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REVIEW ARTICLE

Nina Singh
Timothy Gayowski
Ignazio R. Marino

Hemolytic uremic syndrome in solid-organ transplant recipients

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N. Singh (✉) · T. Gayowski · I.R. Marino
Infectious Disease Section,
VA Medical Center,
University Drive C,
Pittsburgh, PA 15240, USA
Fax: + 1 412 683 6928

Abstract Post-transplant hemolytic uremic syndrome characterized by microangiopathic hemolysis, thrombocytopenia, and renal failure is an infrequent but potentially serious complication in organ transplant recipients. Hemolytic uremic syndrome developed in 2 % (2/100) of our consecutive liver transplants. We report our patients and review a total of 91 cases of hemolytic uremic syndrome in adult solid organ transplant recipients reported in the literature. Ninety percent were observed in renal transplant recipients, 8 % in liver, and 1 % each in lung and heart transplant recipients. Eighty percent and 96 % of cases occurred within 90 days and 1 year, respectively, post-transplantation. In renal transplant recipients, 23 % of cases were due to post-transplant recurrence of hemolytic uremic syndrome. In 50 % of renal transplant recipients and in all nonrenal solid-organ transplant recipients, hemolytic uremic syndrome was attributed to cyclosporin or tacrolimus therapy. Notably, infections were not a significant precipitating factor for post-transplant hemolytic uremic syndrome. Graft loss attributable to hemolytic uremic syndrome occurred in 43 % of renal transplant recipients while renal transplantation and hemodialysis were required in the lung and heart transplant recipients due to hemolytic uremic syndrome induced renal failure. The overall mortality was 13 % (12/91). Physicians caring for transplant recipients need to be aware of this potentially severe graft and life-threatening disorder since prompt recognition and removal of identifiable risk factors is critical in the management of post-transplant hemolytic uremic syndrome.

Key words Hemolytic uremic syndrome · Thrombocytopenia, hemolytic uremic syndrome · Solid-organ transplantation, hemolytic uremic syndrome

Introduction

Hemolytic uremic syndrome, first described in 1955, is a serious disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [36]. Until recently, this syndrome had been associated with virtually 100 % mortality [3].

Hemolytic uremic syndrome is a well-recognized complication of bone marrow transplantation [12, 29, 35]. Cyclosporin A-induced microangiopathy, resulting from defective vascular prostacyclin (PGI_2) synthesis, has been proposed to be the major risk factor for post-transplant hemolytic uremic syndrome [12]. Graft-versus-host disease, cytomegalovirus infection, mitomycin C therapy, and total body irradiation as part of the preparative regimen have also been proposed as risk factors for hemolytic uremic syndrome in bone marrow transplant recipients [35].

Hemolytic uremic syndrome is an uncommon but nevertheless serious complication in solid-organ trans-

plant recipients as well [9, 10, 31]. Since most cases have been reported as individual case reports, the overall role of putative triggering factors and the effect of therapy on graft and patient survival are difficult to discern. Over a 5-year period, hemolytic uremic syndrome developed in 2% (2/100) of our consecutive liver transplant recipients. We describe our patients and review additional cases of hemolytic uremic syndrome in adult solid-organ transplant recipients reported in the literature.

Case reports

Case 1

A 38-year-old male underwent orthotopic liver transplantation for alcohol-related end-stage liver disease. Medication consisted of tacrolimus, 1 mg intravenously b.i.d, methylprednisolone, 20 mg intravenously daily, and trimethoprim-sulfamethoxazole, 80/400 mg orally daily. Twelve days postoperatively, anemia, thrombocytopenia, elevated bilirubin, and renal dysfunction ensued. Hemoglobin and hematocrit were 6 g/dl and 18.5%, respectively. Platelet count was 15,000/mm^3 and serum creatinine was 2.7 mg/dl. Microangiopathic hemolytic anemia was diagnosed based on elevated lactate dehydrogenase (2458 IU/l), a decreased haptoglobin level (< 20 mg/dl, normal level 60–270 mg/dl), an elevated free hemoglobin level (3.6 mg/dl), elevated direct bilirubin (20.7 mg/dl), and the presence of schistocytes on peripheral blood smear. Tacrolimus was continued and plasmapheresis was administered for 10 days with reversal of microangiopathic hemolysis.

