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Case report

Toxic 'Toxo' in the heart: Cardiac toxoplasmosis following a hematopoietic stem cell transplant- a case report

Padmastuti Akella*, Isha Bhatt, Mustapha Serhan, Dilip D. Giri, Stephen M. Pastores

Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, United States

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ABSTRACT

Toxoplasmosis is a rare but potentially severe complication after allogeneic hematopoietic cell transplantation. Toxoplasma gondii-associated cardiac involvement can cause myocarditis, pericarditis, arrhythmias, and congestive heart failure. Most cases with cardiac toxoplasmosis following BMT have been fatal and diagnosed at autopsy. We present an unfortunate case of sudden onset congestive heart failure symptoms and delayed post-transplant Toxoplasma PCR testing that ultimately led to the diagnosis of cardiac toxoplasmosis on autopsy in our patient.

Introduction

Toxoplasmosis is a life-threatening parasitic infection that can affect hematopoietic stem cell (HSCT) and solid organ transplant recipients [1–3]. In HSCT recipients, the major risk of toxoplasmosis results from the reactivation of a pre-transplant latent infection with *Toxoplasma gondii* in seropositive recipients. Cardiac involvement in toxoplasmosis is very uncommon and can manifest with myocarditis, pericardial effusion, constrictive pericarditis, arrhythmias, and congestive heart failure [1,3]. We present an uncommon and unique case of cardiac toxoplasmosis following allogeneic HSCT causing acute decompensated heart failure leading to multisystem organ failure and death.

Case description

A 69-year-old man with history of chronic kidney disease, hypothyroidism, atrial fibrillation and follicular lymphoma was admitted to the hospital for worsening dyspnea and increased swelling of the lower extremities.

The diagnosis of follicular lymphoma was originally made 20 years earlier after a needle biopsy of a palpable left groin mass. The patient received six cycles of Rituximab, Cyclophosphamide, Prednisone, Doxorubicin and Vincristine and went into remission for 13 years. He developed relapse of the lymphoma six years ago with a notable left axillary lymph node and was treated with rituximab and bendamustine for six cycles. This was followed by weekly treatment with rituximab but he continued to have progression of disease. He then began a trial of buparlisib (P13 K inhibitor) and ibrutinib which were discontinued one year later due to an adverse reaction. Further treatment was pursued with trials of Pembrolizumab (anti-programmed death-1 inhibitor) and Etinostat (histone deacetylase inhibitor) followed by lenalidomide and rituximab until early 2020. He achieved complete remission after maintenance therapy with lenalidomide. Of note, the patient acquired asymptomatic coronavirus disease-19 (COVID-19) infection in April 2020 when the pandemic started.

After conditioning with cyclophosphamide, fludarabine, total body irradiation, and horse anti-thymocyte globulin, he underwent an unmodified mismatched unrelated donor peripheral blood stem cell transplant. Pre-transplant workup was negative for donor and recipient cytomegalovirus, *Toxoplasma gondii*, and Epstein Barr virus serologies and hepatitis panel (Table 2). He was maintained on tacrolimus, sirolimus, and methotrexate for graft-versus-host disease (GVHD) prophylaxis and was planned for Rituximab x 4 cycles post-transplant with the first dose given 3 days prior to this hospital admission. As an outpatient, he was maintained on fluconazole, pentamidine and acyclovir prophylaxis. The post-conditioning course was complicated by diarrhea (Day -3), acute kidney injury (Day -4) and transaminitis (Day -3). The post-transplant course was complicated by hemorrhagic mucositis (Day +6), non-infectious hemorrhagic cystitis (Day +12), febrile

* Corresponding author at: Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, United States.
E-mail address: akellap@mskcc.org (P. Akella).

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Table 1
Pertinent laboratory parameters during hospitalization.

