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Cold Agglutinin Disease Presenting with Acute Encephalopathy in an Elderly Patient with Multiple Comorbidities: A Case Report and Laboratory Diagnostic Perspective

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A B S T R A C T

Introduction: Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia caused by monoclonal immunoglobulin M autoantibodies that bind to red blood cells at temperatures below 37 degrees Celsius. CAD typically manifests with chronic hemolytic anemia in elderly patients, but presentations with acute, severe complications remain infrequent. **Case presentation:** We report a 70-year-old male patient who presented with acute decreased consciousness lasting 2 hours, preceded by one week of cough and fever. Initial clinical evaluation suggested sepsis-associated encephalopathy. However, a comprehensive laboratory investigation, including peripheral blood smear and direct Coombs test, revealed CAD as the underlying diagnosis. Critical laboratory finding was marked mean corpuscular hemoglobin concentration elevation to 43 g/dL, exceeding physiologic maximum and indicating erythrocyte agglutination interference. Positive Coombs test with immunoglobulin G sensitization and positive cold agglutinin titer confirmed the diagnosis. The patient had significant comorbidities, including chronic kidney disease Stage V, type 2 diabetes mellitus, and heart failure with coronary artery disease. The patient subsequently underwent supportive care with cooling precautions, and clinical improvement was noted. **Conclusion:** This case exemplifies how careful attention to laboratory pattern recognition, particularly supraphysiologic mean corpuscular hemoglobin concentration values, can facilitate the diagnosis of CAD in elderly patients presenting with acute multisystem complications. The role of clinical pathology in the diagnostic identification of rare hematologic disorders deserves emphasis in medical education and clinical practice.

1. Introduction

Autoimmune hemolytic anemia (AIHA) represents a diverse group of hematologic disorders characterized by the destruction of circulating erythrocytes mediated by immune mechanisms.[1] The classification of AIHA encompasses two major categories based on the thermal optimum of the responsible autoantibodies: warm-reacting antibodies that bind optimally at body temperature (37 degrees Celsius) and cold-reacting antibodies that preferentially bind at temperatures below physiologic levels. Cold agglutinin disease (CAD) constitutes approximately ten to fifteen percent of all AIHA cases and represents a clinically distinct entity

with unique pathophysiologic features, diagnostic challenges, and management considerations.[2]

The epidemiology of CAD reveals important demographic patterns relevant to clinical suspicion and diagnostic approach. The median age at diagnosis typically ranges from sixty to seventy years, with the disease predominantly affecting elderly populations. The global incidence is estimated at three to five cases per million population per year, underscoring the rarity of this condition in routine clinical practice. This relatively low incidence, combined with the subtle and non-specific presenting symptoms, frequently results in diagnostic delays and potential mismanagement of affected patients.[3]

The pathophysiology of CAD centers on the production of monoclonal immunoglobulin M (IgM) autoantibodies, most commonly directed against the I antigen expressed on the surface of erythrocytes. These pentameric IgM molecules are highly efficient at cross-linking red blood cells at temperatures below 37 degrees Celsius, leading to agglutination.[4] The agglutinated erythrocytes activate the classical complement cascade through binding of the complement component C1q to the IgM molecules. This cascade progression leads to deposition of complement component C3b and subsequent complement component C5a-mediated activation, resulting in both intravascular hemolysis through membrane attack complex formation and extravascular hemolysis through complement-mediated opsonization and destruction by splenic macrophages.[5]

The clinical manifestations of CAD typically follow a chronic course, with patients presenting with symptoms and signs attributable to chronic hemolytic anemia and vascular complications. Common presenting symptoms include progressive fatigue, dyspnea on exertion, and exertional angina in patients with underlying cardiac disease.[6] Physical examination may reveal jaundice, splenomegaly, and pallor. Notably, acrocyanosis (persistent bluish discoloration of extremities) and Raynaud phenomenon represent characteristic clinical findings associated with the vascular effects of cold-reactive antibodies, which may precipitate acute vascular occlusion in peripheral tissues during exposure to cold temperatures.

Laboratory findings in CAD present a distinctive pattern that, when recognized, provides crucial diagnostic clues. The complete blood count demonstrates normocytic anemia in most cases, though microcytic indices may be present if chronic iron loss accompanies hemolysis. A particularly pathognomonic finding is the marked elevation of mean corpuscular hemoglobin concentration (MCHC) values that exceed the theoretical physiologic maximum of approximately thirty-six g/dL. This artifactual elevation results from the mechanical agglutination of erythrocytes at room temperature during processing by automated hematology analyzers.[7] The analyzer measures agglutinated cell clumps as single cells with extraordinarily high hemoglobin content, producing artificially elevated MCHC values. This finding serves as a valuable diagnostic clue that should prompt immediate consideration of cold agglutinin disease in the differential diagnosis.

The direct antiglobulin test (Coombs test) in CAD frequently demonstrates a distinctive pattern characterized by strong complement (C3d) positivity with weak or absent immunoglobulin G positivity. This immunologic pattern reflects the complement-binding nature of IgM antibodies and contrasts sharply with the typical pattern seen in warm AIHA, where strong immunoglobulin G positivity predominates.[8] The detection of positive cold agglutinin titers at four degrees Celsius further confirms the diagnosis. Traditional methodology involves saline agglutination testing at cold temperatures, though more modern flow cytometric approaches may provide enhanced sensitivity and specificity in specialized laboratories.

