Case Report
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Cytomegalovirus-Associated Hemophagocytic Syndrome Diagnosed by Liver Biopsy in a Kidney Transplant Recipient

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Hemophagocytic syndrome (HPS) is a rare but potentially life-threatening disease in kidney transplant recipients, and is caused by systemic proliferation of macrophages actively phagocytizing other blood cells in the bone marrow, lymph nodes, and the spleen. Here, we report a 40-year-old male kidney transplant recipient who presented with fever, bicytopenia, and elevated liver enzymes 2 months after transplantation. Given that cytomegalovirus antigenemia and real-time polymerase chain reaction tests were positive, liver biopsy was performed under an assumption of cytomegalovirus-induced hepatitis. Hepatic histology revealed multifocal microabscess with cytomegalovirus inclusion bodies, marked Kupffer cell hyperplasia, and erythrophagocytosis by activated macrophages. As laboratory findings such as hyperferritinemia, elevated serum lactate dehydrogenase, low natural killer cell activity, and high soluble interleukin-2 receptor were also compatible with HPS, the recipient was diagnosed as having cytomegalovirus-induced hepatitis combined with reactive HPS. Following intravenous ganciclovir therapy with continuous administration of tacrolimus and corticosteroid, the symptoms resolved and laboratory findings were normalized. As far as we know, this is the first report of cytomegalovirus-induced hepatitis combined with reactive HPS in a kidney transplant recipient that is diagnosed by liver biopsy.

Key Words: Cytomegalovirus, hemophagocytic syndrome, kidney transplantation

INTRODUCTION

Hemophagocytic syndrome (HPS) is a clinicopathologic entity characterized by systemic proliferation of macrophages actively phagocytizing other blood cells in the bone marrow, lymph nodes, and the spleen.[1,2] HPS is caused by impaired function of natural killer and cytotoxic T-cells leading to activation of macrophages.[3] Overproduction of cytokines, including tumor necrosis factor alpha and interferon gamma, are also implicated in the pathogenesis of HPS that some of the symptoms are related to the cytokine overproduction.[2,4] The most common clinical features of HPS include fever, hepatosplenomegaly, and cytopenia.[5] HPS may develop in the context of genetic predisposition, infection, malignancy, and autoimmune disease.[6] Most of all, viral infection, especially herpes virus infection, is the most frequent trigger of HPS both in healthy people and immunosuppressed patients.[3]

Cytomegalovirus infection is the single most frequent cause of infectious morbidity and mortality in kidney transplant recipients.[7,8] However, cytomegalovirus-associated HPS has rarely been described in kidney transplant recipients since the first report of reactive HPS in kidney transplant recipient by Risdall, et al.[9-16] In this rare disease, hepatic dysfunction is often present, but liver biopsy has not been performed on the suspicion of HPS. Here, we report a rare case of cytomegalovirus-induced hepatitis combined with reactive HPS in a kidney transplant recipient that was confirmed by hepatic histology.

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CASE REPORT

A 40-year-old male received deceased donor kidney transplantation 8 years after starting hemodialysis due to IgA nephropathy. The immunosuppression regimen consisted of tacrolimus, corticosteroid, and mycophenolate mofetil (MMF) with induction therapy of basiliximab. Both donor and recipient were positive for IgG and negative for IgM of cytomegalovirus. The patient had an uneventful postoperative course with stable allograft function, and he was discharged on postoperative day 8. The prophylaxis for cytomegalovirus was not performed in the patient. Two months after transplantation, the patient was re-admitted for fever, epigastric discomfort, and mild weight loss. Physical examination was unremarkable with no evidence of hepatosplenomegaly or lymphadenopathy. The graft function remained stable with a serum creatinine of 1.04 mg/dL. Laboratory findings showed bicytopenia and mild liver enzymes elevation, but no other specific findings were observed.

At initial assessment, MMF-induced bone marrow suppression was suspected. With discontinuation of MMF and administration of granulocyte colony stimulating factor, absolute neutrophil count increased, but low grade fever persisted with continuous elevation of liver enzymes (Table 1). In addition to elevation of liver enzymes, the patient started to develop dyspnea, and computed tomography scan for lung showed bilateral lower lung ground glass opacity (Fig. 1). With an assumption of viral disease, several serological viral tests were performed. Serological studies for Epstein-Barr virus, BK virus, hepatitis A, B, and C, and human immunodeficiency virus were all negative, but active cytomegalovirus infection was confirmed by cytomegalovirus antigenemia and real-time polymerase chain reaction (a viral load of 216879 copies) tests. Under an assumption of cytomegalovirus-induced hepatitis, the patient underwent ultrasound-guided percutaneous gun biopsy of the liver. The liver biopsy showed multifocal microabscess including cytomegalovirus inclusion bodies, marked kupffer cell hyperplasia, and erythrophagocytosis by activated macrophages (Fig. 2), and the patient was diagnosed as having cytomegalovirus-induced hepatitis combined with reactive HPS. Additional tests showed hyperferritinemia, low natural killer cell activity, elevated serum lactate dehydrogenase, and high soluble interleukin-2 receptor, supporting our diagnosis of the patient.