Laboratory parameters	Normal Values	Pre-Transplant Labs	Day of Admission (T)	Day of ICU admission (T + 2)	Last Day of Admission (T + 6)
Sodium	133–143 mEq/L	140	138	138	136
Potassium	3.3–4.9 mEq/L	4.5	4.9	4.7	4.7
Chloride	98–108 mEq/L	105	102	97	104
Bicarbonate	18–29 mEq/L	28	21	27	21
Blood Urea nitrogen	6–20 mEq/L	15	37	50	35
Creatinine	0.6–1.3 mg/dL	1.3	2.9	3.5	2
Glucose	70–140 mg/dL	83	122	144	163
Calcium	8.5–10.5 mg/dL	8.7	8.9	8.5	8.6
Magnesium	1.6–2.6 mg/dL	1.9	1.7	1.7	2
Total Protein	6.3–8.5 g/dL	5.3	5.4	5.6	5
Albumin	3.8–5.0 mg/dL	3.8	3.8	3.8	2.8
Aspartate Aminotransferase	< = 37 U/L	21	33	51	947
Alanine Aminotransferase	< = 55 U/L	17	34	49	464
Alkaline Phosphatase	< = 130 U/L	64	62	70	98
Total Bilirubin	< = 1.2 mg/dL	0.9	0.7	0.7	1
White Cell Count	4.0–11.0 K/mcL	2.3	7	6.7	3.6
Red Cell Count	3.95–5.54 M/mcL	3.41	2.74	2.63	4.09
Hemoglobin	12.5–16.2 g/dL	11.6	8.4	8.1	12.3
Hematocrit	37.5–49.3 %	34.5	25.4	24.7	35.4
Platelets	160–400 K/mcL	107	12	31	6
Neutrophils	32.5–74.8%	64.7	84.1	85.4	98
Monocytes	0.0–12.3 %	11.2	11.9	11.8	1
Eosinophils	0.0–4.9 %	4.3	0	0.1	1
Basophils	0.0–1.5 %	1.7	0.1	0.1	0
Lymphocytes	12.2–47.4 %	18.1	2.3	1	0
Absolute Neutrophil Count	1.5–7.5 K/mcL	1.5	5.9	5.7	3.5
Absolute Monocyte Count	0.0–1.3 K/mcL	0.3	0.8	0.8	0
Absolute Eosinophil Count	0.0–0.7 K/mcL	0.1	0	0	0
Absolute Basophil Count	0.0–0.2 K/mcL	0	0	0	0
Absolute Lymphocyte Count	0.9–3.2 K/mcL	0.4	0.1	0.1	0
Prothrombin time	11.1–15.2 sec	13.2	15.1	16.7	20.2
Activated Partial Thromboplastin Time	22.5–36.5 sec	34.8	29.5	31.7	36
INR	0.80–1.20 INR	1	1.19	1.36	1.73
BNP	0–100 pg/mL	–	4596	>5000	–
D-Dimer	< = 50 mcg/mL FEU	–	1.57	2.5	–
Fibrinogen	150–400 mg/dL	–	–	569	617
Ferritin	22–415 ng/mL	–	5989	19,361	167,157
LDH	130–250 U/L	161	337	1028	3536
Haptoglobin	40–240 mg/dL	–	104	200	124
IL-6	< = 5.0 pg/mL	5	272.5	331.2	–
CRP	< = 0.30 mg/dL	0.2	13.67	20.98	–
Procalcitonin	<=0.49 ng/mL	–	0.43	0.6	1.7
Troponin	< = 0.02 ng/mL	–	0.32	2.39	36.21
Lactic Acid	0.5–2.0 mM/L	1	4.2	2.6	2.6
Sirolimus level	ng/mL	–	9.2	7.8	7.9
Tacrolimus Level	ng/mL	–	10.7	6	7.3

neutropenia (Day +12) with no infectious etiology identified and ongoing pancytopenia with host engraftment. Repeat bone marrow biopsy showed improving chimerism (host 13 %, donor 87 %).