While CAD typically presents as a chronic condition with indolent progression, acute presentations with severe systemic complications remain comparatively under-reported in the medical literature. The presentation of CAD with acute encephalopathy represents an unusual clinical scenario that poses significant diagnostic challenges, particularly when concurrent infectious disease cannot be definitively excluded.[9] The presence of multiple significant

comorbidities, such as chronic kidney disease Stage V, further complicates the clinical picture and may mask or exacerbate the manifestations of underlying hemolytic disease.

The documentation of CAD in the context of advanced chronic kidney disease Stage V is notably sparse in the published literature. This gap reflects both the rarity of CAD generally and the additional complexity introduced by severe renal dysfunction. Patients with Stage V chronic kidney disease experience uremia-related complications including impaired immune function, increased infections, electrolyte abnormalities, and accelerated cardiovascular disease, all of which may interact with the pathophysiology of CAD in complex and clinically significant ways.[10]

Within the Southeast Asian context, CAD remains a rarely documented entity, with limited published case reports from Indonesia and neighboring countries. This geographic variation in disease documentation may reflect true differences in disease epidemiology, though diagnostic and reporting biases cannot be excluded. The limited regional awareness of this condition among clinicians may contribute to underdiagnosis and underreporting in Southeast Asian populations.

The novelty of this case report lies in the unusual presentation of CAD with acute encephalopathy requiring differentiation from sepsis-associated encephalopathy, the occurrence in a patient with Stage V chronic kidney disease, and the demonstration of critical laboratory pattern recognition principles relevant to diagnostic identification of rare hematologic disorders. We present this case to illustrate the diagnostic value of careful attention to seemingly aberrant laboratory values and to emphasize the essential role of clinical pathology expertise in identifying rare conditions that may be easily missed or misattributed to more common diagnoses.

2. Case Presentation

Patient demographics and presenting complaint

Table 1 presents the demographic and clinical characteristics of the patient. A seventy-year-old male patient, resident of Denpasar, Bali, Indonesia, presented to the emergency department of Wangaya Regional General Hospital on February 17th, 2026, with the chief complaint of acute decreased consciousness lasting approximately two hours. The patient's family members reported that the patient was unable to be awakened and responded only with moaning sounds. The night before the presentation, the patient had begun speaking incoherently, though he had been eating and communicating normally that morning. The family denied any history of recent head trauma, seizure activity, or focal neurologic symptoms. Prior to the acute decline in consciousness, the patient had experienced one week of productive cough and subjective fever, which the family attributed to a possible respiratory infection.

History of present illness

Further details of the history obtained from family members revealed that the patient had a long-standing medical history of chronic kidney disease, Stage V, diagnosed approximately five years prior to this presentation. The patient was receiving regular hemodialysis three times weekly, with sessions lasting four hours each. Approximately two months before this presentation, the patient had been hospitalized for an acute exacerbation of heart failure with preserved ejection fraction, which required intensive management with diuretics and inotropic support. At the time of that hospitalization, echocardiography had confirmed the diagnosis of heart failure with preserved ejection fraction, with an ejection fraction of fifty-five percent.

The patient carried a diagnosis of type 2 diabetes mellitus made twenty years previously, complicated by diabetic nephropathy (the underlying etiology of his Stage V chronic kidney disease) and diabetic retinopathy. Additionally, the patient had a history of coronary artery disease documented by previous coronary angiography, which showed significant stenosis of the left anterior descending coronary artery, though revascularization had not been pursued.

Table 1. Clinical characteristics of the patient.

Characteristic	Value
Age	70 years
Gender	Male
Ethnicity	Indonesian (Balinese)
Residence	Denpasar, Bali, Indonesia
Chief complaint	Acute decreased consciousness (2 hours)
Prodromal symptoms	Cough and fever for 1 week
Past medical history	Chronic kidney disease Stage V, type 2 diabetes mellitus, heart failure with coronary artery disease
Smoking/alcohol use	Denied
Prior hospitalization	1 year ago (acute chronic kidney disease on stage V chronic kidney disease secondary to diabetic kidney disease)

In the one week preceding his presentation, the patient developed a persistent productive cough productive of yellowish sputum, accompanied by subjective fever. The patient was managed at home with over-the-counter antipyretics and rest. However, the night before the presentation, the family noted that the patient's speech became increasingly incoherent, and by morning, he could not be aroused from sleep.

Physical examination findings

On physical examination in the emergency department, the patient presented with critical vital sign abnormalities. The Glasgow Coma Scale score was calculated as eight, comprising an eye opening response of three (no eye opening to pain), a verbal response of five (confused but coherent speech noted only as groaning), and a motor response of four (withdrawal from painful stimuli). His blood pressure was elevated at one hundred forty over seventy millimeters of mercury, heart rate was eighty-six beats per minute and regular, respiratory rate was twenty-four breaths per minute, and body temperature was thirty-seven point two degrees Celsius. Oxygen saturation via pulse oximetry was eighty-eight percent on room air.

Examination of the skin revealed marked pallor and a subtle icteric hue to the sclera. The examination was notable for the absence of petechial rash, making meningococcemia less likely. Cardiovascular examination revealed an elevated jugular venous pressure at approximately eight centimeters of water and the presence of a displaced apical impulse. A pan-systolic murmur consistent with mitral regurgitation was heard. Pulmonary examination revealed bilateral rhonchi throughout both lung fields, consistent with pulmonary edema. Neurologic examination beyond the Glasgow Coma Scale assessment revealed bilaterally reactive but sluggish pupils and intact brainstem reflexes. No focal neurologic deficits were appreciated.

