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BRIEF REPORT

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Hemophagocytic syndrome and T-cell lymphoma after kidney transplantation: a case report

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Abstract Lymphoma in immunocompromised transplant patients is a feared cause of morbidity and mortality. Superimposed on the lymphoma and the transplantation immunosuppression is a rare condition: hemophagocytic syndrome (HS). HS is characterized by fever, hepatosplenomegaly and lymphadenopathy, skin rashes, jaundice, coagulopathy, and phagocytosis of blood elements with pancytopenia. Here we describe a rare but fatal case of a kidney transplant patient who developed T-cell lymphoma and HS, without evidence of EBV replication. A short review of the diagnosis, treatment, and prognosis of HS is given.

Key words Hemophagocytic syndrome, kidney transplantation · T-cell lymphoma, kidney transplantation · Kidney transplantation, T-cell lymphoma, hemophagocytic syndrome

Introduction

Hemophagocytic syndrome (HS) is a clinicopathological condition characterized by fever, hepatosplenomegaly, lymphadenopathy, skin rash, lung infiltration, jaundice, coagulopathy, multiple organ failure, and prominent phagocytosis of blood elements with profound cytopenia [22]. This disorder may represent a reaction to infection [11, 17, 20] or hematopoietic neoplasm, especially T-cell lymphoma [5, 7, 9] The majority of HS cases that have developed post-transplantation have been related to infection. We were able to trace 23 renal transplant [2, 3, 6, 10, 16, 17, 19], 1 kidney-pancreas [19], 1 heart [14], and 2 bone marrow transplant [12, 15] recipients with HS. Here we report on a third case of a non-EBV-related T-cell lymphoma and HS following kidney transplantation.

Case report

A 51-year-old male, on peritoneal dialysis since 1988 for end-stage renal disease due to nephrosclerosis, received a cytomegalovirus (CMV)-negative renal transplant in March 1994. There were two mismatches at the HLA-A locus, one at HLA-B, and one at HLA-DR. Immediate graft function was achieved. Maintenance immunosuppression included cyclosporin (5 mg/kg per day), azathioprine (150 mg/day), and prednisolone (30 mg/day). On the 5th postoperative day, Banff classification grade III acute rejection occurred, and the patient was treated with methylprednisolone pulses (750 mg) for 4 days. On the 14th postoperative day, ongoing rejection was documented and successfully controlled with antithymoglobulin (ATG, 375 mg Merieux).

In the meanwhile, a percutaneous nephrostomy was performed because of distal donor ureter leakage. Vancomycin was administered for urosepsis with a methicillin-resistant strain of *Staphylococcus aureus*. The nephrostomy catheter was successfully removed and ureter reimplantation was performed 2 months later. Felodipine was added to control hypertension.

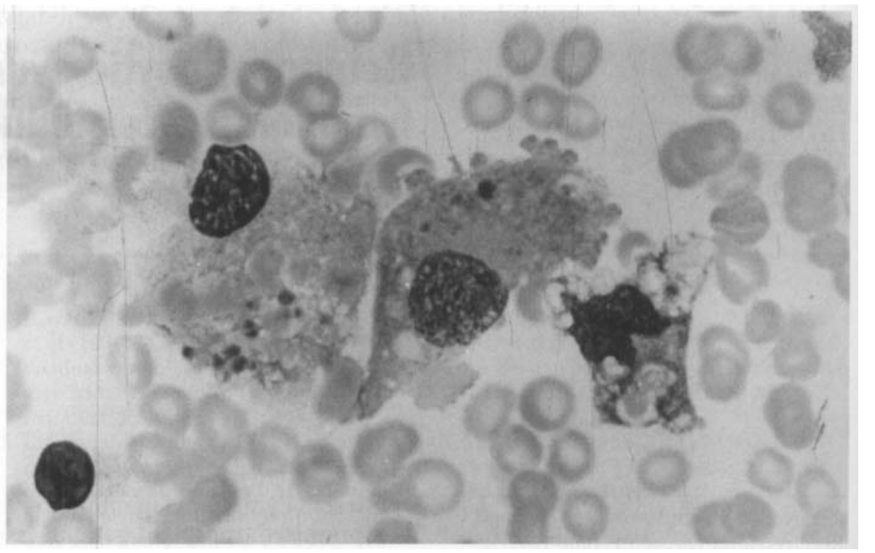

Fig. 1 Histiocytes with erythrophagocytosis

In September 1994, an aseptic necrosis of the right humeral head was diagnosed, attributed at that time to the use of steroids. A deep venous thrombosis of the left femoral vein required prolonged anticoagulation. However, a thorough check-up at 12 months post-transplantation was normal.

