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Understanding Disseminated Intravascular Coagulation and Hepatobiliary Dysfunction Multiple Organ Failure in Hyperferritinemic Critical Illness

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In the present issue of the journal Goldman and colleagues¹ report in a case series of 43 patients treated with antibiotics for sepsis who were considered to have Hemophagocytic Lympho Histiocytosis (HLH), that the Multiple Organ Failure (MOF) pattern of combined Disseminated Intravascular Coagulation (DIC) and Hepatobiliary Dysfunction was associated with 77% mortality compared to 0% without either of these organ failures. This organ failure pattern was seen in 1 of 3 patients with genetically defined familial HLH (33% overall mortality), 5 of 6 patients with cancer associated secondary HLH (100% overall mortality), 1 of 3 patients with autoimmune associated macrophage activation syndrome / secondary HLH (33% mortality overall), and 14 of 31 patients with hyperferritinemic sepsis induced multiple organ failure / idiopathic secondary HLH (42% mortality overall). This organ failure pattern has been described by Shakoory et al² as diagnostic of sepsis associated macrophage activation syndrome (MAS) in adults; whereas, Kyriazopolou et al³ has defined adult sepsis associated macrophage activation like syndrome by a Histiocytosis Score > 151 or the combination of DIC and hepatobiliary organ failure.

What is known about the pathobiology of this MOF pattern in the critical care setting?

In 1988, Suster and colleagues⁴ reviewed bone marrow, lymph node, and spleen histology from 230 consecutive adult autopsies to identify cases of Histiocytic Hyperplasia with Hemophagocytosis (HHH) a relatively rare condition that had initially been mistaken for a neoplastic order. They reported moderate to severe HHH in 102/230 bone marrows (44%), 79/191 lymph nodes (41%) and 16/209 spleens (8%). There was a strong dose related relationship to blood transfusions (adjusted odds ratio 59.9 5 compared 0) and bacterial

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sepsis (adjusted risk ratio 4.10). Surgery and viral infections were only marginally associated. The authors concluded that reactive HHH represented a frequent secondary phenomenon in critically ill patients undergoing transfusions that should not be mistaken for an ominous sign or for the development of superimposed malignancy. In 2004, Strauss and colleagues⁵ evaluated 107 consecutive MICU patient autopsies and found mild to severe HHH in 69 (64.5%). The authors similarly found HHH to be associated with sepsis and blood transfusions. Patients with HHH were less likely to have died due to cardiovascular causes (HHH 22/69, 32% vs. no HHH 28/38, 74%; $p<0.01$) and more likely to die due to MOF (HHH 27/69, 39% vs. no HHH 7/38, 18%; $p<0.05$) with elevated bilirubin, liver enzymes, and disseminated intravascular coagulation. Patients with HHH also required more catecholamine infusions, mechanical ventilation, and CRRT. The authors correlated severe HHH with more siderosis and CD8 T-cells in bone marrow suggesting T-cell activation and hence the clinical name Macrophage Activation Syndrome (MAS) / Secondary Hemophagocytic Lympho Histiocytosis (HLH).⁶⁻⁹

Several experimental models produce macrophage activation induced MOF. Steinberg et al developed the sterile model of zymosan (saccharomyces A) plus mineral oil intraperitoneal injection induced MOF.¹⁰ This model results in initial hypovolemic shock followed by persistent macrophage activation. Injection of either zymosan or mineral oil alone does not induce MOF because the combination of Toll-Like Receptor (TLR) stimulation and unremitting particulate irritation is required for persistent macrophage activation to occur. Behrens et al.¹¹ similarly reported that repeated, not single time, TLR stimulation with CpG oligodeoxynucleotides transforms an otherwise innocuous endotoxin challenge into a MOF model with cytopenias, splenomegaly, hyperferritinemia, and hepatitis. Similarly, in a murine model of cecal ligation and perforation induced peritonitis and liver injury, CpG injection induces cytokine production by macrophages and hepatic mononuclear cells with MODS induced mortality.¹² The MAS/2°HLH phenotype associated with repeated TLR9 stimulation can be exacerbated in knockout mice deficient in native hepatic IL-1ra production and ameliorated by IFN- α induced production of IL-1ra or with direct administration of recombinant IL-1ra (anakinra) itself *in vivo*.¹³ Liver dysfunction is related in part to IL-1 mediated inflammation.¹⁴

Macrophage activation syndrome/2°HLH is classically defined by the presence of 5 of 8 clinical criteria which include Ferritin > 500ng/ml, two line cytopenia, organomegaly, hypertriglyceridemia, hypofibrinogenemia, elevated sCD25, absent NK cytotoxic activity, and hemophagocytosis.⁷ Demirkol et al evaluated organ dysfunction patterns in a center specific cohort study of Turkish children using these criteria to identify hyperferritinemic sepsis MAS/2°HLH.¹⁵ To reduce the likelihood that familial HLH patients were being studied, the authors eliminated children who were under 2 years, had consanguinity, or a history of a previous young family member dying from fever. All the children with MAS/2°HLH had 5 to 6 organ failure MODS with hepatobiliary dysfunction and DIC. Centers in one treatment cohort administered dexamethasone and/or chemotherapy with daily plasma exchange and observed a 50% survival rate; whereas, centers in the other treatment cohort administered methylprednisone and/or IVIG with daily plasma exchange and observed a 100% survival rate. MOF resolved as ferritin levels became normal. Patients who did not resolve MODS

had persistent hyperferritinemia (persistent macrophage activation) and infection and likely died from too much immune suppression.

