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Acute Kidney Injury in Patients with Systemic Sclerosis Participating in Hematopoietic Cell Transplantation Trials in the United States

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Recipients of hematopoietic cell transplantation may be at risk for developing acute kidney injury (AKI), and this risk may be increased in patients who undergo transplantation for severe systemic sclerosis (SSc) due to underlying scleroderma renal disease. AKI after transplantation can increase treatment-related mortality. To better define these risks, we analyzed 91 patients with SSc who were enrolled in 3 clinical trials in the United States of autologous or allogeneic hematopoietic cell transplantation (HCT). Eleven (12%) of the 91 patients with SSc in these studies (8 undergoing autologous HCT, 1 undergoing allogeneic HCT, 1 pretransplantation, 1 given i.v. cyclophosphamide on a transplantation trial) experienced AKI, of whom 8 required dialysis and/or therapeutic plasma exchange. AKI injury in the 9 HCT recipients developed a median of 35 days (range, 0-90 days) after transplantation. Ten of 11 patients with AKI received angiotensin-converting enzyme inhibitor (ACE-I) therapy. The etiology of AKI was attributed to scleroderma renal crisis in 6 patients (including 2 with normotensive renal crisis), to AKI of uncertain etiology in 2 patients, and to AKI superimposed on scleroderma kidney disease in 3 patients. Eight of the 11 patients died, one each because of progression of SSc, multiorgan failure, gastrointestinal and pulmonary bleeding, pericardial tamponade and pulmonary complications, diffuse alveolar hemorrhage, pulmonary embolism, graft-versus-host disease, and malignancy. Limiting nephrotoxins, cautious use of corticosteroids, renal shielding during total body irradiation, strict control of blood pressure, and aggressive use of ACE-Is may be of importance in preventing renal complications after HCT for SSc.

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INTRODUCTION

Acute kidney injury (AKI) has been reported in up to 26% of patients with systemic sclerosis (SSc), and scleroderma renal crisis (SRC) can develop in up to 19% of patients [1-3]. Recipients of hematopoietic cell transplantation (HCT) for hematologic malignancies can develop AKI and chronic kidney injury between 1 and 12 months after preparative conditioning and

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Table 1. Classification/Staging System for AKI*

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine of ≥0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2†	Increase in serum creatinine to >200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3‡	Increase in serum creatinine to >300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL [≥354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L])	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

Modified from RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria [51]. The proposed staging system is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum creatinine influences outcome. Only one criterion (creatinine or urine output) must be fulfilled to qualify for a stage.

*Adapted from Mehta et al. 2007 [13].

†A 200%-300% increase = a 2- to 3-fold increase.

‡Given the wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3, regardless of the stage at the time of RRT.

transplantation [4-8]. The degree of renal impairment posttransplantation has been shown to impact the mortality rate [9]; therefore, patients with SSc who receive high-dose immunosuppression followed by autologous or allogeneic HCT may be at increased risk for developing renal complications. In a pilot study of lymphoablation with a total body irradiation (TBI)-containing regimen followed by CD34+ selected autologous HCT in patients with severe SSc, dramatic improvement/resolution of dermal fibrosis and stabilization/improvement of pulmonary function was observed; however, 6 of the 34 patients (18%) developed AKI [10].

This report characterizes renal complications and outcomes observed in patients with poor-prognosis SSc (diffuse cutaneous disease with internal organ involvement) who participated in 3 clinical trials of HCT in the United States, and offers guidelines for prevention of AKI. The subjects described in this report are derived from the pilot study of high-dose therapy and autologous HCT (34 subjects), the ongoing randomized study of chemotherapy versus autologous HCT in the SCOT (Scleroderma Cyclophosphamide or Transplantation) trial (55 subjects randomized to date), and a study of allogeneic HCT (2 subjects).

