

Warm Autoantibodies in a Patient with Hemophagocytic Lymphohistiocytosis: A Case Report

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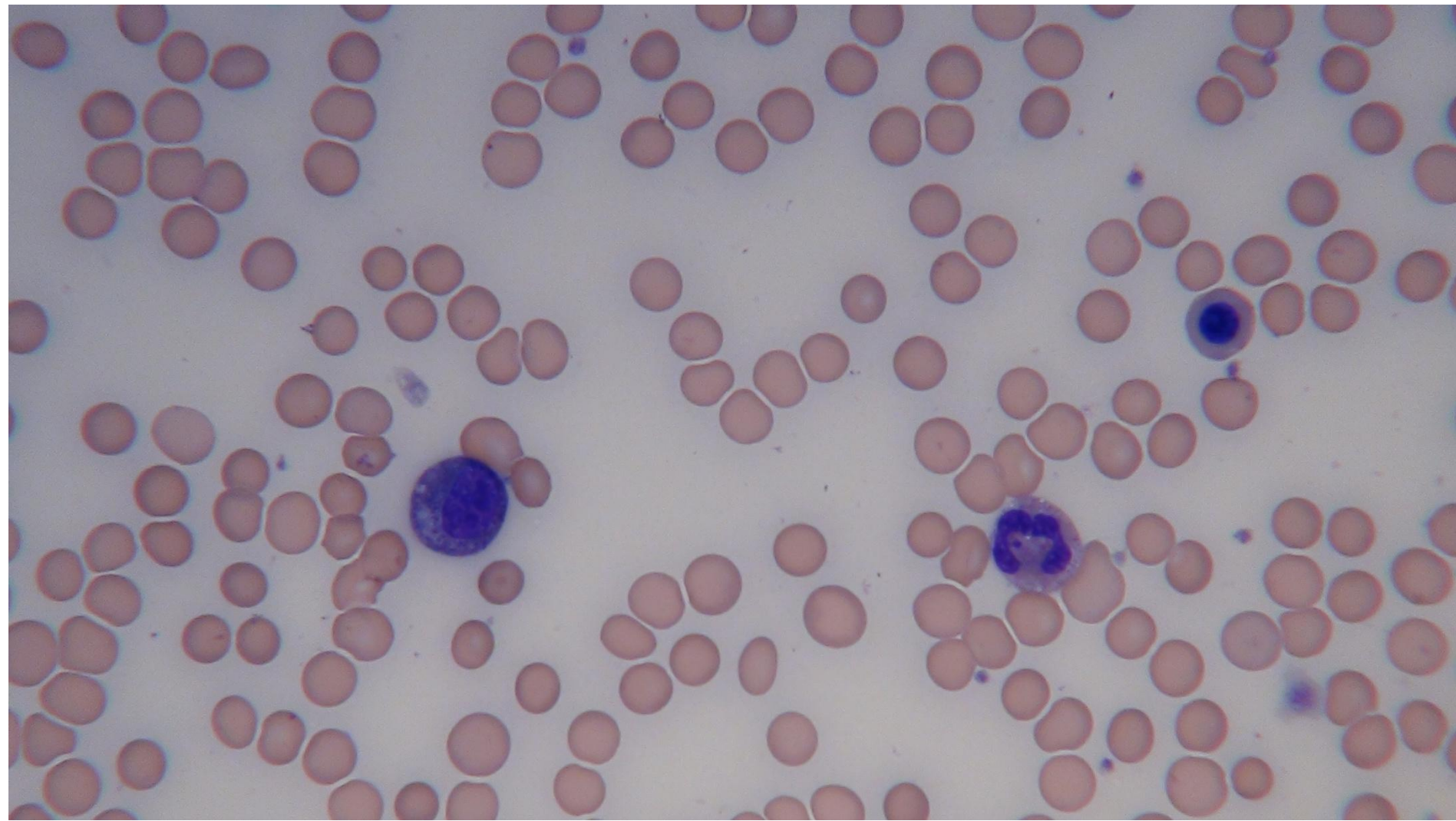
Case Presentation

- 58 y/o female admitted with a one week history of fatigue, weakness and jaundice.
 - A few weeks prior to the onset of symptoms, she had a respiratory infection for which she took amoxicillin.
 - Past medical history of hypothyroidism treated with levothyroxine. No other home medications.
 - She has three children. No previous transfusions. No history of illegal drug use.

