Catastrophic Antiphospholipid Syndrome: Atypical presentation in the Setting of Chronic Graft Versus Host Disease: Case Report and Review of the Literature

A 44-year-old female developed a catastrophic thrombotic syndrome following allogeneic stem cell transplantation for acute lymphoblastic leukemia. In the context of chronic graft versus host disease, she developed a lethal multi-system thrombotic state as evidenced by stroke, renal failure and cardiac thrombi in association with elevated anticardiolipin antibody. The case is discussed in the framework of the existing literature and derives clinical practice recommendations for this rare but clinically devastating entity.

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Catastrophic antiphospholipid antibody syndrome (CAPS) is an uncommon and potentially lethal variant of the antiphospholipid syndrome. Antiphospholipid syndrome is a constellation of arterial or venous thrombotic events, such as recurrent fetal loss, deep vein thromboses, and cerebrovascular accidents in the presence of antiphospholipid antibodies. In contrast to classic antiphospholipid syndrome, CAPS is more fulminate, usually manifesting itself over few weeks as opposed to years. It is characterized by multiorgan system failure due to widespread microvascular thromboses, culminating in a mortality rate of 50%.[1] A recent international consensus established the following definitive criteria for CAPS: involvement of three or more organs; clinical manifestations within one week; histopathologic evidence of microvascular occlusion; and two positive antiphospholipid antibodies titers at least six weeks apart. CAPS is considered probable if the first three criteria are met but positive serial titers are not available.[2] Autoantibody formation has been described in association with acute and chronic graft versus host disease (GVHD) following allogeneic stem cell transplantation (allo-SCT).[3,4] There are only a handful of cases of antiphospholipid antibody associated thrombosis and definitive antiphospholipid syndrome reported following allo-SCT.[5-7] We describe the first case of a fatal thrombotic event due to probable antiphospholipid syndrome in the context of chronic GVHD, highlighting need to make this diagnosis promptly and initiate appropriate therapy to optimize patient outcome.

Case Report

A 44-year-old woman with no history of thromboembolic complications presented with poor-risk ALL. After achieving a complete remission, she underwent an allo-SCT. The graft was T cell depleted, with a total of 5.4×10^6 CD-34 positive cells/kg and 1.6×10^5 CD-3+ cells/kg from an HLA matched sibling. The conditioning regimen consisted of TBI (1200 cGy), Thiotepa, and Cyclophosphamide. Despite prophylactic methylprednisolone, the post-transplant course was complicated on day 40 by biopsy-proven grade II skin GVHD. This resolved with high-dose steroids that were tapered without incident over six months. Seven months post-transplant she developed an unprovoked right lower extremity deep venous thrombosis. Initial evaluation revealed a PT of 14.2 seconds (11.6-13.8), INR of 1.1, and PTT of 43 seconds (24-36), no mixing study was done. She had platelet count of 170,000 mcl and normal LDH, +1 schistocytes on peripheral smear examination.

Evaluation for Factor V Lieden mutation, protein C deficiency and anticardiolipin antibodies were unremarkable. She received un-fractionated heparin followed by six months of warfarin with a target INR of 2-3. She had maintained normal platelet count and LDH through this therapy, with no evidence of TTP. One month following the DVT, steroids were reinitiated for a flare-up of skin GVHD, then again tapered upon adequate control, her platelet count decreased to the 30,000-50,000 range with no evidence of bleeding and normal LDH. She was concomitantly noted to have worsening renal function with a creatinine of 2.0 mg/dL and nephrotic range proteinuria. A renal biopsy revealed focal glomerular deposits consistent with cryoglobulin, and a positive qualitative serum cryoglobulin assay. Despite initiation of plasmapheresis with disappearance of detectable serum cryoglobulins, the renal function continued to worsen with a peak creatinine of 4.5 mg/dL (0.7-1.2) and 6.86 g protein loss per 24 hours. A repeat biopsy revealed a membranoproliferative glomerulopathy with subendothelial fibrillar deposits, again suggestive of cryoglobulin deposition. Eventually, dialysis was initiated. She continues in complete remission from leukemia. Fifteen months post-transplant, she had a sudden change in mental status. MRI revealed a moderate sized infarction in the medial left occipital lobe and a small infarction in the right parietal lobe with microvascular ischemic changes. There was no evidence of fungal or bacterial infections. The Patient's viral studies, including herpes, adenovirus, and preemptive testing for CMV antigenemia were negative. Repeat MRI revealed multiple areas of acute infarction with hemorrhage in the posterior cerebral artery territory (Figure III.). Carotid Doppler and echocardiogram failed to disclose an embolic focus. Repeat measurement of anticardiolipin antibodies now revealed an IgM titer of 1:32 with negative IgG. The PTT was normal, thus mixing studies were not performed. Despite pulse methylprednisolone her clinical condition deteriorated, aggressive measures were withdrawn, and she expired.

