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LETTER TO EDITOR

Rescue of Cytokine Storm Due to HLH by Hemoadsorption in a CTLA4-Deficient Patient

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To the Editor,

Systemic inflammatory response to infections with viral or bacterial pathogens triggering excessive cytokine release is life-threatening. In systemic inflammatory response syndrome (SIRS), increased mortality correlates with elevated levels of pro- and anti-inflammatory mediators. SIRS is not only observed in the context of infection but also after serious trauma, burns, or due to primary and secondary hemophagocytic lymphohistiocytosis [1]. HLH is characterized by fever, splenomegaly, bicytopenia, highly elevated serum levels of ferritin and soluble interleukin-2 receptor (sIL-2R), decreased natural killer (NK) cell activity, hypertriglyceridemia, and detection of hemophagocytosis in bone marrow or other tissues. To confirm the diagnosis, at least five of these eight criteria are required [2]. Primary HLH is caused by a defined set of monogenetic defects disabling cytotoxic effector function of NK and T cells and thus causing bouts of increased cytokine release and severe inflammation due to persistent stimuli. Secondary HLH is most commonly seen in the context of EBV infection, other infections, or lymphoma. In the last years, an increasing number of primary immunodeficiencies with an elevated risk of secondary HLH have been identified. Thus, not only X-chromosomal lymphoproliferative disorders and other disorders with reduced EBV control but also chronic granulomatous disease or disorders of immune dysregulation can present as HLH.

CTLA-4 deficiency is caused by a heterozygous germ line mutation of the *cytotoxic T lymphocytic antigen-4 (CTLA-4)* gene leading to a syndrome with prominent features of immune dysregulation [3]. It is associated with autoimmune manifestations, granulomatous or T cell inflammatory infiltration in CNS, lungs, gastrointestinal tract and others, splenomegaly, lymphadenopathy, and recurrent infections due to progressive hypogammaglobulinemia. To date, no report of HLH in CTLA4-deficient patients has been described. Beside immunoglobulin replacement therapy, most patients require immunosuppressive therapy for their lymphoproliferative and inflammatory complications. Recently, as a targeted therapy successful treatment with abatacept, a fusion protein of the IgG1 Fc-region and the extracellular CLTA-4 domain mimicking CTLA-4 action has been described for patients with a related immunodeficiency syndrome [4].

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Here, we describe the first CTLA4-deficient patient who developed secondary HLH due to EBV-induced Hodgkin lymphoma under the treatment with abatacept and the first successful supportive treatment of HLH with hemoadsorption in a patient with underlying immunodeficiency.

The 50-year-old patient was admitted to the intensive care unit (ICU) with SIRS and multi-organ failure in April 2015. One year beforehand, he had been tested positive for a heterozygous germ line mutation in *CTLA-4* as the asymptomatic brother of a female patient with clinically overt CTLA-4 deficiency presenting with antibody deficiency and severe autoimmune enteropathy [3]. In September 2014, he had developed first symptoms with fever, night sweats, and generalized lymphadenopathy. Extensive diagnostic examination did not reveal a cause for the inflammation beside a low copy number of EBV in the peripheral blood. Initiation of immunoglobulin replacement therapy for mild hypogammaglobulinemia and empirical antibiotic treatment as well as corticosteroids could not control the progressive symptoms. Hence, treatment with abatacept was initiated in January 2015.

After transient improvement, the patient was hospitalized for recurrent fever in March 2015. At ICU admission, he presented with highly elevated inflammatory parameters: CRP 173 mg/l (norm <5 mg/l), procalcitonin 13 ng/ml (norm <0.05 ng/ml), and IL-6 5168 pg/ml (norm <17 pg/ml). No pathogens were identified in samples of blood, urine, and bronchial secretion. The CT scan of the whole body did not detect an infectious focus, and the diagnosis of HLH was confirmed with 5/8 positive criteria: fever, splenomegaly, cytopenia (710/μl leukocytes, 4.000/μl platelets, hemoglobin 6.9 g/dl), hypertriglyceridemia (250 mg/dl), elevated ferritin (11.448 ng/ml), and sIL-2R (60.573 U/ml). NK cell activity