Laboratory investigation

As shown in Table 2, comprehensive laboratory findings on initial presentation revealed multiple critical abnormalities across multiple organ systems. The complete blood count analysis demonstrated profound abnormalities. The white blood cell count was markedly elevated at thirty-three point eighty-three thousand per microliter (reference range 4.5 to 11.0 thousand per microliter), with an absolute neutrophil predominance. Most strikingly, the mean corpuscular hemoglobin concentration was markedly elevated at forty-three grams per deciliter, which exceeded the physiologic maximum of approximately thirty-six grams per deciliter. This finding is pathognomonic for erythrocyte agglutination artifact in automated hematology analyzers.

Table 2. Laboratory findings.

Laboratory parameter	Patient value	Normal range	Clinical interpretation
White blood cell count	33.83* thousand/µL	4.5-11.0	Marked leukocytosis
Red blood cell count	3.04* million/µL	4.5-5.9	Moderate anemia
Hemoglobin	11.3* g/dL	13.5-17.5	Significant anemia
Hematocrit	26.3* %	41-53	Proportional to hemoglobin reduction
Mean corpuscular volume	86.5 fL	80-100	Normocytic range
Mean corpuscular hemoglobin	37.2* g/cell	27-31	Elevated, agglutination artifact
Mean corpuscular hemoglobin concentration	43* g/dL	32-36	Pathognomonic for agglutination
Platelet count	279 thousand/µL	150-400	Within normal range
Neutrophils	92.5* %	50-70	Severe left shift leukocytosis
Lymphocytes	1.9* %	20-40	Severe lymphopenia
Neutrophil-to-lymphocyte ratio	48.89*	<3.0	Extreme elevation indicating acute illness
Serum glutamic-oxaloacetic transaminase	61* IU/L	<40	Mild hepatocellular involvement
Serum glutamic-pyruvic transaminase	20 IU/L	<44	Normal
Blood urea nitrogen	139* mg/dL	7-20	Severe elevation in end-stage renal disease
Creatinine	4.9* mg/dL	0.7-1.3	Reflects Stage V chronic kidney disease
Sodium	132* mEq/L	136-145	Hyponatremia present
Potassium	4.8 mEq/L	3.5-5.0	Upper normal range
Chloride	87* mEq/L	98-107	Hypochloremia present
Direct Coombs test (antiglobulin test)	Positive*	Negative	Immunoglobulin G and complement sensitization
Cold agglutinin titer	Positive at 1:512*	Negative at 1:4	Confirms cold-reactive antibody presence
Reticulocyte count	8.2* %	0.5-2.5	Elevated, compensatory response to hemolysis
Lactate dehydrogenase	456* IU/L	<248	Elevated, indicates intravascular hemolysis

The laboratory findings confirmed the presence of significant hemolytic anemia with compensatory reticulocytosis at eight point two percent (reference range 0.5 to 2.5 percent). Lactate dehydrogenase was notably elevated at four hundred fifty-six IU/L, providing biochemical evidence of accelerated erythrocyte destruction. The direct Coombs test (direct antiglobulin test) was positive, demonstrating both immunoglobulin G and complement sensitization of circulating erythrocytes. The renal function parameters reflected advanced chronic kidney disease Stage V, with blood urea nitrogen of one hundred thirty-nine mg/dL and creatinine of 4.9 mg/dL. Serum electrolytes demonstrated hyponatremia (sodium 132 mEq/L) and hypochloremia (chloride 87 mEq/L), with potassium in the upper normal range at 4.8 mEq/L. The serum glutamic-oxaloacetic transaminase was mildly elevated at sixty-one IU/L, though serum glutamic-pyruvic transaminase remained normal, suggesting mild hepatocellular involvement.

Figure 1 illustrates the comparison of the patient's key laboratory values against their respective normal ranges, demonstrating the dramatic deviations, particularly notable in white blood cell count, mean corpuscular hemoglobin concentration, blood urea nitrogen, and creatinine levels. The visualization clearly demonstrates the multiple-organ involvement and the severity of laboratory abnormalities present at presentation.