PATIENTS AND METHODS

From the two published studies, we identified patients with severe SSc who developed AKI after undergoing autologous or allogeneic HCT [10,11]. We also identified subjects with AKI among those randomized to date on the SCOT study (www.sclerodermatrial.org). Subjects on the SCOT protocol are randomized to 12 monthly i.v. infusions of 750 mg/m^2 cyclophosphamide (Cy) or to myeloablative conditioning followed by CD34+ selected autologous HCT. The subjects undergoing autologous HCT received conditioning with 120 mg/kg Cy, 90 mg/kg antithymocyte globulin (ATGAM), and 800 cGy TBI. TBI was given in four 200-cGy fractions over 2 days, with lung shielding to 200 cGy pulmonary transmission. Subjects enrolled on the SCOT trial also received kidney shielding to 200 cGy renal transmission [12]. Patients given ATGAM received methylprednisolone 0.5 mg/kg/day from day +6 through day +21 posttransplantation and then tapered through day +37, to reduce allergic reactions to ATGAM and damage to organs. The allogeneic HCT recipients received conditioning ATGAM, busulfan, and Cy, followed by cyclosporine and methotrexate for graft-versus-host disease (GVHD) prophylaxis [11].

AKI was defined as an abrupt (within 48 hours) reduction in kidney function, as measured by an absolute increase in serum creatinine of ≥0.3 mg/dL or a percentage increase in serum creatinine of ≥150% (1.5-fold) from baseline. Information on urine output was not available [13]. Staging of AKI is detailed in Table 1. Results were analyzed as of August 4, 2009. All patients participating in these trials gave informed consent in accordance with local institutional review board standards.

RESULTS

A total of 34 individuals with SSc were enrolled in the pilot study of autologous HCT [10]. To date, the SCOT trial has randomized 28 patients to SCT and 27 patients to monthly i.v. Cy. The third study included 2 patients who underwent allogeneic HCT [11]. Of the 91 patients with severe SSc treated on these 3 trials, 11 (12%) developed significant AKI. Of the 64 patients who underwent allogeneic or autologous HCT, 9 (14%) developed AKI. Six of the 11 patients who developed AKI were on the pilot study of autologous HCT, 4 were enrolled on the SCOT study (1 patient randomized to the Cy arm, 1 patient who underwent granulocyte-colony stimulating factor–induced hematopoietic cell mobilization but did not receive preparative conditioning or transplantation, and 2 patients who received autologous HCT), and 1 patient received allogeneic HCT.

Table 2 presents characteristics of the 11 patients who developed AKI. Patients 1-4 were from the

Table 2. Patient Characteristics

Patient Number	1	2	3	4	5	6	7	8	9	10	11
Study	SCOT Randomized Study				Allogeneic HCT	Pilot Autologous HCT					
Institution	U Michigan	Duke University	MDACC	UT Houston	FHCRC	FHCRC	FHCRC	Wayne State	FHCRC	FHCRC	FHCRC
Age, years	52	43	60	59	31	50	43	42	47	41	53
Sex	Male	Male	Female	Female	Female	Female	Female	Female	Female	Male	Male
Transplant type	Autologous	Autologous	None (pre-transplantation)	None (monthly cyclophosphamide)	Allogeneic	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous
Previous H/O SRC	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Day of onset of AKI (days from transplantation)	D+6	D+23	NA	NA	D+39	D+24	D+44	D+85	+35	+90	0
Neurologic dysfunction	No	No	Yes	No	Yes (seizures)	No	No	No	No	No	Yes (decreased level of consciousness)
Hypertension	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Thrombocytopenia	Yes*	Yes	Yes	No	Yes	No†	Yes (nadir 54,000)	Yes (nadir 7000)	No	No	Yes*
LDH	Normal	High	High	NA	High	High	High	High	Normal	NA	Normal
Coombs test	ND	Negative	Negative	ND	ND	ND	ND	ND	ND	NA	ND
Schistocytes	None	Present	None	NA	Few	Moderate	None	Few	Few	NA	None
Haptoglobin	NA	Low	Normal	ND	Low	ND	ND	ND	ND	NA	Normal
Serum creatinine at baseline, mg/dL	1.6	0.7	1.0	1.4	0.6	0.5	0.7	1.3	1.4	0.7	1.6
Maximum serum creatinine, mg/dL	2.4	1.1	2.6	3.5	3.8	2.7	7.3	2.9	2.7	2.4	2.8
Absolute increase in serum creatinine over baseline,mg/dL	0.8	0.4	1.6	2.1	3.2	2.2	6.6	1.6	1.3	1.7	1.2
ACE-I	Yes	Yes	Yes	Yes	Yes	Started D+24	Yes	Yes after diagnosis of SRC	Yes	No	Yes
Hemodialysis	Yes	No	Yes	No	Yes for volume	Yes	Yes	Yes	No	No	Yes
Plasma exchange	No	Yes × 5 days	Yes × 3 days	No	No	Yes	No	No	No	No	No
Final diagnosis	AKI	Normotensive SRC	AKI	SRC	SRC	SRC	AKI super-imposed on SSc kidney disease	SRC	AKI super-imposed on SSc kidney disease	Normotensive SRC	AKI superimposed on SSc kidney disease
Outcome	Alive	Alive	Dead	Dead	Dead	Dead	Alive	Dead	Dead	Dead	Dead
Cause of death	NA	NA	DAH	Pulmonary embolism	GVHD	GI and pulmonary bleeding	NA	Pericardial effusion (near tamponade), pulmonary complications	Disease progression at 5 years	Secondary MDS/AML	Multiorgan failure