Case 2

A 44-year-old male underwent orthotopic liver transplantation for end-stage liver disease due to hepatitis C virus. Postoperative immunosuppression consisted of tacrolimus, 4 mg p.o.b.i.d., and prednisone, which had been tapered down to 10 mg orally daily by 4 weeks post-transplantation. Thirty-one days postoperatively the patient reported no symptoms, although the platelet count was noted to be 11,000/mm^3.Other medications included carafate, sodium bicarbonate, and nifedipine. Hematocrit was 22% and serum creatinine was 1.9 mg/dl. Evidence of microangiopathic hemolytic anemia was present as indicated by a reticulocyte count of 6.2% (normal count 0.9%–2.71%), a haptoglobin level below 20 mg/dl (normal level 60–270 mg/dl), a serum lactate dehydrogenase level of 506 IU/l (normal level 90–180 IU/l), and the presence of schistocytes on peripheral blood smear. There was no evidence of cytomegalovirus or other infections. The diagnosis of hemolytic uremic syndrome was made. Prednisone was increased to 40 mg daily for 3 days, tapered to 30 mg daily for 3 days, and then maintained at a dose of 20 mg daily. Gradual resolution of thrombocytopenia and anemia ensued, and no further recurrences of hemolytic uremic syndrome were noted.

English-language articles describing hemolytic uremic syndrome in solid-organ transplant recipients were identified through a Medline search. Bibliographies of identified articles were also manually searched to find additional descriptions of such cases. A total of 91 cases of hemolytic uremic syndrome after adult solid-organ transplantation are reviewed. The criteria for hemolytic uremic syndrome were as previously defined [29, 35, 36] and included: (1) anemia with microangiopathic hemolysis, i.e., increased bilirubin, increased lactate dehydrogenase enzymes, decreased haptoglobin, and reticulocytosis with schistocytes or fragmented red blood cells in the peripheral blood smear; (2) thrombocytopenia; and (3) renal failure.

Epidemiology

Hemolytic uremic syndrome developed in 2% of our liver transplant recipients and in 0.5%–3.4% of the renal transplant recipients in two European studies [9, 10]. Of 91 cases of hemolytic uremic syndrome in solid organ transplant recipients (Table 1), 90% (82/91) occurred in renal transplant recipients, including 9 patients with kidney-pancreas transplants [10, 21], and 8% (7/91) in liver transplant recipients. One case was reported in a lung transplant recipient and one in a heart transplant recipient. Fifty percent of the patients were male. Their mean age was 38 years (range 17–61 years). In three renal transplant recipients and one liver transplant recipient, hemolytic uremic syndrome occurred after retransplantation [15, 17, 27, 41].

Time of onset

Hemolytic uremic syndrome occurred earlier post-transplantation in renal than in liver, lung, and heart transplant recipients. The median time to onset in renal transplant recipients was 19 days (range 2 days to 40 months); 76% of cases occurred within 6 weeks post-transplantation. The median time to onset was 30 days in liver transplant recipients (range 8 days to 9 months). The only case in a lung transplant recipient occurred 3 months post-transplantation and one case in a heart transplant recipient occurred 33 days post-transplantation [8, 16]. It is noteworthy that all but four (96%) cases of hemolytic uremic syndrome in solid-organ transplant recipients occurred within 1 year of transplantation.

Underlying diseases

The most common underlying disease leading to transplantation was renal failure due to hemolytic uremic syndrome in 23% (19/82) of the renal transplant recipients. The underlying renal diseases in the other renal transplant recipients were diabetic nephropathy (16%), acute or chronic glomerulonephritis (15%), Alport's syndrome (5%), polycystic kidney disease (5%), lupus nephritis (5%), nephrosclerosis (2%), hypertensive renal disease (1%), hereditary nephritis (1%), vesiculouretheral reflux (1%), congenital renal hypoplasia (1%), chronic analgesic use (1%), and unknown or unavailable in 23%.

