CEN Case Reports (2019) 8:252–255
https://doi.org/10.1007/s13730-019-00402-7

CASE REPORT

Hemophagocytic syndrome with acute kidney injury accompanied by erythrophagocytic macrophages in the tubular lumen

Hiroyuki Hashimoto[1] · Takeshi Sugiura[1] · Hideki Matsushima[1]

Received: 5 February 2019 / Accepted: 14 May 2019 / Published online: 4 June 2019

Abstract
Hemophagocytic syndrome (HPS) is a life-threatening syndrome involving excessive immune activation. It is often accompanied by renal involvement known as acute kidney injury (AKI), which is a poor prognostic factor of HPS. Thus, early diagnosis and treatment are very important. However, it is rarely identified in renal biopsy specimens, and its major manifestation is acute tubular necrosis. We report a rare case of erythrophagocytic macrophage presence in the tubular lumen of a patient with HPS-associated AKI. A kidney biopsy showed acute tubular necrosis, interstitial massive macrophage infiltration, and phagocytic macrophage casts without glomerular change. Some arteriolar vascular smooth muscle cells showed vacuolization because they were positive for α-smooth muscle actin. The patient's renal function improved after methylprednisolone pulse therapy followed by oral prednisolone after a month. Our case presents a new pathologic pattern of HPS. Careful urinalysis could suggest renal involvement with HPS. Having knowledge of this pathologic pattern of HPS is important to recognize the disease and to treat it appropriately.

Keywords Histiocytic glomerulopathy · Hemophagocytosis · Hemophagocytic syndrome · Macrophage activation syndrome · Acute kidney injury · Acute tubular necrosis · Acute tubular injury · Kidney biopsy

Introduction

Hemophagocytic syndrome (HPS) is a life-threatening syndrome involving excessive immune activation. It is often accompanied by renal involvement known as acute kidney injury (AKI) [1]. The prognosis of HPS with AKI is poor [2]. Thus, early diagnosis and treatment are very important. HPS is rarely identified in renal biopsy specimens, and major manifestation includes acute tubular necrosis [3]. A previous study investigated the histologic patterns of HPS in nine children [3], which were found to include ischemic/necrotic changes (44%), interstitial nephritis (33%), lymphohistiocytic infiltration (22%), and erythrophagocytosis (11%). Cases of HPS with glomerulopathy are rare. Until now, a report by Santoriello et al. has described a case of HPS with histiocytic glomerulopathy and intraglomerular hemophagocytosis [4]. Furthermore, erythrophagocytic macrophages were observed in the urinary sediments in that case. In addition, there is only one case report of the presence of urinary phagocytic macrophages in HPS [5]. In that case report, renal biopsy revealed macrophage infiltration around the tubules and macrophage casts with typical features of acute postinfection glomerulonephritis. In our study, we report a rare case of erythrophagocytic macrophage presence in the tubular lumen of a patient with HPS-associated AKI, which was successfully treated.

Case report

A 38-year-old woman was referred to our department because of rapid deterioration of renal function. She had a medical history of mixed connective tissue disease (MCTD) and HPS 4 years prior. She was taking antibiotics for the treatment of pneumococcal pneumonia 2 weeks before presentation at our department. Although her fever and laboratory data improved upon antibiotic administration, her fever and fatigue subsequently recurred. Her blood pressure was 118/70 mmHg and body temperature was 39.7 °C. She had systemic edema, with an 11-kg increase in body weight

✉ Hiroyuki Hashimoto
naruhodo.hasshi777@gmail.com

[1] Department of Nephrology, Seirei Mikatahara General Hospital, 3454, Mikatahara, Kita-ku, Hamamatsu, Shizuoka 433-8558, Japan

(87.6 kg) and peripheral lymphadenopathy. Investigations (Table 1) revealed anemia (hemoglobin, 7.9 g/dL), thrombocytopenia (platelet count, 5.6×10^4/μL), leukopenia (white blood cell (WBC) 1080/μL), and AKI with a serum creatinine (Scr) level of 4.1 mg/dL. Her C-reactive protein was 23.7 mg/dL, erythrocyte sedimentation rate was 51 mm/h, ferritin level was 2913 ng/mL, sIL-2Rα level was 7920 U/mL, and triglyceride level was 211 mg/dL. Urinalysis showed proteinuria (0.63 g/day) and 10–19 red blood cells and granular casts per high- and low-power fields, respectively. Her urine β_2 microglobulin level was 85,500 μg/L and serum antinuclear antibody titer was 1:1280, with a speckled pattern. Computed tomography revealed cervical and axillary lymphadenopathy and splenomegaly. Bone marrow biopsy revealed erythrophagocytic macrophages. The present case met five out of the eight diagnostic criteria of HPS (HLH-2004), namely fever, splenomegaly, cytopenia, hyperferritinemia, and elevated IL-2Rα level. Subsequently, she was diagnosed with HPS. We commenced the administration of intravenous pulse methylprednisolone (1000 mg three times daily), followed by 60 mg of oral prednisolone. After 2 weeks of treatment, her thrombocytopenia improved, but the high serum creatinine level persisted. Therefore, we performed a kidney biopsy on day 35 after admission to evaluate the cause of renal involvement.

