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Fatal Hematologic Alphabet Soup: A Complicated Case with Overlapping Features of TTP, AIHA, and HLH

Daniel B. Aruch* and Louis Aledort

Division of Hematology and Medical Oncology, Tisch Cancer Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1079, New York, NY 10029, USA

***Corresponding author:** Daniel B. Aruch, Division of Hematology and Medical Oncology, Tisch Cancer Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1079, New York, NY 10029, USA, Tel: 212-241-4705; Fax: 212-241-2684; E-mail: aruchd13@yahoo.com

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Abstract

Here we describe the case of an unfortunate 26 year old woman who developed a fatal combination of autoimmune hemolytic anemia (AIHA), hemophagocytic lymphohistiocytosis (HLH), and thrombotic thrombocytopenic purpura (TTP). Her initial clinical picture looked that of typical autoimmune hemolytic anemia but when she was refractory to standard therapy and her course progressed, alternative diagnoses were evaluated despite the lack of schistocytes on her peripheral smear. The case highlights consideration of TTP in severe hemolysis in absence of schistocytes and investigation of HLH in severe multiorgan dysfunction even after a primary diagnosis, in this case AIHA, has been made.

Keywords: Hemolytic anemia; Hemophagocytic syndrome; ADAMTS13

Introduction

Acute non-malignant hematologic diseases are rare but account for significant mortality if not quickly recognized and appropriate treatment instituted. Among the most aggressive include hemophagocytic lymphohistocytosis (HLH), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy (DIC) and autoimmune hemolytic anemia (AIHA). While diagnostic criteria have been accepted, in complicated cases, recognition can be elusive and complicate therapeutic decisions. Here we present a case of a patient who had features of each followed by a review of subjective and objective findings.

Case

A 26 year old female presented with syncope, and hypotension, and severe anemia. She suffered a cardiac arrest at presentation and was resuscitated.

Her past medical history was consistent with immune thrombocytopenic purpura (ITP) and autoimmune neutropenia complicated by neutropenic fever that responded to steroids with 2 relapses as well as 1 unexplained episode of anemia in the previous 4 years. Imaging showed generalized lymphadenopathy and a biopsy demonstrated reactive lymphadenopathy. A bone marrow examination was nondiagnostic. She had been noted in the past to have a positive direct antibody test (DAT) without any evidence of hemolysis as well as borderline low IgG with normal IgM, IgE, and IgA.

Initial evaluation (Table 1) demonstrated anemia, hyperbilirubinemia, predominantly indirect, normal renal function, reticulocytopenia, thrombocytopenia, and a positive DAT IgG+C3-. Peripheral smear lacked schistocytes or microspherocytes while evaluation of the reticulocytopenia revealed parvovirus viremia. Treatment with immune globulin therapy (IVIG) and glucocorticosteroids, including a course of pulse dosing, were administered. Her hemolysis was refractory to steroids as she required 3-5 units of packed red blood cells daily in the absence of bleeding and a splenectomy was performed on hospital day 8. Her course was complicated by multiorgan failure including renal failure requiring hemodialysis, hepatic failure, vasopressor dependence, thrombocytopenia, DIC, and postoperatively, gastrointestinal bleeding. Concomitantly, she was given broad spectrum antimicrobials, including antifungals after a positive urine histoplasma antigen was found. Additional evaluation for co-existing rheumatologic disease (negative rheumatoid factor as well as antinuclear and double stranded DNA antibodies) and hematologic malignancy (peripheral blood flow with mature myeloid lacking CD33 though bone marrow examination was not repeated) were non-revealing while immunodeficiency (low IgG, complement C4 and C4, and CD4 count) evaluation was inconclusive in setting of acute illness though suggestive of primary immunodeficiency. Evaluation for hepatitis B and C as well as HIV were also negative. HLH was suggested by initial hyperferritinemia and she ultimately met criteria for this diagnosis as well (ferritin >500, bicytopenia, elevated IL-2R, triglycerides > 265, and fibrinogen <150, and splenomegaly). She died on hospital day 12 and an autopsy was declined. Post mortem, her ADAMTS13 level was found to be 6% and splenic pathology demonstrated red pulp extramedullary hematopoiesis and erythrophagocytosis, consistent with hemolysis, without evidence of microthrombi.