On hospital admission (HSCT day 41), he was dyspneic with increasing oxygen requirement and bilateral lower extremity edema. He had an isolated fever of 100.6 °F, worsening acute kidney injury, lactic acidosis, anemia, and thrombocytopenia. He was empirically started on cefepime for antimicrobial coverage. Blood, urine and sputum cultures, and urinalysis were negative (Tables 1,3). Chest radiograph showed diffuse bilateral opacities. Computed tomography of the chest revealed new multifocal bilateral ground-glass opacities and consolidations with smooth interlobular septal thickening, superimposed pulmonary edema, and moderate bilateral pleural effusions with bibasilar atelectasis (Fig. 1). The electrocardiogram showed normal sinus rhythm. An echocardiogram showed a new decreased ejection fraction of 40 %, grade I diastolic dysfunction, mild to moderate global hypokinesis of both ventricles, with borderline pulmonary arterial hypertension, and increased mitral regurgitation. Despite aggressive diagnostic workup and treatment, his condition continued to worsen, ultimately requiring admission to the Intensive Care Unit (ICU) where his course was complicated by atrial fibrillation with rapid ventricular rate and worsening renal function requiring continuous renal replacement therapy. On day 3 of ICU admission, the patient was intubated for worsening respiratory failure and required vasopressor therapy to maintain adequate blood pressure. His antimicrobial coverage was broadened to meropenem and methylprednisolone 0.5 mg/kg IV daily was added due to concerns for hemophagocytic lymphohistiocytosis (HLH). HLH studies revealed fever of 38.1 °C, anemia of 8.4 g/dL, thrombocytopenia of 12,000, elevated ferritin of 5989, fibrinogen 569 and triglycerides 196 (Table 1). Blood cultures showed Pseudomonas fluorescens and coagulase-negative staphylococcus. Despite full supportive measures, he continued to deteriorate and died from multiorgan failure on ICU day 5.

A limited autopsy of the heart was granted by the patient's family. The heart weighed 393 g. There was minimal accumulation of pericardial fluid. The visceral pericardium appeared glistening and edematous. On microscopy, the myocardial interstitium showed edematous change. On higher power examination (200X and 400X magnification) random individual myocardial

Table 2
Pre-transplant infectious workup.

Pre-Transplant Patient Infectious Markers:	Result
Laboratory test	Negative
CMV IgG Antibody	Negative
CMV IgM Antibody	Negative
EBV VCA IgG Antibody	Negative
EBV VCA IgM Antibody	Negative
EBVNA (Nuclear) Antibody	Negative
Hepatitis B Virus Core Antibody, Total	Negative
Hepatitis B Surface Antibody	Negative
Hepatitis C Virus Antibody	Negative
HIV - 1/2 Ab/Ag Immunoassay	Negative
HTLV I/II Antibodies	Negative
RPR	Negative
Toxoplasma IgG Antibody	Negative
Toxoplasma IgM Antibody	Negative
Varicella Zoster (IgG) Antibody	Negative
COVID19 RNA PCR	Negative
SARS-COV 2 IgG	

Pre-Transplant Donor Infectious Markers:	Result
Donor CMV IgG Antibody	Positive
Donor CMV IgM Antibody	Negative
Donor Toxo IgG Antibody	Negative
Donor Toxo IgM Antibody	Negative
EBV VCA IgG Antibody	Positive
EBV VCA IgM Antibody	Negative
EBVNA (Nuclear) Antibody	Positive

Table 3
Microbiological workup during hospitalization.

