e-ISSN: 2747-2051

Archives of the Medicine and Case Reports

[AMCR]

https://hmpublisher.com/index.php/amcr

Transfusion-Refractory Warm Autoimmune Hemolytic Anemia with Dual Direct Antiglobulin Test Positivity and Marked Monocytosis in an Elderly Patient: A Case Report

I Gusti Ngurah Bayu Paramartha[1*], Dewa Gde Agung Wikananda Besang[2], Desak Agung Indah Praharsini Dewi[3]

[1]Internship Doctor, Bangli Medika Canti Hospital, Bangli, Indonesia

[2]Internship Doctor, Klungkung Regional General Hospital, Klungkung, Indonesia

[3]Internship Doctor, Bhayangkara Lumajang Hospital, Lumajang, Indonesia

ARTICLE INFO

Keywords:
Complement activation
Corticosteroid refractoriness
Direct antiglobulin test
Immunosuppressive therapy
Warm autoimmune hemolytic anemia

***Corresponding author:**
I Gusti Ngurah Bayu Paramartha

E-mail address:
ignbayuparamartha@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/amcr.v7i2.882

A B S T R A C T

Warm autoimmune hemolytic anemia represents a significant clinical challenge in adult hematology, with corticosteroid refractoriness occurring in approximately thirty to forty percent of cases. Management becomes substantially more complex in elderly patients with multiple comorbidities, where standard immunosuppressive therapy frequently fails and alternative therapeutic strategies become necessary. A sixty-three-year-old male with three months of documented warm autoimmune hemolytic anemia presented with acute hemolytic crisis manifested by severe anemia (hemoglobin declining from five point three to four point four grams per deciliter over four days) and accelerated hemolysis. Direct antiglobulin testing demonstrated dual positivity with immunoglobulin G one plus and complement component three-d two plus, indicating complement-mediated hemolysis. Notably, marked monocytosis ranged from seventy to seventy-four percent across serial complete blood counts. The patient demonstrated rapid immunosuppressive treatment failure with escalated triple therapy (methylprednisolone, mycophenolate mofetil, azathioprine) failing within four days of initiation. Transfusion refractoriness was evident despite premedication protocols. Concurrent medical conditions included hypertensive heart disease with documented coronary artery disease, newly diagnosed type two diabetes mellitus with suboptimal glycemic control, benign prostatic hyperplasia requiring catheterization, and clinical immunosuppression complications. The patient was referred to a tertiary academic medical center for advanced therapeutic decision-making. In conclusion, this case illustrates the diagnostic and therapeutic complexity of warm autoimmune hemolytic anemia with complement activation in an elderly population, highlighting the necessity for rapid escalation to advanced therapeutic modalities beyond conventional immunosuppression when clinical deterioration occurs despite maximal standard therapy.

1. Introduction

Autoimmune hemolytic anemia represents one of the most important acquired disorders affecting erythrocyte survival in adult populations worldwide.[1] Classified into distinct pathophysiological subtypes including warm autoimmune hemolytic anemia, cold agglutinin disease, and mixed variants, this group of conditions results from loss of self-tolerance with subsequent generation of autoantibodies targeting red blood cell surface antigens. The incidence of

autoimmune hemolytic anemia ranges from approximately one to three cases per one hundred thousand individuals annually, with warm autoimmune hemolytic anemia accounting for seventy to eighty percent of all autoimmune hemolytic anemia presentations in developed nations. The fundamental pathophysiological mechanism involves production of primarily immunoglobulin G class autoantibodies directed against red blood cell membrane proteins, with resultant Fc receptor-mediated cellular phagocytosis occurring predominantly within the splenic macrophage system. Activation of the classical complement cascade through direct antiglobulin test immunoglobulin G binding leads to progressive complement component deposition, including C3b, iC3b, C3d, and C4d fragments on erythrocyte surfaces, amplifying the hemolytic process through both complement-dependent cellular cytotoxicity and direct membrane attack complex formation.[2]

Direct antiglobulin testing, historically termed the Coombs test, remains the diagnostic cornerstone for confirming warm autoimmune hemolytic anemia and distinguishing this condition from other hemolytic processes. Traditionally, direct antiglobulin testing results are categorized as immunoglobulin G monospecific positivity or dual positivity with concurrent immunoglobulin G and complement component three-d detection. The clinical significance of dual direct antiglobulin test positivity has become increasingly appreciated in recent years, as emerging evidence demonstrates that patients with simultaneous immunoglobulin G and complement component three-d deposition on erythrocyte surfaces experience more severe hemolytic disease compared with those demonstrating immunoglobulin G-only positivity.[3] The complement cascade involvement through classical pathway activation, initiated by immunoglobulin G binding to Fc receptors, results in progressive C3 cleavage to generate C3d fragments that remain covalently bound to red blood cell membranes throughout the lifespan of complement-mediated hemolysis. Patients with dual direct antiglobulin test positivity demonstrate significantly higher transfusion requirements, more rapid disease progression, heightened refractoriness to conventional corticosteroid therapy, and ultimately worse clinical outcomes compared with monospecific immunoglobulin G-positive populations. These findings have profound implications for therapeutic decision-making and prognostic counseling.[4]

The modern treatment landscape for warm autoimmune hemolytic anemia reflects an evolving understanding of disease pathophysiology and expanding therapeutic armamentarium. Corticosteroids, specifically prednisolone and methylprednisolone administered at immunosuppressive dosages, represent first-line therapy with overall response rates ranging from seventy to eighty-five percent in unselected patient populations.[5] However, corticosteroid-refractory disease, defined as failure to achieve adequate hemoglobin responses at clinically acceptable steroid doses or development of severe steroid-related adverse effects, occurs in approximately thirty to forty percent of patients. Second-line therapeutic options include rituximab monoclonal antibody targeting CD20-positive B lymphocytes, demonstrating response rates between fifty and seventy percent in corticosteroid-refractory populations, though with variable durability. Splenectomy remains an important surgical option with overall response rates between forty and seventy percent, particularly in patients with demonstrable splenic sequestration on indium-one-hundred-one labeled red blood cell imaging. Emerging complement-targeted therapies, including pegcetacoplan and other components C3/C5 inhibitors, have demonstrated promising efficacy in clinical trials and are increasingly utilized for patients with complement-prominent hemolytic phenotypes. Additional options include azathioprine, mycophenolate mofetil, danazol, and intravenous immunoglobulin, though supporting evidence varies

considerably. The selection among these modalities requires careful consideration of disease severity, patient age, comorbid conditions, prior treatment responses, and institutional expertise.[6]

Managing warm autoimmune hemolytic anemia in elderly patients presents distinctive clinical and therapeutic challenges that frequently exceed those encountered in younger populations. Older adults typically present with multiple chronic medical conditions requiring polypharmacy, including cardiovascular diseases, diabetes mellitus, chronic kidney disease, and previous cerebrovascular events, all of which substantially complicate immunosuppressive therapy. The physiologic reserve of elderly patients is inherently reduced, such that the profound anemia accompanying hemolytic crisis precipitates rapid decompensation of cardiovascular function, heightening risk for acute myocardial infarction, arrhythmia, and cardiogenic shock.[7] Corticosteroid administration, essential for initial therapy, frequently triggers or exacerbates hyperglycemia, hypertension, and infections in elderly populations, requiring intensive concurrent management of these adverse effects. The pharmacokinetics of immunosuppressive agents may be substantially altered by age-related changes in renal and hepatic function, resulting in unpredictable drug accumulation and increased toxicity. Elderly patients demonstrate reduced tolerance for blood transfusions due to more fragile cardiovascular systems and heightened alloimmunization risk from chronic transfusion requirements. Additionally, cognitive decline and reduced social support in older age may compromise medication adherence and follow-up compliance, further complicating disease management. These factors collectively necessitate individualized therapeutic approaches that carefully balance efficacy requirements against toxicity tolerability in elderly patients with significant comorbidities.[8]

Novelty and Aim of Study: This case report presents a clinically distinctive and educationally valuable example of warm autoimmune hemolytic anemia occurring in an elderly patient with multiple complicating factors. The case features several noteworthy diagnostic findings, including dual direct antiglobulin test positivity with immunoglobulin G one plus and complement component three-d two plus detection, indicating active complement-mediated hemolysis alongside antibody-mediated mechanisms.[9] Markedly elevated monocytic percentage, consistently exceeding seventy percent across serial complete blood counts, suggests either reactive monocytosis secondary to hemolytic stress and compensatory erythropoiesis, or potentially underlying hematologic dyscrasia not yet fully characterized. The patient demonstrated rapid and complete failure of escalated triple immunosuppressive therapy within only four days, suggesting either inadequate immunosuppression dosing, pharmacokinetic factors limiting drug bioavailability, or disease phenotype predominantly driven by complement-mediated rather than antibody-mediated mechanisms amenable to conventional immunosuppression. Transfusion-refractory hemolysis despite maximal premedication protocols points toward unusually active hemolytic processes or potential alloimmunization complicating transfusion therapy. The presence of significant comorbidities, including hypertensive heart disease with documented coronary artery disease, newly diagnosed type two diabetes mellitus requiring insulin therapy with suboptimal glycemic control in acute illness, and benign prostatic hyperplasia requiring urinary catheterization, substantially complicated clinical management and therapeutic decision-making.[10] The aims of this case report are to illustrate the diagnostic complexity of warm autoimmune hemolytic anemia with dual direct antiglobulin test positivity in an elderly population, to analyze the factors contributing to immunosuppressive treatment failure, to discuss advanced therapeutic

considerations appropriate for corticosteroid-refractory disease, and to provide clinically relevant learning points regarding management of hemolytic crisis in older adults with multiple chronic conditions.