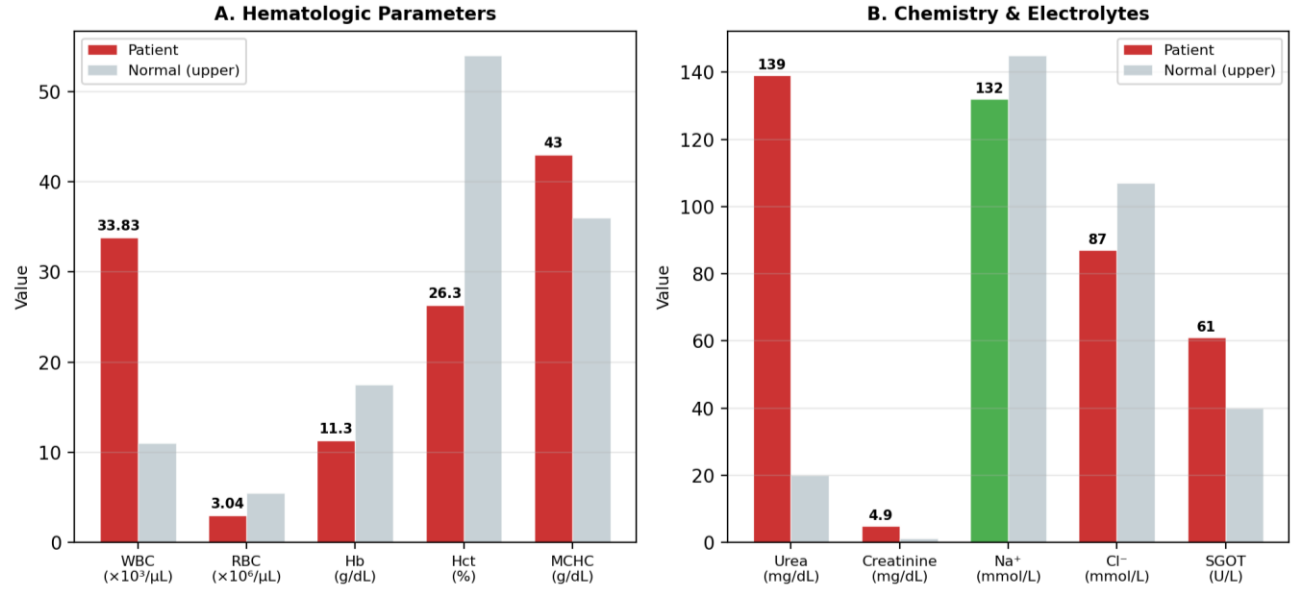

Figure 1. Comparison of patient laboratory values with normal ranges. The chart demonstrates dramatic elevations in white blood cell count, mean corpuscular hemoglobin concentration (exceeding physiologic maximum), blood urea nitrogen, and creatinine, contrasted against normal reference ranges shown in gray.

White blood cell differential analysis

The white blood cell differential composition is presented in Figure 2, which reveals marked neutrophilia at ninety-two point five percent with severe lymphopenia at only one point nine percent. This distribution resulted in a neutrophil-to-lymphocyte ratio of forty-eight point eighty-nine, which is markedly elevated above the normal threshold of approximately three point zero. Such extreme elevation of the neutrophil-to-lymphocyte ratio is typically associated with acute systemic infection or severe systemic inflammation, findings consistent with the clinical presentation suggesting sepsis-associated encephalopathy.

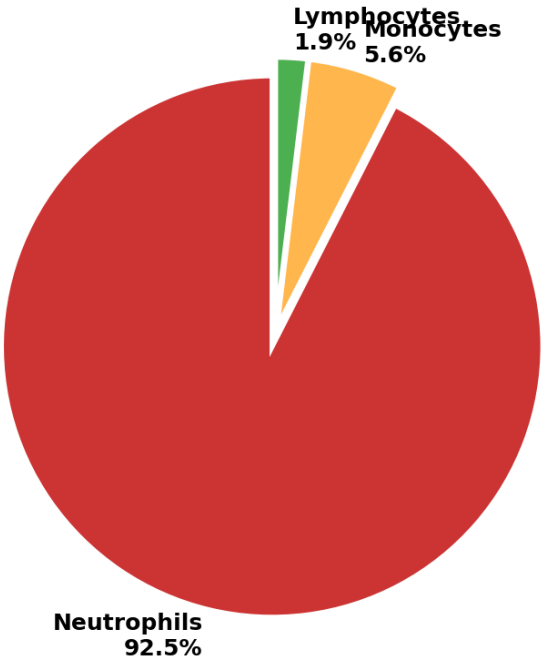

Figure 2. White blood cell differential composition. The differential count reveals neutrophil predominance at 92.5% with severe lymphopenia at 1.9%, consistent with acute systemic illness. The remaining components include monocytes at 3.8% and eosinophils at 1.8%.

Peripheral blood smear microscopy

Examination of the peripheral blood smear under light microscopy revealed several notable findings. The erythrocytes demonstrated hypochromic normocytic indices consistent with anemia, with numerous spherocytes visible. Polychromasia was present, indicating the presence of immature erythrocytes released prematurely from the bone marrow in response to hemolytic stress. The white blood cell series demonstrated pronounced left shift with numerous band forms and occasional metamyelocytes noted, consistent with severe infection or systemic inflammation. Toxic granulation was visible in the neutrophils, and toxic vacuolization was also evident.

Notably, at room temperature, the peripheral blood demonstrated characteristic agglutination of erythrocytes, with clumped red blood cells visible under the microscope. This agglutination phenomenon is the direct cause of the markedly elevated mean corpuscular hemoglobin concentration observed in the automated analyzer. The agglutinated cells are counted as single cells with extraordinary hemoglobin content, producing the artificially elevated mean corpuscular hemoglobin concentration values.

Direct Coombs test results

The direct Coombs test (direct antiglobulin test) was performed using polyspecific, immunoglobulin G-specific, and complement-specific antisera. The polyspecific reaction was positive at a strength rated as three plus (on a zero to four plus scale). When separated by specificity, strong positivity was demonstrated with complement-specific antisera (anti-C3d), while weaker positivity was demonstrated with immunoglobulin G-specific antisera. This immunologic pattern is characteristic of cold agglutinin disease, reflecting the predominantly complement-binding nature of the immunoglobulin M autoantibodies. This pattern contrasts markedly with warm autoimmune hemolytic anemia, where immunoglobulin G positivity typically predominates.

