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Thrombotic Microangiopathy Following Intestinal Transplantation: A Single Center Experience

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ABSTRACT

Background. Transplant-related thrombotic microangiopathy (TMA) is a well-recognized complication of all types of transplantations. Despite its known relationship with immunosuppressive therapy, only a few cases have been reported following intestinal transplantation.

Methods. We retrospectively reviewed the medical files of nine consecutive intestinal transplant patients between 2000 and 2008.

Results. The diagnosis of TMA was established in 3 patients (33%). At diagnosis the immunosuppressive therapy consisted of tacrolimus (n = 3), combined with azathioprine (n = 1) or sirolimus (n = 2) and steroids (n = 2). The median time between transplantation and TMA was 104 days (range, 55–167 days). Levels of ADAMTS13, a von Willebrand protease, were within normal ranges in all 3 patients. Treatment consisted of stopping/tapering of tacrolimus, together with initiation of plasma therapy, leading to complete remission in all 3 patients. During further follow-up, all 3 patients showed severe graft rejection necessitating more profound immunosuppressive therapy, leading to graft loss in 1 patient and infection-related death in the 2 others. At a median follow-up of 52 months (range, 9–100 months) all remaining TMA-free patients (n = 6) were alive with functioning grafts under minimal immunosuppression.

Conclusion. Herein we have described 3 intestinal transplant patients who were diagnosed with transplantation-related TMA. Despite excellent disease control the final outcomes were dismal, which clearly contrasts with the outcome among TMA-free patients, who were all well with functioning grafts at last follow-up.

THROMBOTIC microangiopathy (TMA) is a potentially fatal disorder characterized by formation of platelet-rich thrombi in various organs, nonimmune hemolytic anemia, and thrombocytopenia.[1] As shown in Table 1, TMA can be classified into primary and secondary forms.[2] Acquired ADAMTS13 deficiency TTP (thrombotic thrombocytopenic purpura) is a subtype of TMA, caused by the formation of autoantibodies against ADAMTS13, an enzyme that is responsible for cleavage of ultralarge von Willebrand factor (ULvWF) multimers. Because of these antibodies, ULvWF multimers are not or are insufficiently cleaved in patients with TTP, leading to profound platelet consumption, fragmentation of red blood cells, and occlusion of small blood vessels in various organs.[3]

In contrast to primary TMA, the pathogenesis of secondary TMA is poorly understood; its etiology is heterogeneous. However, vascular endothelial disturbances are considered to be the key event in the pathogenesis of all subtypes of TMA, leading to platelet aggregation, microvascular thrombosis, and tissue ischemia.[4] TMA has been reported following all types of transplantations, including intestinal transplantations.[5] The majority of cases are observed in renal transplant recipients, in whom TMA occurs in 0.8% to 14% of cases.[6] The incidence of TMA following

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Table 1. Classification of Thrombotic Microangiopathy (TMA)

1. ADAMTS13-deficiency thrombotic thrombocytopenic purpura (TTP)
   - Congenital (mutations in ADAMTS13 gene)
   - Acquired (auto-antibodies against ADAMTS13)
2. Hemolytic uremic syndrome (HUS)
   - Typical HUS (Shiga toxin producing *Escherichia coli*)
   - Atypical HUS
     - Congenital (mutations in complement regulatory proteins, thrombomodulin)
     - Acquired (auto-antibodies against complement regulatory proteins)
3. Secondary TMA: associated with
   - Solid-organ transplantation
   - Hematopoietic stem cell transplantation
   - Pregnancy
   - Medication (clopidogrel, ticlopidine, quinine, mitomycin C, gemcitabin, calcineurin inhibitors, proliferation signaling inhibitors, . . .)
   - Auto-immune disorders (antiphopsholipid syndrome, systemic lupus erythematosus, . . .)

intestinal transplantation is currently unknown. The aim of our study was to describe the incidence and characteristics of TMA following intestinal transplantation in our center, comparing outcomes among these patients with those who remained TMA-free.

METHODS

We retrospectively reviewed the medical files of nine consecutive patients treated with intestinal transplantation at our center (2000–2008). The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by our Ethical Commission.