The kidney biopsy sample had 11 glomeruli, which were examined by light microscopy. There were no global sclerotic glomeruli. All glomeruli were intact (Fig. 1a, b), but typical features of acute tubular necrosis and tubulointerstitial nephritis were observed. Erythrophagocytic macrophage casts were observed on Elastica–Masson staining (Fig. 1c). Immunohistochemical staining for CD68 revealed massive macrophage infiltration in the tubular lumen (Fig. 1d). However, there were no intraglomerular macrophages. Although there was a marked interstitial macrophage infiltration in CD68 staining, the cells only showed a slight interstitial erythrophagocytic macrophage infiltration in hematoxylin and eosin staining (Fig. 1e-f). Some arteriolar vascular smooth muscle cells were vacuolated because they were positive for α-smooth muscle actin (Fig. 1f, g).

After 8 weeks of treatment with prednisolone, the Scr level improved to 0.76 mg/dL (eGFR, 68 mL/min/1.73 m^2), and the hemoglobin, platelet, and WBC levels returned to normal.

Discussion

Hyperactivation of cytotoxic T cells and natural killer (NK) cells causes HPS. Fever, cachexia, elevated serum triglyceride levels, high serum ferritin level, AKI, and tubular necrosis observed in HPS are all attributed to the high cytokine levels [1, 6].

Table 1 Laboratory findings

Parameter	Value (reference range)
SCr, mg/dL	4.92 (0.2–0.8)
eGFR, mL/min/1.73 m^2	9 (> 90)
SUN, mg/dL	41 (8–22)
Serum albumin, g/dL	2.5 (3.9–4.9)
AST, U/L	205 (13–30)
ALT, U/L	96 (10–40)
Hemoglobin, g/dL	7.9 (11.0–15.0)
WBC count, $\times10^3$	1080 (3000–9000)
Differential blood count, %	
Neutrophils	92.9 (41.9–79.0)
Monocytes	1.0 (3.5–8.5)
Lymphocytes	3.0 (21.0–51.0)
Eosinophils	0.0 (0.3–1.4)
Platelets, 10^3/μL	8 (14.5–35.0)
PT, s	17.4 (11.6–14.6)
PT-INR	1.45 (0.9–1.10)
LDH, U/L	1137 (110–210)
Haptoglobin, mg/dl	171 (30–178)
Urine dipstick protein	2+
Urine RBC/HPF	10–19 (0.0–4.9)
Urine WBC/HPF	5–9 (0.0–5.0)
Spot urine PCR, g/day	0.63 (< 0.15)
Urine culture	No growth
Blood cultures	No growth
Urinary pneumococcal antigen	Positive
CH50, mg/dL	54.1 (31–49)
C3, mg/dL	118 (75–148)
C4, mg/dL	37 (14–38)
ANA	1:1280 titer; speckled
Anti-dsDNA antibody	Negative
MPO-ANCA	< 1.0 (< 3.5)
PR3-ANCA	< 1.0 (< 3.5)
Rheumatoid factor	22 (0–15)
Lupus anticoagulant	1.27 (< 1.3)
Anticardiolipin and anti-β2-glycoprotein I antibody	< 1.2 (< 3.5)
HIV antibody	Negative
HCV antibody	Negative
HBV surface antigen	Negative
HBV surface antibody	Positive
Soluble IL-2Rα, U/mL	7920 (220–530)
Ferritin, ng/mL	2913 (5.0–152.0)
Triglycerides, mg/dL	211 (40–149)

ALT alanine aminotransferase, *ANA* antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibody, *AST* aspartate aminotransferase, *dsDNA* double-stranded DNA, *eGFR* estimated glomerular filtration rate, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HPF* high power field, *IL-2Rα* interleukin 2 receptor α, *LDH* lactate dehydrogenase, *MPO* myeloperoxidase, *PCR* protein-creatinine ratio, *PR3* proteinase 3, *PT* prothrombin time, *RBC* red blood cell, *Scr* serum creatinine, *SUN* serum urea nitrogen, *WBC* white blood cell