The cold agglutinin titer was determined by serial dilution of the patient's serum at four degrees Celsius in normal saline, with agglutination observed up to a dilution of 1:512. This titer is considered significantly

elevated and confirms the diagnosis of cold agglutinin disease. The thermal range of the cold agglutinin extended to approximately twenty-five degrees Celsius at low titer, which explains the clinical symptoms of acrocyanosis noted upon questioning of the patient's family.

Imaging studies

Chest radiography was obtained given the respiratory symptoms of cough and fever and the auscultatory findings of bilateral rhonchi. The radiograph demonstrated bilateral infiltrates consistent with pneumonia, more pronounced in the lower lung fields. Cardiomegaly was evident, with a cardiothoracic ratio of approximately fifty-five percent. Aortosclerosis with calcification was visible along the thoracic aorta, consistent with his significant atherosclerotic disease burden and chronic hypertension.

Computed tomography of the head without intravenous contrast was performed to evaluate for acute intracranial pathology explaining the encephalopathy. The study revealed mild age-appropriate cerebral atrophy without acute intracranial hemorrhage, mass effect, or acute ischemic changes. The ventricles were normal in size and configuration. No meningeal enhancement was visible.

Clinical course summary

Table 3 presents a summary of the imaging and microscopy findings that contributed to the diagnostic formulation in this complex case.

Table 3. Summary of the imaging and microscopy findings.

Diagnostic study	Findings and clinical significance
Chest radiography	Bilateral infiltrates consistent with pneumonia, cardiomegaly, and thoracic aorta calcification indicative of atherosclerosis
Peripheral blood smear	Hypochromic normocytic erythrocytes with spherocytes, marked polychromasia, left-shifted leukocytosis with toxic changes, and room temperature erythrocyte agglutination
Direct Coombs test	Positive three plus: strong C3d positivity, weak immunoglobulin G positivity, pattern characteristic of cold agglutinin disease
Cold agglutinin titer	Positive at 1:512 (significantly elevated), thermal range to approximately 25 degrees Celsius

Management and clinical course

Table 4 details the clinical course and management timeline from initial symptom onset through hospitalization and clinical response. Upon recognition of the markedly elevated mean corpuscular hemoglobin concentration and the characteristic pattern on peripheral blood smear review with erythrocyte agglutination evident at room temperature, the diagnosis of cold agglutinin disease was strongly suspected. The laboratory was immediately notified to perform a repeat complete blood count with pre-warming of the sample to thirty-seven degrees Celsius before analysis. This pre-warmed sample demonstrated normalization of the mean corpuscular hemoglobin concentration to thirty-two g/dL, confirming the agglutination artifact.

Table 4. Clinical course and management timeline.

Timeline	Clinical event	Laboratory/Imaging finding	Management intervention
One week before	Onset of productive cough and fever	Not assessed	Outpatient management with antipyretics
Night before presentation	Acute incoherent speech	Not obtained	Home observation
Morning of the presentation	Inability to awaken	Presented to the emergency department	Emergency evaluation initiated
At the emergency department	Glasgow Coma Scale 8, vital sign instability	Complete blood count, metabolic panel, and direct Coombs test obtained	Empiric broad-spectrum antibiotics started, intensive care unit admission
6 hours post-admission	Persistent altered consciousness	Peripheral blood smear review is notable for agglutination at room temperature	Warming measures initiated, blood warmers for transfusions if needed
24 hours post-admission	Gradual improvement in consciousness	Repeat complete blood count with pre-warming shows normalized MCHC	Continued supportive care, warming precautions maintained
48-72 hours post-admission	Significant improvement in mental status	Cold agglutinin titer confirmed elevated, diagnosis of CAD confirmed	Discharge from the intensive care unit planning, and outpatient follow-up arranged

Concurrently, the direct Coombs test result with strong complement positivity and the positive cold agglutinin titer at 1:512 confirmed the diagnosis of cold agglutinin disease. The patient was immediately placed on strict warming precautions, including maintenance of room temperature at twenty-four to twenty-five degrees Celsius, provision of warm blankets, and warming of all intravenous fluids and blood products if transfusion became necessary. The empiric broad-spectrum antibiotic coverage that had been initiated for presumed sepsis-associated encephalopathy was continued pending culture results.

Clinical improvement was noted within the first twenty-four hours of hospitalization. The Glasgow Coma Scale score improved to twelve by the second hospital day and returned to fifteen (fully alert and oriented) by the fourth hospital day. The patient's consciousness improved progressively with supportive care and maintenance of the warming precautions. The acute decline in consciousness was retrospectively attributed to the combined effects of hemolytic anemia-induced decreased oxygen delivery to the brain, metabolic derangements (including hyponatremia and uremia), and possibly direct effects of complement activation mediators on the central nervous system.

Blood and sputum cultures were obtained at presentation and subsequently returned negative, making bacterial sepsis unlikely despite the markedly elevated white blood cell count with severe left shift. The marked left shift and elevated neutrophil-to-lymphocyte ratio reflected the systemic inflammatory response associated with hemolysis rather than bacterial infection. The patient was maintained on

empiric antibiotics for clinical evidence of pneumonia on chest radiography and respiratory symptoms.