Labs

Bilirubin	45.7 mg/dL	WBC	4.6 10 ³ /mcL
Direct Bili	>10 mg/dL	Hemoglobin	11.1 g/dL
ALT	942 unit/L	Platelet	177 10 ³ /mcL
AST	1,036 unit/L	Ferritin	6,084.0 ng/mL

- Within less than 24 hours of admission, hemoglobin dropped from 11.1 g/dL to 9.7 g/dL → 8.8 g/dL → 8.2 g/dL. No obvious source of bleeding.
- A peripheral smear was ordered...



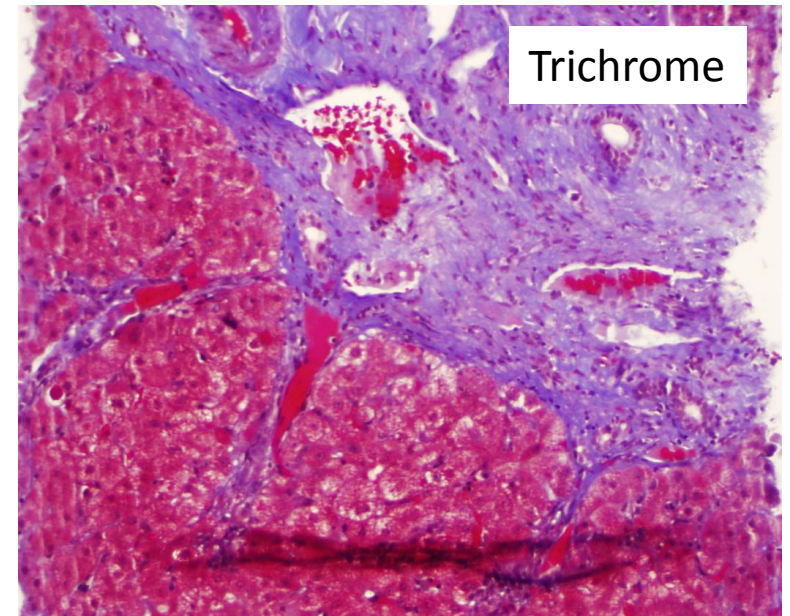
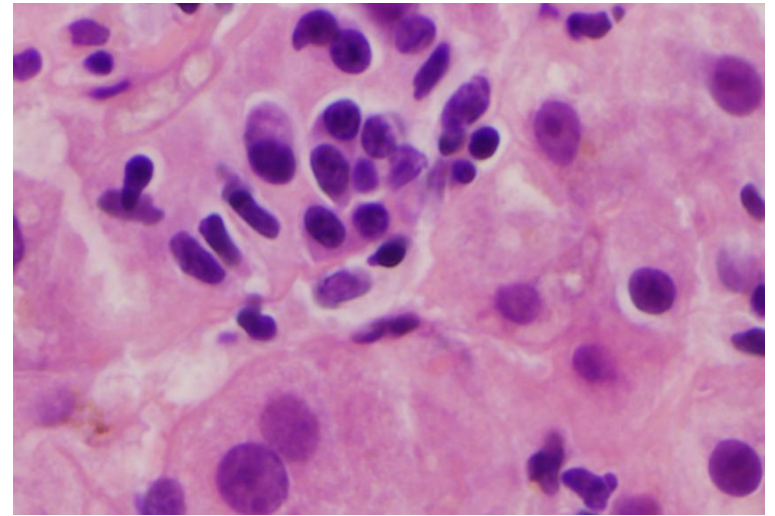
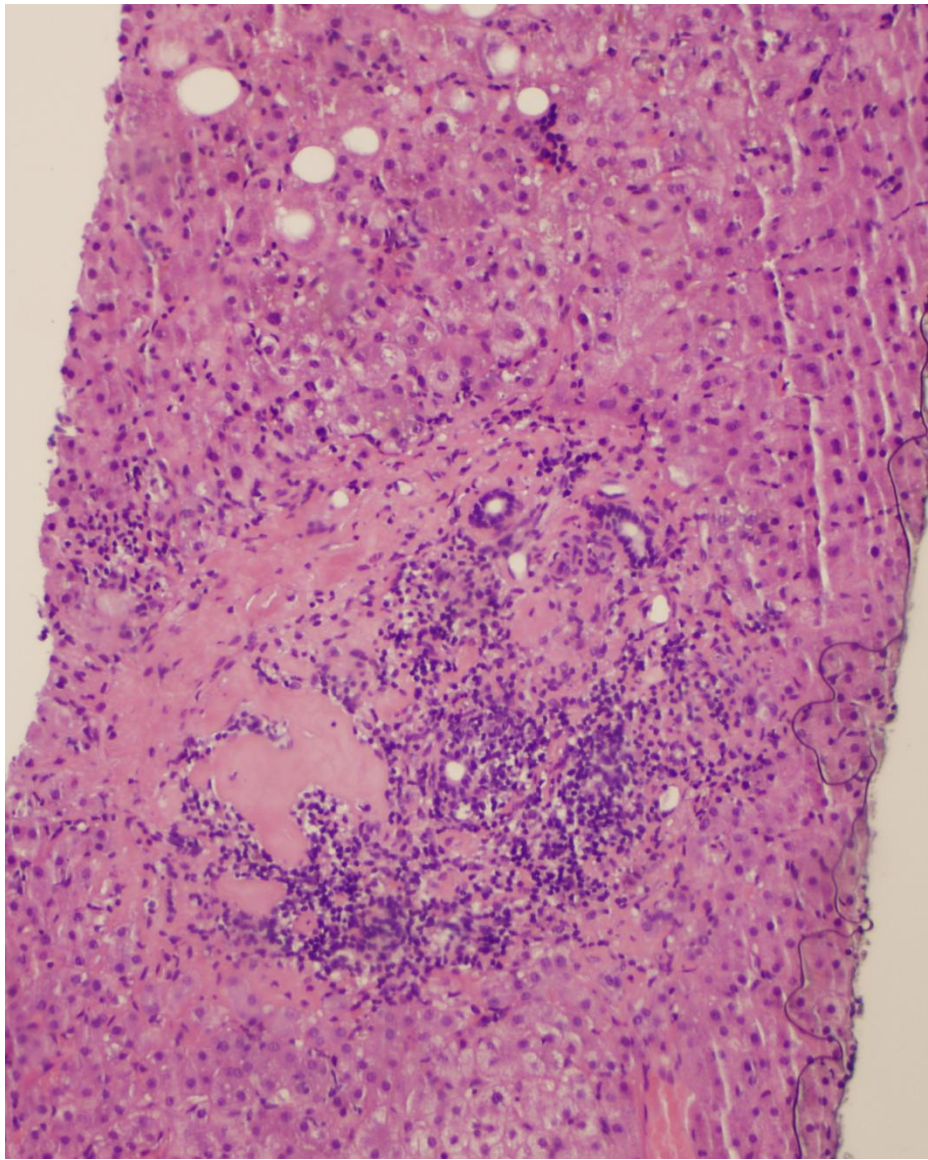
Macrocytic, normochromic anemia with anisopoikilocytosis and polychromasia. Rare schistocytes and teardrop cells. Leukopenia with left shift and neutrophil vacuolation. Scattered large form platelets.