2. Case Presentation

Informed consent statement

Written informed consent was obtained from the patient (and authorized family representative) for the use of deidentified clinical data, laboratory findings, imaging results, and clinical narrative in this case report publication. The patient was informed that his case would be presented as a medical education and clinical learning tool for healthcare providers, with all personally identifiable information removed. The patient granted permission for the case to be submitted to peer-reviewed medical journals for potential publication. The institutional review board or ethics committee approval was obtained as required by the host institution for case report publication involving patient data. The patient understood that publication in a peer-reviewed journal would make this deidentified case information publicly available to the medical and scientific community.

Patient demographics and clinical history

The patient is a sixty-three-year-old male of Indonesian descent residing in Bali. He was born without documented genetic abnormalities or congenital hematologic disorders, with a normal perinatal history. Family history is notable for the absence of documented autoimmune disease, hemolytic anemia, or hematologic malignancy in first-degree or second-degree relatives. The patient is married, nonsmoking, and denies any history of alcohol consumption or illicit substance use. He worked as a merchant prior to retirement. Sexual history and blood transfusion history prior to the current illness are not documented. The patient initially presented with warm autoimmune hemolytic anemia three months prior to the current hospitalization, occurring in January twenty twenty-five. The diagnosis was established at a secondary care facility through clinical presentation of jaundice, fatigue, and dyspnea, with supporting laboratory evidence of severe anemia, unconjugated hyperbilirubinemia, and positive direct antiglobulin testing with immunoglobulin G positivity. Initial presentation three months ago demonstrated hemoglobin of seven point eight grams per deciliter with reticulocyte count elevated at four point eight percent. The patient was initiated on methylprednisolone at a dose of one mg per kilogram per day administered intravenously, which was subsequently converted to methylprednisolone sixteen mg orally twice daily for maintenance therapy. Clinical response initially occurred with hemoglobin stabilization around six to seven grams per deciliter over the initial four to six weeks. However, over the subsequent six to eight weeks, the patient experienced gradual hemoglobin decline despite continued corticosteroid therapy, necessitating addition of mycophenolate mofetil at one gram orally twice daily approximately six weeks prior to current admission. Despite mycophenolate addition, further hemoglobin deterioration persisted, ultimately precipitating current hospital admission for acute hemolytic crisis and management intensification.

The patient's past medical history includes hypertensive heart disease complicated by documented coronary artery disease, diagnosed approximately one year prior to current admission following clinical evaluation for exertional dyspnea. He carries additional cardiovascular risk factors and was prescribed beta-blockers and aspirin-containing regimens. Benign prostatic hyperplasia has been present for approximately two years, causing progressive urinary outflow obstruction with nocturia and decreased urinary stream, recently necessitating urinary catheterization due to acute urinary retention occurring twelve days prior to current admission for urological intervention. Type two diabetes mellitus was

newly diagnosed approximately two months prior to current admission, with initial presentation involving polyuria and polydipsia, now requiring insulin therapy due to inadequate glycemic control on oral agents. The patient denies any known drug allergies or previous anaphylactic reactions. He has not received previous blood transfusions prior to the current illness. Medications prior to hospital admission included methylprednisolone sixteen mg orally twice daily for hemolytic anemia management, mycophenolate mofetil one gram orally twice daily as immunosuppressive therapy, glyceryl trinitrate two point five mg orally twice daily for cardiovascular symptom management, bisoprolol two point five mg orally once daily for cardiac rate control, acetylsalicylic acid eighty mg orally once daily for thromboprophylaxis, isosorbide dinitrate five mg orally as needed for anginal symptoms, paracetamol six hundred fifty mg orally three times daily for symptomatic analgesia, insulin glargine fourteen units subcutaneously once daily at bedtime for basal glycemic control, and rapid-acting insulin analogue twelve units subcutaneously three times daily with meals for postprandial glucose management (Table 1).

Table 1. Patient demographics, past medical history, risk factors, and medications.

Parameter	Details
Age and gender	63-year-old male
Ethnicity	Indonesian
Occupation	Retired merchant
Social history	Nonsmoker, no alcohol use, no illicit drugs
Family history	No autoimmune disease, hemolytic anemia, or hematologic malignancy in first/second-degree relatives
Congenital/Genetic disorders	None documented
Past medical history - Hematologic	Warm autoimmune hemolytic anemia, diagnosed 3 months prior
Past medical history - Cardiac	Hypertensive heart disease with coronary artery disease (diagnosed 1 year ago)
Past medical history - Genitourinary	Benign prostatic hyperplasia (2 years, catheterized 12 days prior for urinary retention)
Past medical history - Endocrine	Type 2 diabetes mellitus (newly diagnosed 2 months ago)
Drug allergies	None reported
Previous transfusions	None prior to the current illness
Current medications - Hematologic	Methylprednisolone 16 mg PO BID; Mycophenolate mofetil 1 g PO BID
Current medications - Cardiac	GTN 2.5 mg PO BID; Bisoprolol 2.5 mg PO daily; ASA 80 mg PO daily; ISDN 5 mg PO PRN
Current medications - Analgesic	Paracetamol 650 mg PO TID
Current medications - Endocrine	Insulin glargine 14 IU SC daily at bedtime; Rapid insulin analogue 12 IU SC TID with meals

Physical examination

Physical examination conducted upon hospital admission revealed a moderately ill-appearing male patient who appeared older than his stated chronological age. Vital signs at presentation documented blood pressure one hundred seven per sixty-five millimeters mercury, heart rate eighty-three beats per minute with regular rhythm, respiratory rate

nineteen breaths per minute, core body temperature thirty-seven point one degrees Celsius, and oxygen saturation ninety-seven percent while breathing ambient air. Glasgow Coma Scale assessment demonstrated full alert and oriented status with eye opening four, verbal response five, and motor response six, indicating normal consciousness without any signs of acute neurological compromise. Examination of the head and face revealed notably pale conjunctivae bilaterally, consistent with severe anemia and reduced hemoglobin concentration. The sclerae demonstrated icteric discoloration bilaterally without exudates or other abnormalities. No jaundice was appreciated on palmar or plantar surfaces, suggesting the unconjugated hyperbilirubinemia was mild despite the hemolysis. Examination of the oral mucosa revealed pale coloring without ulceration, exudate, or lymphoid tissue enlargement. The neck was supple without palpable lymphadenopathy, thyromegaly, or cervical mass. Cardiovascular examination revealed a regular rate and rhythm without murmur, rub, or gallop on auscultation. No peripheral edema was appreciated in the lower extremities, and no jugular venous distension was observed. Respiratory examination revealed clear bilateral air entry without wheezing, crackles, or other adventitious sounds, and normal percussion note throughout all lung fields.

Abdominal examination revealed a moderately distended abdomen that was soft and nontender to palpation (table 2). Hepatomegaly was present with a liver edge palpated three centimeters below the right costal margin, firm, without nodularity, and nontender. Splenomegaly was appreciated with splenic edge palpable on deep inspiration approximately two centimeters below the left costal margin, firm, and nontender. No ascites was appreciated by percussion or shifting dullness. No rebound tenderness or guarding was noted on deep palpation. Abdominal aorta was not enlarged to palpation. Bowel sounds were present and normal in character and frequency. Extremity examination revealed no peripheral edema, no clubbing or cyanosis, and normal capillary refill time. Peripheral pulses were palpable and symmetric in the upper and lower extremities. Skin examination revealed no petechiae, purpura, ecchymosis, or other hemorrhagic manifestations. No significant lymphadenopathy was palpated in the cervical, axillary, or inguinal regions. Neurological examination revealed intact cranial nerves, normal motor strength throughout all major muscle groups, normal deep tendon reflexes with normal symmetry, and intact sensation to light touch and proprioception. Genitourinary examination revealed a catheter in place in the urethral meatus with clear urine collection noted. No scrotal edema or masses were appreciated.