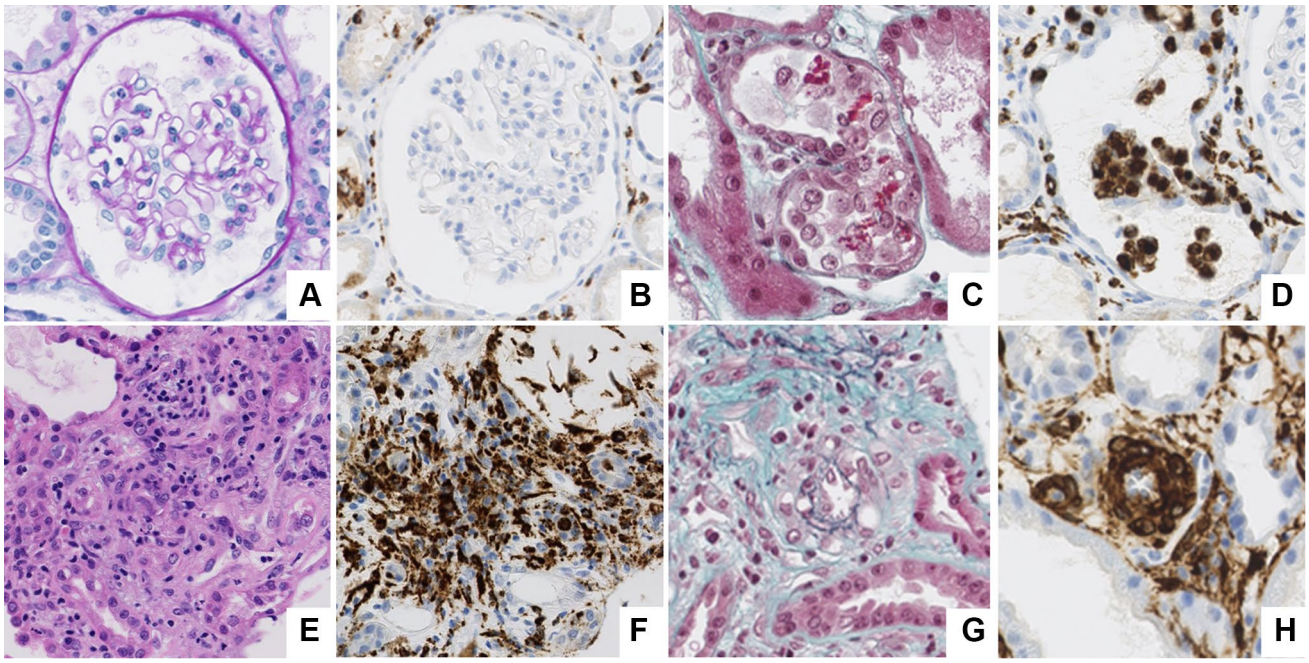

Fig. 1 Light microscopic features. **a** Mesangial proliferation or endocapillary hypercellularity is not observed. **b** No intraglomerular macrophage with immunohistochemical staining for CD68 is observed. **c** Erythrophagocytic macrophages are observed in the tubular lumen. **d** Immunohistochemical staining for CD68 reveals macrophages in the tubular lumen. **e** There was only a slight interstitial erythrophagocytic macrophage infiltration in hematoxylin and eosin staining. **f** Immunohistochemical staining for CD68 highlights interstitial macrophage infiltration. **g** Vacuolization of the arteriole is observed in Elastica–Masson staining. **h** Vacuolization of the smooth muscle cells in the arteriole is observed in α-smooth muscle actin staining

HPS is often triggered by infectious diseases, mainly viral infections, of which Epstein–Barr virus infection is the most frequent trigger [7]. Bacterial infections also cause HPS, and the association of *Staphylococcus* spp. with HPS has also been reported [9, 10]. Therefore, we think that *Staphylococcus pneumonia* infection is the main trigger of HPS in the present case. HPS is also caused by rheumatologic disorders, such as systemic lupus erythematous (SLE), adult-onset Still's disease, systemic vasculitis, and inflammatory bowel disease [7, 11]. Our patient had a history of MCTD; however, MCTD activity was not observed at the onset of the present episode of HPS.

Renal involvement in HPS is most commonly denoted by AKI [1, 12], followed by the nephrotic syndrome. The prognosis of HPS with AKI is poor [2]. HPS-associated AKI may occur as part of multiorgan failure due to the increased capillary permeability and pre-renal condition. It might also be affected by the nephrotoxic effects of antimicrobial therapy.

HPS-associated glomerulopathy is rare. It is often associated with severe nephrotic syndrome with severe renal dysfunction. Collapsing glomerulopathy is the most common pathologic feature, and minimal change is the second most common finding [13, 14]. In our case, the urinary protein was not in the nephrotic level. Light microscopy and electron microscopy findings did not indicate glomerulopathy, although the kidney biopsy was performed after the steroid treatment.