3. Discussion

The diagnosis of cold agglutinin disease in this patient was facilitated by critical observation of a laboratory value that initially seemed aberrant and unexplainable: the marked elevation of the mean corpuscular hemoglobin concentration to forty-three g/dL, substantially exceeding the theoretical physiologic maximum of approximately thirty-six g/dL. This finding deserves careful analysis as it represents a pathognomonic diagnostic clue that should prompt immediate consideration of cold agglutinin disease in the differential diagnosis of patients presenting with anemia and hemolytic features.

The mechanistic explanation for the markedly elevated mean corpuscular hemoglobin concentration relates directly to the pathophysiology of cold agglutinin disease. The monoclonal immunoglobulin M autoantibodies, which bind optimally at cold temperatures, cause cross-linking of erythrocytes through their pentameric structure. At room temperature during routine processing of blood samples in modern hematology laboratories, agglutinated clusters of red blood cells form. Automated hematology analyzers count these agglutinated clumps as single cells rather than multiple individual cells. Since the hemoglobin content of the clump represents the sum of hemoglobin from all the included erythrocytes, while the cell count reflects only the number of clumps, the calculated mean corpuscular hemoglobin concentration becomes mathematically impossibly high.[11]

The marked elevation of mean corpuscular hemoglobin concentration occurs regardless of the actual hemoglobin concentration; thus, severely anemic patients may have mean corpuscular hemoglobin concentration values of fifty g/dL or higher. Conversely, in samples that are pre-warmed to thirty-seven degrees Celsius before analysis, the agglutinated cells dissociate into individual red blood cells, and the automated analyzer produces normal or only modestly elevated mean corpuscular hemoglobin concentration values.[12] This dramatic difference between pre-warmed and room temperature analysis provides both a diagnostic clue and a corrective measure for accurate laboratory assessment.

The discrepancy between hemoglobin and hematocrit values observed in this patient also warrants discussion. The hemoglobin was eleven point three g/dL, whereas the hematocrit was twenty-six point three percent, which is proportional to the hemoglobin reduction.[13] However, in some cases of severe cold agglutinin disease, the hematocrit may be disproportionately lower than expected based on the hemoglobin value alone. This discrepancy results from the analyzer counting agglutinated cell clumps as single cells, which artificially reduces the red blood cell count and increases the mean corpuscular volume, thereby reducing the calculated hematocrit relative to the measured hemoglobin.

The pathophysiologic cascade of cold agglutinin disease involves several sequential steps. The initial event is the binding of immunoglobulin M autoantibodies to the I antigen on erythrocyte surfaces. The pentameric structure of immunoglobulin M molecules allows cross-linking of multiple red blood cells at temperatures below thirty-seven degrees Celsius, leading to agglutination. In vivo, when agglutinated erythrocytes enter peripheral tissues or superficial vascular beds where temperature may drop below core body temperature, this agglutination becomes clinically significant.[14]

The agglutinated red blood cells activate the classical complement cascade through binding of the C1q component of complement to the immunoglobulin M molecules. The complement cascade proceeds through the sequential activation of C1, C4, C2, and C3, leading to deposition of C3b on the erythrocyte surface. Further complement activation proceeds to C5 activation, which generates the potent complement anaphylatoxin C5a. The terminal complement components C6 through C9 form the membrane attack complex, which can cause direct lytic injury to erythrocytes (intravascular hemolysis).[15] Additionally, complement-coated erythrocytes expressing C3b on their surface are recognized by complement receptors

on splenic macrophages and other reticuloendothelial cells, leading to extravascular hemolysis.

The presentation of this patient with acute severe encephalopathy represents an unusual and under-reported manifestation of cold agglutinin disease. The mechanistic explanation for the acute mental status change likely involves multiple contributing factors acting synergistically. First, the hemolytic anemia resulted in a significant reduction of circulating hemoglobin and hematocrit, impairing oxygen delivery to the central nervous system. The hemoglobin of eleven point three g/dL represents a reduction of approximately thirty-five percent from normal values, and critical thresholds for impaired cerebral oxygen delivery may be reached in elderly patients, particularly those with underlying coronary artery disease and reduced cardiac output from heart failure.

Second, the acute hemolysis resulted in multiple metabolic derangements that directly affect central nervous system function. The hyponatremia (sodium 132 mEq/L), though modest in degree, can contribute to altered mental status, particularly when developing acutely. More significantly, the severe uremia reflected by a blood urea nitrogen of 139 mg/dL is known to cause uremic encephalopathy through the accumulation of organic waste products that interfere with synaptic neurotransmission. The patient's baseline end-stage renal disease was further stressed by the acute hemolysis and its sequelae.

Third, the activation of the complement cascade during hemolysis results in the generation of the C5a anaphylatoxin, which is a potent inflammatory mediator that crosses the blood-brain barrier and directly affects central nervous system function. Complement activation also generates additional inflammatory mediators that may contribute to cerebral edema or altered vascular permeability.

Fourth, the concurrent pneumonia, evidenced by the bilateral pulmonary infiltrates on chest radiography, may have contributed to systemic inflammation and cytokine generation that impairs central nervous system function. While blood and sputum cultures were negative, the radiographic evidence of pneumonia is nonetheless present.