Hematological investigations

Serial complete blood count examinations were performed over four consecutive days of hospitalization, revealing dramatically fluctuating hemoglobin concentrations that reflected active ongoing hemolysis inadequately compensated by erythropoiesis despite an appropriate reticulocyte response. On hospital day one, presenting hemoglobin was five point three grams per deciliter with hematocrit sixteen point five percent, indicating severe normocytic or slightly microcytic anemia. Red blood cell count on day one was one point eighty-seven trillion per microliter, also markedly reduced. Platelet count was preserved at four hundred sixteen thousand per microliter, excluding thrombocytopenia as a complicating feature. Total white blood cell count was markedly elevated at twenty-one point zero-one thousand per microliter, predominantly from absolute monocytosis reaching seventy-one point three percent. Mean corpuscular hemoglobin was twenty-eight point three picograms, and mean corpuscular hemoglobin concentration was thirty-two point one grams per deciliter, indicating hypochromic red blood cells. Mean corpuscular volume was eighty-eight point two femtoliters, borderline microcytic. By hospital day two,

despite transfusion of packed red cells, hemoglobin had further declined to four point six grams per deciliter with hematocrit fourteen point four percent and red blood cell count one point sixty-seven trillion per microliter, indicating accelerated hemolysis exceeding transfusion replacement. Platelet count had dropped to three hundred seventeen thousand per microliter, displaying minor thrombocytopenia. Total white blood cell count had normalized to six point zero thousand per microliter, but monocyte percentage remained elevated at sixty-six point five percent. By hospital day three, hemoglobin showed slight improvement to five point seven grams per deciliter with hematocrit seventeen point three percent and red blood cell count two point zero-four trillion per microliter. Platelet count recovered to three hundred eighty-three thousand per microliter. However, total white blood cell count rose again to thirteen point five thousand per microliter with marked monocytosis of seventy-four point four percent. By hospital day four, hemoglobin had again declined to four point four grams per deciliter, reaching a nadir, with hematocrit thirteen point one percent and red blood cell count one point fifty-six trillion per microliter. Platelet count remained at three hundred seventeen thousand per microliter. White blood cell count was ten point zero-six thousand per microliter with persistent monocytosis of seventy point three percent. The striking pattern of monocytic predominance throughout hospitalization, consistently exceeding seventy percent in absolute numbers, remained unexplained by standard reactive causes and warranted further investigation to exclude hematologic dyscrasia (Table 3).

Table 2. Physical examination findings with clinical significance.

System	Findings	Clinical significance
General	Moderately ill-appearing, older than stated age	Reflects chronic illness burden and acute hemolytic stress
Vital signs	BP 107/65, HR 83 regular, RR 19, T 37.1°C, O2 sat 97% RA	Hemodynamically compensated despite severe anemia
Mental status	GCS E4V5M6, alert and oriented	No acute encephalopathy or cardiopulmonary compromise
HEENT	Pale conjunctivae bilateral, icteric sclerae, pale oral mucosa	Consistent with severe anemia and hemolysis
Neck	Supple, no lymphadenopathy, no thyromegaly	No evidence of lymphoproliferative disease
Cardiac	Regular rate and rhythm, no murmur/rub/gallop	No acute cardiac decompensation or valvular disease
Pulmonary	Clear bilateral air entry, normal breath sounds, normal percussion	No pulmonary edema or respiratory compromise
Abdomen	Soft, nontender, no ascites	No peritonitis or portal hypertension
Hepatomegaly	3 cm below the costal margin, firm, nontender	Likely from extramedullary hematopoiesis and hemolysis
Splenomegaly	2 cm below left costal margin, firm, nontender	Consistent with hemolysis and reticuloendothelial activity
Extremities	No edema, normal capillary refill, symmetric pulses	No signs of peripheral hypoperfusion or edema
Skin	No petechiae, purpura, or ecchymosis	No evidence of bleeding disorder or sepsis
Lymph nodes	No palpable cervical, axillary, or inguinal lymphadenopathy	Against lymphoproliferative disease
Neurologic	Intact cranial nerves, normal motor/sensory/reflex exam	No acute neurological compromise from anemia
Genitourinary	Foley catheter in place with clear urine	Catheterized for urinary retention from BPH

Table 3. Serial complete blood count with four-day monitoring.

Parameter (Reference Range)	Day 1	Day 2	Day 3	Day 4	Clinical significance
Hemoglobin (13.5-17.5 g/dL)	5.3	4.6	5.7	4.4	Severe anemia with downward trend; Day 4 nadir
Hematocrit (41-53%)	16.5%	14.4%	17.3%	13.1%	Corresponds to hemoglobin decline; indicates severe anemia
RBC (4.7-6.1 trillion/µL)	1.87	1.67	2.04	1.56	Markedly reduced; accelerated decline suggests hemolysis exceeds transfusion replacement
Platelets (150-400 thousand/µL)	416	317	383	317	Mild thrombocytopenia on Day 2; otherwise preserved
WBC (4.5-11.0 thousand/µL)	21.01	6.00	13.50	10.06	Markedly elevated Day 1 and Day 3; reflects hemolytic stress and inflammation
Monocytes (%)	71.3%	66.5%	74.4%	70.3%	Persistently elevated (>70%); unusual pattern warrants further investigation
Lymphocytes (%)	17.2%	29.3%	23.0%	23.4%	Relatively preserved despite monocytosis
Neutrophils (%)	11.4%	4.2%	2.5%	6.1%	Relative neutropenia correlates with elevated monocytes
MCH (27-31 pg)	28.3	27.5	27.9	28.2	Low-normal, consistent with hypochromic RBCs
MCHC (32-36 g/dL)	32.1	31.9	32.9	33.6	Low-normal, confirms hypochromia
MCV (80-100 fL)	88.2	86.2	84.8	84.0	Borderline microcytic; may reflect acute erythropoiesis

Biochemical and hemolysis markers

Laboratory evaluation revealed marked evidence of hemolysis with severe unconjugated hyperbilirubinemia and other hemolysis-associated laboratory abnormalities. Serum aspartate aminotransferase was thirty units per liter, within the normal range of eight to forty units per liter, suggesting the absence of significant hepatocellular injury. Serum alanine aminotransferase was twenty-eight units per liter, also within the normal range of three to thirty units per liter, further excluding hepatic parenchymal disease as a contributor to the clinical presentation. Total bilirubin was markedly elevated at four point four milligrams per deciliter, substantially

exceeding the normal range of zero point two to one point zero milligrams per deciliter. Direct or conjugated bilirubin was mildly elevated at one point, three milligrams per deciliter, within the normal range of zero point one to zero point five milligrams per deciliter. Indirect or unconjugated bilirubin was markedly elevated at three point one milligrams per deciliter, normal range zero point two to zero point seven milligrams per deciliter. The disproportionate unconjugated hyperbilirubinemia with preserved hepatocellular function, as evidenced by normal aminotransferases, conclusively established the hyperbilirubinemia as resulting from hemolysis rather than hepatic dysfunction. This biochemical pattern is pathognomonic for hemolytic disease and confirms the diagnosis of warm autoimmune hemolytic anemia with substantial daily red blood cell turnover. The bilirubin fractionation pattern indicates unconjugated hyperbilirubinemia exceeding hepatic conjugation capacity despite normal liver synthetic function. Additional hemolysis-associated markers, such as lactate dehydrogenase and haptoglobin values, were not measured during this hospitalization, representing a limitation in the biochemical assessment of hemolysis severity (Table 4).

Table 4. Biochemical and hemolysis markers with interpretation.

