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Tacrolimus-associated hemolytic uremic syndrome in a pediatric heart transplant recipient

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Abstract: HUS is a well-known entity primarily associated with bacterial infection and is characterized by a classic triad of anemia, thrombocytopenia, and kidney injury. Its atypical form has been associated with calcineurin inhibitors and has been extensively discussed in renal transplantation. We present a case of tacrolimus-associated HUS in a pediatric heart transplant recipient, which we believe to be previously unreported in the literature.

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Key words: heart transplantation – hemolytic uremic syndrome – calcineurin inhibitors – pediatrics

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HUS has been associated with the use of calcineurin inhibitors, particularly tacrolimus. Renal transplant recipients appear to be particularly susceptible to tacrolimus-associated HUS; however, it has been reported in adult heart transplant recipients as well (1–5). To the extent of our knowledge, it has not been previously reported in a pediatric heart transplant patient.

Case

A five-yr-old female with isolated truncus arteriosus repaired in infancy who subsequently developed complete heart block and dilated cardiomyopathy received an orthotopic heart transplant at the age of six months. She was maintained successfully on cyclosporine and mycophenolate for five yr, but developed cyclosporine-related side effects, including hirsutism and hypertension. While on cyclosporine, her renal function, hemoglobin, and platelet count were normal. Due to her new side effects, the calcineurin inhibitor was changed to tacrolimus. She was initially started on 0.5 mg twice daily, but this was increased one wk later to 1 mg twice daily in order to meet her goal tacrolimus level of 5–10 μg/L. The new dose was then tolerated without adjustment, with her levels remaining in the range of 6–8 μg/L.

However, she presented three months later with severe periumbilical abdominal pain, cramping, and bloody stool. On admission, her mycophenolate was stopped with concern for mycophenolate-induced colitis, but her tacrolimus was continued. Infectious causes were also investigated, and a stool culture for SSCE, and Shiga toxin 1 and 2 was negative, as was a *Clostridium difficile* toxin PCR. Her hemoglobin was 14.4 mg/dL (normal 10.5–14.0 mg/dL), and she had a normal urinalysis, prothrombin time, partial thromboplastin time, and liver function tests. Her stool was hemoccult positive. An esophagogastroduodenoscopy was unremarkable; however, a colonoscopy showed edema with patches of erythema and multiple petechiae throughout the colon. A colon biopsy specimen contained a single blood vessel with a microthrombus.

On the third day of admission, the patient developed anemia (hemoglobin 5.6 mg/dL) and thrombocytopenia (platelet count 30 000/L, normal 150 000–450 000/L) along with an increased blood urea nitrogen (39 mg/dL, normal 9–22 mg/dL) and creatinine (0.92 mg/dL, normal

Abbreviations: HUS, hemolytic uremic syndrome; SSCE, *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*; TTP, thrombotic thrombocytopenic purpura.

0.15–0.53 mg/dL). A peripheral blood smear showed schistocytes and a direct antibody test was negative, suggestive of a microangiopathic hemolytic anemia, such as HUS, TTP, or disseminated intravascular coagulation. Her urinalysis was notable for the presence of blood and protein. A repeat stool SSCE was negative. She had no neurological symptoms and ADAMTS13 activity was normal, making TTP unlikely. Given her continued acute kidney injury, anemia and thrombocytopenia, recent initiation of tacrolimus therapy, and no evidence of infection with Shiga toxin-producing *E. coli*, a diagnosis of tacrolimus-associated atypical HUS was made.

Tacrolimus was discontinued and the patient was transitioned to sirolimus at a dose of 1 mg daily, with a goal level of 4–6 μg/L, along with resumption of her mycophenolate. Her thrombocytopenia and acute kidney injury resolved over the next week, and she was discharged from the hospital. Her hemoglobin returned to normal approximately two wk after discharge. Further follow-up has shown excellent tolerance of sirolimus without need for further dose adjustment.

Discussion

HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury. In its typical form, it is most commonly associated with Shiga toxin-producing *E. coli*, especially in children (6). However, atypical HUS can be associated with a variety of drugs, including interferon, chemotherapeutic agents, sirolimus, and calcineurin inhibitors (1, 7).

The use of tacrolimus in pediatric orthotopic heart transplant is widespread (2). It has been shown to be associated with atypical HUS (7), including in adult heart transplant recipients (3–5), although to our knowledge there have been no cases reported in pediatric heart transplant. The mechanism of tacrolimus-associated HUS is not well understood, and it appears to be most common in association with renal transplant (1, 7), where allograft biopsy has indicated microthrombi formation (8). The cause of renal microthrombus formation is unclear, but it has been postulated that tacrolimus may affect the coagulation cascade via disturbance of the balance between thromboxane A2 and prostaglandin PGI_2 (8). It may also induce endothelial injury and subsequent dysfunction via release of von Willebrand multimers and platelet-aggregating factor (9). Interestingly, in this case, a colonic biopsy showed a single microthrombus in a colonic vessel as well, suggesting that thrombus formation is not isolated solely to the kidney. Nephrotoxicity related to prolonged calcineurin use may also contribute to HUS via interstitial injury and fibrosis which may explain the cases of later-onset HUS (8, 9). Notably, while withdrawal of the offending agent and commencement of replacement immunosuppression is essential, sirolimus has also been associated with HUS (1, 10). In conclusion, while not a common complication, this first report in pediatric heart transplant should serve as a reminder that tacrolimus-associated HUS is an important consideration in patients with anemia, thrombocytopenia, and kidney injury receiving tacrolimus.

Authors' contributions

James M. Gray and Rebecca K. Ameduri: Contributed to the concept, design, literature review, drafting, and final revision of the article.

References

1. Al-Nouri Z, Reese J, Terrell D, Vesely S, George J. Drug-induced thrombotic microangiopathy: A systematic review of published reports. Blood 2015: 125: 616–618.
2. Dipchand AI, Kirk R, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth official pediatric heart transplantation report. J Heart Lung Transplant 2013: 32: 979–988.
3. Walder B, Ricou B, Suter PM. Tacrolimus (FK 506)-induced hemolytic uremic syndrome after heart transplantation. J Heart Lung Transplant 1998: 17: 1004–1006.
4. Mach-Pascual S, Samii K, Beris P. Microangiopathic hemolytic anemia complicating FK506 (tacrolimus) therapy. Am J Hematol 1996: 52: 310–312.
5. Vardas PN, Hashmi ZA, Hadi MA. Identification and management of atypical hemolytic uremic syndrome immediately post-heart transplantation. J Card Surg 2015: 30: 373–375.
6. Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol 2005: 16: 1035–1050.
7. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009: 361: 1676–1687.
8. Randhawa PS, Starzl TE, Demetris A. Tacrolimus (FK506)-associated renal pathology. Adv Anat Pathol 1997: 4: 265–276.
9. Lin C-C, King K-L, Chao Y-W, et al. Tacrolimus-associated hemolytic uremic syndrome: A case analysis. J Nephrol 2003: 16: 580–585.
10. Lobach N, Pollock-Barziv S, West L, Dipchand A. Sirolimus immunosuppression in pediatric heart transplant recipients: A single-center experience. J Heart Lung Transplant 2005: 24: 184–189.