Case Report

Haemophagocytic–histiocytic syndrome in renal transplantation

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Introduction

The haemophagocytic–histiocytic syndrome (HHS) is a rare syndrome characterized by fever, weight loss, profound pancytopenia, lymphadenopathy, hepatosplenomegaly. This syndrome is a result of prominent haematophagocytosis [1] caused by phagocytizing histiocytes. After the first cases of HHS were reported by Chandra et al. [2], Risdall et al. were the first to establish this disorder as a distinct clinicopathological entity in 1979 [3]. Thirteen of the 19 cases reported by Risdall were renal transplant recipients who had been treated with splenectomy, prednisolone, and azathioprine, and one had SLE and was treated with the same drugs. The remaining five were otherwise healthy persons who had no precipitating condition. Risdall ascribed 15 of 19 cases to viral aetiology (herpes viruses in 14 and adenovirus in 1). To underline the fact that viral aetiology was present in almost all cases, the entity was designated as virus-associated haemophagocytic syndrome. While 13 individuals recovered, four renal transplant recipients and two healthy patients died from opportunistic infections and haemorrhage.

Since then, HHS has been documented to occur with infections by many different micro-organisms (viral—CMV, herpes simplex virus, adenovirus; bacterial—M. tuberculosis; fungal), tumours (haematological malignancies, mainly T-cell neoplasms), and drugs (phenytoin), viruses again being the most frequently encountered aetiological agents [4,5]. This aetiological classification comprises reactive HHS. Later familial erythrophagocytic lymphohistiocytosis cases, most of whom had been from Israel, were described with an autosomal mode of inheritance [6].

If a patient has fever of unknown origin, a variable degree of pancytopenia, and the progressive development of multiorgan dysfunction, especially in the context of immunosuppression, HHS must always be considered in the differential diagnosis.

We here would like to present four cases of HHS in our renal transplantation unit observed in a very short time, namely 2 months.

Case report

Patient 1

One-haplotype matched living related kidney transplantation was performed in a 27-year-old female in June 1994; her primary disease was nephrolithiasis. Right nephrectomy had been performed 5 years before the transplantation, and at the time of the transplant operation the left kidney was also removed. She received triple immunosuppression. At the 10th month post-transplant she presented with high-grade fever (39°C), chills, and weight loss. Hb was 0.8 mmol/l, corrected reticulocyte count 1.5%, WBC 3600/mm³, neutrophil percentage 85%, platelets 27 000/mm³. At the right posterior cervical region three separate enlarged lymph nodes were found. On abdominal ultrasound, fluid and splenomegaly were found. Serum creatinine was 143 μmol/l, prior values being around 115 μmol/l. Total bilirubin was 32 μmol/l, indirect bilirubin 18 μmol/l, AST 10 U/l, ALT 5 U/l, alkaline phosphatase 105 IU/l, albumin 493 μmol/l; on protein electrophoresis decrease in albumin and increase in alpha-1, alpha-2 and beta globulin. Both PT and APTT were moderately prolonged. FDP was in the normal range. On peripheral blood film there was normochromia and normocytosis. Bone marrow aspiration revealed macrophages showing phagocytic activity against erythroid, granulocytic cells and platelets. Chest X-ray showed bilateral pleural effusion and heterogeneous infiltration on the right middle zone. With several investigations including bronchoalveolar lavage, no infectious agent was detected. Herpes simplex type 1, type 2 (by the absence of fourfold increase in IgG and the absence of IgM antibodies), Epstein–Barr (by the absence of fourfold increase in IgG and the absence of IgM antibodies against viral capsid antigen), and CMV (negative antigenaemia test) infections were
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outcomes, vancomycin, ceftazidime, and imipenem were immunological tests as in case 1. Despite this negative result, direct bilirubin to 32 \(\mu\)mol/l, indirect bilirubin 19 \(\mu\)mol/l, ALT/AST 55/87 IU/l, CMV antigenemia negative, PT 18 s, APTT 48 s. On peripheral blood smear there was anisocytosis, slight hypochromia, and basophilic stippling. Again bone marrow aspiration revealed many macrophages that had phagocytosed numerous erythroid cells, platelets, and granulocytes. There was no positive result from virological (including HSV type 1 and 2, EBV, CMV), bacteriological, parasitological, and mycological studies. Yet with the thought that pancytopenia might be a result of CMV infection, gancyclovir was initiated at a dose of 5 mg/kg/day, but without any beneficial result. Despite additional supportive therapy against haemorrhagic diathesis and thrombocytopenia, the patient died from multiple organ failure following a subfebrile course 20 days after her admission.

