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BRIEF REPORT

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Hemolytic uremic syndrome in small-bowel transplant recipients: the first two case reports

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Abstract Post-transplant hemolytic uremic syndrome (HUS) is an uncommon but well-described complication in solid organ transplant recipients. Believed to be secondary to immunosuppressive therapy, it has been reported after kidney, liver, pancreas, heart, and lung transplants. In all reported cases, the primary organ affected was the kidney (transplant or native). But until now, no cases after small-bowel transplants and no cases in which the kidney was not the primary organ affected have been reported. We report two cases of HUS in small-bowel transplant recipients. In our first case, clinical presentation was with renal failure; biopsy of the native kidney demonstrated the typical histological changes seen with HUS, namely occlusion of the microcirculation by thrombi and platelet aggregation. Immunosuppression was changed from tacrolimus to cyclosporin, but with no improvement in renal function. In our second case, the transplanted bowel was the primary organ affected. This recipient presented with ulcers in the bowel mucosa, which were believed to be ischemic in origin, secondary to occlusive vascular lesions affecting the small vessels in the transplanted bowel. Her tacrolimus dose was decreased with resolution of ulcers and no evidence of rejection. These two cases represent the first reports of HUS after small-bowel transplants; in addition, our second case represents the first report of an extrarenal graft as the primary organ affected. When caring for small-bowel transplant recipients, physicians must be alert to the possibility of HUS and its various presentations.

Key words Thrombotic microangiopathy – Hemolytic uremic syndrome – Small-bowel transplantation

Introduction

Post-transplant hemolytic uremic syndrome (HUS) has been described as a complication of cyclosporin or tacrolimus therapy. The exact mechanism is unclear, but a link has been suggested to defective vascular prostacyclin synthesis [4, 14]. HUS is characterized clinically by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure [11]. It may occur after a kidney or kidney–pancreas transplant, in which case the transplanted kidney demonstrates the typical histological features [2, 15, 18]. Numerous cases have also been reported after extrarenal transplants, including liver [9], lung [1], and heart [6]; in these cases, the typical histological changes of thrombotic microangiopathy were demonstrated in the kidney. Until now, HUS has not been reported in small-bowel transplant recipients. This report describes two small-bowel transplant recipients who developed HUS and outlines their clinical presentation, pathology, treatment, and clinical course.

Case reports

Patient no. 1

A 34-year-old male with a longstanding history of Crohn's disease and numerous small-bowel resections underwent a cadaver small-bowel transplant. Indications were short-gut syndrome with chronic total parenteral nutrition (TPN) dependence and numerous episodes of central line sepsis. Postoperative immunosuppression consisted of tacrolimus, mycophenolate mofetil (MMF), prednisone, and OKT3 induction therapy. His initial course was complicated by an anastomotic leak on postoperative day 7, which was successfully repaired.

The patient developed severe acute rejection of the bowel graft, as demonstrated by an endoscopic biopsy performed at 1 month post-transplant. He was treated with a 7-day course of OKT3, with good response, and discharged home at 6 weeks post-transplant. Unfortunately, he was readmitted 2 weeks later with acute renal failure [blood urea nitrogen (BUN), 140 mg/dl; serum creatinine, 4 0 mg/dl]. He had thrombocytopenia (platelets 36,000 × 109/l) and anemia (hemoglobin 7.4 g/dl), with evidence of hemolysis on a peripheral smear including the presence of schistocytes. The serum lactate dehydrogenase (LDH) was markedly elevated at 1920 U/l (normal range 325–750 U/l). Hemodialysis was instituted and a kidney biopsy was performed, which demonstrated typical lesions of thrombotic microangiopathy (Fig. 1). While these occlusive vascular lesions may be seen with conditions such as scleroderma or accelerated hypertension, the biopsy findings combined with the clinical features were most consistent with a diagnosis of HUS secondary to tacrolimus therapy. The patient was switched to cyclosporin A (CSA), and plasmapheresis was initiated in an effort to salvage the kidney. But after 3 weeks, he was still hemodialysis dependent. At that time, CSA was discontinued and rapamycin was obtained on an emergency basis. Immunosuppression was then maintained with rapamycin, MMF, and prednisone. He continued on this regimen for more than 3 weeks with no evidence of acute rejection (according to weekly endoscopic bowel biopsies) and no significant side effects such as bone-marrow suppression. Despite the discontinuation altogether of CSA, his renal failure persisted. While his overall condition was good, he became very depressed about being hemodialysis dependent. He died 2 months after the onset of renal failure, secondary to a self-inflicted injury. Autopsy studies demonstrated a systemic granulomatous vasculitis with giant cells containing polarizable material consistent with talc, most likely from intravenous injection of tablets intended for oral administration. Microangiopathic (non-granulomatous) lesions were present in the kidney.