Parameter	Value	Reference Range	Interpretation
SGOT (AST)	30 U/L	8-40 U/L	Normal; no hepatocellular injury
SGPT (ALT)	28 U/L	3-30 U/L	Normal; normal liver synthetic function
Total bilirubin	4.4 mg/dL	0.2-1.0 mg/dL	Markedly elevated; indicates severe hemolysis
Direct bilirubin (Conjugated)	1.3 mg/dL	0.1-0.5 mg/dL	Mildly elevated; reflects hepatic processing capacity
Indirect bilirubin (Unconjugated)	3.1 mg/dL	0.2-0.7 mg/dL	Markedly elevated; pathognomonic for hemolysis
Bilirubin pattern	Predominantly indirect	Predominantly indirect in hemolysis	Confirms hemolytic mechanism rather than hepatic dysfunction

Serological investigations

Direct antiglobulin testing, performed using the gel-based method at body temperature, demonstrated polyspecific antiglobulin positive findings. The polyspecific antiglobulin globulin test at thirty-seven degrees Celsius was two plus positive, confirming the presence of red blood cell surface-bound immunoglobulins and complement components. Monospecific testing revealed immunoglobulin G positivity at one plus intensity, indicating IgG-mediated autoimmunization. Complement component three-d testing was two plus positive, demonstrating complement deposition on erythrocyte surfaces. The control specimen was negative, excluding technical error. This pattern of dual positivity with both immunoglobulin G one plus and complement component three-d two plus is indicative of active complement-mediated hemolysis alongside antibody-dependent cellular cytotoxicity. The relatively low immunoglobulin G positivity despite the clinically severe hemolysis and rapid hemolytic deterioration suggests that complement-dependent mechanisms may be disproportionately contributing to the hemolytic process in this patient. Indirect antiglobulin testing, performed using low-ionic-strength saline at thirty-seven degrees Celsius with appropriate controls,

revealed panel cell one at one plus positivity with mixed-field reaction pattern, indicating pan-reactive alloantibody or autoantibody reactivity. The patient's own autocontrol was two plus positive, consistent with direct antiglobulin test positive warm autoimmune hemolytic anemia and confirming that detected antibodies are bound to patient red blood cells rather than representing free serum antibodies. The mixed-field reaction pattern on indirect antiglobulin testing may reflect the variable intensity of surface antibody binding on heterogeneous red blood cell populations or may indicate dual populations of antibody-coated and uncoated red blood cells. No unexpected alloantibodies against defined red blood cell antigens were identified that would contraindicate transfusion or predict hemolytic transfusion reactions (Table 5).

Table 5. Serological investigations with detailed interpretation.

Test	Result	Method	Interpretation
Direct Antiglobulin Test (DAT) - Polyspecific	2+ positive	Gel method, 37°C	Confirms RBC-bound immunoglobulin and complement
DAT - IgG Monospecific	1+ positive	Gel method, 37°C	Indicates IgG-mediated autoimmunization, relatively weak
DAT - Complement C3d	2+ positive	Gel method, 37°C	Indicates active complement deposition and complement-mediated hemolysis
DAT - Control Specimen	Negative	Gel method, 37°C	Excludes technical error in testing procedure
Indirect Antiglobulin Test (IAT)		LISS 37°C	
IAT - Panel Cell 1	1+ positive	LISS 37°C	Pan-reactive indicating autoantibody; mixed-field pattern
IAT - Autocontrol	2+ positive	LISS 37°C	Confirms RBC-bound antibody consistent with warm AIHA
Unexpected Alloantibodies	Not identified	Standard panel testing	No defined alloantibodies; transfusion can proceed with caution

Peripheral blood smear analysis

Morphologic examination of peripheral blood smears revealed multiple abnormalities consistent with hemolytic anemia and compensatory erythropoiesis. The overall red blood cell population demonstrated normochromic to hypochromic appearance, with variable morphology. Marked anisopoikilocytosis was evident, indicating substantial variation in red blood cell size and shape. Microcytes and macrocytes were both present within the same smear. Specific abnormal red blood cell morphologies included ovalocytes, teardrop cells, stomatocytes, and spherocytes. Polychromasia was prominent, reflecting the presence of reticulocytes and other immature red blood cells representing the bone marrow's compensatory response to hemolysis. Normoblasts (nucleated red blood cells) were present, indicating accelerated erythropoiesis with premature release of immature red blood cells from the bone marrow into peripheral circulation, consistent with severe hemolytic stress. The white blood cell population was notable for marked monocytosis, with absolute

monocyte numbers substantially elevated compared with neutrophil and lymphocyte populations. Atypical lymphocytes were present, demonstrating increased cytoplasmic volume, abundant cytoplasm, and irregular cell borders. No blast cells or immature myeloid precursors were identified. Platelet count appeared normal on smear examination, with normal platelet morphology and no abnormal giant platelets. The combination of severe monocytosis with atypical lymphocytes raised concerns for possible underlying hematologic dyscrasia, requiring further evaluation such as bone marrow examination or flow cytometry to exclude chronic myelomonocytic leukemia or other myeloproliferative or lymphoproliferative disorders (Table 6).

Table 6. Peripheral blood smear findings with clinical significance.

Finding	Observation	Clinical significance
Overall RBC color	Normochromic to hypochromic	Consistent with anemia; suggests iron adequacy
RBC size variation	Marked anisopoikilocytosis; mixed microcytes and macrocytes	Indicates variable erythropoiesis and ongoing hemolysis
Ovalocytes	Present	May reflect chronic hemolysis and membrane stress
Teardrop cells	Present	Associated with hemolytic processes and marrow fibrosis
Stomatocytes	Present	Can occur in warm AIHA and membrane disorders
Spherocytes	Present (implied by ovalocytes)	Expected in antibody-coated RBCs
Polychromasia	Prominent	Indicates reticulocytosis and compensatory erythropoiesis
Normoblasts	Present	Indicates accelerated erythropoiesis with premature marrow release
Monocytes	Marked elevation (71-74%)	Persistent monocytosis; concerning for dyscrasia if sustained
Atypical lymphocytes	Present	May represent a reactive response or a potential underlying dyscrasia
Myeloid blasts	Absent	Excludes acute leukemia
Giant platelets	Absent	No evidence of MDS or specific bleeding disorders
Platelet count (morphology)	Normal	Adequate platelet reserve

Imaging studies

Abdominal ultrasonography was performed to assess for hepatosplenomegaly, portal hypertension, and other structural abnormalities that might contribute to hemolysis or explain the clinical presentation. The liver demonstrated normal echogenicity without focal lesions, masses, or evidence of cirrhosis. However, the liver was enlarged, measuring approximately fourteen to fifteen centimeters in cranial-caudal dimension, confirming clinical hepatomegaly. The spleen was markedly enlarged, measuring approximately thirteen to fourteen centimeters in the longest dimension, significantly exceeding the normal upper limit of approximately eleven centimeters. The splenic parenchyma demonstrated normal echogenicity

without focal lesions. Portal vein diameter was normal at ten to twelve millimeters, and hepatic veins demonstrated appropriate flow patterns. No ascites was identified within the peritoneal cavity. The gallbladder was normal without gallstones or wall thickening. The common bile duct was normal. The pancreas was normal without focal lesions or ductal dilation. Both kidneys were normal in size, echotexture, and position, with normal collecting systems and no hydronephrosis. The prostate gland was enlarged, consistent with benign prostatic hyperplasia, measuring approximately forty to forty-five millimeters in anteroposterior dimension. No focal lesions were identified within the prostate. The bladder was partially distended with a Foley catheter visible in place. No evidence of portal hypertension or esophageal varices was identified on sonography. The imaging findings support the clinical suspicion that hepatomegaly and splenomegaly result from hemolytic disease with compensatory extramedullary hematopoiesis and reticuloendothelial hyperactivity rather than from cirrhosis, malignancy, or other primary liver or splenic disease (Table 7).

Table 7. Imaging studies with organ-specific findings.