Table 1 Clinical features of hemolytic uremic syndrome in solid-organ transplant recipients

Type or transplant	Number of patients	Age in years (range)	Primary immunosuppression	Renal graft loss or permanent renal failure	Mortality	Reference
Renal	18	20–56	Cyclosporin ($n = 17$) Tacrolimus ($n = 1$)	22 % (4/18)	6 % (1/18)	[1, 9, 11, 17, 18, 30, 39, 40, 41, 44, 45]
	16	20–52	Azathioprine	87 % (14/16)	31 % (5/16)	[13, 19, 20, 24, 26, 27, 28, 33, 34, 36, 40, 42]
	45	17–61	Cyclosporin + azathioprine	33 % (15/45)	11 % (5/45)	[10, 14, 21, 40, 43]
	3	21–52	Not reported	66 % (2/3)	0 % (0/3)	[5, 20, 21, 23]
Liver	7	32–59	Cyclosporin ($n = 3$) Tacrolimus ($n = 3$) Cyclosporin + azathioprine ($n = 1$)	0 % (0/6)	0 % (0/6)	[4, 15, 21, 22, 31; Present cases]
Lung	1	33	Cyclosporin + azathioprine	100 %[a] (1/1)	0 % (1/1)	[8]
Heart	1	50	Cyclosporin + azathioprine	100 %[b] (1/1)	100 % (1/1)	[16]

[a] Patient required renal transplantation
[b] Patient required hemodialysis

The underlying causes of end-stage liver disease in liver transplant recipients were alcoholic liver disease in two patients and chronic active hepatitis, hepatocellular carcinoma, primary biliary cirrhosis, hepatitis C, and cryptogenic cirrhosis in one patient each. Lung transplantation was performed for saccular bronchiectasis in one patient and heart transplantation for ischemic cardiomyopathy in one other patient.

Predisposing factors for hemolytic uremic syndrome

Role of immunosuppressive therapy

A number of factors have been proposed as etiologies for hemolytic uremic syndrome. Immunosuppression with cyclosporin has been implicated as a significant risk factor for post-transplant hemolytic uremic syndrome. The association between hemolytic uremic syndrome and cyclosporin was first established by Leithner et al in renal transplantation [27]. A number of reports on transplant recipients have since recognized cyclosporin-induced hemolytic uremic syndrome as a distinct entity and a potentially serious complication of cyclosporin A administration [4, 36, 42]. Hemolytic uremic syndrome has also been reported after nontransplant use of cyclosporin, e.g., in Behcet's syndrome [2].

The pathogenesis of hemolytic uremic syndrome involves a cascade of biochemical events triggered by vascular endothelial damage that lead to the formation of thrombi in the microcirculation [36]. Endothelial cells normally synthesize a number of factors that prevent thrombogenesis. Prostacyclin (PGI_2) is the most potent endogenous inhibitor of platelet aggregation [32, 36]. Endothelial damage mediated through the inhibition of PGI_2 is believed to be the pathogenetic mechanism of cyclosporin-induced hemolytic uremic syndrome [32]; reduced PGI_2 levels result from inhibition of prostacyclin-stimulating factor. Cyclosporin can also cause direct endothelial damage; exposure of endothelial cells in culture induced a time and dose-dependent cell injury [6].

In renal transplant recipients, cyclosporin therapy was believed to be the cause of hemolytic uremic syndrome in 50 % (41/82) of the patients. In an additional 22 % (18/82) of renal transplant recipients, post-transplant hemolytic uremic syndrome was a result of recurrence of the original disease. Antilymphocyte preparations (antilymphocyte globulin in one case and OKT3 antibodies in two cases) were believed to contribute to recurrence in 3 of 82 patients [13, 14, 20]. Monoclonal antibodies including OKT3 can induce tumor necrosis factor – $\propto$ release, which stimulates endothelial cell procoagulant activity [13]. In one patient, an estrogen-containing oral contraceptive preparation was believed to have triggered the recurrence of hemolytic uremic syndrome 24 months after transplantation [42]. By lowering prostacyclin production, estrogen-containing contraceptives have been shown to trigger hemolytic uremic syndrome [36]. In 13 % (11/82) of the patients, graft rejection was believed to be the precipitating factor for post-transplant hemolytic uremic syndrome [10, 26]. The causative factor was believed to be tacrolimus in one case [39], while the etiology of post-transplant hemolytic uremic syndrome was undetermined or unknown in 10 % of the patients.