Postmortem examination revealed a subacute infarct of left cerebral hemisphere. Recent and remote infarcts were also present in the left cerebellar hemisphere. The presence of infarcts of varying ages in multiple vascular distributions could be attributed to extensive thrombosis in the intra-myocardial vessels (Figure 1), as well as thrombi in the mitral and tricuspid valves. Renal examination revealed multiple fibrin thrombi of the capillary loops of glomeruli (Figure 2). Electron microscopy of the glomeruli revealed evidence of chronic thrombotic microangiopathy that was consistent with antiphospholipid syndrome: there was reduplication of capillary basement membranes with accumulation of amorphous, granular and cellular material in the subendothelial spaces; mesangial sclerosis; tuft collapse and wrinkling of the basement membranes; and partial effacement of foot processes.

Discussion

To our knowledge this is the first case report of suspected CAPS in the setting of chronic GVHD. The patient developed newly elevated titers of antiphospholipid antibodies associated with microvascular thromboses in multiple organs, with rapid clinical deterioration.

Traditionally, GVHD is attributed to interactions between donor-derived T cells and host histocompatible antigens. However recent reports suggest a more global immune dysregulation in this setting. Several *auto* anti-

Figure 1. An organizing thrombus occluding a blood vessel within the myocardium.

Figure 2. Occlusive thrombi in several glomerular capillary loops (arrows), in contrast to other patent and congested capillaries.

bodies have been associated with GVHD, such as rheumatoid factor, antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody, and antithyroid peroxidase antibody.[4,8] Antiphospholipid antibodies comprise a subset of GVHD-associated auto-antibodies, and while some reports found them to be non-pathologic,[9,10] several groups have found associations between antiphospholipid antibodies and various thrombotic complications (Table 1).[5-7,11] Immune dysregulation in the context of conditioning, infections, medications, GVHD, and endothelial damage common in the transplant setting may lead to the generation of autoantibodies and ultimately antiphospholipid antibodies.

Mengarelli *et al.* prospectively studied the impact of allogeneic stem cell transplantation (allo-SCT) on development of antiphospholipid antibodies in 32 patients, finding significantly greater rise in antiphospholipid antibodies titers among patients who received unrelated grafts compared with related,[9] and because this paralleled a significantly greater incidence of CMV antibody seroconversion among the unrelated grafts, they postulated that CMV infection might be implicated in the development of these antibodies. In this series of patients, no relationship was noted between antiphospholipid antibodies and type of conditioning regimen, or whether GVHD developed, furthermore, no thromboembolic events were observed. Gharavi et al. suggested a relationship between CMV infection and antiphospholipid antibodies production, in a murine model, they induced antiphospholipid antibodies in mice by immunization with phospholipid binding viral peptides, and demonstrated resulting pathologic effects.[12] Others have described the association of antiphospholipid antibodies with GVHD and hepatic veno-occlusive disease.[6,11]