Patient no. 2

A 6-year-old girl with short-bowel syndrome and TPN-induced cirrhosis underwent a combined cadaver liver-bowel transplant. Born with gastroschisis, she had lost 80% of her bowel shortly after birth, leaving her TPN dependent since shortly after birth. Postoperative immunosuppression consisted of tacrolimus, prednisone, and OKT3 induction therapy. At 2 weeks post-transplant, she experienced acute rejection, which was treated by a 7-day course of OKT3 and an increase in her steroid dose. At 4 weeks post-transplant, she had anemia, thrombocytopenia, a blood smear demonstrating schistocytes, and renal dysfunction, which raised the possibility of HUS. Her platelet count had decreased to 26 × 109/l, associated with a rise in the serum LDH level to 4990 U/l. Renal dysfunction was manifested by a rise in the serum BUN to 90 mg/dl

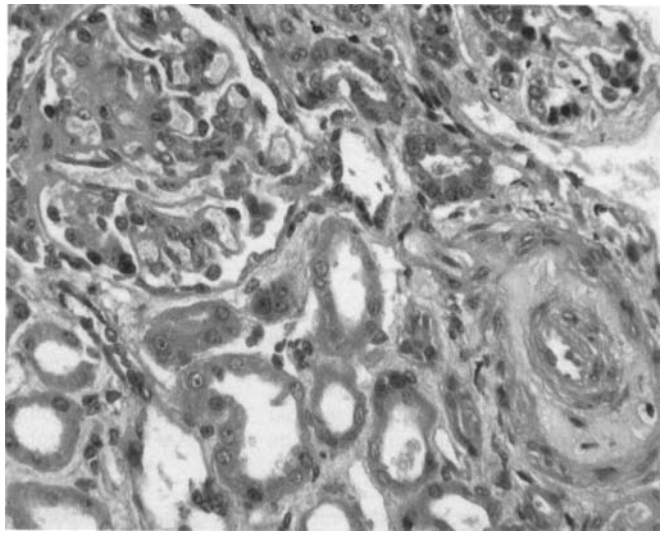

Fig. 1 Renal biopsy from patient no. 1 showing an acute occlusive vasculopathy with intimal edema. The adjacent glomerulus contains numerous intracapillary fibrin thrombi (hematoxylin and eosin stain; original magnification × 200)