Infectious Markers During Admission	Result
Central venous Catheter Blood Cultures:	Negative
MRSA Nasal Swab DNA PCR	Negative
SARS- CoV-2 IgG Antibody	Negative
COVID19 Rapid Qualitative RNA	Negative
Urine Culture	Negative
Legionella Urinary Antigen	Negative
Streptococcus pneumoniae Urine Antigen	Negative
Cytomegalovirus PCR	Negative
HHV-6 Quantitative PCR, Plasma	Negative
EBV Quantitative PCR, Plasma	Negative
Serum BD Glucans	< 31 (< 80 pg/mL)
Serum Aspergillus galactomannan Antigen	Negative
Mycoplasma pneumoniae Antibody Panel (IgG and IgM)	Negative
Respiratory NAAT Panel	Negative
BK virus Urine PCR	Negative
COVID 19 Nasal PCR swab	Negative

fibers were involved by minute cyst forms of *Toxoplasma gondii* organisms (Fig. 2A). Several foci showed rupture of the cyst forms with dissemination of the merozoite forms of *Toxoplasma* (Fig. 2B). There was evidence of destruction of myocardial fibers. The diagnosis of cardiac toxoplasmosis was confirmed by immunostaining (Fig. 2C). The immunostaining was done using Rabbit Polyclonal antibody to *Toxoplasma gondii* (Cell Marque, 1:200 dilution with Optiview Detection kit on Ventana Benchmark ultra-platform) [4].

Discussion

Toxoplasma gondii in HSCT recipients can cause encephalitis, pneumonitis, cardiac involvement and disseminated infection [1,5,6]. Toxoplasma infection of the myocardium can trigger a local inflammatory response with subsequent myocarditis or cardiomyopathy leading to a life-threatening cardiac event [1,6]. The myocarditis and resulting cardiac dysfunction are commonly associated with involvement of other organs especially the brain and the lungs.

We did not suspect toxoplasmosis as the primary cause for the sudden cardiac dysfunction and heart failure with reduced ejection fraction in our patient at the time of ICU admission. We did not perform serologic polymerase chain reaction (PCR) testing for *T gondii* during his brief ICU stay and our patient was not on chemoprophylaxis for Toxoplasma. Diagnosing toxoplasmosis in HSCT recipients is often difficult because of the non-specific signs and symptoms of the infection. Furthermore, pre-transplant donor and recipient serologies for *T gondii* were negative. It is likely that the conditioning regimen and immunosuppressive therapy (corticosteroids, tacrolimus, sirolimus) significantly impaired our patient's immune response, rendering him more susceptible to developing toxoplasmosis. Despite reports of acute toxoplasmosis in recipients who were seronegative for *T gondii*, suggesting transmission of infection after HSCT, the source of infection in those cases has not been clearly ascertained as to whether it is due to the transplant procedure by itself or from an environmental source (e.g., ingestion of raw or undercooked meat containing bradyzoites within tissue cysts from infected animals) [7,8].

Toxoplasma PCR serology is a useful tool in defining the patient's immune status. A combination of reactive IgM with non-reactive IgG antibodies would suggest an acute Toxoplasma infection [4]. Given the time between the HSCT and hospital admission and risk of acquiring toxoplasmosis in the interim period, it may be important to consider post-transplant serologic testing. The time between HSCT and onset of cardiac symptoms in our patient was 40 days. Case reports have shown a median time of onset to acute infection of 52.5 days [7]. However, HSCT recipients may not be able to reliably mount an IgM response or increase their IgG titers in response to an acute infection and obtaining biopsies in patients who are acutely ill or profoundly thrombocytopenic is difficult [7,9].

Finally, *T gondii* detected by histopathology such as in brain or heart tissue is rarely obtained in the antemortem period given the atypical clinical presentation and risks associated with invasive diagnostic methods. Thus, the diagnosis is usually made postmortem, as in our patient. Our case highlights the need for a high level of suspicion for toxoplasmosis in immunocompromised patients presenting with undetermined cause of heart failure post-HSCT.

In patients with acute myocarditis after transplantation, the diagnosis is best made by endomyocardial biopsy, which often demonstrates *T. gondii* tachyzoites [1]. Histopathological changes include myonecrosis, edema, and an inflammatory cell infiltrate consisting of plasma cells, macrophages, lymphocytes, and eosinophils. The most sensitive technique for the demonstration of tachyzoites in biopsy specimens is the peroxidase-anti-toxoplasma antibody technique or immunostaining [2,4].