At 15 months post-transplantation, the patient presented with asthenia, vomiting, a 5 % weight reduction, and fever (39 °C). On physical examination, mobilization of the right shoulder was painful and hepatosplenomegaly was present. Biochemical investigation showed profound leukopenia (700/mm^3 WBC with 62 % neutrophils, 29 % lymphocytes, 6 % monocytes, and 3 % atypical lymphocytes), an erythrocyte sedimentation rate of 23 mm/h, fibrinogen 604 mg/dl (normal range 200–400 mg/dl), hemoglobin 9.8 g/dl, and platelets 207 · 10^3/mm^3. Lactate dehydrogenase (LDH) was 1086 (normal level < 512 IU/l) with elevated LDH isoenzyme fractions 2 (29 %) and 3 (25 %). Hepatic tests were initially within the normal range. Serum creatinine was 1.26 mg/dl and creatinine clearance was 73 ml/min.

Broad-spectrum antibiotherapy with ceftazidime and vancomycin was started; azathioprine was stopped. Hemocultures, retinal examination, a chest x-ray, urinalysis, and transesophageal echocardiography were negative. There was no urinary CMV excretion and serology for CMV, herpes, adenovirus, parainfluenza, hepatitis B virus, measles, *Legionella, Mycoplasma, Borrelia,* and *Burcella* was negative. Recent Epstein-Barr virus (EBV) infection was excluded (IgM < 1/40; IgG 260; EB early antigen 1/16; EB nuclear antigen-positive: all indicative for past infection). Anti-nuclear antigen was negative. Abdominal and transplant echography showed only marked hepatosplenomegaly. A search for *Mycobacterium* in sputum and urine was negative. Magnetic resonance imaging of the right shoulder confirmed aseptic necrosis and chronic osteitis of the humeral head. Tc ^{99}m-mAb-granulocyte scintigraphy also demonstrated hepatosplenomegaly and discrete hypercaptation of the right shoulder.

Despite treatment with antibiotics, high fever and leukopenia persisted. Liver and renal function deteriorated (creatinine clearance 27 ml/min). Thrombocytopenia (70000/mm^3) and monocytosis (60 % of 2400 WBC/mm^3) developed. A bone marrow biopsy showed a large population of histiocytes (37 %) with hemophagocytosis of platelets, white blood cells, and red blood cells (Fig. 1). A population of large lymphoid cells with atypical morphology (moderately elevated nuclear to cytoplasmic ratio, irregular nuclei, and granular cytoplasm) and abnormal phenotype (CD2, CD7, CD8, and HLA-DR-positive but CD3, CD16, CD56 and CD57-negative) was present. T-cell lymphoma and HS were diagnosed.

A modified regimen of cyclophosphamide, 375 mg/m^2 (50 % dose reduction), and methylprednisolone, 120 mg/day, was administered. Cyclosporin was stopped. However, the clinical situation degraded further into respiratory failure. A ventilator-associated pneumonia and sepsis with multiresistant *Klebsiella oxytoca* occurred, and imipenem was started. Jaundice, hepatic insufficiency, a macular rash, and diffuse intravascular coagulopathy (DIC) developed.

The patient evolved further into multiple organ failure with septic shock, acute renal failure, pancytopenia and coagulopathy, and respiratory and liver failure. Finally, he developed a massive subdural hemorrhage and died of cerebral edema 18 days after being admitted to the hospital.

Bone marrow, lymph nodes, spleen, and liver were infiltrated by a lymphoma on autopsy. The large atypical lymphoid cells were immunohistochemically positive for T-cell markers UCHL1 (CD45R0) and Ber-H2 (CD30) and negative for B-cell markers MB2 and LN2 (CD20). The erythrophagocytes were positive for KP1 (CD68). Bone marrow was dominated by macrophages with hemophagocytosis. Immunohistochemistry for the late membrane protein of EBV and the PCR analysis for the EBV genome in liver, lung, bone, spleen, and lymph nodes were negative. T-cell antigen receptor gene rearrangement was not observed.

Discussion

In their initial description of the hemophagocytic syndrome, Risdall et al. distinguished this condition from malignant histiocytosis [17]. Since then, many associated conditions have been described. The clinicopathological picture of the hemophagocytic syndrome is characterized by a myriad of signs including fever, hepatosplenomegaly, lymphadenopathy, skin rashes, lung infiltration, jaundice, coagulopathy, multiple organ failure,

and phagocytosis of blood elements with cytopenias. However, minimal diagnostic criteria have not yet been clearly established.