DAH indicates diffuse alveolar hemorrhage; ACE, angiotensin converting enzyme; FHCRC, Fred Hutchinson Cancer Research Center; LDH, lactate dehydrogenase; MDACC, M.D. Anderson Cancer Center; MDS/AML, myelodysplastic syndrome/acute myelogenous leukemia; MOF, multiorgan failure; NA, not applicable; ND, not determined/available; UT, University of Texas.

Patient 1 remains on dialysis at last follow-up. Patient 3 was able to discontinue dialysis. Patient 5 underwent dialysis for a few days for volume control. Patient 6 discontinued dialysis for a while but then developed other complications; she required dialysis again before her death. Patient 7 underwent dialysis for 21 months, and is now free from dialysis for 6 years. Patients 8 and 11 died while receiving dialysis.

*Posttransplantation.

†History of gastric antral vascular ectasia. The patient required platelet transfusions to maintain a platelet count >50 × 10^9 /L; she never became platelet transfusion–independent and died 6 months post-HCT.

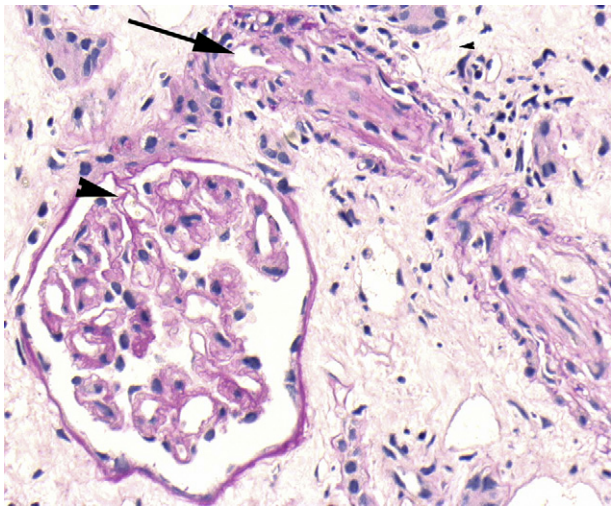

Figure 1. Periodic acid-Schiff–stained section of renal biopsy from patient 6. The glomerulus exhibits duplication of the basement membrane (arrowhead), segmental collapse of capillary loops, and mesangiolysis. An adjacent longitudinally oriented arteriole (arrow) has a small residual eccentric lumen nearly obliterated by myointimal matrix. (Original magnification, 40×.)

randomized SCOT protocol, patient 5 was from the allogeneic HCT study, and patients 6-11 were from the autologus HCT pilot study. All but one subject received angiotensin-converting enzyme inhibitor (ACE-I) therapy to prevent or treat SRC; patient 10 did not, because he was not hypertensive. After developing AKI, 3 patients underwent plasma exchange for presumed diagnosis of transplantation-associated thrombotic microangiopathy (TA-TMA)/thrombotic thrombocytopenic purpura (TTP), and 7 patients required hemodialysis. The final diagnosis was SRC in 6 patients (normotensive SRC in 2), AKI of uncertain etiology in 2 patients, and AKI superimposed on SRC in 3 patients. The diagnosis was based on clinical and laboratory data. Renal tissue was available for histopathological evaluation in 2 patients (patients 6 and 8). At last follow-up, 3 of the 11 patients are alive, 1 of whom (patient 1) remains on dialysis. The surviving patients are 7, 31, and 72 months posttransplantation. Two patients died while on dialysis. All others were able to discontinue dialysis. Eight of the 11 patients died, one each because of progression of SSc, multiorgan failure, gastrointestinal and pulmonary bleeding, pericardial tamponade and pulmonary complications, diffuse alveolar hemorrhage, pulmonary embolism, GVHD, and malignancy. None of these deaths was directly attributable to AKI.