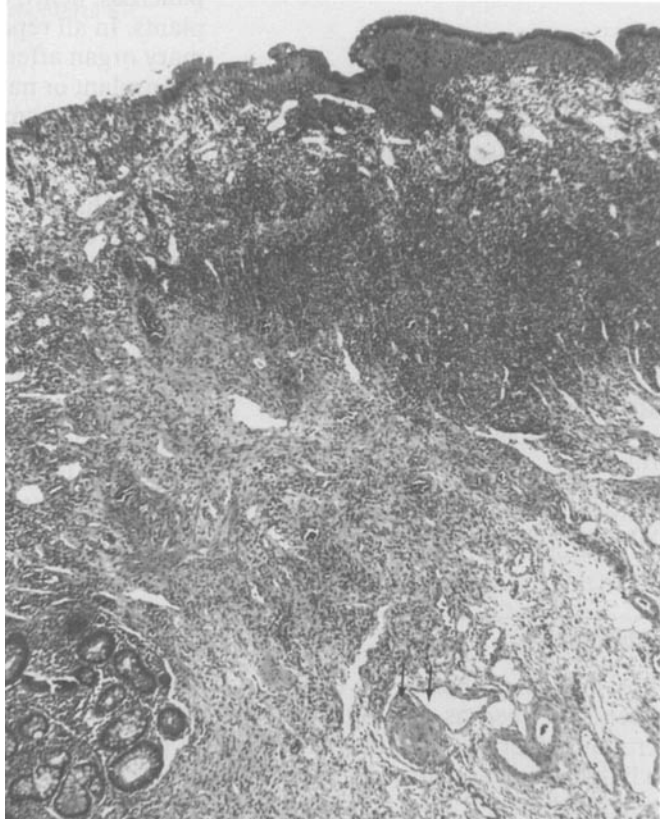

Fig. 2 Small-bowel transplant resection specimen from patient no. 2. Multifocal ischemic mucosal lesions were present. An obliterated vessel is apparent in the submucosa (*arrows*) (hematoxylin and eosin stain; original magnification × 75)

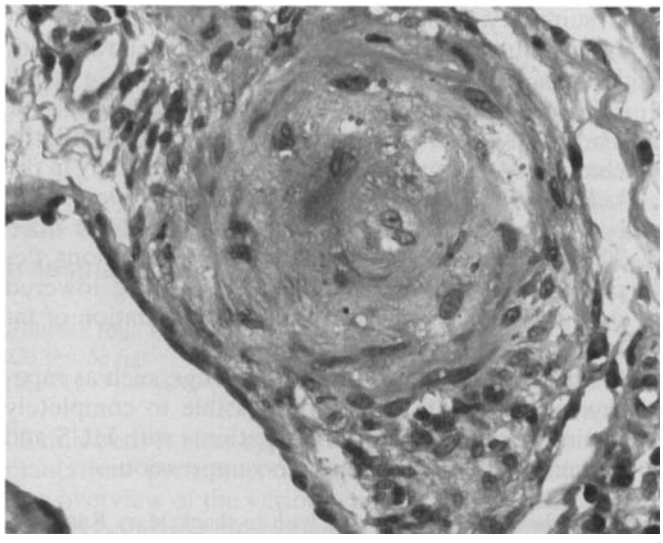

Fig. 3 High magnification of the submucosal vessel showing total luminal occlusion (hematoxylin and eosin stain; original magnification × 400)

and a doubling of the serum creatinine to 0.9 mg/dl. An endoscopic bowel biopsy demonstrated an ulcer, regenerating intestinal mucosa, and occlusive arteriolar lesions. The lesions were similar to those that develop in renal arteries in cases of HUS, consisting of endothelial damage, "mucoid" intimal edema, and fibrin deposition (Fig. 2). She later developed bowel perforation at the biopsy site and underwent a segmental resection of the graft. Pathologic examination confirmed the presence of the characteristic occlusive vascular lesions of HUS and the absence of rejection (Fig. 3).

The patient's tacrolimus dose was lowered (target level 7–10 ng/ml), which resulted in gradual resolution of the thrombocytopenia and anemia, improvement of renal function, and healing of the intestinal ulcers. She did not require either dialysis or plasmapheresis. At 1 year post-transplant, she continues to do well, with normal renal function (BUN, 12 mg/dl; serum creatinine, 0.3 mg/dl) and hematology lab values. Her maintenance immunosuppressive regimen consists of prednisone and low-dose tacrolimus; MMF was recently added because of a mild acute rejection episode.

Discussion

HUS occurs in 0.5–3 % of solid organ transplant recipients [2, 3]. More than 90 % of reported cases have been in kidney transplant recipients, primarily affecting the graft. In all reported cases of HUS in liver, heart, and lung transplant recipients, the native kidneys were affected.

