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Case Report

Heart Transplant Rejection in the Setting of Glyphosate Herbicide Exposure; A Case Report

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Abstract:

Glyphosate is a common herbicide utilized worldwide with known exposure related toxicities. Numerous adverse effects related to glyphosate exposure have been documented, specifically in non-human models, however literature is lacking on cardiotoxic effects specific to heart transplant patients. Rejection is the most common post-transplant complication and the diagnosis of such is vital in order to guide immediate and appropriate treatment. In addition to the endomyocardial biopsy, noninvasive genetic testing can aid in rejection diagnosis and distinguish between cell-mediated and antibody-mediated rejection. We describe a case of glyphosate exposure in a post orthotopic heart transplant and the subsequent heart transplant rejection, patient's clinical course, treatment, and follow up.

Key words: heart transplant; transplant rejection; glyphosate; cardiotoxicity

Abbreviations:

dd-cfDNA: Donor derived cell free DNA

DSA : Donor specific antibodies

ECG : Electrocardiogram

GBH : Glyphosate-based herbicide

HLA : Human leukocyte antigen

ISHLT : International Society for Heart and Lung Transplantation

LVEF : Left ventricular ejection fraction

MMF : Mycophenolate mofetil

OHT : Orthotopic heart transplantation

RHC : Right heart catheterization

RV : Right ventricle

TAC : Tacrolimus

TTE : Transthoracic echocardiogram

TR : Tricuspid regurgitation

QT : QT wave interval

1.Introduction

Glyphosate is the most common herbicide in the world since the 1970s.[1] It is a non- selective, broad-spectrum herbicide that inhibits the 5-enolpyruvoylshikimate-3-phosphate synthase enzyme utilized in amino acid synthesis in plants, one vertebrate species lack.[1,2] The mixture containing glyphosate and the surfactant polyoxyethyleneamine is found in commercial herbicides such as RoundUp™, and associated with cytotoxic, genotoxic, and teratogenic effects.[3]

Although most literature on acute glyphosate-based herbicide (GBH) toxicity has focused on non-human models, acute human toxicity of glyphosate occurs.[4] Specific to cardiotoxicity, glyphosate in both non-human and human models has caused tachycardia or bradycardia, QT wave interval (QT) prolongation, and atrioventricular block.[1,5-7] However, data is limited on cardiotoxic effects in post heart transplants recipients. Here we describe a post orthotopic heart transplant recipient with accidental glyphosate exposure resulting in allograft dysfunction.

2.Clinical Case:

A 64-year-old man with chronic kidney disease, rheumatoid arthritis, and recurrent deep vein thromboembolisms presented with 10 days of cough, diarrhea, dyspnea, and weight gain following inadvertent toxin exposure. He had undergone orthotopic heart transplantation (OHT) two years prior for nonischemic cardiomyopathy, likely Plaquenil-mediated, without subsequent rejections or development of post transplantation antibodies. At baseline, he had New York Heart Association class 1 symptoms and walked five miles daily. Immunosuppression medications included prednisone (due to coexistent rheumatoid arthritis), mycophenolate mofetil (MMF), and tacrolimus (TAC). A transthoracic echocardiogram (TTE) nine months prior showed normal allograft function and cardiac catheterization showed minimal intimal hyperplasia of the left anterior descending artery and 10% occlusion of the mid right coronary artery.

His inhalation exposure to RoundUp resulted in immediate mucosal irritation and subsequent diarrhea, abdominal pain, cough, six-pound weight gain, and sinus congestion. He presented nine days following exposure for a previously scheduled clinic visit with new dyspnea on exertion. TTE revealed a new reduction in right ventricle (RV) function with normal left ventricular ejection fraction (LVEF) 55-60%. Poison control was contacted, who recommended observation.

On admission, he was afebrile, heart rate 101 bpm, with blood pressure 128/96. Labs significant for B natriuretic peptide 648 pg/ml, creatinine 2.01 mg/dl (baseline 1.2), alkaline phosphatase 177 IU/L (prior 66), tacrolimus level 4.3 ng/ml (at target goal), and remaining labs were unchanged. Infectious workup negative for CMV-PCR, EBV IgM, Rocky Mountain spotted fever IgM/IgG, Lyme disease, and COVID. Presenting electrocardiogram (ECG) noted sinus tachycardia, low voltage, new axis right deviation, incomplete right bundle branch block and poor R wave progression (Figure 1) compared with prior ECG (Figure 2). Physical exam revealed jugular venous distention and peripheral pitting edema.

