G39 Hemophagocytic Lymphohistiocytosis: A Case Report and Review of the Literature

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The goal of this presentation is to discus a case of a rare hematologic syndrome (Hemophagocytic Lymphohistiocytosis), and a literature review. New data has shown, that in the infection associated form of hemophagocytic syndrome, a selective loss of cytotoxic function in antigen presentation to T cells, creates an imbalance in the immune system, and promotes abnormal/excessive production of T cell derived cytokines, such as Interferon gamma (IFNã), which is quite toxic, and leads to the characteristic clinical and histopathologic features of HLH. This is a rare entity, yet important, because it has a primary and secondary form, which may occur in the young, and in individuals with no known underlying immune deficiency/lymphoproliferative disorder.

This presentation will impact the forensic community and/or humanity by identifying and discussing the different forms of this syndrome, i.e., primary and secondary; its clinical, laboratory and histopathologic findings and its unusual cause of death in those individuals affected by this syndrome. The entity is a hematologic and anatomic/forensic curiosity, with remarkable gross and microscopic findings.

Statement of Methods: This poster will present a case report and literature review of: Sporadic Hemophagocytic Syndrome, and its clinical, laboratory, and histopathologic manifestations, with a focus on its sometimes innocuous presentation as a viral illness, leading to rapid (within 14 days) death in both young and older patients.

Abstract: The focus of this case report is patient EC, a 77-year-old male, who was transferred from an outside hospital to the institution with confusion, ataxia, pancytopenia, diffuse lymphadenopathy/ splenomegaly, and a flu-like illness with temperature spikes to 103° F. His past medical history included CAD s/p MI, dermoid tumors, and hypercholesterolemia. He underwent a cervical lymph node biopsy during admission, which demonstrated a non-clonal proliferation of T-cells with Ebstein-Barr virus positivity (by in-situ hybridization, consistent with mononucleosis). EC was treated with steroids without improvement of his lymphadenopathy. Labs during admission: WBC **2.6**; Hgb **9.5**; Plt **34** Neut: 40.9%; Lymphs: **51.5** %; Eos: 3.6% Absolute Neutrophil Count: **5650**. Serology tests showed EBV IgG positive/Ig negative, CMV IgG positive/IgM negative, RPR negative, HIV negative, toxoplasmosis negative. For his entire hospital admission, he had no bacterial growth in his blood cultures, but did have *S. aureus* positive respiratory cultures.

Within two weeks of admission, EC suffered a non-Q wave myocardial infarction, with an echocardiogram study showing an EF of 25
– 30%. Although the work up of his hematologic aberrancies continued, the patient's medical status deteriorated following his MI.

The patient developed hypoxic respiratory failure and cardiogenic shock, and expired on 15 days after admission.

At autopsy, the body was that of a cachectic older male with marked generalized lymphadenopathy. Histologic findings included a newly diagnosed pleomorphic high-grade large B-cell lymphoma, which showed EBV positivity and systemic hemophagocytic lymphohistiocytosis. The presence of the stain LMP-1 in most of the lymphoma cells is consistent with an EBV-driven disorder. There was also evidence of a remote myocardial infarct and pleural fibrosis.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by uncontrolled hyper-inflammation on the basis of various inherited or acquired immune deficiencies. It is also characterized by clinical, laboratory and histologic findings. The clinical symptoms/signs include: fever, severe constitutional symptoms, lymphadenopathy, hepatosplenomegaly, icterus/jaundice, neurologic symptoms (seizures, CN palsies, encephalitis, meningismus) and rash (maculopapular/nodular eruptions). Laboratory criteria include: pancytopenia (cytopenia in at least two cell lineages), hypertriglyceridemia, high ferritin, transaminases, bilirubin, and LDH. Also, hypofibrinogenemia, high levels of the á chain of the soluble IL-2 receptor and Impaired function of Natural Killer Cells and cytotoxic T cells. Histopathologic findings are: reactive and systemic proliferation of benign histiocytes that phagocytose blood cells and their precursors in bone marrow, and or spleen. EC fulfilled the criteria for the acquired form of hemophagocytic syndrome, due either to an EBV infection, lymphoma, or a combination of both: an EBV-driven high-grade lymphoma.

Familial forms (FHLH) hemophagocytic lymphohistiocytosis is the entity where HLH is the primary and only manifestation, occurring in approximately in 1/50,000 births. FHLH is associated with immune deficiencies such as: Chédiak-Higashi Syndrome, Griscelli Syndrome, and X-linked lymphoproliferative

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Syndrome. Secondary (Sporadic) HLH is associated with the trigger of a benign or neoplastic disease (most patients have no known underlying immune deficiency), such in the patient, EC. Various infectious microorganisms, mostly viruses, such as EBV, but also bacteria, protozoa and fungi, induce secondary HLH. In a review article from 1996 of children with infection-associated hemophagocytic syndrome (IAHS) EBV was found to be the triggering event in 74% of cases. HLH may also occur as a complication of rheumatologic disorders (macrophage activation syndrome), malignancies (especially T cell lymphomas), also known as Lymphoma associated Hemophagocytic Syndrome (LAHS). EBV was detected only rarely in those with B- cell lymphomas, and much more so, 80%, in patients with T/NK lymphomas. The median survival time with pts with LAHS is about 11 days.

New data about what the possible etiologies are for sporadic hemophagocytic syndrome have shown that uncontrolled secretion of cytokines may stimulate the proliferation and phagocytic activity of macrophages, and therefore cause widespread inflammation, and the severe pancytopenia seen in this entity. More specifically, a selective loss of cytotoxic function in antigen presentation to T cells, creates an imbalance in the immune system, and promotes abnormal/excessive production of T cell derived cytokines, such as Interferon gamma (IFNã), which is quite toxic, and leads to the characteristic clinical and histopathologic features of HLH.

In conclusion, in the presented case, the clinical, laboratory, and autopsy findings demonstrate case of Secondary Hemophagocytic Lymphohistiocytosis. The disease entity has specific clinical, laboratory and histopathologic findings, and when sporadic, can present as an innocuous viral illness, as in EC's case, with fatalities occurring within two weeks of presentation, due to uncontrolled hyper-inflammation and activated macrophages/histiocytes that kill/ingest all hematopoietic elements, causing widespread pancytopenia.

Hemophagocytic Lymphohistiocytosis, Ebstein Barr Virus (EBV), Interferon Gamma (IFNã)

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