontributory. Given the ST elevations and elevated troponins, the patient was diagnosed with an ST elevation myocardial infarction (STEMI). The patient was referred to the emergency department where troponins were repeated and trended 3 hours apart (0.13 to 0.2 ng/mL). Urine drug screen was positive for cannabinoids. Echocardiography showed normal global biventricular systolic function (ejection

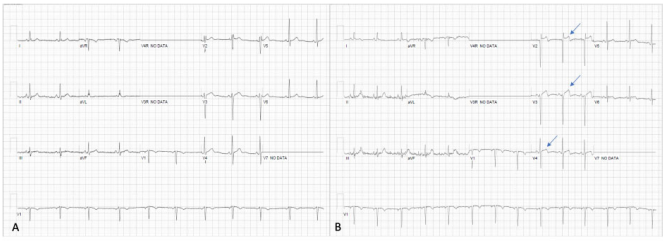


Figure 1: (A) Baseline ECG. Normal sinus rhythm with a heart rate of 64 beats per minute, incomplete right bundle branch block, and normal pattern of repolarization. (B) ECG at presentation. Sinus rhythm with interval loss of R waves in V1, new Q waves in V2, 2 mm ST elevations (arrow) and biphasic T waves in V2, 2–3 mm ST elevations in V3 (arrow), 1 mm ST elevation in V4 (arrow).

Table 1: Laboratory values before and after PCI

Test (normal value)	Prior to PCI	After PCI
Na (135–148)	137 mmol/L	138 mmol/L
K (3.2–4.5)	3.61 mmol/L	3.54 mmol/L
Cl (96–109)	96 mmol/L	101 mmol/L
Bicarbonate (22–33)	29 mmol/L	28 mmol/L
Glucose (70–199)	91 mg/dL	108 mg/dL
BUN (7–18)	13 mg/dL	12 mg/dL
Cr (0.6–1.3)	0.83 mg/dL	0.71 mg/dL
Ca (8.4–10.5)	9.7 mg/dL	9.1 mg/dL
Ph (2.7–4.9)	3.8 mg/dL	3.0 mg/dL
Mg (1.6–2.6)	2.1 mg/dL	1.9 mg/dL
AST (2–40)	28 units/L	25 units/L
ALT (3–30)	40 units/L	30 units/L
Alkaline phosphatase (30–120)	104 units/L	92 units/L
Total bilirubin (0.3–1.2)	0.6 mg/dL	0.6 mg/dL
Direct bilirubin (0.0–0.4)	<0.2 mg/dL	<0.2 mg/dL
Triglycerides (<90 mg/dL)	199 mg/dL	240 mg/dL
LDL (<110 mg/dL)	121 mg/dL	65 mg/dL

Other than elevated lipids, the patient had a mildly elevated ALT at presentation, which was downtrending from his previous levels from his outpatient visits.

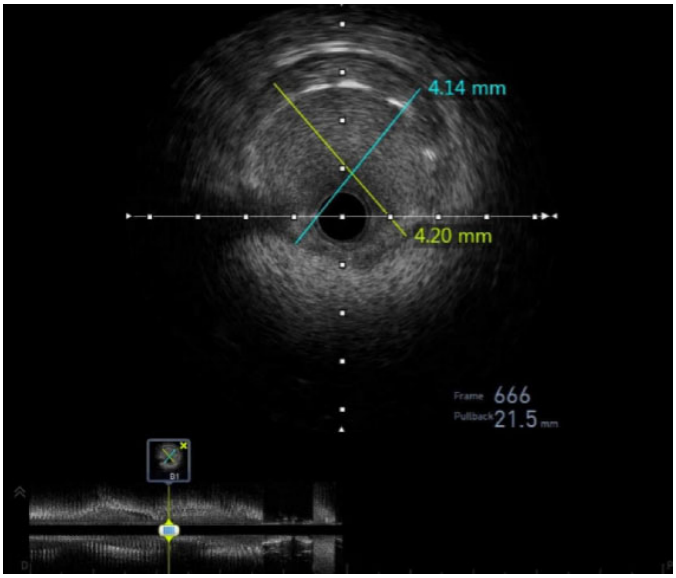
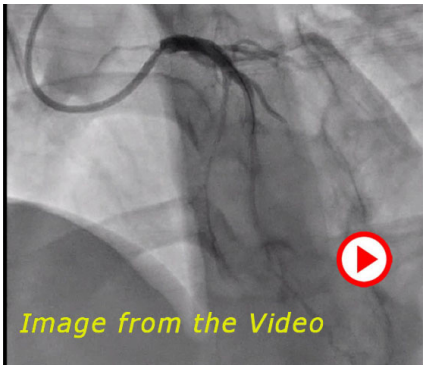