Although there are no randomized controlled trials evaluating the efficacy of toxoplasma prophylaxis, universal prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) for at least 6 months is recommended for high-risk pre-HSCT toxoplasma-seropositive recipients on the basis of several observational studies [10]. Alternative agents include dapsone-pyrimethamine and leucovorin or atovaquone with or without pyrimethamine and leucovorin; clindamycin and azithromycin when TMP/SMX or pyrimethamine/sulfadiazine cannot be used. Prophylaxis with pyrimethamine 25 mg/day for 6 weeks after HSCT or with TMP/SMX has also been successful in seronegative recipients [1,2].

In HSCT patients, pyrimethamine (25–75 mg/day) and sulfadiazine (4–8 g m/day) with folinic acid (5–10 mg/day) for a minimum of 6 weeks is the treatment of choice [1]. Concerns about the bone marrow suppressive effects of pyrimethamine and sulfadiazine limits their use as empiric therapy [9,11].

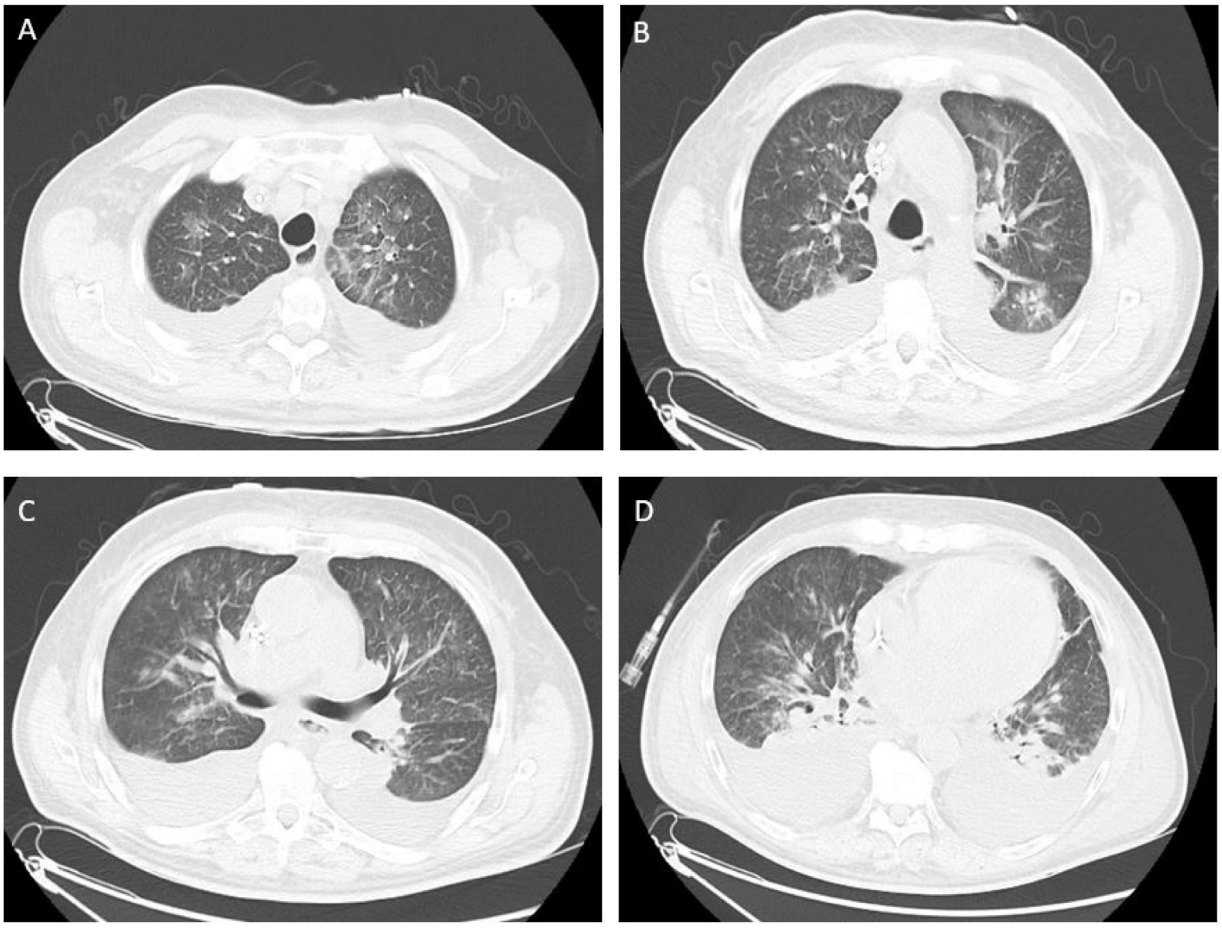

Fig. 1. Computed tomography scan images showing new multifocal bilateral ground-glass opacities and consolidations with smooth interlobular septal thickening, superimposed pulmonary edema, and moderate bilateral pleural effusions with bibasilar atelectasis.

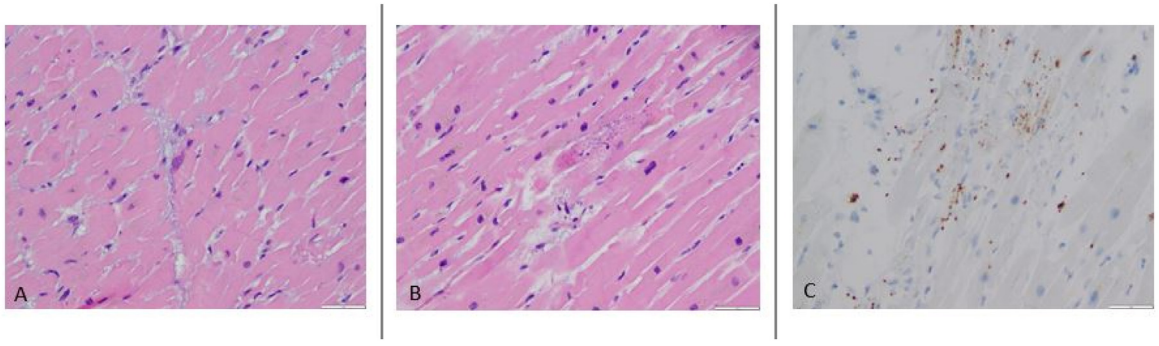

Fig. 2. A, Section of myocardium showing cyst form of Toxoplasma organisms in an individual myocardial fiber. The interstitial space between myocardial fibers is edematous. (Hematoxylin & Eosin stain, magnification 200X) B, Section of myocardium showing dispersed merozoite forms of Toxoplasma organisms causing destruction of myocardial fibers. (Hematoxylin & Eosin stain, magnification 200X) C, Immunostaining confirms the diagnosis of cardiac Toxoplasmosis. Individual merozoites are identified as stained with the Toxoplasma antibody. (Magnification 200X).

In conclusion, we present a unique case of cardiac toxoplasmosis following allogeneic HSCT manifested by acute decompensated heart failure leading to multisystem organ failure and death. Clinicians should have a high clinical suspicion for parasitic causes of heart failure such as toxoplasmosis, perform Toxoplasma PCR serologic testing in blood or other body fluids, and initiate prompt treatment, given the high mortality rate associated with this opportunistic infection in immunocompromised patients.

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Informed consent statement

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

CARE checklist (2013) statement

The authors have read the CARE Checklist (2013), and the manuscript was prepared and revised according to the CARE Checklist (2013).

Declaration of Competing Interest

The authors declare that they do not have any conflict of interest.

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