Organ/Structure	Finding	Clinical significance
Liver	Enlarged (14-15 cm cranial-caudal); normal echogenicity; no focal lesions or cirrhosis	Hepatomegaly from hemolysis and extramedullary hematopoiesis; normal synthetic function
Spleen	Markedly enlarged (13-14 cm); normal echogenicity; no focal lesions	Splenomegaly from hemolysis; splenic sequestration expected
Portal vein	Normal diameter (10-12 mm); normal flow pattern	No portal hypertension; excludes cirrhotic complications
Hepatic veins	Normal flow patterns; no Budd-Chiari features	Normal hepatic venous drainage
Ascites	Absent	No evidence of portal hypertension or hepatic decompensation
Gallbladder	Normal; no gallstones or wall thickening	No biliary obstruction or cholecystitis
Common bile duct	Normal caliber	No biliary obstruction
Pancreas	Normal; no focal lesions or duct dilation	No pancreatitis or pancreatic disease
Kidneys	Normal size, echotexture, and collecting systems; no hydronephrosis	Preserved renal function; no obstruction
Prostate	Enlarged (40-45 mm AP); no focal lesions	Consistent with benign prostatic hyperplasia
Bladder	Partially distended; Foley catheter visible	Catheterized for urinary retention from BPH

Metabolic parameters and glycemic control

Glycemic monitoring was performed serially throughout the hospitalization to assess diabetes control in light of acute illness stress and concurrent corticosteroid therapy, both of which increase insulin resistance and hyperglycemia. On hospital day one, random blood glucose was recorded at one hundred sixty-one milligrams per deciliter. On hospital day two, fasting glucose was measured at one hundred fifty-four milligrams per deciliter, indicating inadequate

overnight glycemic control despite insulin glargine therapy. Additional random glucose measurement on day two was elevated at two hundred nine milligrams per deciliter. On hospital day three, fasting glucose had further increased to one hundred eighty-four milligrams per deciliter, reflecting deteriorating glycemic control. Random glucose on day three was measured at one hundred fifty-one milligrams per deciliter, providing conflicting data. On hospital day four, fasting glucose was markedly elevated at two hundred twenty-seven milligrams per deciliter, representing severe hyperglycemia. Concurrent random glucose on day four was two hundred fourteen milligrams per deciliter. The overall trend demonstrated progressive hyperglycemia despite continuation of insulin glargine at fourteen units subcutaneously once daily and rapid-acting insulin at twelve units subcutaneously three times daily. The escalation of methylprednisolone dosage from sixteen mg twice daily orally to sixty-two point five mg twice daily intravenously certainly contributed to the deteriorating glycemic control. Adjustments to insulin dosing were not documented during this hospitalization, representing a potential management gap. The patient would benefit from more frequent glucose monitoring and insulin dose escalation during acute illness and high-dose corticosteroid therapy. Hemoglobin A1c was not measured during this acute hospitalization, limiting assessment of chronic glycemic control prior to current presentation (Table 8).

Table 8. Metabolic parameters and glycemic control.

Day	Fasting glucose (mg/dL)	Random glucose (mg/dL)	Clinical significance
Day 1	Not measured	161	Baseline hyperglycemia from stress and diabetes
Day 2	154	209	Fasting acceptable but random elevated; steroid effect
Day 3	184	151	Deteriorating fasting control; variable random
Day 4	227	214	Marked hyperglycemia; inadequate insulin dosing
Insulin Therapy	Glargine 14 IU SC daily	Rapid 12 IU SC TID	Doses not adjusted despite worsening hyperglycemia
Contributing Factors	IV methylprednisolone escalation (16→62.5 mg BID)	Acute hemolytic illness	Both significantly increase insulin resistance

Hospital course and therapeutic management

The patient's hospital course was marked by progressive hemolytic deterioration despite escalating immunosuppressive therapy, ultimately necessitating referral to tertiary care for advanced therapeutic interventions. The patient presented on hospital admission (designated as hospital day one) with hemoglobin five point three grams per deciliter and icteric appearance consistent with acute hemolytic crisis. Immediate management included establishment of intravenous access and initiation of supportive care with normal saline infusion at twenty milliliters per kilogram body weight daily to maintain hydration and support renal perfusion during

hemolysis. Packed red cell transfusion was initiated at two units per day, with premedication consisting of dexamethasone five milligrams intravenously and diphenhydramine ten milligrams intravenously administered thirty minutes prior to each transfusion unit to minimize transfusion reactions. Antibiotic therapy was begun with cefuroxime one gram intravenously three times daily and levofloxacin seven hundred fifty milligrams intravenously once daily to provide broad-spectrum coverage pending culture results. Methylprednisolone dosage was escalated from the outpatient dose of sixteen milligrams orally twice daily to sixty-two point five milligrams intravenously twice daily, representing a four-fold increase in daily steroid exposure to maximize initial immunosuppression. Azathioprine at fifty milligrams orally twice daily was newly initiated as a second immunosuppressive agent to address corticosteroid refractoriness. Mycophenolate mofetil was continued at one gram orally twice daily as previously established. Esomeprazole was initiated at forty milligrams once daily to provide gastric protection against ulceration from high-dose steroids. Intravenous albumin was administered twice daily to provide nutritional support and improve plasma oncotic pressure. All prior cardiac medications including beta-blockers, nitrates, and antiplatelet therapy were continued. Insulin therapy was maintained at the baseline regimen without dose escalation despite progressive hyperglycemia.

On hospital day two, despite transfusion of two additional packed red cell units, hemoglobin declined further to four point six grams per deciliter, indicating hemolysis exceeding transfusion replacement. The patient remained clinically stable without evidence of acute coronary syndrome or decompensated heart failure despite the severe anemia. Transfusion was continued at two units daily. The escalated immunosuppressive regimen was maintained unchanged. By hospital day three, hemoglobin showed minimal recovery to five point seven grams per deciliter, suggesting possible early response to intensified therapy or transfusion effect. White blood cell count dramatically increased to thirteen point five thousand per microliter from the day two nadir of six thousand per microliter, with monocyte percentage remaining persistently elevated at seventy-four point four percent. The marked leukocytosis may have represented inflammatory response to the hemolytic process or adverse effect of the immunosuppressive regimen. Transfusion and all other therapies were continued unchanged. By hospital day four, hemoglobin had declined again to a nadir of four point four grams per deciliter, with accompanying decline in hematocrit to thirteen point one percent and red blood cell count to one point fifty-six trillion per microliter. This pattern of severe fluctuating anemia with progressive deterioration despite four days of escalated triple immunosuppressive therapy (methylprednisolone sixty-two point five mg IV twice daily, mycophenolate mofetil one gram PO twice daily, and azathioprine fifty mg PO twice daily) demonstrated clear treatment failure. The patient's hemoglobin had declined further than baseline by the end of four days of intensified therapy. This rapid therapeutic failure, occurring within days of initiating escalated immunosuppression, indicated that conventional immunosuppressive strategies were inadequate for this patient's hemolytic disease. The possibility of complement-predominant hemolysis not adequately addressed by conventional immunosuppression became increasingly apparent. At this juncture, the decision was made to refer the patient urgently to Professor Ngoerah Hospital, a tertiary academic medical center with capabilities for advanced therapeutic interventions including rituximab therapy, complement inhibitors, and potential splenectomy evaluation. The patient was transferred to the tertiary center on hospital day five for specialized management beyond the capabilities of the secondary care facility (Tables 9 & 10).

Table 9. Hospital course timeline with hemoglobin trends and interventions.

Hospital day	Hemoglobin (g/dL)	Key clinical events	Interventions	Response
Day 1 (Admission)	5.3	Acute hemolytic crisis presentation; severe icteric appearance; moderate illness	IV access, NS 20 mL/kg/day, PRC 2U with premedication, cefuroxime+levofloxacin, methylprednisolone escalation to 62.5 mg IV BID	Baseline hemodynamically compensated
Day 2	4.6	Further hemolysis despite transfusion; hemolysis exceeds replacement	Continue PRC 2U daily, all prior therapy continued, azathioprine initiated 50 mg BID	Continued decline; transfusion refractoriness evident
Day 3	5.7	Minimal recovery; marked leukocytosis to 13.5K with monocytosis 74.4%	Continue all therapies unchanged; ESO 40 mg daily, albumin BID added	Partial recovery; leukocytosis concerning for dyscrasia
Day 4	4.4 (nadir)	Hemoglobin reaches nadir; triple therapy failure evident; clinical deterioration	Maintain current regimen; tertiary referral decision made	Clear therapeutic failure; inadequate response
Day 5	Transferred	Transferred to a tertiary academic center for advanced therapies	Referred for rituximab, complement inhibitors, and splenectomy evaluation	Expected advanced interventions

Table 10. Complete medication list with doses, routes, frequencies, and indications.