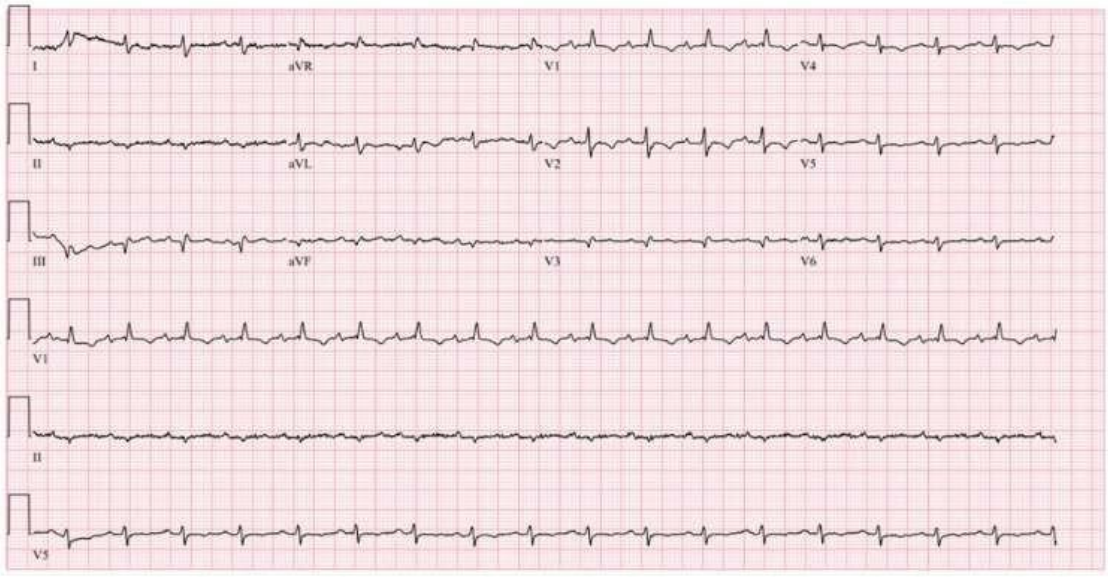

Figure 1. Presenting ECG: sinus tachycardia, incomplete right bundle branch block, low voltage QRS, poor R wave progression.

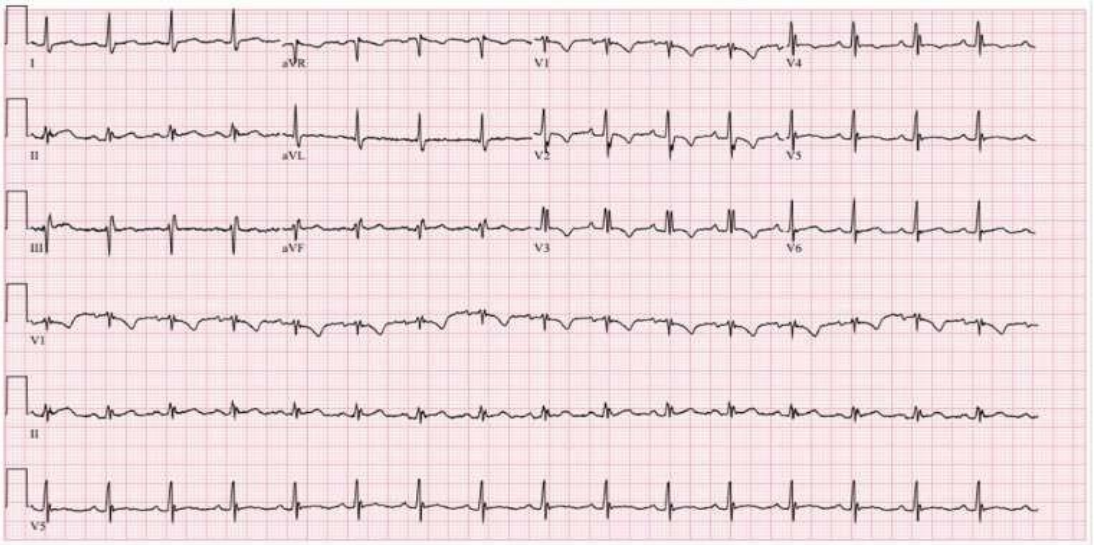

Figure 2. Baseline ECG: sinus rhythm, incomplete right bundle branch block.

Transplant specific work up included elevated AlloSure Heart (cell-free DNA) at 3.5% (high: > 0.15%); elevated AlloMap (gene expression profiling) at 37 (high: >34 if > six months post-transplant). New class I and II donor specific antibodies (DSA) were identified on human leukocyte antigen (HLA) testing. Right heart catheterization (RHC) noted a right atrial pressure 16 mmHg, pulmonary artery pressure 34/18/23

mmHg, pulmonary capillary occlusive pressure of 16 mmHg with v-waves to 24, pulmonary artery saturation 61.5%, cardiac output and index by Fick 3.4 L/min and 1.7 L/min/m2. Endomyocardial biopsies noted mild acute cellular rejection with International Society for Heart and Lung Transplantation (ISHLT) grade 1R and negative C4d staining. Treatment included intravenous steroids, followed by a prednisone taper, an increase in MMF dose, and TAC continuation. He was discharged following 6L diuresis.