Figure 1 illustrates the renal pathology in patient 6. Myointimal proliferation of arterioles and venules as well as abnormalities in the glomerular capillaries, including thickening and collapse of the walls and widening of the subendothelial spaces, were seen. Marked interstitial fibrosis associated with tubular atrophy was present. Autopsy kidney sections from patient 8 (Figure 2) showed widespread arterial and arteriole myointimal thickening with mucoid degeneration. The thickened myointimal layers within the interlobular and afferent arterioles contained fibrinoid material. There were multiple foci of segmental cortical necrosis with sclerosis of glomeruli. Remaining glomeruli showed a loss of capillary loops with necrosis of the endothelium. These vascular changes were consistent with scleroderma vasculopathy. In addition, there was interstitial fibrosis with tubular atrophy. The kidney changes seen in patients 6 and 8 are consistent with chronic kidney injury from severe SSc with some superimposed changes of AKI.

DISCUSSION

The etiology of AKI in HCT recipients is multifactorial and can be attributable to the effects of high-dose chemotherapy, TBI, ATGAM, nephrotoxic drugs and anti-infective agents, sepsis, hypotension, viral infection, TA-TMA, or i.v. contrast dyes used for imaging studies. In allogeneic HCT recipients, this list expands to include hepatic veno-occlusive disease and administration of a calcineurin inhibitor (tacrolimus or

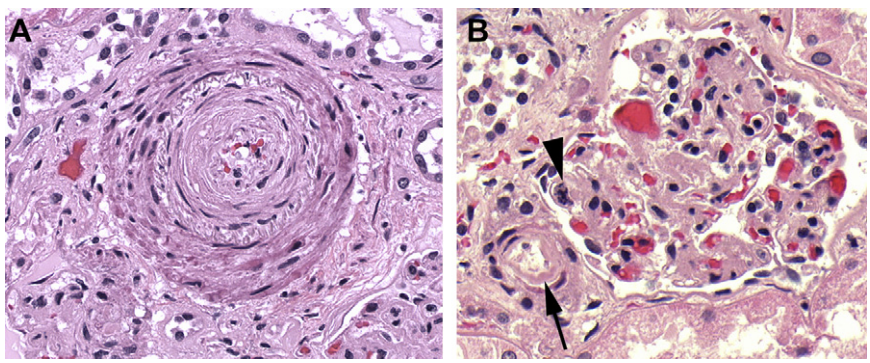

Figure 2. Autopsy kidney from patient 8 with SRC. (A) Interlobular arteriole with severe luminal narrowing from "onion skin–like" myointimal hyperplasia. (Hematoxylin and eosin; original magnification, 40×.) (B) The shrunken glomerulus exhibits a collapse of capillary loops with focal necrosis of endothelial cell (arrowhead). A contiguous afferent arteriole shows fibrinoid necrosis (arrow) within the thickened intimal layer. (Hematoxylin and eosin; original magnification, 40×.)

cyclosporine) for the prevention and treatment of GVHD [14-18]. Development of AKI increases the treatment-related mortality rate in both allogeneic and autologous HCT [7,9]. Zager and coworkers [9] reported that posttransplantation mortality increased with worsening degree of renal impairment. In their study, mortality exceeded 80% in patients who required hemodialysis, and patients who survived were at an increased risk for chronic kidney disease (CKD).

The incidence of AKI is frequently underestimated in patients with SSc, because serum creatinine is a less-robust marker of renal function in these patients, presumably because of renal vasculopathy and decreased muscle mass resulting from scleroderma [19]. Whether or not the combination of SSc and HCT magnifies the risk of subsequent renal complications is unclear.

