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Editorial Reviews

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Haemophagocytic syndrome—a life-threatening complication of renal transplantation

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Introduction

Haemophagocytic syndrome (HPS), also referred as macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis, is a clinicopathologic entity caused by systemic proliferation of benign haemophagocytic cells of the monocyte–macrophage–histiocyte lineage. Criteria for diagnosis include fever, hepato-splenomegaly, neurological dysfunction, pancytopaenia, hypertriglyceridaemia, hypofibrinogenaemia, hyperferritinaemia and haemophagocytosis. Five of the following eight diagnostic criteria needed to be met: (1) fever, (2) cytopaenia of two lines, (3) hypertriglyceridaemia and/or hypofibrinogenaemia, (4) hyperferritinaemia (>500 μg/L), (5) haemophagocytosis, (6) elevated soluble interleukin-2 receptor (CD25), (7) decreased natural killer (NK)-cell activity and (8) splenomegaly can also commonly be found in patients with sepsis, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS) and MAS [1–3]. A tissue biopsy, but more commonly bone marrow aspiration examination, may reveal haemophagocytosis characterized by proliferation of mature histiocytes actively ingesting other blood cells. However, the typical haemophagocytic features may be absent in 30% of cases. [1–4]. Two forms of the syndrome have been well characterized: a familial HPS and a reactive HPS.

Primary HPS

The familial, or primary, HPS is a genetic disorder that mainly affects young children. Two autosomal recessive gene defects underlie that, accounting for 40–50% of primary cases: perforin, a major immune cytotoxic protein [5], and MUNC 13–4, a protein involved in exocytosis of perforin-bearing cytotoxic granules during apoptosis [6]. Biallel mutations of syntaxin 11 have also been reported in ∼20% of families with haemophagocytic lymphohistiocytosis, being particularly frequent in Turkish families [7]. Until recently, the prognosis of familial HPS was almost always fatal. However, over last decade, clinical outcomes have significantly improved. About 75% of children improved after 2 months of immunomodulating therapy. After allogeneic haematopoietic cell transplantation, the disease-free survival currently ranges from 50 to 70% [8].

Reactive HPS

Reactive, or secondary, HPS may develop at any age and can occur during systemic infection, immunodeficiency or malignancy. HPS secondary to infection is mainly observed not only in association with viral infections, but also with infections due to intracellular bacteria, parasites and fungi [1–3]. HPS may also develop as a complication of malignancies such as lymphoma and metastatic carcinomas [4,9] or inflammatory/autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis and Still's disease [10–12]. No underlying cause may be identified in some 20% of HPS occurring in adults [1–3]. The pathogenesis is poorly understood. However, the strong link between systemic inflammatory syndrome response and haemophagocytosis coupled with peripheral T-cell expansion and deficient NK activity often found in patients with HPS [13] strongly supports the hypothesis of a defective regulation in the inflammatory and immune response. Previous reports found elevated concentrations of IL-6, tumour necrosis factor (TNF)-α and interferon (IFN)-γ in the sera of patients with HPS [14–16]. IFN-γ is the prominent Th-1 cytokine and a well-known activator of macrophages. An important role in the pathogenesis of HPS might be played by an imbalance between IL-18 and its binding protein, IL-18BP [17,18]. IL-18 is a member of the IL-1 family and requires the intracellular cysteine protease caspase-1 for biological activity [19]. It is a pro-inflammatory cytokine that is not only able to increase adhesion molecule expression, nitric oxide synthesis and chemokine production but also plays an important immunoregulatory role through induction of IFN-γ in association with IL-12, increase activity of

cytotoxic T and NK cells and most notably the expression of Fas ligand [20]. Recently, new proteins regulating the processing and release of IL-1 have been discovered. Among chief of those are the purinergic ATP-gated P2X(7) receptor (P2X(7)R) and its downstream signalling molecule Pannexin-1 (Panx-1). Both proteins are involved in the control of the activation and the release of mature IL-1alpha, IL-1beta and IL-18 [21]. The activation of the P2X7 receptor is a powerful event in the regulation of the caspase-1 inflammasome, as well as of in the activation and secretion of proinflammatory cytokines. It can also lead directly to killing of intracellular pathogens in infected macrophages and epithelial cells [22].