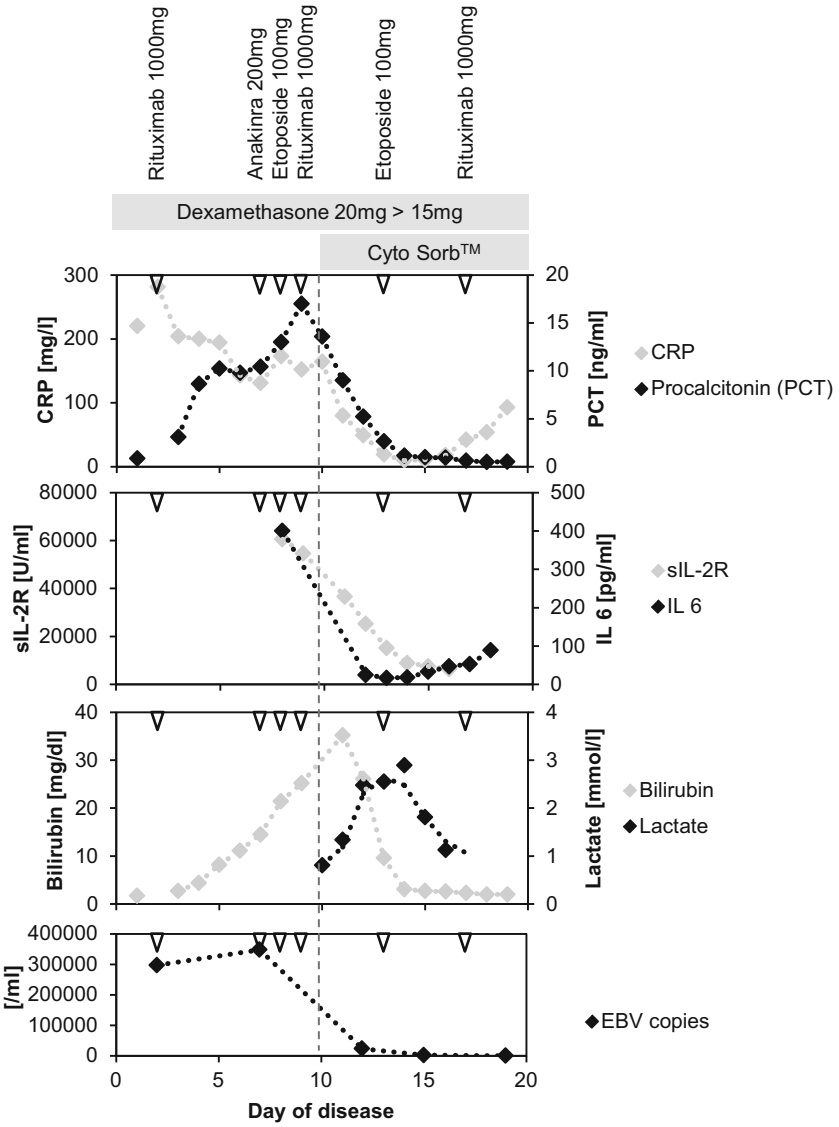

Fig. 1 Profile of inflammatory and HLH parameters: C-reactive protein (*CRP*), procalcitonin (*PCT*), interleukin-6 (*IL-6*), soluble interleukin-2 receptor (*sIL-2R*), bilirubin, lactate, and EBV copies. The *dotted line* indicates the initiation of the hemoadsorption

was not analyzed because of the known underlying genetic defect. Bone marrow examination showed no detectable signs of hemophagocytosis. As a probable trigger, highly replicating EBViremia was identified (350,000 copies/μl).

Oligo-anuric acute renal failure (maximum creatinine 2.34 mg/dl) requiring continuous veno-venous hemodiafiltration occurred due to prerenal acute kidney injury in the context of a hypotonic state requiring catecholamine therapy. Renal biopsy was forgone due to SIRS-induced coagulopathy (INR 1.62, PTT 72 s) and liver failure. Cholestatic hepatopathy rapidly worsened (maximum bilirubin of 35.2 mg/dl, norm <1.4 mg/dl). Mechanical ventilation was initiated for reduced consciousness due to encephalopathy and hypoxic/hypercapnic respiratory failure.