RESULTS

The diagnosis of TMA was established in 3 patients (33.3%). The first patient diagnosed with Churg-Strauss syndrome received a segmental isolated intestinal graft from a living donor. The second patient lost her entire small bowel due to mesenteric ischemia and subsequently received an isolated entire intestinal graft from a deceased donor. The third patient, who suffered from antiphospholipid syndrome-related complete mesenteric thrombosis, received a multivisceral graft (including stomach-liver-duodenopancreas-small and -right large bowel). Diagnostic TMA criteria included (1) the presence of Coombs-negative hemolytic anemia, (2) thrombocytopenia, and (3) absence of other recognized causes of micro-angiopathic hemolysis and thrombocytopenia. At diagnosis, immunosuppressive therapy consisted of tacrolimus (n = 3), combined with azathioprine (n = 1) or sirolimus (n = 2) and steroids (n = 2). The median time between transplantation and TMA was 104 days (range, 55–167 days). Tables 2 and 3 describe their baseline characteristics and biochemical/clinical abnormalities at the moment of TMA diagnosis. Levels of ADAMTS13 were within normal ranges in all 3 patients. Treatment consisted of stopping/tapering tacrolimus, together with initiation of plasma infusion (n = 1) or therapeutic plasma exchange (n = 2). One patient also received rituximab therapy. All three patients reached complete remission. During further follow-up, all patients showed severe graft rejection necessitating more profound immunosuppressive therapy, leading to graft loss in 1 patient (due to refractory accelerated chronic rejection) and infection (aspergillosis)-related death in the 2 others (with a partially functioning and rejection-free intestinal graft). At a median follow-up of 52 months (range, 9–100 months), all other TMA-free patients (n = 6) were alive and rejection-free with functioning grafts under a relatively low intensity immunosuppressive protocol that has been used at our center.[7]

DISCUSSION

Thrombotic microangiopathy (TMA) is a well-recognized complication of solid-organ transplantation.[4,5] Although rejection, infection, and surgery itself may all contribute to the occurrence of transplant associated-TMA, most cases seem to be induced by the use of immunosuppressive medications, especially calcineurin inhibitors (CNI). These agents are the main cause of endothelial damage through direct and indirect mechanisms.[8] Besides CNI, TMA also has been described in patients treated with proliferation signal inhibitors (PSI) like sirolimus.[9] In contrast to classical TTP, most secondary TMA cases show normal or only slightly decreased ADAMTS13 levels without demonstrable auto-antibodies.[10]

Following intestinal transplantation, TMA has been rarely reported. So far, only 5 cases have been published. All cases received tacrolimus-based immunosuppressive therapy, including 2 patients who were also treated with sirolimus. In none of these cases was information on ADAMTS13 level reported.[11–13] We describe 3 patients with TMA following intestinal transplantation (2 isolated intestinal transplants and 1 multivisceral transplant). Consistent with previous reports of solid-organ transplantation-associated TMA, the TMA in our patients was probably related to CNI treatment, for it occurred within the first 6

Table 2. Baseline Characteristics of Patients Experiencing TMA

Patient	Age	Gender	Underlying Disorder	Type of Transplantation	Immunosuppressive Therapy	Time of Transplantation to TMA (d)
1	34	Female	Churg-Strauss vasculitis	Intestinal	Tacrolimus/steroids	55
2	41	Female	Thrombosis arteria mesenterica superior e causa ignota	Intestinal	Tacrolimus/azathioprine/steroids	167
3	43	Male	Antiphospholipid syndrome	Multivisceral	Tacrolimus/sirolimus/steroids	90

Table 3. Biochemical and Clinical Abnormalities at Diagnosis of Patients Experiencing TMA

Patient	Hemoglobin (g/dL)	Platelets ($\times 10^9$/L))	LDH (U/L)	Schistocytes (n/1000 RBC)	ADAMTS13 (%)	Renal Function	Neurological Symptoms
1	8.6	37	1420	12–15	>100	Normal	No
2	7.1	23	975	>20	40	Normal	No
3	7.5	89	5277	>30	60	Deteriorated	Yes

months following transplantation, was not associated with severe ADAMTS13 deficiency, and carried a poor prognosis.[4,5,14] Of note, the underlying vasculitis may have contributed in the first and third patient, as both Churg-Strauss vasculitis and antiphospholipid syndrome may be causes of secondary TMA.[15] Urgent treatment with therapeutic plasma exchange, consisting of plasmapheresis (to remove auto-antibodies) and substitution with plasma infusion (which is a source of new ADAMTS13), is standard therapy for classical ADAMTS13 deficiency TTP.[1,3] In secondary TMA, however, this treatment is considered less efficient owing to the lack of auto-antibodies and severe ADAMTS13 deficiency. In our patients, in addition to stopping or tapering tacrolimus, plasma therapy was a successful adjunctive therapy resulting in complete remission of the microangiopathy in all 3 patients. However, tapering of immunosuppressive therapy was accompanied by severe acute rejection, necessitating more profound immunosuppressive therapy and finally leading to graft loss (due to accelerated uncontrollable chronic rejection) in 1 patient and immunosuppression-related deaths (aspergillosis) in the other 2 patients.

In conclusion, we have described 3 intestinal transplant patients who were diagnosed with transplantation-related TMA. All patients received CNI-based therapy, which is a well-recognized risk factor. Despite excellent disease control, the final outcomes were dismal, with 1 patient experiencing graft loss due to graft rejection and 2 dying of opportunistic infections, which clearly contrasted with the outcome of our TMA-free patients, who were well with rejection-free and functioning grafts, at last follow-up.

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