In summary, the current view is that the immune system becomes overactive due to its inability to effectively respond to infection and/or shut down the immune response to such infections. Accordingly, the activation of Th-1 cells and the overproduction of their cytokines would lead to macrohage activation and proliferation, escaping control of NK cell cytotoxicity activation [23,24]. The uncontrolled proliferation of highly activated macrophages eventually leads to haemophagocytosis. The discovery of genetic defects in the secretory pathway of NK cells [25] and of effectors of lymphocyte cytotoxicity, such as perforin [5], in some patients with haemophagocytosis further supports this hypothesis. The prognosis of reactive HPS is severe, with mortality occurring in ∼30–50% of patients [1,3].

HPS in renal transplant recipients

In 1979, Risdall *et al*. [26] reported on 19 patients with reactive HPS. Among them, 13 were renal transplant recipients. Since then, a number of cases in organ transplant and bone marrow recipients have been described. To the best of our knowledge, 76 cases of HPS have been reported in renal transplant patients [27–49]. The largest series was reported by Karras *et al*. [41] who collected 17 cases among 4230 renal transplant recipients with an estimated prevalence of 0.4%. HPS more often developed in the first few weeks after transplantation, but in a few patients it occurred years after transplantation, particularly when it was caused by parasitic infection or neoplasia. Most cases were associated with viral infection caused by cytomegalovirus (CMV) [27,30,41–44], adenovirus [38], Epstein-Barr virus (EBV) [31,43], human herpes virus 8 (HHV-8) [32,40], HHV-6 [39], parvovirus B19 [48] or even by BK polyoma virus [45]. Other cases were associated with tuberculosis [41,42], *Escherichia coli* [42] or protozoan infections such as toxoplamosis [47], leishmaniasis [27] or babebiosis, the latter occurring more frequently in splenectomized patients [32,35]. More rarely, HPS occurred in patients with T-cell lymphoma [29,38] or angiosarcoma [37]. One such case has also been described in a recipient of ABO incompatible kidney [50]. However, in a number of cases it was impossible to recognize the cause of HPS.

Diagnosis of posttransplant HPS

The diagnosis of posttransplant HPS is not easy. High fever and constitutional symptoms are almost constant but are not specific at all (Table 1). Lymphadenopathy and skin rash are often present, but these may also be caused by a number of other complications. Hepatosplenomegaly may be absent in ∼50% of patients. Laboratory investigations generally show pancytopaenia. However, it must be borne in mind that in transplant recipients, pancytopenia may be caused by immunosuppressive drugs (including azathioprine, mycophenolic acid, anti-thymocyte globulins, alemtuzumab, etc.). Hypertriglyceridaemia is frequent in transplant recipients, particularly in those receiving high doses of steroids, sirolimus or everolimus. High levels of serum ferritin that are generally associated with HPS are also increased in other inflammatory conditions. However, serum ferritin levels >10 000 ng/ml associated with high levels of CD163 (normal level 1.5 μg/ml; range 0.5–3 μg/ml) and CD 25 (normal levels 605 ± 49 U/ml) are considered to be reliable markers of macrophage activation and are diagnostic for HPS if these findings are associated with the morphological evidence of haemophagocytosis in the bone marrow [51]. About half of the patients may show neurologic dysfunction, including stupor and disorientation until convulsions, and come among the most severe cases. The bone marrow smears may show the characteristic proliferation of mature histiocytes actively ingesting other blood cells (Figure 1). These haematophagic

Table 1. More frequent clinical and laboratory abnormalities in renal transplant patients with haemophagocytic syndrome [27–49]

Clinical signs and symptoms
High fever (100%)
Hepatosplenomegaly (50%)
Lymph node enlargement (11–50%)
Gastrointestinal symptoms (50%)
Stupor, convulsions, coma (45%)
Cough–dyspnoea (45%)
Rash (3–65%)
Laboratory abnormalities
Pancytopaenia (100%)
High serum ferritin levels (86%)
Hypertriglyceridaemia (75%)
Hyponatraemia (59%)
Increased liver enzymes (50%)
Elevated LDH (66%)