**Patient 2**

A 20-year-old woman had undergone renal transplantation from a one-haplotype matched living related donor. At post-transplant 15th month while receiving triple immunosuppressive medication she presented with fatigue and yellow discoloration on the sclera. On laboratory examination, hct was 36%, Hb 1.9 mmol/l, platelets 112 000/\(\mu\)l, corrected reticulocyte 1%, total bilirubin 74 \(\mu\)mol/l, and indirect bilirubin 41 \(\mu\)mol/l. On peripheral blood film there were anisocytosis, normochromia, rare polychromasia, basophilic stippling, the fragmented erythrocyte ratio was 2%. On bone marrow aspiration, increased normoblastic erythropoiesis, numerous macrophages that had phagocytic activity against erythroid cells, granulocytes and platelets were found. ALT/AST were 91/134 IU/l, LDH 750–1050–1270 U/l. Prothrombin time was 20.3 s, APTT 119 s, fibrinogen 5.6 \(\mu\)mol/l. Fibrin degradation products were in the normal range. Chest X ray and abdominal ultrasound were normal. On follow-up, fever appeared in the 10th day. While starting at 37.6°C, it later rose to 38.1°C. There was no growth in the bacteriological and mycotic cultures. CMV antigenemia was negative. Herpes simplex type 1 and EBstein–Barr viruses were excluded by the same immunological tests as in case 1. Despite this negative outcome, vancomycin, ceftazidime, and imipenem were used, but without any clinical benefit. Her immunosuppression was attenuated with the cessation of azathioprine, later cyclosporin, and finally prednisolone. From a review of the literature and large series [7] it seems that HHS occurs at a median age around 50 years with a male/female ratio of between 1.5/1 and 3/1. The median duration of symptoms is between 14 days and 3 months, whereas the median duration of illness is between 18 days and 1 month. Presenting symptoms include fever (75%), gastrointestinal symptoms (36%), chills-sweats (35%), anorexia (28%), weight loss (24%), weakness/fatigue (24%), malaise (21%), and respiratory symptoms (19%). Physical signs present at the time of diagnosis of HHS include splenomegaly (52%), hepatomegaly (50%), lymphadenopathy (43%), and rash (19%). The most prominent laboratory abnormality in HHS is pancytopenia (%70), whereas anaemia, thrombocytopenia, and leuko-
kopenia are found respectively in 85, 83, and 77% of patients [7]. Bone marrow aspirates invariably show phagocytosis of various haematopoietic cells by histiocytes and sometimes hypocellularity, increased numbers of plasma cells, decreased numbers of myeloid and erythroid precursors, and increased numbers of megakaryocytes. Elevated serum aminotransferases and/or bilirubin levels, coagulopathy disorders, and azotaemia are found in respectively 89, 66, and 40% of cases [7].

In our patients, fever was present in all cases, jaundice (3/4), splenomegaly (1/4, ultrasonographically) and lymphadenopathy (1/4). Pancytopenia was present in all cases, resistant to G-CSF, and coagulopathy was excluded by bone marrow biopsy. Thus it is important to look carefully at bone marrow films, for the diagnosis is easily missed.

As a common point, all HHS cases suffer from some sort of immune dysfunction, usually on the basis of a viral infection. Indeed in all reported series, viruses are the most frequently encountered agents [3,8]. Like viruses, other infections that are known to induce neutropenia (Brucellosis, typhoid fever and tuberculosis) may cause this syndrome. Indeed, in one of our patients (Case 4), tuberculosis was responsible for the induction of HHS. There is no satisfactory explanation for the occurrence of HHS in our patients in a very short period like 2 months. The cause of HHS in cases 2 and 3 was obscure, but close temporal relationship between them (only 1 week apart) suggests viral aetiology, although we could not demonstrate any agent. To our knowledge, case 1 represents the first example of HHS related to Kaposi sarcoma. Again in this case, despite the negative virological test results, viral aetiology might play a role in the causation of HHS, because one form of HSV (Kaposi-sarcoma-associated herpesvirus) was reported to be responsible for the causation of Kaposi’s sarcoma [9].

In the context of an extreme immunosuppression, the final result is an unbalanced macrophage proliferation that leads to haemophagocytosis and the secretion of products such as plasminogen activator that is responsible for the decrease in plasma fibrinogen, IL-1 and TNFα. According to some investigators the serum concentration of TNFα is correlated with the severity of HHS [10].

In the literature there are some reports indicating the efficiency of epipodophyllotoxin (VP16) in familial haemophagocytic lymphohistiocytosis (FHLH) [11,12]. Similar speculations are present for the high-dose steroid therapy, especially at the acute phase in conjunction with the treatment of the underlying aetiology, since steroids are able to inhibit the release of cytokines by monocytes/macrophages.

As a result, this syndrome must always be borne in mind in renal transplant recipients, especially in the context of fever and pancytopenia. Aetiological agents must always be searched for so as to give a specific treatment, and immunosuppression attenuated or stopped.

References


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