Figure 2: Pre-stent intravascular ultrasound (IVUS). IVUS revealed a thickened intimal wall at the level of the lesion consistent with an eccentric atherosclerotic plaque.

fraction 60%), no regional wall abnormalities, and no pericardial effusion.

Management

He was given 325 mg of aspirin, started on a heparin drip, and admitted. Cardiac catheterization showed severe high-grade narrowing of the proximal left anterior descending (LAD) artery (>90% stenosis), just after the branch point of the left circumflex (LCx) artery. The distal LAD vasculature was mildly hypoplastic, secondary to underfilling (Video 1). The right coronary artery was widely patent with no obvious lesions. Intravascular ultrasound (IVUS) revealed a thickened intimal wall at the level of the lesion consistent with an eccentric atherosclerotic plaque (Figure 2). The patient was transferred to an adult cardiac center where two drug eluting stents (DES) were placed in the proximal LAD to prevent further myocardial ischemia, as the artery was largely occluded. No intracoronary nitroglycerin was administered prior to DES placement. Intravascular ultrasound confirmed excellent position with 10% residual stenosis (Video 2). No biopsies were obtained due to the risk of inciting a ventricular tachyarrhythmia. He was discharged the following day on lifetime aspirin, ticagrelor for one year, metoprolol succinate, and rosuvastatin.



Video 1: Initial coronary angiography demonstrates a discrete concentric lesion in the proximal LAD with TIMI-2 flow. The left circumflex artery is without lesions and demonstrates good flow.

Video 1 URL: https://www.ijcrioncology.com/archive/article-full-text/100117Z10SB2022#video1

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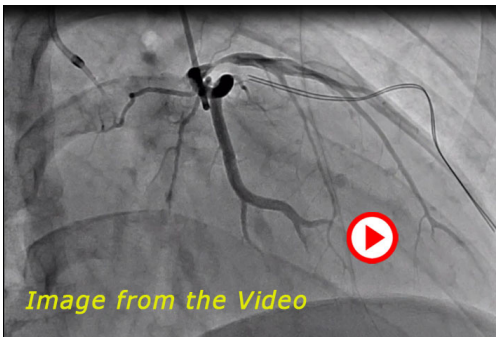

Video 2: Post-stent coronary angiography demonstrates 10% residual stenosis in the LAD.

Video 2 URL: https://www.ijcrioncology.com/archive/article-full-text/100117Z10SB2022#video2

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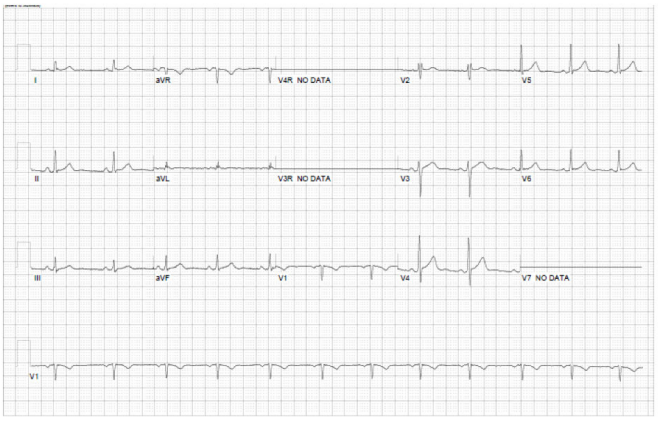

Figure 3: Repeat ECG at 6-month follow-up visit. ECG is notable for normal sinus rhythm.