In a European phase I/II study of autologous HCT in SSc, 5 of 41 patients (12%) were reported to have scleroderma-related renal impairment before transplantation, but only 1 of these patients experienced significantly decreased serum creatinine level at 1 year posttransplantation [20]. Although there was a 10% rise in the final serum creatinine level over baseline, the authors did not report a significant correlation between baseline renal function and survival [20]. Similar results were noted by other European investigators, who found that renal function remained stable after autologous HCT for SSc [21,22]. Of note, most patients who undergo transplantation for autoimmune disease in Europe do not receive TBI for lymphoablation.

In the U.S. pilot trial of high-dose cyclophosphamide, ATGAM, TBI, and autologous HCT, 6 of 34 patients (18%) developed some degree of AKI (patients 6-11 in the present study) [10]. Renal events occurred within 3 months of transplantation, and no late renal abnormalities were noted. Two patients who required dialysis died because of complications of hospitalization. A third patient required dialysis for 21 months, and at 6 years posttransplantation was dialysis-independent with a serum creatinine level of 2.4 mg/dL. Because of an apparent increased incidence of AKI in the pilot U.S. autologous HCT trial compared with the European study, kidney shielding with a limitation to 200 cGy renal transmission was instituted for the subsequent randomized SCOT trial. Other measures adopted in the SCOT trial to minimize nephrotoxicity include the routine administration of ACE-I through day 60 posttransplantation (ie, through glucocorticoid therapy). Use of captopril as an ACE-I is not recommended in HCT recipients, because the sulfa moiety in this agent has been associated with neutropenia. Aggressive control of blood pressure (to below 110/80 mm Hg), restricted use of glucocorticoids, prohibition of i.v. contrast, and close monitoring of renal function, including urinary protein/creatinine ratios, are also standard practice. It is notable that to date, only 2 of the transplant recipients in the SCOT trial have developed transient renal complications after autologous HCT, and both of these individuals are surviving with normal renal function.

As shown in Table 2, AKI can develop in patients with SSc in the absence of HCT. The prevalence of SRC in patients with SSc is estimated to be as high as 19% [1-3]. SRC is more common in individuals with diffuse cutaneous scleroderma and is rare in patients with limited disease. The majority of patients with SRC present within 5-6 years of their initial diagnosis of SSc and classically demonstrate malignant hypertension (90% of patients), microangiopathic hemolytic anemia (MAHA; 43%), and central nervous system abnormalities (11%). However, 10% of individuals with SRC may present with normal blood pressure readings (so-called "normotensive renal crisis") [23]. The etiology of SRC is poorly understood, but renal vascular intimal proliferation, vascular hyperreactivity, decreased cortical blood flow, and activation of the renin–angiotensin–aldosterone axis have all been implicated [24,25]. The primary treatment of SRC is ACE-I therapy, given even in the presence of AKI. With ACE-I administration, the 1-year mortality of SRC has decreased dramatically from 76% to 15% [26,27]. Glucocorticoid administration, particularly at high doses (ie, prednisone $\geq$15 mg/day or equivalent), has been postulated to trigger the onset of SRC [25,28]. However, in the appropriate clinical setting (ie, Rodnan skin hardening score $\geq$20 and large joint contractures), even lower doses of prednisone (mean, 7.4 mg daily) have been associated with SRC. Multivariate regression analysis demonstrated that the nature clinical characteristics was more important than prednisone use in predicting the development of SRC [29,30]. Therefore, systemic steroid use in patients with SSc requires careful renal function and blood pressure monitoring. The use of prophylactic ACE-I is controversial, but should be considered in this particular clinical situation.

Patients undergoing allogeneic HCT appear to be at increased risk for developing renal abnormalities because of administration of calcineurin inhibitors and high-dose corticosteroids for the prevention or treatment of GVHD [31]. Two patients with SSc who underwent allogeneic HCT are included in the present review. No significant renal complications were observed during 7 months of cyclosporine treatment in one patient. In the other patient (patient 5), SRC was temporally associated with the administration of prednisone 2 mg/kg/day. However, the patient died 18 months after allogeneic HCT because of complications of chronic GVHD while tolerating long-term calcineurin inhibitor therapy without significant renal dysfunction [11]. Based on this limited experience, it is not possible to comment on the risk of renal dysfunction in SSc subjects receiving calcineurin inhibitor therapy.