On day 5 of admission, intravenous ganciclovir was started with continuous administration of tacrolimus and corticosteroid. In order to prevent additional bacterial infection and pneumonia aggravation, 4th generation cephalosporin was also started. On day 14 of admission, the patient's complete blood cell count and liver enzyme levels were nearly normalized, and serum ferritin declined to 656.0 μg/L. Two weeks after starting intravenous ganciclovir, the viral load of cytomegalovirus fell to 2617 copies, reaching below 150 copies by the time of discharge. As his symptoms were resolved and general condition improved, the recipient was discharged on day 26 after

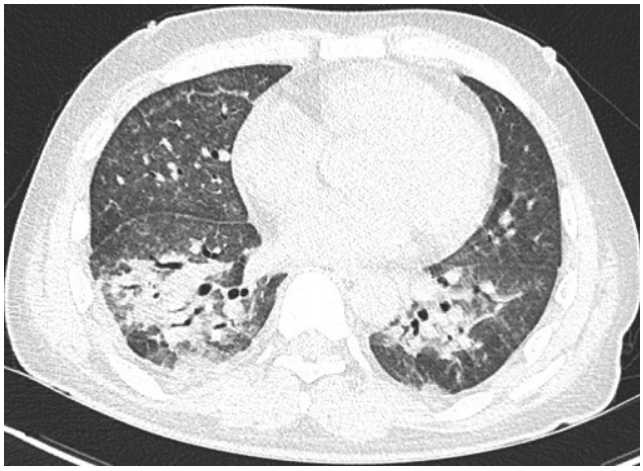

Fig. 1. Computed tomography showing multiple ill-defined tiny nodules, ground glass opacity, peribronchiolar consolidation, and interlobular septal thickening in both lungs.

Table 1. Changes in Laboratory Findings in the Patient

	Normal range	On admission	After 4 days	After 14 days
White blood cell count (/μL)	4000–11000	1800	6600	4700
Absolute neutrophil count (/μL)	-	698.4	5940.0	1936.4
Hemoglobin (g/dL)	12.5–17.5	11.4	12.3	9.3
Platelet count ($\times 10^4$/μL)	13.4–38.7	6.5	7.4	17.3
Creatinine (mg/dL)	0.70–1.20	1.04	0.95	0.81
Alanine aminotransferase (U/L)	5–41	173	422	49
Aspartate aminotransferase (U/L)	5–40	190	560	42
Triglyceride (mg/dL)	37–200	N/A	190	125
Fibrinogen (mg/dL)	182–380	N/A	178	239
Lactate dehydrogenase (U/L)	100–200	N/A	647	N/A
Ferritin (μg/L)	30.0–400.0	N/A	6825.0	656.0
Natural killer cell activity (pg/mL)	251–6000	N/A	91	N/A
Soluble interleukin-2 receptor (U/mL)	158–623	N/A	2528	N/A