In liver transplant recipients, the hemolytic uremic syndrome was attributed to cyclosporin in four patients [4, 15, 21, 31], to tacrolimus in one patient [22], and of unknown etiology in the two present cases. Tacrolimus has been used as therapy for cyclosporin-induced hemo-

lytic uremic syndrome [31]. It has been suggested that a potent immunosuppressive agent such as tacrolimus may have a salutary effect on cyclosporin-induced, immune mediated endothelial injury [31]. In vitro, immunosuppressive doses of tacrolimus did not lower endothelial prostacyclin levels to the same degree as cyclosporin and, therefore, it may be less likely to cause microangiopathy [7]. However, hemolytic uremic syndrome has been reported in transplant recipients receiving tacrolimus [22, 25, 39]. A precipitating factor for hemolytic uremic syndrome was not identified in our patients, and resolution of hemolytic uremic syndrome was observed without discontinuation of tacrolimus.

Role of infections

Cytomegalovirus infection has been associated with hemolytic uremic syndrome in bone marrow transplant recipients [35]. Forty-two percent of the patients in a study of renal transplant recipients had IgM antibodies to cytomegalovirus [21]. Cytomegalovirus infection, however, was not determined to be a causative factor for hemolytic uremic syndrome in any other report on solid-organ transplant recipients. Likewise, infections associated with sporadic and endemic cases of hemolytic uremic syndrome, e.g., *Shigella dysenteriae* and *E. coli* 0157:H7 were not documented in any patient in this review. In a lung transplant recipient, pneumonia due to *S. pneumoniae* preceding hemolytic uremic syndrome was proposed to have a contributory role [8]. Neuraminidase elaborated by pneumococcus can cleave sialic acid residues of von Willebrand factor multimer and thus promote platelet aggregation [8, 36]. Influenza A was considered the cause of hemolytic uremic syndrome in a renal transplant recipient [33].

Role of drugs

The association of trimethoprim-sulfamethoxazole and acyclovir with hemolytic uremic syndrome was assessed by Rabinowe et al in bone marrow transplant recipients [35]. The incidence of hemolytic uremic syndrome (8 %) in patients receiving trimethoprim-sulfamethoxazole was not significantly different from those who did not receive trimethoprim-sulfamethoxazole (16 %). Moreover, discontinuation of trimethoprim-sulfamethoxazole in 91 % of the patients at the onset of hemolytic uremic syndrome did not lead to improvement in hematologic or renal parameters. Likewise, acyclovir prophylactic therapy had no statistical correlation with hemolytic uremic syndrome in that study [35].

Role of rejection

Rejection episodes preceding hemolytic uremic syndrome were reported in 38 % of renal transplant recipients and occurred a median of 28 days (range 7 days to 15 months) before hemolytic uremic syndrome. Rejection was believed to be the triggering event for hemolytic uremic syndrome in 11 patients reported in this review [10, 26]. Rejection was also documented in one liver transplant recipient [22].

Clinical and laboratory features

Presenting symptoms of hemolytic uremic syndrome can be variable. It should be mentioned that the terms "hemolytic uremic syndrome" and "thrombotic thrombocytopenic purpura" are often used interchangeably and describe the different clinical expressions of the same disease characterized by hemolytic anemia of the microangiopathic type, thrombocytopenia, and renal failure [36]. The fundamental pathologic lesion in both syndromes is hyaline thrombi of small vessels; this change predominantly involves the kidneys in hemolytic uremic syndrome and the brain in thrombotic thrombocytopenic purpura.

Reported symptoms in solid organ transplant recipients included flu-like symptoms, jaundice, and hematuria. Fever was reported in five patients and neurologic symptoms were described in three cases [4, 15, 21, 33, 36].

Microangiopathic hemolytic anemia characterized by the presence of schistocytes in the peripheral blood smears was present in all cases. The hemoglobin level ranged between 4.3 and 11 g/dl and the hematocrit between 12 % and 36 %. The median platelet count at nadir was 60,000 mm^3 (range 7–449,000/mm^3). Other reported laboratory test abnormalities included elevated lactate dehydrogenase levels (range 137–7,777 IU/l), elevated total bilirubin (range 1.2–3.8 mg/dl), elevated reticulocyte count (range 6 %–19 %), and a decreased haptoglobin level.