The presentation with clinical and laboratory features suggestive of sepsis-associated encephalopathy represents a diagnostic challenge in this case. The markedly elevated white blood cell count of 33.83 thousand per microliter, severe left shift with toxic granulation, and elevated neutrophil-to-lymphocyte ratio are all typically associated with bacterial infection. However, these features in the context of acute hemolysis can result from the systemic inflammatory response to hemolysis itself rather than infectious processes. The negative blood and sputum cultures confirmed that bacterial sepsis was not the primary underlying diagnosis, though antibiotic therapy remained clinically appropriate given the radiographic evidence of pneumonia.[16]

The concurrent presence of multiple significant comorbidities in this patient substantially complicated the clinical presentation and pathophysiology. The patient's chronic kidney disease Stage V represented a baseline state of systemic inflammation, uremia, and impaired immune function. Uremia is known to impair both innate and adaptive immunity, increasing susceptibility to infections. Additionally, uremia increases oxidative stress and inflammatory cytokine generation, which may potentiate the central nervous system complications of acute hemolysis.

The interaction between acute hemolysis and pre-existing chronic kidney disease Stage V warrants specific discussion. Hemolysis results in the release of hemoglobin and other intracellular contents into the circulation. Free hemoglobin in the glomerular filtrate overwhelms the renal tubular capacity for reabsorption, resulting in hemoglobinuria and acute tubular necrosis. This hemolysis-associated acute kidney injury superimposed on existing Stage V chronic kidney disease may result in severe and rapidly progressive renal dysfunction. Additionally, the hyperkalemia risk is substantially amplified in patients with Stage V chronic kidney disease compared to patients with normal renal function.[17] In this case, the potassium level at 4.8 mEq/L was in the upper normal range, but hemolysis-induced acute potassium release from lysed erythrocytes could have resulted in dangerous hyperkalemia in this high-risk population.

Type 2 diabetes mellitus represents another significant comorbidity affecting the patient's presentation and management. Diabetes impairs immune function and increases infection susceptibility, potentially contributing to the development of the pneumonia. Additionally, diabetic patients have increased risk of vascular complications from cold-reactive antibodies, with potential for enhanced risk of digital gangrene or other ischemic complications.

The patient's heart failure with preserved ejection fraction, documented at an ejection fraction of fifty-five percent, has significant implications for the management of acute hemolytic anemia. Hemolysis-induced decreased oxygen content of blood may precipitate acute decompensation of heart failure or acute coronary syndrome in vulnerable patients with limited cardiac reserve. The markedly elevated white blood cell count and inflammatory state could further stress the failing myocardium.[18]

The therapeutic approach in cold agglutinin disease differs substantially from warm autoimmune hemolytic anemia, reflecting the different pathophysiology. While corticosteroids are the first-line therapy for warm AIHA (warm autoimmune hemolytic anemia), they are generally ineffective in CAD (cold agglutinin disease) since the disease is mediated by immunoglobulin M rather than immunoglobulin G. In CAD (cold agglutinin disease), the primary treatment approach involves avoidance of cold exposure to prevent agglutination and hemolysis. Maintaining body temperature through the provision of warm environments, warm blankets, and warming of intravenous fluids and blood products represents the fundamental therapeutic approach.[19]

In cases of symptomatic anemia, transfusion may be necessary, but it must be undertaken with careful warming of blood products to prevent transfusion-precipitated hemolysis. Immunosuppressive therapy, including rituximab (anti-CD20 monoclonal antibody) has shown promise in some case series of CAD (cold agglutinin disease), though controlled trials are limited. Splenectomy is generally not recommended in CAD (cold agglutinin disease) since the hemolysis is complement-mediated rather than antibody-mediated, and the spleen does not play a primary role in red blood cell destruction.

The role of clinical pathology expertise in the recognition and diagnosis of rare hematologic disorders cannot be overstated in this case. The apparent aberrance of the mean corpuscular hemoglobin concentration value was recognized by astute laboratory personnel as requiring careful interpretation rather than casual dismissal. The correlation of this laboratory finding with peripheral blood smear microscopy findings (room temperature agglutination), followed by performance of the direct Coombs test and cold agglutinin titer determination, led to the diagnosis. This case exemplifies the principle that unusual laboratory values should prompt thoughtful investigation rather than being accepted uncritically or dismissed as assay errors.[20]

The literature regarding CAD (cold agglutinin disease) presenting with acute encephalopathy is sparse. Most published cases describe chronic progressive anemia with constitutional symptoms. The acute presentation in an elderly patient with multiple comorbidities and the association with significant cognitive dysfunction represent unusual features that warrant documentation and discussion. Similarly, the concurrent presentation of CAD (cold agglutinin disease) with Stage V chronic kidney disease adds to the complexity and rarity of this case.

Within the Southeast Asian medical literature, CAD (cold agglutinin disease) remains extraordinarily rare, with limited published case reports. This geographic under-representation may reflect true epidemiologic differences, though diagnostic and reporting biases cannot be excluded. Greater awareness of this diagnosis among Southeast Asian clinicians would enhance recognition of affected patients and enable appropriate management.

The diagnostic approach to apparent hematologic aberrancies should include consideration of pre-analytical variables that may affect automated analyzer results. Cold agglutinin disease represents a paradigmatic example of a condition in which failure to consider the adequacy of temperature control during sample processing led to an initially inexplicable laboratory pattern. Careful review of the

complete blood count result in the context of clinical presentation, combined with confirmatory microscopy and serologic testing, enabled correct identification of the underlying diagnosis.