Because sCD25 levels, NK cytotoxicity, and hemophagocytosis are not easily accessible clinical tests, rheumatologists have sought to redefine autoimmune MAS/2° HLH by organ dysfunction patterns that use more readily available laboratory tests. In this regard Ravelli and colleagues¹⁶ have provided a consensus statement that any child with a known diagnosis of systemic juvenile arthritis (sJIA) who presents with fever and a ferritin > 684 ng/mL with any two of the following; platelet count < 181 K, ALT > 48 IU/L, triglycerides > 156 mg/dL, and fibrinogen < 360 mg/dL can be considered as having met criteria for MAS /2°HLH and therefore eligible for therapy, or clinical trials. In this regard, Shakoory and colleagues considered the combination Hepatobiliary dysfunction and Disseminated Intravascular Coagulation (DIC) as representative of features of MAS in adults with severe sepsis. They hypothesized that if the combination of these two organ dysfunctions represents MAS / 2°HLH then treatment with IL-1 receptor blockade should improve sepsis related MAS as it does sJIA related MAS.^{17, 2} In a secondary analysis of an adult severe sepsis IL-1 receptor blockade trial they compared patients with combined Hepatobiliary dysfunction (HBD) and DIC (HBD + DIC) to those without this combination (non HBD + DIC) and found the following: 1) Only 5.6% of severe sepsis patients had these features of MAS (HBD + DIC), 2) patients with these features of MAS had higher incidence of shock (HBD + DIC = 95% vs non HBD + DIC = 79%), and acute kidney injury (HBD + DIC = 61% vs non HBD + DIC = 29%), but not acute respiratory distress syndrome (HBD + DIC = 21% vs non HBD + DIC = 26%), and 3) although IL-1 receptor blockade had no effect on non HBD + DIC 28 day survival (IL-1 blockade = 71% vs placebo 71%) it significantly increased HBD + DIC 28 day survival (IL-1 blockade = 65.4% vs placebo 35%). If HBD + DIC is indeed reflective of MAS/2°HLH then we can conclude that the condition is rare but associated with a high incidence of MODS and death, and remediable in part by IL-1 receptor blockade.

How do we treat the condition?

More recent case series have similarly shown that outcomes in HLH/MAS/ Sepsis MOF patients with DIC and hepatobiliary dysfunction can be better than expected not when using etoposide and dexamethasone, but rather when using less immune suppressive regimens including methylprednisone, IVIG, anakinra and plasma exchange to reverse organ failure.^{18,19} We recently described the pathophysiologic basis for these observations as well as putative therapies to be considered.²⁰⁻²³ According to our reviews, the MOF pattern of DIC and hepatobiliary dysfunction requires 1) plasma exchange therapy to reverse coagulopathy/ DIC, and to remove ferritin and free hemoglobin which together are important mediators of feed forward inflammation, 2) IVIG to neutralize DNA viremia which stimulates TLR9 activation and induces liver injury, and 3) anakinra to stop cytokine induced liver injury.

Other therapies should also be considered that address the cause of the uncontrolled inflammation leading to organ failure. Benefit or harm of these therapies can be monitored by measuring C-reactive protein and ferritin level response with CRP levels decreasing to < 4 mg / dL and ferritin levels to < 1,000 ng /mL being considered a favorable response.^{24,25} For the most part uncontrolled inflammation is considered to be the result of reduced NK

cell ability to kill viruses, cancer cells and activated immune cells such as host CD8 cells and macrophages. If uncontrolled inflammation is driven by primary HLH with hopelessly qualitatively defunct NK cells and proliferating CD8 cells then etoposide is needed to kill CD8 cells and reduce interferon gamma production. Somewhat similarly, if inflammation is driven by proliferating cancer cells then chemotherapy or preferably immunotherapy will be needed. However, if inflammation is driven by autoimmune disease with NK cell function being present but somewhat diminished then corticosteroids will be needed, preferably methyl prednisone rather than dexamethasone, to control inflammasome overactivation. On the other hand, if inflammation is driven by sepsis with temporarily diminished NK cell and T cell numbers then rapid source control will allow immune cell numbers to recover and then control inflammation. Some of these children who have an atypical HUS like presentation may also have overactivation of complement related to inadequate inhibitory complement production. This too can be remedied with plasma exchange restoring normal inhibitory complement levels. In contrast to primary HLH patients, septic patients have decreased CD8 cell numbers and interferon gamma levels are suppressed rather than elevated so etoposide is not recommended as it prolongs rather than reverses inflammation. Under the circumstance that inflammation is driven by CART mediated lymphocyte and cancer cell lysis therapy, tocilizumab (IL-6 antibody) can be an effective treatment.

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Figure.

Understanding DIC and hepatobiliary multiple organ failure during sepsis