Medication	Dose	Route	Frequency	Indication
Methylprednisolone	62.5 mg (escalated from 16 mg PO)	IV	Twice daily	Primary immunosuppression for wAIHA
Mycophenolate Mofetil	1 g	PO	Twice daily	Second-line immunosuppression
Azathioprine	50 mg (newly added)	PO	Twice daily	Third-line immunosuppression for refractory disease
Dexamethasone	5 mg	IV	Immediately before transfusion	Transfusion premedication
Diphenhydramine	10 mg	IV	Immediately before transfusion	Transfusion premedication antihistamine
Cefuroxime	1 g	IV	Three times daily	Broad-spectrum antibiotic coverage
Levofloxacin	750 mg	IV	Once daily	Broad-spectrum antibiotic coverage
Esomeprazole	40 mg	PO	Once daily	Gastric ulcer prophylaxis from steroids
Albumin	Standard infusion	IV	Twice daily	Nutritional support; plasma oncotic pressure
Glyceryl Trinitrate (GTN)	2.5 mg	PO	Twice daily	Anginal prophylaxis; cardiac afterload reduction
Bisoprolol	2.5 mg	PO	Once daily	Beta-blocker for cardiac rate control
Acetylsalicylic Acid (ASA)	80 mg	PO	Once daily	Antiplatelet therapy for CAD
Isosorbide Dinitrate (ISDN)	5 mg	PO	As needed	PRN anginal symptom relief
Paracetamol	650 mg	PO	Three times daily	Symptomatic analgesia; antipyresis
Insulin Glargine	14 IU	SC	Once daily at bedtime	Basal glycemic control for type 2 DM
Rapid-Acting Insulin	12 IU	SC	Three times daily with meals	Postprandial glucose control for type 2 DM

Patient's perspective

From the patient's perspective, the acute hemolytic crisis represented a profoundly distressing and frightening health event occurring in the context of what had been an increasingly problematic three-month illness with warm autoimmune hemolytic anemia. Prior to the current hospitalization, the patient had experienced progressive fatigue, dyspnea on exertion, and jaundice despite being on what was explained as appropriate treatment with corticosteroids and additional immune-modifying medications. The patient's quality of life had deteriorated substantially, with the inability to continue normal work activities and increasing dependence on medication regimens. The acute hemolytic crisis, with rapid worsening of symptoms including severe dyspnea, dizziness, and worsening jaundice, prompted emergency hospital admission and generated considerable anxiety regarding whether the prescribed treatments were working. Hospital admission involved multiple blood transfusions, intravenous medications, frequent blood draws for monitoring, and discussions regarding escalating the immunosuppressive therapy. The patient experienced the psychological burden of having a chronic disease with unclear prognosis, anxiety regarding future treatment requirements, and uncertainty about whether the escalated therapies at the secondary facility would be effective. The need for referral to a tertiary center conveyed to the patient that the local hospital's standard treatments had failed, generating further anxiety but also hope that specialized center might offer more effective options. The patient expressed concern regarding the need for multiple medications with potential side effects and worry about drug interactions given his other medical conditions. The newly diagnosed diabetes mellitus added additional complexity and burden, requiring the patient to manage blood glucose monitoring and insulin therapy while simultaneously struggling with life-threatening hemolysis. The prolonged catheterization for urinary retention represented an additional indignity and infection risk concern. Throughout this experience, the patient required substantial education regarding his diagnoses, the reasons for various treatments, and realistic expectations for recovery. The patient's perspective should remind healthcare providers that behind the laboratory numbers and clinical findings are real individuals experiencing fear, suffering, and hope for meaningful recovery and return to normal function.

3. Discussion

The direct antiglobulin test result in this patient demonstrated dual positivity with immunoglobulin G one plus and complement component three-d two plus, a pattern carrying important diagnostic, prognostic, and therapeutic implications. In warm autoimmune hemolytic anemia, the direct antiglobulin test positivity pattern reflects the underlying hemolytic mechanism and provides critical prognostic information. Approximately seventy to eighty percent of warm autoimmune hemolytic anemia patients demonstrate isolated immunoglobulin G positivity without complement component deposition on red blood cell surfaces. These patients experience hemolysis predominantly through antibody-dependent cellular phagocytosis wherein immunoglobulin G-coated red blood cells are recognized by Fc gamma receptors on splenic macrophages, leading to extravascular hemolysis within the reticuloendothelial system. In contrast, patients with dual immunoglobulin G and complement component three-d positivity, such as this patient, demonstrate activation of the classical complement cascade initiated by IgG binding to red blood cell surface antigens. This IgG-IgG crosslinking on adjacent red blood cell epitopes activates C1q of the complement cascade, initiating sequential cleavage of C4, C2, and C3 components. The progressive formation of C3 convertase leads to generation of substantial C3b and C3d fragments that covalently

bind to red blood cell membranes. These complement-coated red blood cells are recognized through CR1 (complement receptor one) and CR2 receptors on splenic and hepatic macrophages, amplifying the hemolytic process through complement receptor-mediated extravascular hemolysis. The dual positivity pattern in this patient indicates ongoing complement activation, representing an additional hemolytic mechanism superimposed upon immunoglobulin G-mediated antibody-dependent cellular cytotoxicity. Recent evidence indicates that patients with dual direct antiglobulin test positivity experience significantly more severe hemolytic disease compared with immunoglobulin G-only populations, with higher hemoglobin requirements, more rapid hemolytic deterioration, and reduced responsiveness to corticosteroid therapy. The relatively low immunoglobulin G positivity intensity in this patient (one plus) despite the clinically severe hemolysis suggests that complement-dependent mechanisms may be disproportionately driving the hemolytic process. This finding has therapeutic implications, as conventional immunosuppression targeting antibody production may be insufficient to control complement-mediated hemolysis. The dual positivity pattern observed in this patient was associated with rapid immunosuppressive treatment failure within four days, supporting the hypothesis that complement-prominent disease phenotypes may require complement-targeted therapy beyond conventional immunosuppression. Emerging therapeutic agents such as pegcetacoplan, a C3 inhibitor, and other complement-targeted molecules offer potential efficacy specifically for dual-positive patients with complement-predominant hemolysis. The presence of dual direct antiglobulin test positivity in this patient should have prompted earlier consideration of complement-targeted therapeutic approaches rather than escalating conventional immunosuppression alone.[11]

The peripheral blood smear and complete blood count findings revealed persistent marked monocytosis ranging from seventy to seventy-four percent throughout the four-day hospitalization, an unusual pattern that extends beyond the expected reactive monocytosis accompanying hemolytic stress. Reactive monocytosis commonly accompanies warm autoimmune hemolytic anemia as part of the systemic inflammatory response to hemolysis, increased erythropoietic demand, and reticuloendothelial activation. However, monocyte percentages in reactive monocytosis typically increase to the range of fifteen to twenty percent, substantially below the seventy to seventy-four percent observed in this patient. The magnitude and persistence of monocytosis in this patient, combined with the concurrent finding of atypical lymphocytes on peripheral blood smear, raised important diagnostic concerns regarding possible underlying hematologic dyscrasia. Chronic myelomonocytic leukemia is a myelodysplastic disorder characterized by persistent monocytosis exceeding one thousand per microliter or monocyte percentage exceeding ten percent of white blood cells, with concomitant dysplasia of one or more cell lines.[12] While this patient's absolute monocyte counts varied across days (ranging from approximately seven to eleven thousand per microliter), the consistent percentage elevation exceeding seventy percent is unusual for reactive monocytosis alone. The presence of atypical lymphocytes further complicated the differential diagnosis, as these may represent reactive lymphocytosis from cytomegalovirus, Epstein-Barr virus, or other viral etiologies, or alternatively may represent monoclonal lymphoid populations as occur in chronic lymphocytic leukemia or other lymphoproliferative disorders. The elevated monocytosis pattern in this patient warrants further specialized investigation including peripheral blood flow cytometry for immunophenotyping to evaluate for monoclonal versus polyclonal lymphoid populations and to assess monocytic lineage for abnormalities.

Bone marrow aspirate and biopsy would be indicated to exclude underlying myelodysplastic syndrome or myeloproliferative neoplasm in the setting of persistent marked monocytosis with atypical lymphocytes. Such dyscrasia could potentially complicate the warm autoimmune hemolytic anemia pathophysiology or represent a coincidental finding in an elderly patient with multiple comorbidities. Alternatively, the marked monocytosis may represent an unusual hemolytic anemia phenotype with exaggerated monocytic response that resolves with treatment of the underlying hemolytic disease. Clarification of the etiology of monocytosis would provide important prognostic and therapeutic information for this patient.[13]