Follow-up

At the patient's one-month follow-up appointment, he remained asymptomatic. He was continued on rosuvastatin, dual anti-platelet therapy, and metoprolol. His ECG six months after the event showed normal sinus rhythm without T wave abnormalities (Figure 3).

DISCUSSION

Graft-versus-host disease is a known complication of HSCT and commonly associated with skin and gastrointestinal disease, but in rare instances, can affect other organs, including the heart [2, 6]. This case describes the second successful PCI for CAD in a pediatric patient with a history of chronic GVHD. Only one other report of a 16-year-old with chronic GVHD who presented with angina showed successful revascularization following PCI after myocardial infarction [3].

The proposed mechanism of CAD in GVHD patients is thought to be similar to that of pediatric allograft cardiac transplant rejection, where endothelial injury occurs secondary to cytotoxic T lymphocyte perivascular inflammation, leading to atherosclerosis and coronary vasculopathy [7]. One patient with GVHD who presented with sudden cardiac death appeared consistent with this theory [4]. Autopsy examination revealed a markedly reduced lumen of the LAD secondary to concentric cellular proliferation, which is similar to allograft heart transplant rejection, in which coronary arteries have diffuse concentric fibro-intimal hyperplasia with variable lymphocytic and plasma cells [8].

In the other pediatric patient who underwent PCI, a mildly elevated LDL was her only risk factor for CAD [3]. Similarly, our patient had elevated triglycerides of 199 mg/dL (NL <90 mg/dL) and LDL cholesterol of 121 mg/dL (NL <110 mg/dL), which may have compounded the endothelial injury from his longstanding GVHD and contributed to accelerated formation of atherosclerosis. Furthermore, our patient was exposed to chronic steroids, a known risk factor for cardiovascular disease [9]. There are other case reports, however, of patients with GVHD and severe coronary artery luminal narrowing, who had no risk factors for CAD [4, 5]. On review of our patient's medications, there were no known medications associated with other etiologies of anginal chest pain, such as coronary vasospasm. His urine drug screen was positive for cannabinoids, which has been associated with ACS [10]. While his risk for cardiovascular disease may be increased due to his cannabis use, only one pediatric case series demonstrated an association between chest pain after cannabis use, but none were due to atherosclerotic disease, as seen in this case [11].

Cardiac manifestations of HSCT or GVHD may be related to chemotherapy toxicity, direct radiation exposure to the chest, or immune-mediated therapies. Similar to previous reports of ACS in patients with chronic GVHD, our patient had previous exposure to anthracyclines, known cardiotoxic chemotherapeutic drugs. The patient was also taking sorafenib, a tyrosine kinase inhibitor. Sorafenib been shown to lead to cardiac events including ACS, but without evidence of atherosclerotic disease [12]. Only one case of atherosclerosis has been reported in an adult patient treated with sorafenib and none have been reported in the pediatric population [13]. In our case, no coronary biopsies were obtained, limiting our ability to examine the coronary vessels and underlying pathology of luminal narrowing. Nonetheless, intravascular imaging was significant for intimal wall thickening, which suggests GVHD contributed to the development of CAD.

CONCLUSION

We describe a rare case of ACS with evidence of atherosclerosis in a pediatric patient with chronic GVHD. Acute coronary syndrome is an underappreciated cause of morbidity that should be considered in patients with GVHD presenting with chest pain and elevated troponins who may benefit from urgent PCI.

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Author Contributions

Sunakshi Bassi – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Addison Gearhart – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

David Liddle – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Pinak B Shah – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jacob Hartz – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jesse Esch – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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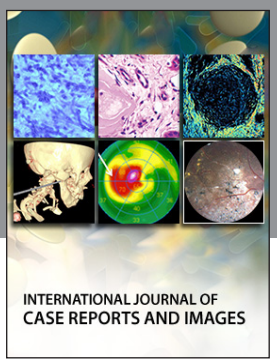

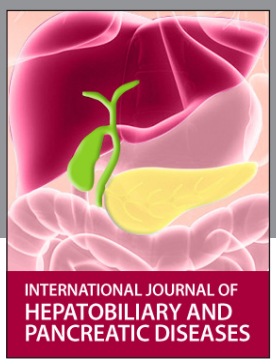

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