Case continued

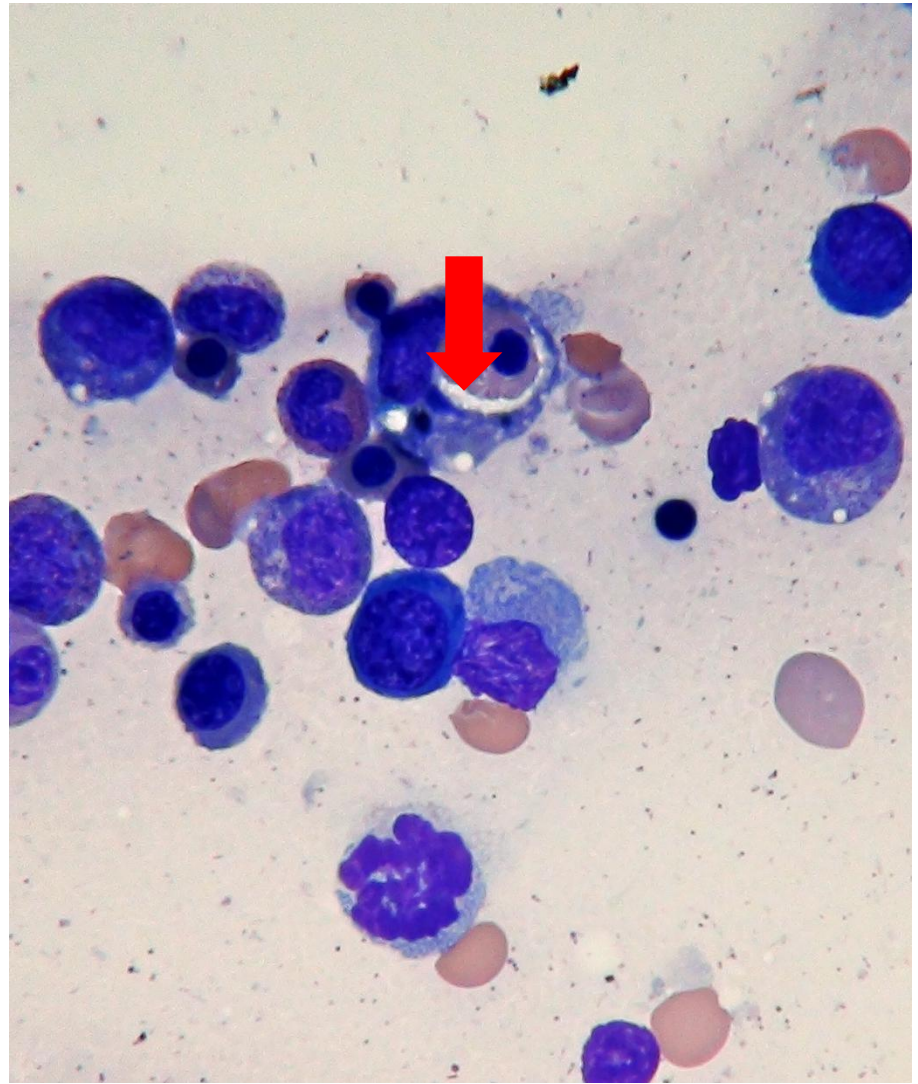
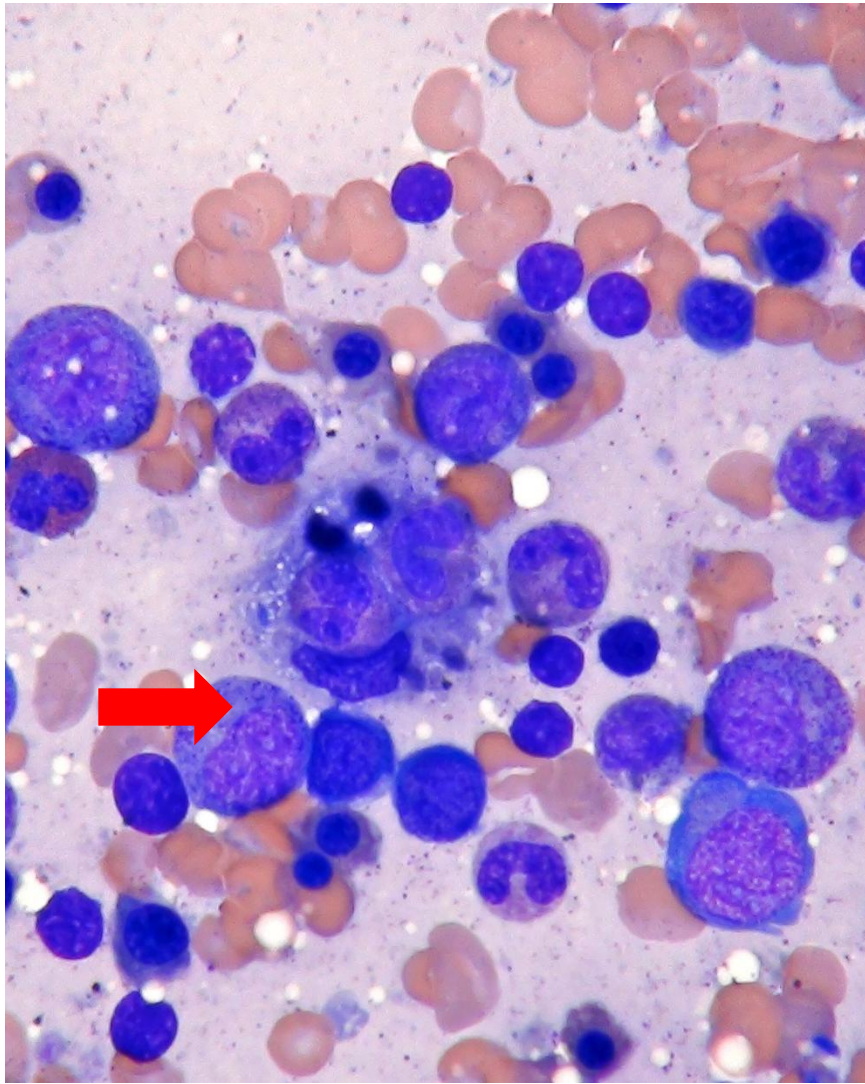
- Type and crossmatch was ordered.
 - ABORH: O positive
 - Gel ABSC: positive (both cells on 2 cell screen)
 - ABID: all cells on gel panel positive with a positive auto control
 - DAT: 3+ with Poly, 3+ IgG, negative with C3
 - Elution: negative
- Sample sent to reference lab for adsorptions.
 - Reference lab report: Broad reactivity detected at LIS-IgG and Gel-IgG. Broad reactivity in the serum alone with a positive DAT and negative eluate is suggestive of drug related antibody. No alloantibodies detected following allogenic adsorption.
- Additional sample sent to different reference lab for drug studies to look for presence of Amoxicillin dependent red cell antibodies.