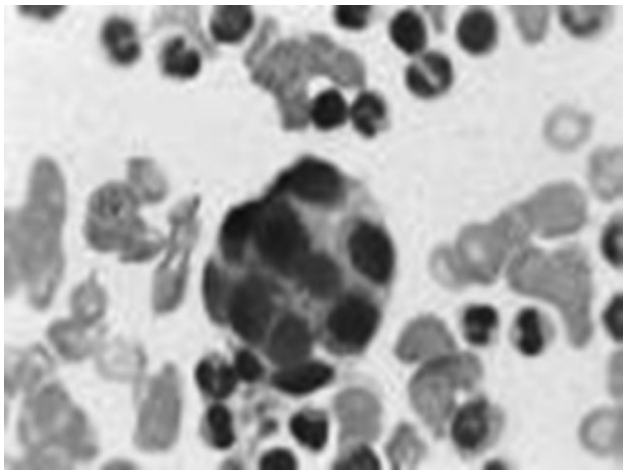

Fig. 1. A bone marrow smear showing the characteristic proliferation of mature histiocytes actively ingesting other blood cells.

histiocytes most commonly involve the bone marrow, but may also be present in the lymph nodes, spleen and liver (Figure 1). However, these findings may be absent in some cases. The differential diagnosis from a posttransplant haemolytic uraemic syndrome or drug-related bone marrow hypoplasia associated with infection may be difficult on clinical grounds. It may also be difficult to distinguish HPS from malignant histiocytosis. The cytologic maturity and the degree of haematophagic activity of the histiocytes may help in the differential diagnosis of these rare diseases. In some patients, however, a clear distinction of malignant from reactive histiocytosis will not be possible until a clonal marker for malignant histiocytes is identified [25].

Pathogenesis of posttransplant HPS

The pathogenesis of posttransplant HPS is not dissimilar to that hypothesized for non-transplant patients. In most cases, HPS was triggered by an opportunistic infection following intensive immunosuppression. In fact, many patients who developed HPS either have been splenectomized [26,32,35], a procedure that renders the patient more susceptible to life-threatening infection [52], or have received the highly immunosuppressive anti-thymoglobulins for induction therapy [41] or have had reinforcement of immunosuppression because of rejection. The high-level production of cytokines, tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) caused by severe infection coupled with abnormalities of CD8+T lymphocyte and NK-cell cytotoxicity caused by immunosuppression may render the immune system incapable of controlling a primary causative infectious agent. This lack of cytotoxicity may explain the excessive Th-1 lymphocyte and macrophage activities, as well as cytokine production, each of which are hallmarks of HPS [53]. The massive tissue infiltration of macrophages explains hepatosplenomegaly, enlargement of lymphnodes and bone marrow inhibition. Fever, cachexia and inflammatory syndrome are consequences of the storm of cytokines. Elevated serum triglyceride levels have been considered to be caused by the inhibition of lipoprotein lipase by cytokines [41].

Prognosis of posttransplant HPS

The prognosis of posttransplant HPS is even more severe in transplant recipients than in non-transplant patients. Reviewing the available literature [26–50], we found that 40 of 76 (53%) renal transplant recipients with HPS died. However, it is possible that a number of deaths (including two cases observed by one of us) have not been reported in the literature. Karras *et al*. [41] found that the cause of HPS was not predictive of the outcome. The risk of death was significantly associated with organomegaly, elevated aminotransferase levels, abnormal prothrombin time and thrombocytopaenia. Only few reports have described the renal outcome in surviving patients. In some patients, the graft function was lost either because patients were nephrectomized as a rescue treatment or because of the onset of an irreversible rejection following a dramatic reduction of immunosuppression or because of graft failure caused by septic shock.