A number of factors may lead to HUS. In transplant recipients, immunosuppressive drugs such as cyclosporin and tacrolimus are believed to be responsible. Pathogenesis involves reduced prostacyclin (PGI_2) levels resulting from the drugs' inhibition of prostacyclin-stimulating factor [10]. These reduced PGI_2 levels lead to vascular endothelial damage, platelet aggregation, and thrombi formation in the microcirculation [11]. Histological changes of HUS characteristically affect the kidney. The basic lesion is thrombotic microangiopathy, with occlusion of smaller cortical vessels followed by glomerular ischemia and cortical infarction. Thus, the main clinical manifestation of HUS is renal dysfunction or failure. Other clinical features include fever and lethargy. Characteristic laboratory abnormalities include anemia with evidence of hemolysis, increased serum LDH levels, decreased serum haptoglobin, and thrombocytopenia. The vascular lesions characteristically affect the kidneys, either native or transplanted. To our knowledge, extrarenal grafts have not been reported to demonstrate the characteristic lesions of HUS in the microcirculation. Microthrombi have, however, been described in the brain, manifesting clinically as neurologic dysfunction – this is generally referred to as thrombotic thrombocytopenic purpura (TTP).

Our two cases are both unique. In our first case, HUS developed after a small-bowel transplant. It manifested as acute and persistent renal failure. The characteristic lesions of thrombotic microangiopathy were demonstrated on the kidney biopsy. In our second case, HUS developed after a combined liver-bowel transplant, again secondary to tacrolimus therapy. It manifested as renal dysfunction (though dialysis was not required), anemia, and thrombocytopenia. The small-bowel graft was directly involved: mucosal biopsies demonstrated the characteristic occlusive lesions of HUS. These lesions likely contributed to the development of ischemic mucosal ulcers and eventual small-bowel perforation. Thus, our second case represents the first report in the literature of an extrarenal graft demonstrating the histological changes of microangiopathy.

The optimal management of HUS is not known. A variety of therapies have been tried, ranging from observation to plasmapheresis. Spontaneous resolution without any specific therapy has been reported in kidney transplant recipients [2], but it is uncommon. Initially, the responsible immunosuppressive drug should be discontinued or reduced [7]. Complete discontinuation may not be possible, especially given the risk of graft loss. Newer drugs such as rapamycin may allow such drugs as CSA and tacrolimus to be discontinued (at least temporarily) without significant detriment, as demonstrated by our first case.

Liver, kidney, and kidney–pancreas transplant recipients with HUS have switched from CSA to tacrolimus with success [7, 8, 12]. In our second case, lowering of the tacrolimus dose to achieve low therapeutic levels was associated with clinical improvement, as manifested by healing of intestinal ulcers, resolution of anemia and thrombocytopenia, and improvement in renal function.

Plasmapheresis has been effective in nontransplant recipients with HUS [13] and has been used successfully in transplant recipients [5, 17]. However, in a literature review, the overall incidence of kidney graft loss in kidney transplant recipients with HUS was no different with or without plasmapheresis [16]; the authors of that review, however, cautioned that the two groups were not matched with respect to disease severity, so those undergoing plasmapheresis may have been more severely affected.

Of our two cases, the first patient had a more severe form of HUS. He had progressed to complete renal failure requiring dialysis. The second patient had renal dysfunction, but had not progressed to renal failure requiring dialysis and responded well to a lowered tacrolimus dose. The first patient underwent plasmapheresis, then switched from tacrolimus to CSA. This was then discontinued, after which the combination of rapamycin, MMF, and prednisone provided adequate immunosuppression (with no episodes of acute rejection). Despite all of this, his renal failure did not improve.

In summary, these two unique cases demonstrate several important aspects of HUS in small-bowel transplant recipients:

1. HUS may be seen in bowel transplant recipients.
2. The small-bowel graft itself may be involved with the characteristic small-vessel lesions (seen usually in the kidney), which can lead to local ischemia, ulcers, and bowel perforation.
3. The treatment of HUS remains unclear. Options, depending on the severity of HUS, include lowered doses of the responsible drug, discontinuation of tacrolimus or CSA, and plasmapheresis.
4. With newer immunosuppressive drugs, such as rapamycin and MMF, it may be possible to completely avoid tacrolimus and CSA in patients with HUS and yet maintain adequate immunosuppression.

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