Case continued

- The patient was transferred to the ICU for transfusion of 'least incompatible' RBCs.
- Radiologic imaging of chest, abdomen and pelvis was significant only for mediastinal and peri-portal lymphadenopathy.
- Based on these findings, the differential diagnosis included:
 - Drug-induced hemolytic anemia and hepatitis/cholestasis (recent amoxicillin use)
 - Autoimmune disease (Still's disease)
 - Hemophagocytic lymphohistiocytosis post viral infection (EBV, CMV)
 - Lymphoproliferative process (mediastinal and peri-portal lymphadenopathy on imaging)
- Liver biopsy and bone marrow biopsy were performed...



Hepatitis with periportal, lobular and bridging necrosis. Fibrosis with septa formation. Comment: Combined with clinical features, these findings support a diagnosis of Autoimmune Hepatitis (AIH).



Trilineage hematopoiesis with erythroid hyperplasia and hemophagocytosis.
Comment: Combined with clinical and morphological features, this case is suspicious for hemophagocytic syndrome.

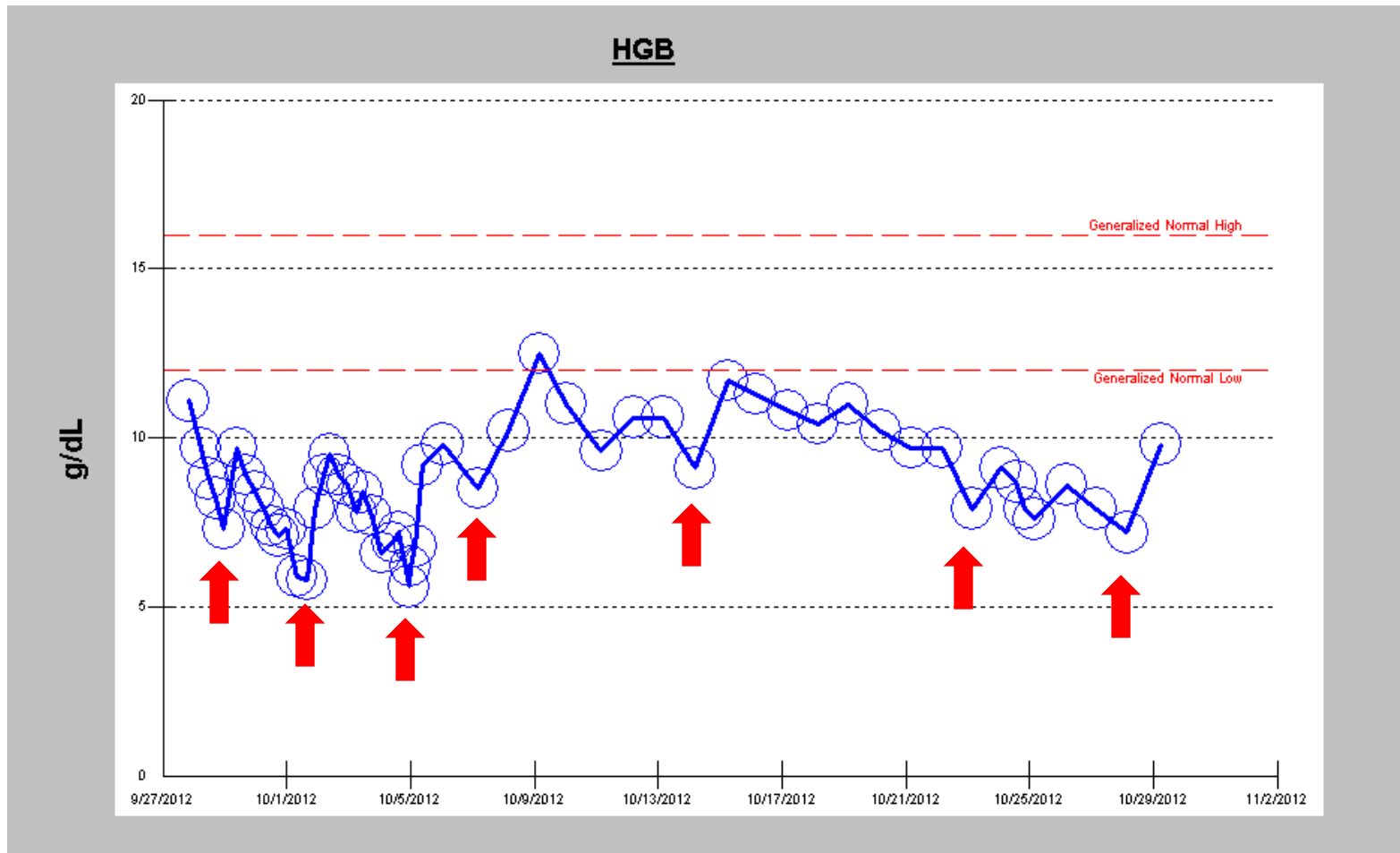
Case continued

- Testing for anti-amoxicillin antibodies
 - Reference lab report: No drug-dependent antibody was detected. Although testing for amoxicillin dependent red cell antibodies was negative, the findings of a strongly positive DAT due to IgG and a negative eluate are suggestive of drug induced hemolytic anemia. Results need to be correlated carefully with patient's clinical course.
- The patient was diagnosed with:
 - Autoimmune hemolytic anemia,
 - Autoimmune hepatitis, and
 - Hemophagocytic lymphohistiocytosis.

Clinical Course

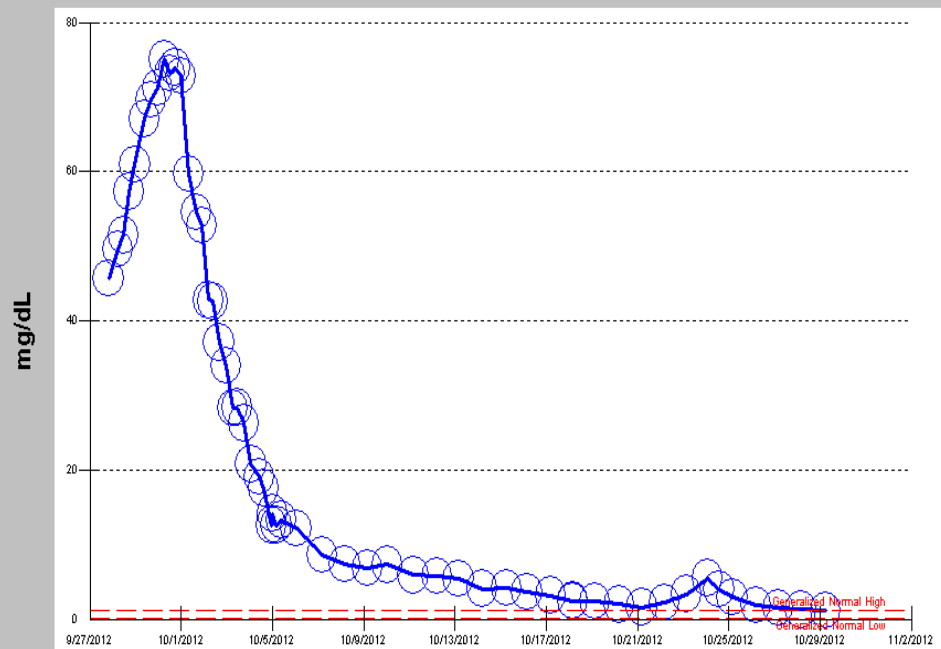
- Total blood products transfused during one month hospital stay: 13 RBCs, 4 PLTs
- She was treated IV steroids, IVIg, Rituximab, and Etoposide.
- After three weeks of treatment, repeat type and crossmatch revealed negative DAT/negative antibody screen.