In 1992, Wong et al. [22] proposed the following diagnostic histological requirements for HS: (1) demonstration of phagocytosis of red cells, white cells, platelets, and erythroblasts by histiocytes (at a minimum of 2 % of all nucleated marrow cells) and (2) cytopenia in at least two cell lines. The cytopenia is due to the hemophagocytosis itself, splenic sequestration, or the underlying disease (lymphoma, lupus, or direct viral suppression of bone marrow). Furthermore, fever is always present. Liver, spleen, and lymph node enlargement are common, probably due to the underlying disease. Hepatic tests are disturbed in two out of three cases. Prolonged prothrombin time and activated partial thromboplastin time are found in one-third of the patients. DIC occurs frequently. Normochromic and normocytic anemia develop within a few weeks. Reticulocyte count is low. The serum level of ferritin can give an indication of disease activity. Atypical lymphocytes may be present in the peripheral blood smear.

Malignant lymphoma seems to be the most common associated pathology in the hematological literature [22]. T-cell lymphoma and anaplastic large cell lymphoma, but also B-cell lymphoma, may coexist. Infections are the second most important associated condition. Initially, HS was thought to occur as a virus-associated disease. In particular, EBV but also Herpes viruses, CMV, adenovirus, parainfluenza, hepatitis B, and Dengue virus have been implicated. Fungi and bacterial infections include *Candida, Histoplasma,* and *Staphyloccus aureus,* beta-hemolytic *Streptococcus, Staphylococcus faecalis* and *milleri,* tuberculosis, *Salmonella typhi, Brucella, Escherichia coli, Acinetobacter* species, *Rickettsia* species, *Chlamydia psitacci,* and also toxoplasmosis and leishmaniasis [1, 18, 19]. In a study of 40 Oriental patients with HS, systemic lupus erythematosus was present in 2 patients [22, 23]. Prior immunosuppression (corticotherapy, chemotherapy, postsplenectomy, or AIDS) induced the syndrome in eight of the cases. Familial forms known as familial lymphophagocytic lymphadenopathy and erythrophagocytic lymphohistiocytosis have been described [4].

Fatality occurs in up to 40 % of all immunodepressed cases and is mainly due to bleeding, opportunistic infection, liver failure, and the underlying pathology. DIC is a bad prognostic factor since, in a series of 11 patients, only one survived [22]. In cases of survival, there is rapid recovery of the blood cell lines within 1 or 2 weeks. Liver tests recover after 3–4 weeks.

The most important differential diagnosis is malignant histiocytosis [21]. Further differential diagnosis includes eliminating histiocytic medullary reticulosis, familial hemophagocytic lymphohistiocytosis, and X-linked lymphoproliferative syndrome [4, 11].

Treatment of HS consists of transfusion of packed cells and platelets, if required, and treating the underlying condition with cytotoxic agents, steroids, or antimicrobial therapy. Intravenous administration of immune globulins is sometimes successful [8].

Infections with bacteria and viruses (EBV, CMV, herpes) are common in immunosuppressed transplant recipients, some of which may, on rare occasions, be associated with hemophagocytosis. In the literature, we were able to trace 21 renal transplant [2, 3, 6, 16, 17, 19], 1 kidney-pancreas [19], 1 heart transplant [14] and 2 bone marrow transplant recipients [12, 15] who were all found to have infection-associated HS. In our patient, however, viral or EBV-associated disease was excluded by negative serological testing, absence of a viral illness in the weeks prior to the disease, the presence of a hypercellular marrow compared to the hypocellular marrow, and the atypical lymphocytes of the infection-related HS, which is different from the original description of HS [17]. In our patient, HS occurred in the setting of disseminated T-cell lymphoma. Post-transplant lymphoproliferative disease (PTLD) complicates intense immunosuppression following organ transplantation in approximately 2 % of cases; the majority of tumors arise from B lymphocytes, whereas 15 % are of T-cell origin [13]. As in our patient, the high-dose immunosuppression that is given to control ongoing rejection post-transplantation very likely contributes to the development of lymphoma cell proliferation. The association of T-cell lymphoma with HS is not totally unexpected. Indeed, neoplastic T cells may secrete cytokines that stimulate histiocytes to proliferate and phagocytize hemopoietic cells, such as tumor necrosis factor (TNF), interferon-α (IFN-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and macrophage colony-stimulating factor (M-CSF). Also, elevation of soluble IL-2 receptor and CD8 has been reported [9, 20]. However, T cell-associated HS is extremely rare following renal transplantation; only two cases have been reported [10, 19].