Table 3. Distinguishing between TTP and SRC*

Characteristic	TTP	SRC	TA-TMA
Thrombocytopenia	Yes	Yes	Yes
MAHA	Yes	Yes	Yes
LDH	Elevated	Elevated	Elevated
Peripheral smear	Schistocytes	Schistocytes	Schistocytes
Bilirubin	Elevated	Elevated	Elevated
Coombs test	Negative	Negative	Negative
Neurologic dysfunction	Yes	Yes	Yes
Hypertension	Possible	Yes	Possible
Hemorrhagic manifestations	Yes	No	Possible
Fever	Yes	No	No
Acute renal impairment	Yes	Yes	Yes
Thrombotic microangiopathy	Yes	Yes	Yes
Coagulation profile	Normal PT, PTT	Normal PT, PTT	Normal PT, PTT
Type of SSc	Usually limited	Usually diffuse	NA
vWF-cleaving protease	Low	Not known	Normal
Therapy	Plasmapheresis	ACE-I	Supportive care

LDH indicates lactate dehydrogenase; PT, prothrombin time; PTT, activated partial thromboplastin time; NA, not applicable.
*Adapted from Manadan et al. 2005 [47].

The inclusion of TBI in the conditioning regimen for patients with malignant disease has been implicated in the development of CKD, TA-TMA, hemolytic uremic syndrome (HUS), and radiation nephritis [8,32]. A recent study found a similar risk of developing AKI after haploidentical allogeneic HCT in groups that did and did not receive TBI in the conditioning regimen; however, the TBI group was more likely to develop CKD [8]. Clinical features of HUS and TA-TMA may be indistinguishable from those of radiation nephritis, which also may present with hypertension, anemia, edema, proteinuria, hematuria, and elevated serum creatinine level [33,34]. Posttransplantation TTP or TA-TMA has been reported in 0.51%-74% of patients undergoing allogeneic HCT [35-38] and in 0.13%-0.25% of those undergoing autologous HCT [39]. TA-TMA appears to be distinct from idiopathic TTP, given different causative events and higher mortality [40]. TA-TMA usually is not associated with deficiency of ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) activity or with the presence of inhibitory antibodies [41]. Moreover, TA-TMA usually does not respond to plasma exchange [42]. The clinical distinctions among TA-TMA, TTP, and normotensive SRC in the absence of ADAMTS 13 determinations can be problematic; for example, the clinical findings in patient 2 in our series were attributed to normotensive SRC, but this patient also was treated for TTP with plasma exchange and had a successful outcome.

In the setting of either SSc or HCT, AKI also may result from the development of TTP. Classic TTP is a relatively rare syndrome characterized by a pentad of AKI, thrombocytopenia, MAHA, neurologic abnormalities, and fever. These signs and symptoms result from microvascular platelet clumping [43,44]. Left untreated, TTP is often rapidly fatal, whereas prompt initiation of plasma exchange can be lifesaving [45,46]. Several reports have noted the coexistence of TTP with SSc [47-49]. True TTP in individuals with SSc may mimic SRC, and radiation nephritis, MAHA, and drug- induced nephrotoxicity also may contribute to the differential diagnosis of posttransplantation AKI. Features that help distinguish TTP from SRC have been detailed by Manadan et al. [47] and are summarized in Table 3. Laboratory testing for ADAMTS-13 (von Wiilebrand factor [vWF] cleaving protease) and the plasma concentration of ultra-large vWF multimers might provide additional clarifying information, but these tests are not readily available in most institutions. Therefore, whenever there is clinical suspicion of TTP, treatment with plasma exchange should be initiated promptly, because a delay can be life-threatening. Plasma exchange can be discontinued if ADAMTS-13 activity is normal.

HCT is an increasingly popular and possibly successful treatment for selected patients with SSc and other autoimmune diseases [50]. AKI in patients with SSc undergoing HCT might be attributable to several causes, making the diagnosis and management of these patients particularly challenging. Renal shielding during TBI, careful blood pressure control, avoidance of i.v. contrast dyes or high-dose glucocorticoids, and aggressive ACE-I therapy may reduce the development of AKI in patients with SSc undergoing autologous or allogeneic HCT. The decrease in AKI should reduce the posttransplantation mortality and the burden of CKD following transplantation.

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