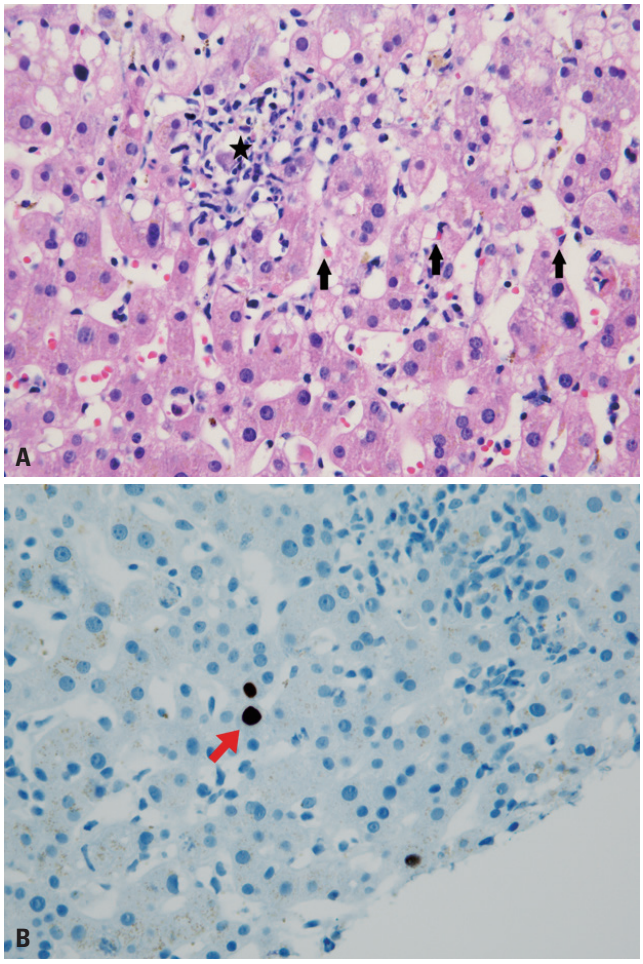

Fig. 2. Pathology results of liver biopsy. (A) Hematoxylin and eosin staininig showing multifocal microabscess, including cytomegalovirus inclusion bodies (star), and marked Kupffer cell hyperplasia with erythrophagocytosis (arrows) (×200). (B) Immunohistochemistry staining showing strong focal cytomegalovirus immunoreactivity with brownish areas (arrow) (×400).

hospitalization. The patient was given oral valganciclovir (900 mg once daily) for an additional 3 months, and MMF was restarted 4 weeks after the discharge. As a screening exam for reactivation, cytomegalovirus antigenemia test was performed every 2 weeks for 3 months, and no reactivation occurred during the follow-up period. Informed consent was obtained from the patient regarding the publication of this case report.

DISCUSSION

HPS is a rare but potentially life-threatening disease in kidney transplant recipients, and it requires early diagnosis and initiation of treatment to improve clinical outcomes. However, its nonspecific clinical presentation makes the diagnosis challenging. In the present case, the patient presented with fever, epigastric discomfort, and mild weight loss. MMF-induced bone marrow suppression was initially suspected, but continuous increase of liver enzymes and positive cytomegalovirus serologic tests led us to perform liver biopsy under an assumption of cytomegalovirus-induced hepatitis. However, contrary to our expectation, the hepatic histology revealed marked Kupffer cell hyperplasia and erythrophagocytosis by activated macrophages, suggesting reactive HPS combined with cytomegalovirus-induced hepatitis. Subsequently, we conducted additional laboratory exams and were able to diagnosis HPS, as elevated serum ferritin, high soluble interleukin-2 receptor, and low natural killer cell activity were also compatible with HPS.

In kidney transplant recipients with HPS, liver dysfunction is often present, but liver biopsy has not been performed on the suspicion of HPS, since bone marrow analysis has been known to be the most sensitive diagnostic test for HPS.[4] In the present case, however, a liver biopsy was performed instead of a bone marrow biopsy, as the patient's main problem was a continuous elevation of liver enzymes and HPS was not suspected at the time of performing liver biopsy. After the diagnosis of HPS, anti-viral agent was started and the patient's condition improved. Therefore, an additional bone marrow biopsy was not required to confirm HPS. To the best of our knowledge, this is the first report of cytomegalovirus-associated HPS that is diagnosed by liver biopsy in a kidney transplant recipient.

Since the spectrum of pathogens responsible for HPS is extremely broad, choosing the most adequate antiviral and antibacterial therapy is crucial. However, what to do with the immunosuppressive regimen still remains an unresolved issue.[1] Immunosuppressive therapy may help in reducing the activation of macrophages and their cytokine production. On the other hand, the reduction or withdrawal of immunosuppressive therapy is needed to improve resistance to infection in kidney transplant recipients. According to Karras, et al.,[4] who reported the largest series of HPS in kidney transplant recipients, majority of the patients experienced a life-threatening conditions including septic shock, acute respiratory distress syndrome, neurologic disorders, or cardiac failure. In these patients, immunosuppressive agents were tapered, with steroid monotherapy in some patients. In the present case, the patient managed to recover without the discontinuation of tacrolimus and corticosteroid. This suggests that, if the patient's disease severity is not severe, the administration of antiviral therapy with minimal withdrawal of immunosuppressive agent during treatment period would be sufficient to treat the cytomegalovirus-associated HPS in a kidney transplant patient.

