T-cell-rich B-cell Lymphoma with Secondary Hemophagocytic Lymphohistiocytosis Presenting as Acute Liver Failure – Chung Ki Wong

**Abstract:**

Malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH) is mostly associated with T/NK cell lymphomas and Hodgkin’s lymphoma, but it is relatively uncommon in patients with B-cell lymphomas. This is a case of a patient with acute liver failure caused by malignant infiltration by T-cell rich B-cell lymphoma and secondary HLH.

**Introduction:**

Hematological malignancies such as Hodgkin’s lymphoma, non-Hodgkin’s lymphomas, and leukemias can cause malignant infiltration of the liver. Malignant infiltration and malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH) can simultaneously present as acute liver failure (ALF) and carry a poor prognosis with > 60% mortality rate.

**Case Report:**

A 62-year-old man presented as a direct admit from PCP office with elevated LFT’s and a 3-month history of generalized weakness, fatigue, daily fevers of 101-102 degrees. His past medical history was significant for Castleman’s disease s/p splenectomy, portal vein thrombosis, asthma, and recently diagnosed sarcoidosis without biopsy. He was a never smoker and consumed alcohol occasionally. Labs on presentation revealed anemia, thrombocytopenia, and transaminitis.

After hospitalization, patient continued to have low-grade fevers with hemoglobin 9.3 g/dL, platelet 77,000/mm3, alanine aminotransferase 268 U/L, aspartate aminotransferase 199 U/L, serum ferritin > 70,000 ng/mL, and serum triglycerides of 348 mg/dL. CT scan of the abdomen and pelvis was significant for multiple nonspecific hepatic lesions with numerous periportal, retroperitoneal, and right iliac lymphadenopathy. Liver biopsy showed patchy areas of lymphohistiocytic infiltrate, while subsequent bone marrow biopsy revealed atypical lymphohistiocytic infiltrate with additional findings suggestive of T-cell-rich B-cell lymphoma. He also met criteria for HLH with fever, anemia, thrombocytopenia, hypertriglyceridemia, and elevated ferritin level. Upon further investigation, he was noted to have markedly elevated soluble IL-2 receptor alpha, which is specific for the diagnosis of HLH. Patient was started on R-CHOP for lymphoma along with etoposide and dexamethasone for HLH . Unfortunately, by his third cycle of chemotherapy, patient developed worsening metabolic acidosis and septic shock secondary to bacteremia and fungemia. Despite aggressive treatment, patient continued to deteriorate rapidly. With full capacity to make his own decision, he opted for supportive care only approach and was discharged to hospice care facility.

**Discussion:**

In addition to T-cell-rich B-cell lymphoma, this patient also presented with secondary HLH. HLH is not a malignancy; it is a syndrome of excessive inflammation and tissue damage caused by a lack of down-regulation of activated macrophages and lymphocytes. While primary HLH refers to HLH caused by a genetic mutation, secondary HLH can be a manifestation secondary to any infection, malignancy, or rheumatologic condition. 27% of secondary HLH is related to malignancy with the majority being hematologic malignancies. According to one retrospective population-based analysis, the estimated annual incidence of M-HLH in adulthood was 0.36/100,000 individuals/year. If left untreated, patients with HLH survive for only a few months secondary to progressive multi-organ failure.

The diagnosis of HLH is difficult because of its rare occurrence, variable clinical presentation, and the non-specific laboratory findings. Nonetheless, the diagnosis is often made by identifying a mutation in an FLH gene, or by fulfilling 5 out of 8 diagnostic criteria. H score is a diagnostic scoring system consisting of 12 variables designed to estimate the probability of HLH; for instance, fever, immunosuppression, hemoglobin level, leukocyte level, and triglyceride level. An H score ≥ 250 confers a 99% probability of HLH, whereas a score of ≤ 90 confers a < 1% probability of HLH. Our patient met 6 out of 8 criteria and had an H score of 254, making the probability of HLH 99%. Based on the HLH-94 protocol, which is the mainstay of HLH treatment, he was initiated on weekly treatment with etoposide and dexamethasone. The goal of therapy is to suppress systemic inflammation by destroying immune cells.

Besides malignant hepatic infiltration by concurrent T-cell-rich B-cell lymphoma, our patient also suffers from M-HLH induced liver failure. Liver involvement in HLH is common and results in marked elevation of liver enzymes. The probable mechanism of liver injury is considered secondary to infiltration of hemophagocytic histiocytes or due to overproduction of cytokines.

Hematologic malignancies and M-HLH can present simultaneously as acute liver failure and are associated with a poor prognosis. Once a high likelihood of HLH is established, evaluation for multi-organ involvement including bone marrow biopsy, liver biopsy, lymph node biopsy, and immunologic profiling should be initiated as soon as possible. Prompt induction of immunosuppressive treatment and chemotherapy are crucial for the survival of affected patients but HLH still carries a high mortality.

**Conclusion:**

In conclusion, hematologic malignancies and secondary HLH can present simultaneously as acute liver failure and are associated with a high mortality. In patients presenting with B symptoms such as fever, chills, weight loss, as well as hepatosplenomegaly, malignancy workup should be initiated as soon as possible. While starting chemotherapy and immunosuppressive therapy can be lifesaving, HLH is associated with high mortality rate with an average survival of 2-12 months.

**References:**

1. Machaczka M, Vaktnäs J, Klimkowska M & Hägglund H. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: a retrospective population based analysis from a single center. *Leukemia and Lymphoma*. 2011;52(4):613-19.

2. McClain K, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. In: Rosmarin A, ed. *UpToDate*. Waltham, Massachusetts: UpToDate, 2018.

3. McClain Kenneth. Treatment and prognosis of hemophagocytic lymphohistiocytosis. In: Rosmarin A, ed. *UpToDate*. Waltham, Massachusetts: UpToDate, 2018.

4. Patel K, Lee S, Valasareddy P, Vontela N, Prouet P & Martin M. Genetic analysis of B-cell lymphomas associated with hemophagocytic lymphohistiocytosis. *Blood Advances*. 2016;1:205-07.

5. Patel R, Patel H, Mulvoy W & Kapoor S. Diffuse large B-Cell lymphoma with secondary hemophagocytic lymphohistiocytosis presenting as acute liver failure. *ACG Case Reports Journal.* 2017;4:e68.