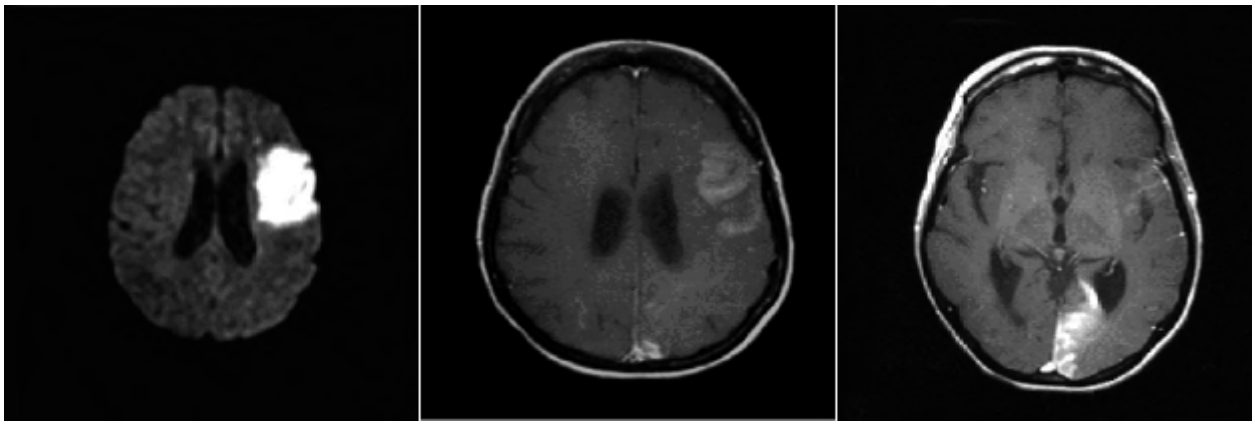

Figure 3. Representative magnetic resonance images demonstrating extensive infarctions in the left parietal and occipital lobes

Table 1. Summary of antiphospholipid syndrome in allogeneic stem cell transplant recipients.

Reference	*Patient age/gender*	*Donor*	*GVHD type Acute/Chronic*	*Thrombotic event Day/presentation*	*Treatment/outcome*
Qasim 1998	4 month old male with Omenn syndrome	HLA matched sibling PSCT	Acute	Day 59-Right-sided focal seizures and hemiplegia. week later V/Q mismatch suggestive of APE (with elevated ACA titers, reduced AT III and protein S levels)	Anticoagulation with coumadin and heparin Resolution of hypercoagulable parameters but residual hemiplegia Methylprednisolone and IVIG
Morio 1991	37 to male with AML,	second matched related PSCT	Acute	On day 23, VOD suspected based on rise in bilirubin, ALP, in setting of positive LA. Shortly, autopsy showed subintimal edema and narrowing of hepatic vein.	Death on day 46, from respiratory failure.
Kharfan-Dabaja 2003	28 yo male with aplastic anemia;	matched-related PSCT	Acute	GVHD on Day 34-No systemic thrombosis but positive LA	Infliximab and steroids 4 months later- normal A coags & negative L
Söhngen 1994	54 yo male with CMML;	sibling SCT and severe thrombocytopenia	Chronic	"7 months later"-VOD with + ACA, +LA	IV immunoglobulin & steroids ineffective, followed by CSA With CSA, normalization of platelet counts, disappearance of signs of chronic GVHD and all autoantibodies

Abbreviations: ACA, anticardiolipin antibody; ALP, antiphospholipid antibody; AT III, antithrombin III; SCT, Stem cell transplant; CMML, chronic myelomonocytic leukemia, CSA, cyclosporine, LA, lupus anticoagulant; PE, pulmonary embolism; AML, acute myelogenous leukemia; IVIG, intravenous immunoglobulin.

Kharfan-Dabaja *et al,* described a patient who developed *de novo* lupus anticoagulant 34 days after allo-SCT, in the setting of acute GVHD. No clinical evidence of systemic thrombosis developed and the lupus anticoagulant resolved after immunosuppressive therapy with steroids and infliximab.[6] Sohngen et al described a patient with MDS who developed anticardiolipin antibody and lupus anticoagulant simultaneously with severe thrombocytopenia 8 months after Allo-SCT. Notably, therapy with cyclosporin brought about resolution of the thrombocytopenia and the antibodies.[7] In another study, the preconditioning incidence of antiphospholipid antibodies was not found to be significantly increased in patients with bone marrow transplant-related organ dysfunction.[13] However, in a retrospective review Greeno *et al.* observed that lupus anticoagulant was associated more significantly with conditioning regimens of Busulphan plus cyclophosphamide as well as cyclosporine or those receiving a T-cell depleted marrow.[10]

