Case Report
Multi-organ dysfunction syndrome following infectious mononucleosis: case study

Giorgio Berlot1, Ariella Tomasini1, Lorenzo Zandonà2, Eugenio Leonardo2, Rossana Bussani2

1Department of Anesthesia and Intensive Care, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste 34149, Italy; 2Department of Pathology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste 34149, Italy

Received May 16, 2017; Accepted December 30, 2017; Epub November 15, 2019; Published November 30, 2019

Abstract: The authors describe the case of a young woman who developed a clinical picture resembling a septic shock-related multiple organ dysfunction syndrome (MODS) occurred a couple of months after having been diagnosed as a hemophagocytic lymphohistiocytosis (HLH) associated with an infectious mononucleosis. Despite the aggressive treatment, which included antibiotics, vasopressors, iv immunoglobulins and the use of an extracorporeal device aimed to remove mediators released both during sepsis and the HLH-associated cytokine storm, the patient died. At the autopsy, an extremely uncommon aggressive lymphoma of Epstein-Barr virus-positive T-lymphocytes with systemic involvement was discovered.

Keywords: Multiple organ dysfunction syndrome infectious mononucleosis, hemophagocytic lymphohistiocytosis, septic shock, lymphoma

Introduction
Although most patients with infectious mononucleosis (IM) due to a primary infection with Epstein-Barr virus (EBV) recover without major clinical sequelae, in the acute phase of the disease a number of harmful complications can occur, including encephalitis, hepatitis, splenic rupture and hematological abnormalities [1]; however, these latter are not restricted to the acute phase only, as they can develop even later on due to the persistence of EBV in the tissues. The IM-related hemophagocytic lymphohistiocytosis (HLH) is particularly relevant because is characterized by the massive production and release of inflammatory mediators caused by the dysregulated activation of T-lymphocytes, NK-cells and macrophages and the ensuing clinical picture resembles septic shock and can be associated with the occurrence of a multiple organ dysfunction syndrome (MODS) carrying a particularly poor prognosis [2-5]. The tropism of EBV for B-lymphocyte accounts for the occurrence of B-cells lymphoproliferative diseases, including Burkitt, Hodgkin and diffuse large cell lymphomas [6] whereas the involvement of epithelial cells and T-lymphocytes is rather uncommon and has been reported more in Asian and Latin American patients than in European ones [7, 8].

Here we describe the case of a patient who developed a rapid-evolving MODS a couple of months after the occurrence of an IM complicated by HLH.

Case description
A 24-year-old woman was transferred to our ICU with the diagnosis of septic shock from the Dept. of Infectious Disease where she had been admitted thirty-six hours before due to fever attributed to a relapse of an EBV-associated HLH. The history revealed that two months prior to the current hospitalization the patient had been treated in that Department due to an IM complicated by a HLH. The diagnosis of IM was confirmed by the presence of EBV DNA in the bloodstream and the diagnosis of HLH was suspected on the basis of the clinical findings such as persisting fever, the enlargement of the liver and the spleen as well as of blood abnormalities including pancytopenia, abnormally elevated values of ferritin (>
15.000 mcg/ml), triglycerides (789 mg/dl) and of liver enzymes (AST 175 U/L, AST 120 U/L); a bone marrow biopsy confirmed the presence of HLH and demonstrated both the presence of hemophagocytosis and of viral RNA in many cells by means of in-situ hybridization (EBER) [9]. The family history was negative for HLH and a genetic screening excluded the presence of gene mutations associated with its occurrence. The patient was treated with steroids, etoposide, rituximab, cyclosporine, granulocyte-stimulating factor and intravenous immunoglobulins (IvIg) [10] and was ultimately discharged 38 days after the admission; at this time, the viral DNA was no longer detectable in the bloodstream. During her 3-weeks long stay at home, the patient received prednisone, cyclosporine, trimethoprim-sulphamethoxazole and acyclovir through a peripherally inserted central venous catheter (PICC). At the ICU admission, the patient presented high fever (40°C), disseminated intravascular coagulation (DIC), arterial hypotension and acute kidney injury requiring renal replacement therapy (RRT); an oxacillin-resistant Staph. aureus was isolated from the blood cultures and a septic shock-related MODS possibly in association with a cytokine storm caused by the HLH were hypothesized; the patient was intubated and mechanically ventilated and treated with iv. vasopressors at incremental doses, vancomycin, meropenem and caspofungin; the PICC was removed and replaced with a central venous catheter; as the patient remained unresponsive to the treatment, a Coupled Plasma Filtration and Adsorption (CPFA, LYNDAR®, Bellco, Mirandola, Italy) aimed to remove the septic mediators was added to the RTT along with the iv. administration of IgM-enriched IvIg (Pentaglobin®, Biogen; Dreieich, Germany) Despite this increasingly aggressive approach, the MODS further worsened and the patient died 24 hours after the admission.