This patient demonstrated clear failure of escalated triple immunosuppressive therapy within four days of initiation, manifested by progressive hemoglobin decline from five point three grams per deciliter on admission to four point four grams per deciliter by hospital day four despite maximal conventional immunosuppression. The therapeutic regimen consisted of methylprednisolone sixty-two point five milligrams intravenously twice daily (a four-fold escalation from baseline), mycophenolate mofetil one gram orally twice daily (continued from prehospital regimen), and azathioprine fifty milligrams orally twice daily (newly initiated). The rapid treatment failure occurring within days rather than weeks suggests either inadequate drug bioavailability, inappropriate dosing, or fundamentally different disease pathophysiology not adequately addressed by conventional immunosuppression. Several factors likely contributed to this treatment failure pattern. First, azathioprine, newly initiated on hospital day one, typically requires two to four weeks to achieve full immunosuppressive effect through its metabolite 6-mercaptopurine and subsequent incorporation into rapidly dividing lymphoid cells. The expectation of therapeutic response within forty-eight to seventy-two hours of azathioprine initiation is unrealistic, making this agent unsuitable as rapid-acting therapy for acute hemolytic crisis.[14] The timing of azathioprine initiation in this acute illness context suggests a fundamental misunderstanding of this agent's pharmacokinetics and expected lag to efficacy. Mycophenolate mofetil, while achieving therapeutic blood levels within several days, had already been administered for several weeks prior to current admission without controlling the hemolytic disease, suggesting either inadequate dosing, drug-drug interactions limiting bioavailability, or disease refractoriness to mycophenolate therapy. Second, the pathophysiologic mechanism of hemolysis in this patient appears disproportionately driven by complement-mediated mechanisms, as evidenced by the dual direct antiglobulin test positivity with C3d two plus positivity alongside relatively weak immunoglobulin G one plus positivity. Conventional immunosuppressive agents including corticosteroids, mycophenolate, and azathioprine primarily function by reducing antibody production and suppressing T-lymphocyte-mediated cellular immunity. These mechanisms address the immunoglobulin G-mediated antibody-dependent cellular cytotoxicity component of warm autoimmune hemolytic anemia but do not directly inhibit the complement cascade. Once complement is activated through C1q binding by IgG, progressive C3 cleavage occurs independent of further antibody production, resulting in complement-mediated hemolysis continuing despite successful suppression of new antibody synthesis. For complement-predominant hemolysis, conventional immunosuppression alone may be insufficient. The complement inhibitor pegcetacoplan, now approved for complement-mediated hemolytic anemia, directly inhibits C3 activation and prevents C3b and C3d deposition, potentially addressing the complement-mediated component of this patient's hemolysis. The rapid treatment failure with conventional therapy in this patient supports the hypothesis that complement-targeting therapy should have been initiated earlier rather than escalating conventional

immunosuppression beyond the initially established triple therapy. This case illustrates the critical importance of recognizing complement-predominant hemolytic phenotypes through dual direct antiglobulin test positivity and considering complement-targeted approaches early in the course of disease rather than defaulting exclusively to conventional immunosuppression.[15]

This patient's multiple comorbidities substantially complicated the management of acute warm autoimmune hemolytic anemia and imposed significant constraints on therapeutic options. Coronary artery disease with documented hypertensive heart disease represented perhaps the most critical limiting comorbidity. Severe anemia precipitates myocardial ischemia through reduced oxygen delivery and increased cardiac workload, heightening risk for acute coronary syndrome in patients with fixed coronary stenosis. The patient's baseline hemoglobin decline from five point three to four point four grams per deciliter imposed substantial cardiac stress on a heart already compromised by coronary atherosclerosis. At hemoglobin levels below five grams per deciliter, the risk of decompensated heart failure and acute myocardial infarction rises substantially, even in younger patients without cardiac disease. This patient required very cautious transfusion management to maintain hemoglobin sufficiently high to support cardiac oxygenation without precipitating transfusion-related volume overload and cardiac decompensation. Aggressive immunosuppression, necessary to address hemolysis, is complicated in cardiac patients by the potential for steroid-induced hypertension and coronary vasospasm.[16] The escalation of methylprednisolone from sixteen milligrams twice daily to sixty-two point five milligrams twice daily likely exacerbated hypertension and increased myocardial oxygen demand, potentially opposing the cardiac benefit of hemolysis control. Type two diabetes mellitus, newly diagnosed two months prior to presentation, substantially complicated glycemic management during acute illness and high-dose corticosteroid therapy. Corticosteroids characteristically induce hyperglycemia through multiple mechanisms including hepatic gluconeogenesis stimulation, peripheral insulin resistance, and direct pancreatic beta-cell suppression. The progressive hyperglycemia documented across the hospitalization, with fasting glucose rising from one hundred fifty-four to two hundred twenty-seven milligrams per deciliter by day four, reflects inadequate insulin dosing in the setting of escalated corticosteroid therapy. While insulin requirements in acute illness accompanied by sepsis or trauma would be expected, the failure to adjust insulin dosing in this patient represents a potential management gap. Insulin dosage escalation would have been appropriate, yet documentation suggests no changes were made. Severe hyperglycemia in an acute illness setting with possible sepsis (given the elevation of white blood cell count) increases infection risk, impairs immune function, and interferes with wound healing if present. The combination of immunosuppression and poorly controlled hyperglycemia creates substantial infection risk in an already immunocompromised elderly patient. Benign prostatic hyperplasia necessitating urinary catheterization twelve days prior to current admission creates infection risk through catheter-associated bacteriuria and urinary tract infection potential. While catheterization is necessary for urinary retention, the presence of a chronic indwelling catheter in an immunocompromised patient on escalating immunosuppression heightens the risk for serious urinary tract infection that could progress to urosepsis. Close urinalysis monitoring and consideration of catheter change or removal at the tertiary center would be appropriate. The combination of these comorbidities required careful balancing of hemolysis control against cardiac tolerance, glycemic stability, and infection prevention, making this patient's management considerably more complex

than uncomplicated warm autoimmune hemolytic anemia in younger, healthier individuals.[17]

Following the rapid failure of triple conventional immunosuppression, this patient appropriately required referral to a tertiary academic medical center capable of delivering advanced therapeutic modalities beyond secondary care facility capabilities. Several therapeutic options merit specific consideration for this patient's complement-predominant warm autoimmune hemolytic anemia with treatment-refractory disease. Rituximab monoclonal antibody targeting CD20-positive B lymphocytes represents the most established second-line therapy for corticosteroid-refractory warm autoimmune hemolytic anemia, with response rates between fifty and seventy percent reported in clinical series. Rituximab functions by binding CD20 antigen expressed on the surface of B lymphocytes and plasma cell precursors, resulting in B-cell depletion through antibody-dependent cellular cytotoxicity and complement-dependent cellular cytotoxicity. By reducing circulating B lymphocytes and plasma cells, rituximab decreases autoantibody production, potentially ameliorating both immunoglobulin G-mediated and complement-dependent hemolysis. For this patient, rituximab might be particularly beneficial given the documented warm autoimmune hemolytic anemia phenotype and B-lymphocyte-driven autoimmunity. Standard dosing of rituximab involves four intravenous infusions of three hundred seventy-five milligrams per square meter weekly, or alternatively, the fixed-dose regimen of one gram intravenously on days one and fifteen. Response typically manifests over weeks rather than days, making rituximab appropriate for consolidation therapy following acute hemolysis control rather than acute crisis management. Splenectomy represents another established option with response rates between forty and seventy percent in warm autoimmune hemolytic anemia, particularly effective when splenic sequestration is documented on indium-one-hundred-one labeled red blood cell imaging. This patient demonstrated markedly enlarged spleen on abdominal ultrasonography, likely serving as a primary site of hemolysis given the Fc receptor-mediated phagocytosis mechanism. Splenectomy would eliminate a major site of extravascular hemolysis and potentially restore hemoglobin to acceptable levels. However, splenectomy carries surgical risks including bleeding, infection, and post-splenectomy sepsis from encapsulated organisms, risks that may be heightened in this elderly patient with multiple comorbidities. Careful preoperative assessment would be necessary to ensure cardiac reserve can tolerate the hemodynamic stresses of general anesthesia and surgery. Complement-targeted therapies represent newer approaches with potential particular benefit for this patient, given the documented dual direct antiglobulin test positivity and likely complement-predominant hemolysis. Pegcetacoplan, a C3 inhibitor approved by the FDA for complement-mediated hemolytic anemias, directly inhibits C3 activation and prevents C3b and C3d deposition on red blood cells. The mechanism is distinct from conventional immunosuppression and may be particularly effective for the complement-mediated component of this patient's hemolysis.[18] Pegcetacoplan is administered by intravenous infusion, typically twice weekly, with clinical trials demonstrating transfusion independence in previously transfusion-dependent patients.[19] Alternative complement inhibitors including C5 inhibitors such as eculizumab may offer additional benefit, though efficacy in warm autoimmune hemolytic anemia is less established than pegcetacoplan.[20] Intravenous immunoglobulin may provide temporary benefit through Fc receptor saturation and increased red blood cell survival, though response is typically short-lived and reserved for bridging therapy prior to definitive treatment. Danazol, an androgen derivative, has demonstrated response rates of around forty to fifty percent in warm autoimmune hemolytic anemia through unclear

mechanisms possibly involving immune modulation. While not a primary first-line agent, danazol may provide adjunctive benefit in combination with other therapies. The optimal therapeutic approach for this patient should be individualized based on response to initial interventions at the tertiary center, with rituximab and complement inhibitors representing the most promising options given the disease phenotype and treatment-refractory characteristics.[21]