Hemoglobin

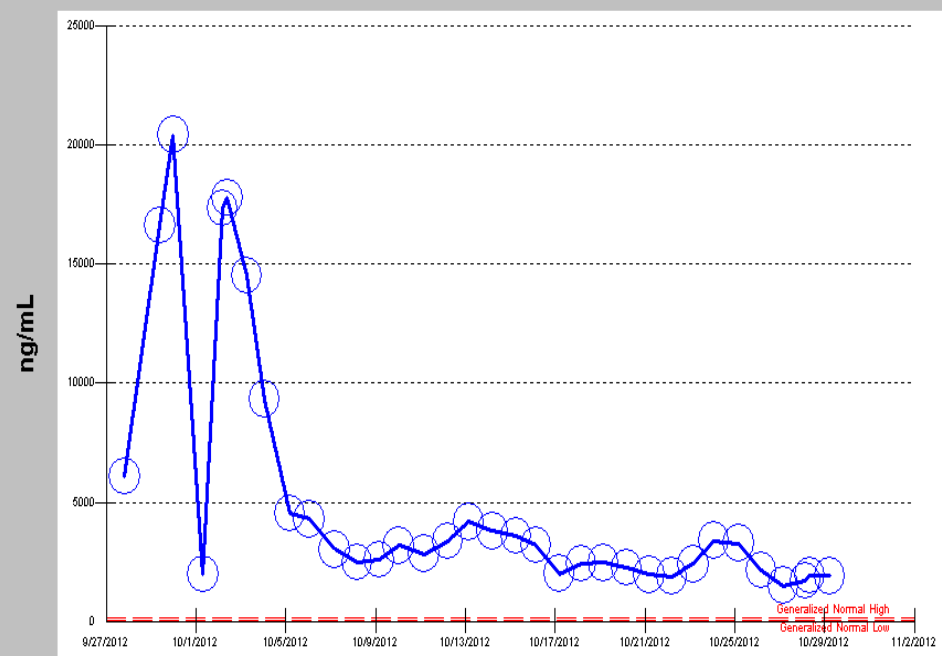


↑ = RBC transfusion

Total Bilirubin



Ferritin Level



Hemophagocytic Lymphohistiocytosis

- Rare clinical syndrome triggered by a variety of conditions characterized by a highly stimulated, but ineffective, immune response to antigens. This leads to a life-threatening cytokine storm and inflammatory reaction.
- Caused by inherited or acquired defect in NK cells and T-lymphocytes, resulting in uncontrolled proliferation of activated T lymphocytes and histiocytes, which phagocytose other cells.
- Death in >90% of patients if untreated.

Hemophagocytic Lymphohistiocytosis

- AKA Hemophagocytic syndrome, Macrophage-Activation Syndrome, or Malignant Histiocytosis
- Types
 - Primary: Rare autosomal recessive disorder presenting in infancy or early childhood, 6 types based on different genetic mutations.
 - Secondary: triggered by infections (EBV, CMV, HSV, influenza, adenovirus, bacteria, fungi, ehrlichiosis), autoimmune disease (SLE, Still's disease, RA), immunosuppression from organ transplants, hematologic malignancies.

Diagnostic Criteria for HLH (must meet at least 5 criteria)

- Fever
- ★ • Splenomegaly
- ★ • Cytopenia involving two or more cell lines
- ★ • Hypertriglyceridemia or hypofibrinogenemia
- ★ • Hemophagocytosis
- ★ • Low or absent natural killer cell activity
- ★ • Serum ferritin level >500 $\mu\text{g/L}$
 - Soluble CD25 >2400 U/mL
- ★ Present in our patient

Hemophagocytosis

- Not required to diagnose HLH
- Not specific for HLH
 - Can also be seen in patients who have received blood transfusion and incidentally in lymph node biopsies
 - One study found 64.5% of ICU patients with fatal sepsis had hemophagocytosis at autopsy

Ferritin

- Acute Phase Reactant
- Ferritin > 500 is 82% sensitive and 42% specific for HLH.
- Ferritin $> 10,000$ is 90% sensitive, 96% specific for HLH.
- Ferritin $> 10,000$ is seen in a limited number of conditions: HLH, histiocytic malignancies, adult-onset Still's disease

Treatment

- HLH-94 protocol: 55% survival at 5 years
 - IV dexamethasone, etoposide, intrathecal methotrexate (if neurologic symptoms), and antifungal therapy

Summary

- Patient has continued to follow with hematology/oncology as an outpatient and has had some fatigue, but is otherwise doing well!
- All HLH medications discontinued at March appointment.

References

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