It is interesting to note that in certain cases where lupus anticoagulant was present prior to transplantation due to a secondary antiphospholipid syndrome, disappearance of lupus anticoagulant was noted after allo-SCT. One such report describes a 19 year-old female with SLE and elevated titers of anticardiolipin antibody and lupus anticoagulant. After repeated thrombotic events manifested as arterial and venous thrombosis, thrombocytopenia and auto-immune hemolytic anemia, she received an autologous CD34+ SCT which was followed 8 months later by a normal hematological state requiring no further treatment.[14] Olalla et al described a 23 year old female with chronic myeloid leukemia with elevated lupus anticoagulant prior to transplantation which fully resolved by day 27 and remained in resolution for 4 years after transplantation from an identical HLA sibling.[15]

Based on the most recent proposed diagnostic criteria, the diagnosis of CAPS in our case is not definitive, as only one set of elevated antiphospholipid antibodies titers was available with a prolonged course. However, the clinical context is most consistent with CAPS, as confirmed histopathologically.

In practice, differentiating CAPS from conditions such as thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation, or even heparin induced thrombocytopenia (HIT), is challenging because of overlapping clinical and laboratory characteristics. For example, thrombocytopenia with microangiopathy, renal failure, and neurologic events can occur in both CAPS and TTP. TTP is more likely to follow infection or use of certain medications (such as cyclosporine or tacrolimus), and to cause a profound thrombocytopenia and overt hemolytic anemia with numerous schistocytes on peripheral blood smear. With no evidence of infection on cultures or post-mortom in our case is against TTP. Also, the Recurrence is common in TTP, but rare in CAPS. Finally the pathologic features appear to differ in distribution, character, and consequences between TTP and CAPS. TTP shows striking involvement of myocardial arteries and variable degrees of vascular involvement in kidney, pancreas, brain, and adrenal glands. The thrombi of TTP are composed predominantly of platelets with a trivial component of fibrin, consistent with previous studies. CAPS on the other hand is characterized by diffuse vascular damage. The thrombi of CAPS appear to be composed predominantly of fibrin with few platelets.[16,20]

Our patient developed renal insufficiency that progressed to end stage renal disease following allo-SCT. Acute renal insufficiency affects about 40% allogeneic BMT patients, sometimes requiring dialysis.[17,18] The etiology of renal failure in this setting is often multifactorial. This patient's initial renal insufficiency was attributed to cryoglobulinemia, prompting plasma exchange; however there was ultimately autopsy evidence of renal microthrombi, suggesting that antiphospholipid antibodies was likely the key etiology of the renal failure. Asherson et al, drawing conclusions from the largest published case series reports of CAPS, theorized that in a fraction of cases, CAPS was precipitated by a flare of the underlying autoimmune disease, specifically systemic lupus erythematosus[1] It seems plausible that our patient's

CAPS also commenced with a flare of her immunologic dysfunction.

Implications For Management

The literature on CAPS, primarily comprised of case series, supports the use of anticoagulation and potentially immunosuppressives, whereas the benefits of plasmapheresis and IVIG are controversial.[1,2] Therapy for potential inciting factors, such as infections, should be initiated. Early removal of catheters is advocated in an attempt to remove additional stimuli for thrombosis. Analyses of some patient series showed the best survival in the subgroup receiving combination therapy with anticoagulants, corticosteroids, and plasma exchange or gammaglobulin.[19] Other series showed questionable benefit of the latter two approaches, while confirming the role of anticoagulation and steroids[2] Therapy with anticoagulation is particularly challenging in the post SCT setting, because of frequent thrombocytopenia, risk of gastrointestinal bleeding from GVHD, and risk of drug interactions given frequent need for multiple antibiotics.

Conclusion

This case underscores the potential utility of early screening for antiphospholipid antibodies when unexpected or multiple thrombotic events occur. The mortality from CAPS remains high. Although rare, the diagnosis should be considered when extensive thrombotic complications develop in a transplant recipient without a clear precipitant. It is important to attempt to distinguish this entity from others with similar clinical features, especially TTP, but even HIT, as treatment strategies can markedly differ.

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