Renal biopsy was performed in 68 of 82 renal transplant recipients, in the lung transplant recipient, and in the heart transplant recipient. The basic pathologic lesion in post-transplant hemolytic uremic syndrome is an arteriopathy associated with intimal proliferation and thrombotic occlusion of smaller cortical vessels with subsequent glomerular ischemia, cortical infarction, and renal allograft loss. This type of arterial vasculopathy is in sharp contrast with the predominantly glomerular thrombotic microangiopathy observed in infantile or childhood hemolytic uremic syndrome in which vascular PGI_2 levels are normal [36].

It has been suggested that autologous platelets labeled with indium-111 can noninvasively identify cy-

closporin arteriopathy in transplant recipients prior to the development of microangiopathy, although validation of this observation in follow-up studies has not been carried out [38].

Therapy and outcome

A variety of therapeutic options have been attempted as treatment for sporadic and endemic acute hemolytic uremic syndrome. These include antiplatelet drugs, corticosteroids, platelet transfusions, intravenous immunoglobulin, plasma infusions, and plasma exchange. Platelet transfusions should be avoided as much as possible. An abrupt clinical deterioration with an increase in the frequency of hemorrhage and a rise in serum creatinine was observed when platelet transfusions were employed for hemolytic uremic syndrome in nontransplant settings [3]. A major benefit of plasma therapy, delivered either by exchange or infusion, was observed in the late 1970s. Plasmapheresis or plasma exchange was more effective than plasma infusion in a randomized study in nontransplant recipients [37]. Besides replacing deficient factors, plasma exchange, as opposed to plasma infusion, was also thought to remove the offending platelet-aggregating factors [37]. It is noteworthy that, despite plasmapheresis, a 22 % mortality rate was still observed in that study [37].

Therapy in renal transplant recipients

In 18 renal transplant recipients who received only cyclosporin-[17] or tacrolimus [1]-containing immunosuppressive regimens, the treatment of hemolytic uremic syndrome consisted of discontinuation of, or reduction in, cyclosporin in seven patients (with graft loss in one case), discontinuation of cyclosporin and conversion to azathioprine in five (with cure in all cases), cessation of cyclosporin, plasmapheresis, and conversion to another immunosuppressive (azathioprine in one and tacrolimus in one case) in two patients (with graft loss in the patient switched to azathioprine), plasmapheresis in two (with graft loss in one case), and discontinuation of tacrolimus, conversion to azathioprine, and plasmapheresis in one case, with eventual cure. No specific therapy was administered in one case diagnosed at autopsy [11]. The overall incidence of graft loss in this group was 22 % (4/18) and mortality was 6 % (1/18); the death (and thus graft loss) in one patient was due to disseminated malignant lymphoma and aspergillosis [11].

Amongst 16 patients who received only azathioprine containing immunosuppressive regimens, the therapies employed consisted of discontinuation of the putative triggering agents e.g. antilymphocyte globulin ($n = 1$), estrogen-containing oral contraceptive ($n = 1$), and OKT3 monoclonal antibody ($n = 1$); the graft was lost in one of these three cases; i.e., in a patient who received plasmapheresis in addition to discontinuation of OKT3. Four patients received heparin; graft loss occurred in all four, and three of the four died (one patient sustained cerebral hemorrhage after institution of heparin). It should be noted that antiplatelet agents including aspirin and Persantine have no efficacy in the treatment of this disease. On the contrary, the use of such agents has been associated with increased bleeding complications. Two of 16 patients received corticosteroids as therapy for hemolytic uremic syndrome (one in conjunction with splenectomy); graft loss occurred in two, and one patient died. Five patients received plasmapheresis; the graft was lost in all. One patient was diagnosed at autopsy and another underwent nephrectomy and therapy. Overall 87 % (14/16) of the patients in this group lost their graft and the mortality was 31 % (5/16).

Forty-five renal transplant recipients (including nine with combined kidney-pancreas transplants) received both cyclosporin and azathioprine as primary immunosuppressive agents. Cyclosporin was discontinued in 31; 24 of these 31 patients also received plasmapheresis. There was one death in this group. Although the incidence of graft loss was 39 % (12/31), 6 of the 12 graft losses were due to rejection episodes occurring 6 months later. In eight patients, the cyclosporin dosage was decreased; one of eight patients also received intravenous immunoglobulin [21]. There were four graft losses and two deaths among these patients. Two patients underwent transplant nephrectomy as therapy and survived. In one patient hemolytic uremic syndrome resolved without patient or graft loss upon cessation of OKT3 [14]. Three patients received no therapy with death in two of these three patients. Overall graft loss due to hemolytic uremic syndrome was observed in 33 % (15/45) of the patients receiving cyclosporin and azathioprine as immunosuppressive agents, and death occurred in 11 % (5/45) of the patients.