HLH therapy was initiated with high-dose systemic corticosteroids, etoposide, and rituximab because of EBV reactivation. This regimen including additional application of anakinra was not able to overcome SIRS. Because of rapid clinical worsening with progressive multi-organ failure, a cytokine removal column (CytoSorb^{TM}) was added into the circuit of hemodiafiltration after case presentation at the HLH reference center (www.hlh-registry.org). Extracorporeal therapy was continued for 4 days with replacement of the column according the manufacturer's suggestions after 24 h.

Cytokine adsorption resulted in an immediate decrease in inflammatory parameters (Fig. 1); the clinical condition improved in parallel. The patient was discharged to the regular ward 9 days after CytoSorb^{TM} initiation.

Histological analysis of a lymph node removed after the acute phase provided retrospective evidence of an EBV-associated Hodgkin lymphoma as the likely reason for secondary HLH. After finalizing HLH therapy 4 weeks after onset, the patient received one cycle of AVD chemotherapy and a hematopoietic stem cell transplantation from a fully matched non-familial donor. A recent clinical control 12 months after initial diagnosis confirmed a complete remission and complete donor chimerism.

Despite improved treatment protocols, HLH still remains a clinical challenge with a high mortality due to the cytokine storm-induced SIRS. Adjuvant therapies bridging the time from diagnosis to definite therapy of the underlying cause in secondary HLH and stem cell transplantation for primary HLH may be lifesaving. Here, we report the first case of a successful application of extracorporeal hemoadsorption in a patient with CTLA-4 deficiency and SIRS due to secondary HLH triggered by EBV-associated Hodgkin lymphoma. Secondary HLH has been reported in primary immunodeficiencies including X-linked lymphoproliferative syndrome, ITK, and CD27 deficiency [2], less commonly in severe combined immunodeficiency or chronic granulomatous disease, but so far not in patients with CTLA-4 deficiency. In our patient, EBV-associated lymphoma was the probable trigger of HLH. Interestingly, the patient as well as his sister (data not shown) had lost the control over EBV under abatacept therapy. This has been rarely observed in patients with rheumatoid arthritis on abatacept [5] and might point towards a particular risk of patients with predisposing immunodeficiency, which needs to be carefully observed in additional patients.

HLH was treated using the pediatric HLH-1994 protocol [6]. Since the addition of rituximab and anakinra did not stop the progressing inflammatory state, additional hemoadsorption was initiated, which instantly stopped the cytokine storm and enabled an impressive and rapid clinical recovery.

Cytokine adsorbing devices like the CytoSorb^{TM} column (CytoSorbents Corporation, Monmouth Junction, NJ) play an increasing role in the treatment of critically ill patients with severe inflammatory response and hypercytokinemia by continuously removing molecules up to 50 kD through highly porous polymer beads. So far, its usage has been described recently in one patient with fulminant liver failure and HLH due to generalized HSV-1 infection as bridge to transplant with a sufficient removal of bilirubin [7]. We observed rapid reduction of all measured pro-inflammatory cytokines and of severe hyperbilirubinemia in our patient. The instant response within hours after onset of cytokine removal therapy suggests that CytoSorb^{TM} was the decisive therapeutic intervention in this case. The positive outcome warrants further studies exploring column-based cytokine removal as a potentially lifesaving bridging component of treatment strategies in rapidly progressing and refractory secondary and possibly also primary HLH patients.

Compliance with Ethical Standards

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Conflict of Interest KW has received a research grant from BMS, honoraria for consultant services from LFB, and for speaking engagements from Octapharma and Baxalta. FR has received an educational grant and speaker honorarium from Pfizer. Our ICU team received technical support during the CytoSorb^{TM} application by the supplier. CG, PLR, BG, and DD declare that they have no conflict of interest.

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