In conclusion, HS is rarely associated with malignancy or infection in febrile, immunosuppressed transplant recipients with pancytopenia. Prominent hemophagocytic activity in bone marrow will confirm this condition. Exhaustive microbiological screening may reveal infection-related HS, whereas the presence of lymphocytes with atypical morphology and phenotype should raise suspicion of lymphoma-associated HS.

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References

1. Bell MD, Wright RK (1992) Fatal virus-associated hemophagocytic syndrome in a young adult producing nontraumatic splenic rupture. J Forensic Sci 37: 1407–1417
2. Boehler A, Schaffner A, Salomon F, Keusch G (1994) Cytomegalovirus disease of late onset following renal transplantation: a potentially fatal entity. Scand J Infect Dis 26: 369–373
3. Broeckaert-Van Orshoven A, Michielsen P, Vandepitte J (1979) Fatal leishmaniasis in renal-transplant patient. Lancet II: 740–741
4. Cline MJ (1994) Histiocytes and histiocytosis. Blood 84: 2840–2853
5. Craig FE, Clare CN, Sklar JF, Banks PM (1992) T-cell lymphoma and the virus-associated hemophagocytic syndrome. Am J Clin Pathol 97: 189–194
6. Drut R, Drut RM (1994) EBV-associated Kaposi's sarcoma in a pediatric renal transplant recipient. Pediatr Pathol 14: 863–872
7. Falini B, Pileri S, De Solas I, Martinelli MF, Mason DY, Delsol G, Gatter KC, Fagioli M (1990) Peripheral T-cell lymphoma associated with hemophagocytic syndrome. Blood 75: 434–444
8. Freeman B, Rathore MH, Salman E, Joyce MJ, Pitel P (1993) Intravenous administered immune globulin for the treatment of infection-associated hemophagocytic syndrome. J Pediatr 123: 479–481
9. Jaffe ES, Costa J, Fauci AS, Cossman J, Tsokos M (1983) Malignant lymphoma and erythrophagocytosis simulating malignant histiocytosis. Am J Med 75: 741–749
10. Kaplan MA, Jacobson JO, Ferry JA, Harris NL (1993) T-cell lymphoma of the vulva in a renal allograft recipient with associated hemophagocytosis. Am J Surg Pathol 17: 842–849
11. Kikuta H (1995) Epstein-Barr virus-associated hemophagocytic syndrome. Leuk Lymphoma 16: 425–429
12. Levy J, Wodell RA, August CS, Bayever E (1990) Adenovirus-related hemophagocytic syndrome after bone marrow transplantation. Bone Marrow Transplant 6: 349–352
13. Penn I (1990) Cancers complicating organ transplantation. N Engl J Med 323: 1767–1769
14. Pucci A, Grasso M, Arbustini E (1989) Myocardial involvement due to a disseminated human cytomegalovirus infection in a heart transplant recipient. A case report. G Ital Cardiol 19: 230–233
15. Reardon DA, Roskos R, Hanson CA, Castle V (1991) Virus-associated hemophagocytic syndrome following bone marrow transplantation. Am J Pediatr Hematol Oncol 13: 305–309
16. Reiner AP, Spivak JL (1988) Hemophagic histiocytosis. A report of 23 new cases and a review of the literature. Medicine 67: 369–387
17. Risdall RJ, Mc Kenna RW, Nesbit ME, Krivit W, Balfour HH, Simmons RL, Brunning RD (1979) Virus-associated hemophagocytic syndrome. Cancer 44: 993–1002
18. Risdall RJ, Brunning RD, Hernandez JI, Gordon DH (1984) Bacteria-associated hemophagocytic syndrome. Cancer 54: 2968–2972
19. Rostaing L, Fillola G, Baron E, Cisterne J-M, Durand D (1995) Course of hemophagocytic histiocytic syndrome in renal transplant patients. Transplantation 60: 506–509
20. Shirono K, Tsuda H (1995) Virus-associated haemophagocytic syndrome in previously healthy adults. Eur J Haematol 55: 240–244
21. Su IJ, Hsu YH, Lin MT, Cheng AL, Wang CH, Weiss LM (1993) Epstein-Barr virus-containing T-cell lymphoma presents with hemophagocytic syndrome mimicking malignant histiocytosis. Cancer 72: 2019–2027
22. Wong K, Chan JKC (1992) Reactive hemophagocytic syndrome – a clinicopathologic study of 40 patients in an Oriental population. Am J Med 93: 177–180
23 Wong K, Hui P, Chan JKC, Chan Y, Ha S (1991) The acute lupus hemophagocytic syndrome. Ann Intern Med 113: 387–390