Treatment of posttransplant HPS

The treatment of posttransplant HPS in renal transplant recipients is still a conundrum. Since the clinical picture is dominated by the signs and symptoms of infection, efforts should be made to recognize promptly and treat the etiological microorganism. As pointed out above, the spectrum of microorganisms responsible for HPS is extremely broad, ranging from viral (the most common) to prozoan agents. Cytomegalovirus (CMV) infection should be treated with intravenous ganciclovir resorting to foscarnet or cidofovir, which are both nephrotoxic, to resistant cases. Two cases of posttransplant HPS associated with HHV-8 infection were rescued by reduction of immunosuppression and the administration of foscarnet. One patient with HPS caused by BK virus infection was successfully treated by withdrawal of sirolimus, infusion of intravenous immunoglobulins (IVIg) and increasing prednisone [45]. Specific therapy is required in the cases caused by bacteria, fungi or protozoans. The use of IVIg may be useful both because of their adjuvant activity on treatment for sepsis [54] and because of their complex interference in macrophage activity [55,56]. The results largely depend on the timeline of diagnosis and the severity of disease. Asci *et al*. [46] reported that out of 13 patients with posttransplant HPS, 6 who recovered were all treated with IVIg.

What to do with immunosuppression is still an unresolved issue. In most transplant patients with HPS, the immunosuppressive drugs are reduced in dose or withdrawn in order to improve the resistance to infection. On the other hand, cyclosporine and antithymocyte globulins, that may reduce the activation of Th-1 lymphocytes and their cytokine production, have been recommended in the treatment of HPS in non-transplant patients [57,58]. Minimizing the administration of immunosuppressive drugs while giving intravenous steroids at high doses might be a reasonable compromise. At high doses, steroids can protect from rejection, can reduce the activation of macrophages [59], as well as the cytokine production and effects [60], and can improve survival in patients with septic shock [61,62]. In confirmation of the potential role of corticosteroids, Karras *et al*. [41] found that steroid dosage at diagnosis of HPS was significantly higher in surviving patients. In cases refractory to the above therapeutical attempts, plasmapheresis, leukocytopheresis or etoposide were shown effective in anecdotal life-threatening cases occurring in non-transplant patients [63–65].

On the basis of the available results, we suggest the following steps as soon as diagnosis is made or even suspected. (1) Maximize the antibacterial or antiviral therapy. Waiting for the confirmation of the etiological agent, it is justified to start with a broad-spectrum antibiotic therapy associated with ganciclovir. (2) Stop immunosuppressive therapy with the exception of steroids. (3) Give a bolus of methylprednisolone of 0.5 per day to be repeated for 2–3 days then followed by doses of 60–80 mg intravenously every day. (4) Administer intravenous immunoglobulins (0.4 g/kg every other day for 6–10 days). (5) In cases refractory to the

above-mentioned therapeutical attempts, plasmapheresis or leukocytopheresis, both of which gave effective results in anecdotal life-threatening cases occurring in non-transplant patients [61.62], may be tried.

Conclusions

In conclusion, HPS appears to be rare after renal transplantation, but it is possible that this syndrome has not been diagnosed in an undefined number of patients. The clinical presentation is pleomorphic but dominated by the signs and symptoms of infection. In most cases, HPS is associated with opportunistic infection or neoplasia, but in ∼20% of cases the etiologic factor cannot be identified. The prognosis is severe with about half of transplant patients dying with a clinical picture of multiorgan failure. There is still little consensus on how to treat posttransplant HPS, and this is still far from being established. Intensive supportive therapy and specific treatment of the responsible microorganism are mandatory. Reduction or withdrawal of calcineurin inhibitors, mTOR inhibitors and anti-nucleotide agents is usually recommended in order to control infection, although there is no clear evidence that such measures are actually useful, in view of the potential interference of these drugs on the activation and proliferation of T cells. Intravenous methylprednisolone may reduce the activation of macrophages and cytokines, but a prolonged administration may worsen the underlying infection. There is agreement that IVIg may be helpful and should be administered as soon as possible.

Some new therapeutic options could become available in the near future. In an animal model, Jordan *et al*. [66] showed that CD8+ T cells are necessary for the development of HPS. IFN-γ, which was uniquely essential as well, appeared to be driven by increased antigen presentation to CD8+ T cells. These data might provide new targets for specific therapeutic intervention in this fatal disorder, such as the administration of monoclonal antibodies directed against IL-18 or of recombinant IL-18-binding protein in order to slow down the activity of IL-18 that may induce IFN-γ production and Th-1 lymphocyte differentiation [17–20]. Therapeutic approaches to inflammation and sepsis will certainly be enhanced by an increased understanding of how purinergic receptors modulate the inflammasomes [21,22].

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