Herein, we report a rare case of cytomegalovirus-induced hepatitis combined with reactive HPS that was confirmed by hepatic histology in a kidney transplant recipient. When a kidney transplant recipient presents with fever, cytopenia, and elevated liver enzymes, and positive cytomegalovirus serologic tests are confirmed, cytomegalovirus-associated HPS must be always suspected and liver biopsy may be considered for the early diagnosis and successful treatment of HPS.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: Eun Ji Choi, Jun Bae Bang, and Young Bae Kim. Formal analysis: Eun Ji Choi and Jun Bae Bang. Investigation: Eun Ji Choi and Jun Bae Bang. Methodology: Eun Ji Choi and Jun Bae Bang. Project administration: Chang-Kwon Oh and Su Hyung Lee. Resources: Eun Ji Choi and Jun Bae Bang. Software: Eun Ji Choi and Jun Bae Bang. Supervision: Chang-Kwon Oh and Su Hyung Lee. Validation: Eun Ji Choi and Jun Bae Bang. Visualization: Eun Ji Choi and Jun Bae Bang. Writing—original draft: Eun Ji Choi. Writing—review & editing: Jun Bae Bang. Approval of final manuscript: all authors.

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REFERENCES

1. Ponticelli C, Alberighi OD. Haemophagocytic syndrome--a life-threatening complication of renal transplantation. Nephrol Dial Transplant 2009;24:2623-7.
2. Ardalan MR, Shoja MM, Tubbs RS, Esmaili H, Keyvani H. Postrenal transplant hemophagocytic lymphohistiocytosis and thrombotic microangiopathy associated with parvovirus b19 infection. Am J Transplant 2008;8:1340-4.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014; 383:1503-16.
4. Karras A, Thervet E, Legendre C; Groupe Coopératif de transplantation d'Ile de France. Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. Transplantation 2004;77:238-43.
5. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007; 48:124-31.
6. Nusshag C, Morath C, Zeier M, Weigand MA, Merle U, Brenner T. Hemophagocytic lymphohistiocytosis in an adult kidney transplant recipient successfully treated by plasmapheresis: a case report and review of the literature. Medicine (Baltimore) 2017;96: e9283.
7. Sagedal S, Nordal KP, Hartmann A, Degré M, Holter E, Foss A, et al. A prospective study of the natural course of cytomegalovirus infection and disease in renal allograft recipients. Transplantation 2000;70:1166-74.
8. Anand S, Yabu JM, Melcher ML, Kambham N, Laszik Z, Tan JC. Cytomegalovirus in the transplanted kidney: a report of two cases and review of prophylaxis. NDT Plus 2011;4:342-5.
9. Yang D, Thamcharoen N, Marcus C, Varkaris A, Aird W, Khankin EV, et al. Unusual presentation of hemophagocytic lymphohistiocytosis in a kidney transplant patient. Case Rep Transplant 2019; 2019:3682378.
10. Rostaing L, Fillola G, Baron E, Cisterne JM, Durand D. Course of hemophagocytic histiocytic syndrome in renal transplant patients. Transplantation 1995;60:506-9.
11. Romiopoulos I, Pyrpasopoulou A, Onoufriadis I, Massa E, Mouloudi E, Kydona C, et al. Fulminant Epstein-Barr virus-associated hemophagocytic syndrome in a renal transplant patient and review of the literature. Transpl Infect Dis 2016;18:795-800.
12. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979;44:993-1002.
13. Lima VACC, Gouvêa ALF, Menezes P, Santos JDF, Rochael MC, Carvalho FR, et al. Hemophagocytic lymphohistiocytosis, a rare condition in renal transplant-a case report. J Bras Nefrol 2018;40:423-7.
14. Gurkan A, Yakupoglu U, Yavuz A, Dikici H, Yakupoglu YK, Tuncer M, et al. Hemophagocytic syndrome in kidney transplant recipients: report of four cases from a single center. Acta Haematol 2006; 116:108-13.
15. Asci G, Toz H, Ozkahya M, Cagirgan S, Duman S, Sezis M, et al. High-dose immunoglobulin therapy in renal transplant recipients with hemophagocytic histiocytic syndrome. J Nephrol 2006;19: 322-6.
16. Alotaibi T, Adel M, Gheith O, Abo-Atya H, Halim MA, Nair P, et al. Successful management of late-onset cytomegalovirus-induced hemophagocytic lymphohistiocytosis in kidney transplant recipient after coronary artery bypass graft surgery. Exp Clin Transplant 2019;17(Suppl 1):207-11.