In three patients the primary immunosuppression was not reported. Graft loss occurred in two of these three patients (in one due to rejection 18 months later). There were no deaths in this group.

A seemingly higher graft loss and mortality in the patients receiving azathioprine-containing immunosuppressive regimens is likely due to the fact that most of these cases occurred nearly two decades ago when understanding of the pathogenesis and therapy for hemolytic uremic syndrome was still evolving. Consequently, nearly a third of these patients received not only ineffective but potentially dangerous therapies, e.g., heparin and/or splenectomy. A pronounced clinical deterioration and even death has been reported after splenectomy, and splenectomy is currently not recommended as a therapy for hemolytic uremic syndrome [3].

Although plasmapheresis remains the only known definitive treatment for hemolytic uremic syndrome, the overall incidence of renal graft loss in patients receiving plasmapheresis – 38 % (13/34) – was not different from those who did not receive plasmapheresis – 42 % (20/48). We, however, caution that because of the retrospective nature of this review, the two groups cannot be matched for severity of the illness. It is conceivable that patients receiving plasmapheresis were more severely ill, as this therapy was often employed when other options for treatment failed. Overall, the incidence of graft loss due to hemolytic uremic syndrome in renal transplant recipients was 43 % (35/82). The overall mortality was 13 % (11/82); 12 % (10/82) of the deaths were attributable to hemolytic uremic syndrome.

Therapy in liver transplant recipients

In five liver transplant recipients, the therapy consisted of discontinuation of cyclosporin and a switch to tacrolimus, discontinuation of cyclosporin and a switch to azathioprine, reduction of tacrolimus and institution of plasmapheresis, plasmapheresis without any change in cyclosporin therapy, and intravenous immunoglobulin with continuation of cyclosporin. There was no mortality or permanent renal dysfunction in any of these patients.

In our patients, plasmapheresis was employed in one patient and corticosteroids in another; tacrolimus was continued in both patients with careful monitoring so as not to exceed therapeutic levels. Resolution of hemolytic uremic syndrome with plasmapheresis, despite continued cyclosporin therapy, has been reported previously in two liver transplant recipients [15, 21]. Spontaneous resolution has also been reported in de novo as well as in cyclosporin-induced hemolytic uremic syndrome in renal transplant recipients [9, 21, 23].

Therapy in heart and lung transplant recipients

The lung transplant recipient received antiplatelet agents (aspirin and dipyridamole) and the cyclosporin dosage was reduced. Despite improvement in platelet count, renal failure persisted with the eventual requirement of renal transplantation. The heart transplant recipient received plasmapheresis along with cessation of cyclosporin, an increase in prednisone, and conversion to an experimental immunosuppressive RS-61 443 [16]. The patient, however, died; autopsy revealed evidence of hemolytic uremic syndrome in the kidneys.

In summary, hemolytic uremic syndrome is a rare but serious disease in solid-organ transplant recipients. Eighty percent and 96 % of cases occurred within 3 months and 1 year, respectively, of transplantation. Immunosuppressive therapy with cyclosporin and recurrence of the original disease (in renal allograft recipients) were the most commonly identifiable predisposing risk factors. Unlike sporadic or endemic cases of hemolytic uremic syndrome, infections were not significant initiating events in post-transplant hemolytic uremic syndrome. Hemolytic uremic syndrome was associated with graft loss in 43 % of cases in renal transplant recipients. Renal transplantation was required in a lung transplant recipient and hemodialysis was necessary in a heart transplant recipient for hemolytic uremic syndrome induced renal failure. Overall, mortality in solid-organ transplant recipients attributable to hemolytic uremic syndrome was 13 % (12/91). A clearer elucidation of the pathophysiology of hemolytic uremic syndrome in transplant recipients should lead to more definitive treatment. Until then, prompt recognition, removal of identifiable risk factors, and institution of plasmapheresis represent one of the best management strategies presently available against this potentially graft and life-threatening disorder in transplant recipients.

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