The patient was readmitted 2-weeks later due to tachycardia, a decline in LVEF to 35- 40%, and mild tricuspid regurgitation (TR). Repeat RHC demonstrated persistent elevated intracardiac filling pressures and reduced cardiac output. Readmission labs were similar to prior, AlloMap 39 but AlloSure Heart 0.84%. HLA testing negative for DSAs. Repeat endomyocardial biopsy was ISHLT grade 1R rejection. Pathology showed multifocal vacuolization and ballooning of myocytes concerning for ischemic injury. Coronary angiogram was unchanged.

Cardiac magnetic resonance imaging showed late gadolinium enhancement pattern suggestive of myopericarditis. Treatment included intravenous pulse-dose steroids and oral taper, administration of anti-thymocyte globulin (rabbit), with subsequent allergic reaction, causing a change to anti-thymocyte globulin (equine), increase MMF dose, continuation TAC (target trough 6-8), and intravenous diuresis. At outpatient follow up, repeat TTE noted improved LVEF of 50-55% with normal RV size, trace TR, mild mitral regurgitation, repeat AlloMap and AlloSure showed improvement at 29 and 0.51%, respectively, and RHC noted improved hemodynamics.

3. Discussion:

Heart transplantation is a common treatment for end-stage heart failure. Despite advanced immunosuppressive therapy, patients are subject to some degree of rejection, with most occurring in the first six months. After one year, the incidence of rejection significantly decreases.[8] In this case, new DSA, elevated cell free DNA, and gene expression profiling, with therapeutic FK level supported the hypothesis of GBH toxicity mediated heart transplant injury, which likely precipitated acute allograft rejection, and subsequent allograft dysfunction.

Cardiac manifestations of GBH toxicity include arrhythmias such as conduction blocks, bradycardia, and ventricular arrhythmia due to interference with calcium homeostasis.[4,5] The mechanism of toxicity is complex but felt to be largely cellular-mediated by surfactant interference that disrupts the mitochondrial wall proton gradient needed for energy production.[4] Oxidative stress and oxidative phosphorylation interruption secondary to GBH, plays a role in coronary artery disease when exposure-related oxidative stress over time induce cardiac subintimal inflammation.[9] Animal models found glyphosate increased myocardial contraction, while the surfactant in GBH decreased cardiac output, left ventricular stroke index, and mean arterial pressure.[10,11]

Heart transplant rejection can manifest as allograft failure with new heart failure, arrhythmias, or death. Invasive diagnosis is made with endomyocardial biopsy and microscopic examination. The ISHLT developed a standardized grading method to quantify rejection based on endomyocardial biopsy severity; 0R, 1R, 2R & 3R.[12] Cellular mediated rejection (CMR) is most commonly T-cell mediated and more common than antibody (B-cell) mediated rejection (AMR).[13] In AMR, antibodies can be DSA against human leukocyte antigen (HLA) class 1 or 2, non-DSA, or non-HLA. Together, both AlloMap and Allosure provide a noninvasive means to detect rejection/injury. AlloMap® Molecular Expression Testing assesses the gene expression profile of ribonucleic acid isolated from peripheral blood mononuclear cells. While AlloSure® Heart measures the amount of donor derived cell free DNA (dd-cfDNA) in the blood. A result >0.15% dd-cfDNA is associated with a higher probability of rejection; our patient's AlloSure level of 3.5% supported rejection.[14]

Our patient's endomyocardial biopsy showed ISHLT 1R (mild rejection), with histopathologic findings consistent with interstitial and/or perivascular infiltrates, with vacuolization, ballooning of myocytes, and myocytolysis. Myocytolysis is characterized by gradual vacuolization of muscle fibers and thought to be due to myocardial strain. Myocytolysis is commonly associated with ischemia and observed in a variety of other conditions including cardiomyopathies, myocarditis, and endocarditis.15

4. Conclusion:

Here we present the first known case of GBH toxic exposure mediated heart transplant rejection. Our patient had prior OHT presented with symptomatic GBH exposure and clinical evidence of impaired cardiac function with AMR, based on new DSA and a markedly elevated AlloSure. GBH cardiotoxicity is largely cell-mediated with oxidative stress manifesting in arrhythmias. Genetic testing can aid in noninvasive detection of rejection along with endomyocardial biopsy to confirm cellular and/or antibody mediated rejection leading to efficient and effective treatment.

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