There were erythrophagocytic macrophage casts in the tubular lumen in the present case. Oki et al. [5] reported urinary phagocytic macrophages in HPS. Urinary sediments might provide a diagnostic clue for detecting renal involvement in HPS. A limitation of this case report is that a detailed analysis of the urinary sediments was not performed.

Although the origin of the erythrophagocytic macrophages is not clear, it is speculated that they might have infiltrated the tubular lumen through the damaged tubuli because there were no macrophages in the glomeruli. In the present case, the interstitial macrophages were not erythrophagocytic. The activated macrophages might have phagocytosed red blood cells after infiltrating into the tubular lumen and into the blood stream. The cause of arteriole smooth muscle vacuolization is unclear. However, this finding is often observed in allograft samples obtained 1 h after kidney transplantation. This vacuolization may be due to ischemia or arteriolar spasm.

Although HPS with AKI has a poor prognosis, our patient's renal function almost completely recovered. The optimal treatment of HPS remains undefined. Elimination of triggers of HPS is crucial. Li et al. reported that patients with

viral infection-related HPS had better outcomes compared to those with malignancy-related HPS, which has high mortality rates [8]. Their study suggested that patients with older age at onset, male sex, splenomegaly, or thrombocytopenia were prone to having poor outcomes.

Our patient was young, female, and her HPS was not related to any malignancy. Moreover, we were able to treat the pneumonia, which was a trigger of HPS, and promptly started steroid treatment. These factors contributed to her good clinical course.

In conclusion, our report presents a new pathologic pattern of HPS. When erythrophagocytic macrophages infiltrate the tubular lumen in a patient with HPS-associated AKI, these cells may be observed in the urinary sediments. Careful urinalysis could provide evidence for renal involvement in HPS. Knowledge of this pathologic pattern of HPS is important to recognize the disease and treat it appropriately.

Acknowledgements We would like to thank Editage (www.editage.jp) for English language editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the participant included in the article.

References

1. Karras A. What nephrologists need to know about hemophagocytic syndrome. Nat Rev Nephrol. 2009;5(6):329–36.
2. Esmaili H, Mostafidi E, Mehramuz B, Ardalan M, Mohajel-Shoja M. An update on renal involvement in hemophagocytic syndrome. J Nephropathol. 2016;5(1):8.
3. Fitzgerald NE, MacClain KL. Imaging characteristics of hemophagocytic lymphohistiocytosis. Pediatr Radiol. 2003;33(6):392–401.
4. Santoriello D, Hogan J, D'Agati VD. Hemophagocytic syndrome with histiocytic glomerulopathy and intraglomerular hemophagocytosis. Am J Kidney Dis. 2016;67(6):978–83.
5. Oki R, Kono M, Kubo K, Tojo A, Yamamoto K. Urinary phagocytic macrophages in hemophagocytic lymphohistiocytosis. Kidney Int. 2016;90(4):908.
6. Mlner JD, Orekov T, Ward JM, Cheng L, Torres-Velez F, Junttila I, et al. Sustained IL-r exposure leads to a novel pathway for hemophagocytosis, inflammation, and tissue macrophage accumulation. Blood. 2010;116(14):2476–83.
7. Ramos-casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503–16.
8. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, Tian X. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine (Baltimore). 2014;93(2):100–5.
9. Hoshino C, Satoh N, Sugawara S, Kuriyama C, Kikuchi A, Ohta M. Community-acquired Staphylococcus aureus pneumonia accompanied by rapidly progressive glomerulonephritis and hemophagocytic syndrome. Intern Med. 2007;46(13):1047–53.
10. Song M, Ni F, Gao X, Wang JJ, Tian T, Duan LM, Pan SY, Qiu HX. Clinical analysis of staphylococcus septicemia-associated hemophagocytic lymphohistiocytosis: seven case reports. Zhonghua Xue Ye Xue Za Zhi. 2017;38(5):437–9.
11. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases; analysis of 30 cases. Rheumatology (Oxford). 2008;47(11):1686–91.
12. Aulagnon F, Lapidus N, Canet E, et al. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. Am J Kidney Dis. 2015;65(6):851–9.
13. Thaunat O, Delahousse M, Fakhouri F, Martinez F, Stephan JL, Noel LH, et al. Nephrotic syndrome associated with hemophagocytic syndrome. Kidney Int. 2006;69(10):1892–8.
14. McCarthy T, Sharma R, Sharma M, Li JZ, GeXL Dileepn KN, et al. TNF-α increases albumin permeability of isolated rat glomeruli through the generation of superoxide. Jam Soc Nephrol. 1998;9(3):433–8.