At the autopsy, the liver and the spleen appeared extremely enlarged, weighting 3110 g and 1230 g, respectively. Microscopically, the spleen showed lymphocyte depletion or punctiform necrosis of Malpighi’s follicles (Figure 1A) and a subversion of the general architecture due to a proliferation of T-lymphocytes (CD3+) with predominant expression of CD8 (Figure 1B). The lymphocyte population B (CD20+, PAX-5+) was virtually absent, while there was a significant increase in monocyte-macrophage component sometimes with hemophagocytic
phenomena. The EBER highlighted several lymphocytes with integrated EBV RNA in the nucleus (Figure 1C). The liver showed numerous perivascular infiltrates of polymorphic lymphocytes like those found in the spleen and many monocyte-macrophage cells (CD14+, CD64+). In the bone marrow there were multiple lymphocyte with polymorphic or “bizarre” nuclei (Figure 2A), that appeared to be almost exclusively CD8+ T-lymphocytes (Figure 2B). Most of these cells were EBER positive (Figure 2C); B-lymphocytes (CD20+, PAX-5+) were almost absent while there was an expansion of the monocyte-macrophage series (CD14+, CD64+).

Discussion

Independently from the cause(s), the current treatment of septic shock is based on the prompt administration of large-spectrum antibiotics and on the cardio-respiratory support [11]; these measures in some ICUs can be associated with the administration of IVIG and with the extracorporeal removal of endotoxin and/or septic mediators. The very same principles of treatment apply to hematological cases, who are increasingly admitted to the ICU. In these patients, the MODS can represent the final common pathway of different conditions, including the primary disease, the treatment-related immunosuppression and the occurrence of HLH, making a precise diagnosis challenging [12]. To further complicate an already compromised condition, the therapeutic options may be in contrast with each other.

This scenario fully applies to our patient.

Initially, the presence of relevant risk factors such as an indwelling PICC and the long-lasting immunosuppressive treatment addressed us toward the diagnosis of a Staph. Aureus-related septic shock which was treated accordingly; however, the failed response to the extremely aggressive treatment implemented led us to hypothesize a possible concomitant relapse of the previously diagnosed EBV-associated HLH; unfortunately, the treatment of this latter, primarily consisting in the administration of strong immunodepressant agents is contraindicated in patients with septic shock [13]; consequently, aiming to remove the mediators which are produced both during HLH and septic shock, we added the CPFA to the already running therapies, but also this approach failed to modify the clinical course and the patient ultimately died.

The autopsy findings revealed that both diagnostic hypothesis were substantially wrong and that the long-term treatment with immunosuppressant agents, albeit indicated for the treatment of the HLH, may have determined the evolution of the underlying chronic active EBV infection towards the aggressive EBV-positive T-cell lymphoma with systemic (splenic, liver, mediastinic and bone marrow) involvement.

It appears that in patients with EBV-related infections the chronic persistence of an elevated viral load represents a risk factor for HLH as well for other severe hematologic complications, including DIC and lymphoma [2, 13, 14]. In the described patient, however, viral DNA
was no more present at the discharge from the dept. of Infectious Disease and this finding contrasts with the massive presence of EBV in all tissues. It is likely that the immunosuppressant agents given to treat the HLH and to prevent its relapse acted as a double-edged sword: from one side they reduced of hemophagocytosis which was present only in marginal amounts at the post-mortem examination of the bone-marrow, but from the other one they triggered the reactivation of the EBV. Actually, lymphoma of EBV-positive T lymphocytes is exceedingly uncommon in western populations and has been attributed either to a possible antiapoptotic action exerted by the viral DNA hosted in the infected T-cells and/or to proliferating signals transmitted by some viral proteins such as Latent Membrane Protein 1 causing the continuous stimulation of members of the TNF receptors [8].

Conclusions

The occurrence of EBV infection-associated HLH and the prevention of its relapse consists in the prolonged administration of immunosuppressant agents possibly associated with bone-marrow transplantation. Likewise other conditions associated with the decrease of the immune capabilities, this treatment exposes the patients to infectious complications, including viral reactivation and overwhelming bacterial infections. The occurrence of aggressive hematologic tumours is uncommon but must kept into consideration in patients with HLH admitted with conditions resembling septic shock.

Disclosure of conflict of interest

None.

Address correspondence to: Giorgio Berlot, Department of Anesthesia and Intensive Care, Catrinara Hospital, University of Trieste, Strada di Fiume 447, Trieste 34149, Italy. Tel: +390403994540; Fax: +39040912278; E-mail: berlot@inwind.it

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