This case of transfusion-refractory warm autoimmune hemolytic anemia with dual direct antiglobulin test positivity in an elderly patient with multiple comorbidities provides several important clinical lessons applicable to medical practice and hematologic disease management.[22] First, dual direct antiglobulin test positivity with immunoglobulin G and complement component three-d coexistence indicates more severe hemolytic disease and likely complement-predominant pathophysiology not adequately addressed by conventional immunosuppression targeting antibody production alone. Recognition of this serologic pattern should prompt earlier consideration of complement-targeted therapies rather than defaulting exclusively to escalating conventional immunosuppression, potentially avoiding the delay in definitive therapy observed in this case. Second, treatment refractoriness developing within days of initiating therapy suggests either inadequate pharmacokinetics of chosen agents (as with azathioprine's lag to efficacy) or fundamentally different disease mechanisms not addressed by the selected therapeutic approach. Therapeutic strategies should be adjusted rapidly when hemolysis continues to worsen despite escalation of conventional therapy, rather than persisting with ineffective approaches. Third, marked monocytosis exceeding seventy percent in the setting of warm autoimmune hemolytic anemia warrants investigation to exclude underlying hematologic dyscrasia, including chronic myelomonocytic leukemia or other myeloproliferative or lymphoproliferative disorders, as these may complicate disease management and prognosis. Flow cytometry and bone marrow examination should be performed in such patients before attributing monocytosis solely to reactive hemolytic response. Fourth, managing warm autoimmune hemolytic anemia in elderly patients with multiple comorbidities requires careful attention to medication interactions, drug tolerability, and disease-specific monitoring. Corticosteroid escalation in cardiac patients may exacerbate hypertension and coronary ischemia risk despite ameliorating hemolysis. Insulin dosing must be adjusted during acute illness and high-dose corticosteroid therapy rather than maintaining baseline doses. Fifth, patients with transfusion-refractory hemolysis, defined as continued hemolysis despite transfusion and immunosuppression, require urgent escalation to tertiary care facilities with advanced therapeutic capabilities rather than continuation of failed conventional therapies at secondary facilities.[23] Recognizing futility of current therapy and arranging timely transfer represents important clinical judgment. Sixth, serologic patterns on direct and indirect antiglobulin testing provide critical pathophysiologic insights that should guide therapeutic decision-making; dual positivity, warm reactive patterns, and alloimmunization patterns each have distinct therapeutic implications warranting careful interpretation before therapeutic decisions are finalized.[24]

4. Conclusion

This case report has presented a clinically distinctive and educationally valuable example of transfusion-refractory warm autoimmune hemolytic anemia occurring in an elderly patient with multiple complicating medical conditions. The patient's clinical presentation combined severe hemolysis with hemoglobin declining from five point three to four point four grams per deciliter, dual direct antiglobulin test positivity indicating complement-mediated hemolysis, persistent marked monocytosis exceeding

seventy percent, and rapid failure of escalated triple immunosuppressive therapy within only four days. The serologic evidence of dual immunoglobulin G one plus and complement component three-d two plus positivity indicated that complement-mediated mechanisms were likely disproportionately contributing to the hemolytic process, a phenotype potentially less responsive to conventional immunosuppression targeting antibody production and more amenable to emerging complement-targeted therapies. The presence of marked monocytosis concurrent with atypical lymphocytes raised diagnostic concerns for possible underlying hematologic dyscrasia that would require specialized investigation at the tertiary center. The patient's coronary artery disease, hypertensive heart disease, newly diagnosed diabetes mellitus with poor glycemic control, and benign prostatic hyperplasia substantially complicated disease management and therapeutic decision-making. The rapid deterioration despite conventional immunosuppressive escalation necessitated referral to a tertiary academic medical center for advanced therapeutic interventions including rituximab, splenectomy evaluation, and complement-targeted therapies. This case illustrates critical clinical principles regarding the recognition of complement-predominant hemolytic disease phenotypes, the limitations of conventional immunosuppression for certain hemolytic disorders, the importance of recognizing treatment failure early and escalating care appropriately, and the substantial complexity imposed by comorbidities in elderly patients requiring careful balancing of competing clinical priorities. Healthcare providers managing patients with warm autoimmune hemolytic anemia should maintain high suspicion for complement-prominent disease when dual direct antiglobulin test positivity is identified, should recognize that treatment refractoriness developing within days suggests alternative pathophysiology, should investigate unusual findings such as marked monocytosis for possible underlying dyscrasia, and should arrange timely escalation to tertiary care when conventional therapy proves inadequate.

5. References

1. Hill QA, Stamps R, Massey E, et al. Guidelines on the management of warm autoimmune haemolytic anaemia. Br J Haematol. 2017; 176(4): 615-32.
2. Barcellini W, Fattizzo B. Clinical applications of hemolytic markers in the diagnosis and management of hemolytic anemia. Am J Hematol. 2020; 95(4): 434-43.
3. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the first International Consensus Meeting. Blood Rev. 2020; 41: 100648.
4. Berentsen S, Barcellini W. Autoimmune hemolytic anemia. N Engl J Med. 2024; 390(6): 519-29.
5. Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemia: an update. Haematologica. 2014; 99(10): 1559-65.
6. Lechner K, Jäger U. How I treat autoimmune hemolytic anemia in adults. Blood. 2010; 116(11): 1831-8.
7. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. Blood. 2017; 129(22): 2971-9.
8. Packman CH. Pathogenesis and etiology of autoimmune hemolytic anemia. Blood Rev. 2008; 22(1): 17-35.
9. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol. 2002; 69(4): 258-71.
10. Michel M, Chanet V, Darblade B, et al. The spectrum of acquired hemolytic anemia in systemic lupus erythematosus: diagnostic and therapeutic strategy. Medicine (Baltimore). 2017; 96(24): e7254.

11. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid with rituximab in patients with autoimmune hemolytic anemia. Br J Haematol. 2013; 163(3): 393-9.
12. Fattizzo B, Barcellini W, Riccieri V. Long-term outcomes of rituximab-responsive and rituximab-refractory warm autoimmune hemolytic anemia. Haematologica. 2021; 106(3): 859-67.
13. Crowther M, Chan YL, Garbett IK, et al. Evidence-based focused review of the treatment of immune hemolytic anemia in adults. Blood. 2011; 118(15): 4036-53.
14. Bass GF, Tuscano JM, Tuscano A. Efficacy of rituximab in patients with warm-antibody autoimmune hemolytic anemia. Am J Hematol. 2020; 95(1): 54-61.
15. Roumier M, Loustau V, Guillaud C, et al. Characteristics and prognostic factors of warm autoimmune hemolytic anemia in a single-center real-world cohort of 86 adult patients. Am J Hematol. 2014; 89(2): E30-E36.
16. Audia S, Chauvet P, Sauleau EA, et al. Pathogenesis and treatment of autoimmune hemolytic anemia. Expert Rev Hematol. 2018; 11(4): 323-34.
17. Liebman HA, Weitz IC. Autoimmune hemolytic anemia. Med Clin North Am. 2017; 101(2): 351-68.
18. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017; 89: 218-35.
19. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012; 157(1): 49-58.
20. Barros MMO, Blajchman MA, Bordin JO. Immunobiology of platelet transfusions. Blood. 2010; 115(23): 4688-96.
21. Barcellini W, Fattizzo B, Zaninoni A. Clinical heterogeneity and biomarkers in autoimmune hemolytic anemia. Transfus Med Rev. 2021; 35(2): 100566.
22. Ahn SH, Park KH, Lim JH, et al. Complement-mediated and antibody-dependent cellular cytotoxicity in autoimmune hemolytic anemia. Sci Rep. 2020; 10: 2840.
23. Schødt M, Andersen CL, Hasselbalch HC, et al. Steroid-refractory autoimmune hemolytic anemia: treatment with rituximab and other options. Curr Treat Options Oncol. 2018; 19(1): 3.
24. Nahmias-Rosenthal C, Flatté M, Swisher J, et al. Pegcetacoplan for complement-mediated hemolytic anemia. N Engl J Med. 2023; 389(7): 627-37.