	Day 1	Day 4	Day 7	Day 10
WBC (x1000/uL)	4.2	10.3	7	18.6
Hemoglobin (g/dL)	4.9	6.1	6.5	7.5
Hematocrit (%)	14.5	18	19	22
Platelet (x1000/uL)	92	91	34	205

Reticulocyte count (%)	2.2	3.5	1.7	2.3
LDH (U/L)	625	14834	3490	7220
Haptoglobin (mg/dL)	<7	<7	<7	15
Plasma Hgb (%)		117.7	109.8	
Bilirubin, Total (mg/dL)	17.6	76.4	149.5	70.6
Bilirubin, Direct (mg/dL)	5.8	69.1	143.3	62.1
ALT (U/L)	31	6607	1584	242
AST (U/L)	18	4558	371	416
Triglyceride (mg/dL)		360		432
Fibrinogen (mg/dL)	189	210	215	263
Ferritin (ng/mL)	3292	1392	87620	125493
Parvovirus PCR (IU/mL)	66000		578000	
D-dimer (ug/mL)	1.69	15.44	3.74	4
Interleukin 2R (U/mL)	6218			
ADAMTS13 (%)			6	
ADAMTS13 Inhibitor			1.9	

Table 1: Initial evaluation demonstrated anemia, hyperbilirubinemia, predominantly indirect, normal renal function, reticulocytopenia, thrombocytopenia, and a positive DAT IgG+C3-.

Discussion

This case demonstrates a unique combination of pathologies and several diagnostic dilemmas. The initial diagnosis of warm autoimmune hemolytic anemia was supported by a positive direct coombs, laboratory evidence of hemolysis, and by the splenic histology. 80% of patients will have a response to prednisone therapy and of those refractory to steroids, 38-82% responds to splenectomy, suggesting our patient, who was refractory to both, had additional coexisting pathology [1]. Concomitant parvovirus infection and AIHA have been described and most likely parvovirus precipitated the autoimmune phenomena or suppressed the appropriate response in a previously compensated hemolysis [2].

The hallmark of TTP is the presence microangiopathy highlighted by the presence of schistocytes on peripheral smear. While occasional schistocytes can be found on normal peripheral blood smears, any more than 1% of the total population suggests TTP [3]. One case report notes a patient with TTP in the absence schistocytes, though in the setting of relapse [4]. Suspicion is generally confirmed by evaluation of ADAMTS13 activity. ADAMTS13 is a metalloproteinase which cleaves large multimers of von Willebrand factor. In its absence, these multimers can activate platelets leading to microthrombi and tissue injury. However, low ADAMTS13 level, even below 10%, can be seen in alternative diagnoses, including DIC, vasculitis, and HUS. For example, ADAMTS13 is low in about 16% of cases of DIC. ADAMTS13 activity and inhibitor assays are limited in the setting of hyperbilirubinemia, resulting in falsely low activity and elevated titers, respectively [5]. TTP in the setting of positive DAT has been shown, often resulting in the incorrect diagnosis and patient morbidity [6]. Our patient possibly had concomitant TTP as suggested by refractory hemolysis and a low ADAMTS13 despite the lack of schistocytes on peripheral smear. While thrombi can be found on histologic sections of the spleen after splenectomy, in 2 case series, of the total 38 patients undergoing splenectomy for TTP, only 2 were found to have microthrombi on pathology. Therefore, the lack of microthrombi in our patient's spleen does not rule out TTP as a diagnosis.

HLH is often suggested in the setting of hyperferritinemia. The diagnostic criteria created for HLH based on pediatric cases is controversial in adults, particularly the cutoff used for ferritin (>500). Elevated ferritin can be the result of iron overload, malignancy, hepatocellular injury, autoimmune disease, and infectious conditions [7]. Varying cutoffs, including 2,000 and 10,000 have been suggested as more appropriate. In pediatrics, a ferritin of >10,000 has 96% specificity and 90% sensitivity for HLH while in adults HLH accounts for 60% of patients with a ferritin >10,000 once patients with sickle cell, graft versus host disease, and liver failure are excluded [8]. Another diagnostic marker, soluble interleukin 2-receptor can be elevated in a variety of similar conditions, including neoplasia, infections, allograft rejection, and autoimmune disease [9,10]. Hemophagocytosis or erythrophagocytosis can also be seen in alternative conditions, including immune mediated hemolytic anemia as well as TTP [11]. Treatment for secondary HLH is not clearly established in adults with IVIG, steroids, cytotoxic therapy, and even splenectomy reported as successful [8,12,13] Regardless, mortality with HLH is high, particularly those with a ferritin >50K [14]. HLH has been diagnosed with AIHA, including patients with active parvovirus B19 infection as well as TTP [15-17].

The differential diagnosis of this complicated case includes HLH, TTP, DIC, and parvovirus mediated AIHA. TTP without schistocytes has only been noted once but the ADAMTS13 level in this case supports it as a diagnostic consideration despite the limitations noted above. The diagnostic challenges of the case raise awareness that not only can TTP lack the classical pentad but should be considered in severe cases of hemolysis even in the absence of schistocytes. Additionally it highlights that multiple life threatening hematologic conditions can co-exist complicating diagnostic and treatment decisions with fatal consequences and this is the first case where HLH, TTP, parvovirus infection, and AIHA coexisted in same patient.

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