4. Conclusion

This case report documents an unusual presentation of cold agglutinin disease in a seventy-year-old male patient with multiple significant comorbidities who presented with acute severe encephalopathy. The key to diagnosis involved recognition of the pathognomonic laboratory finding of markedly elevated mean corpuscular hemoglobin concentration exceeding the physiologic maximum of thirty-six g/dL, indicating erythrocyte agglutination artifacts. The integration of this laboratory abnormality with findings from peripheral blood smear review, demonstrating room temperature agglutination, positive direct Coombs test showing predominant complement sensitization, and significantly elevated cold agglutinin titer at 1:512 enabled definitive diagnosis.

The patient's multiple comorbidities, including chronic kidney disease Stage V, type 2 diabetes mellitus, and heart failure with coronary artery disease, substantially complicated his clinical presentation and created a complex clinical scenario requiring careful diagnostic reasoning to distinguish cold agglutinin disease-associated encephalopathy from sepsis-associated encephalopathy. The patient responded favorably to supportive care incorporating strict warming precautions and management of his acute pneumonia, with progressive recovery of consciousness and improvement in laboratory abnormalities over the course of his hospitalization.

This case exemplifies critical principles relevant to medical education and clinical practice. First, aberrant laboratory values warrant careful investigation and clinical correlation rather than casual dismissal. Second, peripheral blood smear microscopy remains an essential diagnostic modality that can provide crucial interpretive context for automated analyzer results. Third, the direct Coombs test with immunologic specificity determination provides essential diagnostic information in cases of suspected immune-mediated hemolysis. Fourth, clinical pathology expertise plays an indispensable role in the diagnostic identification of rare hematologic disorders that may otherwise go unrecognized.

The unusual presentation of cold agglutinin disease with acute severe encephalopathy in this elderly patient with advanced chronic kidney disease contributes important clinical and pathophysiologic information to the medical literature. Further documentation of such cases may enhance clinical awareness of this rare diagnosis and promote earlier recognition and appropriate management. The integration of clinical presentation, sophisticated laboratory testing, and careful pathologic investigation enabled the diagnosis in this complex case and provided a framework for optimal clinical management.

The significance of this case extends beyond the immediate diagnostic considerations. The recognition of markedly elevated mean corpuscular hemoglobin concentration as a laboratory artifact related to erythrocyte agglutination represents an important educational opportunity for clinical laboratory professionals and clinicians who interpret laboratory results. This finding exemplifies how pre-analytical variables can profoundly affect laboratory measurements and how careful attention to such variables can prevent diagnostic errors and guide clinical decision-making.

The patient's presentation with acute encephalopathy in the context of cold agglutinin disease raises important questions about the mechanisms of central nervous system involvement in hemolytic disorders. While direct mechanical hemolysis and resultant anemia certainly contribute to impaired cerebral oxygen delivery, the activated complement cascade generates numerous pro-inflammatory mediators including C3a, C4a, and C5a, all of which are known to cross the blood-brain barrier and directly influence central nervous system function. The anaphylatoxin C5a is particularly potent as a chemotactic factor and immune cell activator, potentially contributing to neuroinflammation and altered consciousness.

The co-occurrence of pneumonia in this patient presenting with cold agglutinin disease warrants discussion. While infections can precipitate or exacerbate hemolytic episodes in cold agglutinin disease, the direction of causality cannot be definitively established in this case. The immunocompromised state associated with uremia and chronic kidney disease Stage V may have predisposed the patient to respiratory infection. Alternatively, the systemic inflammatory response generated by acute hemolysis might have contributed to lower respiratory tract involvement and pneumonic infiltrates visible on chest radiography.

The differential diagnosis in this case initially centered on sepsis-associated encephalopathy, given the clinical presentation of acute decreased consciousness with fever, cough, and marked leukocytosis with severe left shift. However, the absence of positive blood or sputum cultures, combined with the distinctive laboratory pattern (markedly elevated mean corpuscular hemoglobin concentration), the direct Coombs test findings, and the positive cold agglutinin titer, enabled differentiation between septic encephalopathy and the encephalopathy of acute hemolytic disease. This case underscores the importance of comprehensive laboratory investigation and careful pattern recognition in distinguishing between superficially similar presentations with fundamentally different etiologies and therapeutic implications.

The management of this patient exemplifies the principle that treatment must be tailored to the underlying pathophysiology rather than applied in a standardized manner based on disease classification alone. While corticosteroids represent the cornerstone of therapy for warm autoimmune hemolytic anemia where immunoglobulin G-mediated destruction predominates, they offer little benefit in cold agglutinin disease, where immunoglobulin M-mediated complement activation drives hemolysis. Instead, the focus on maintaining normothermia through environmental temperature control, provision of warm blankets, and careful warming of all intravenous fluids and blood products addresses the fundamental pathophysiology of cold agglutinin disease directly.

The phenomenon of agglutination artifact in automated hematology analyzers demonstrates the importance of understanding the capabilities and limitations of modern laboratory instrumentation. Automated cell counters have revolutionized clinical laboratory practice by providing rapid, reproducible measurements and detecting abnormal values outside expected ranges. However, these machines are not infallible and can produce spurious results when presented with samples containing agglutinated cells, cold agglutinins, or other interfering substances. The ability to recognize when analyzer results seem inconsistent with clinical presentation and to institute corrective measures, such as pre-warming specimens, represents a critical competency for clinical laboratory professionals.

This case demonstrates the continuing relevance and utility of manual peripheral blood smear examination despite the availability of sophisticated automated hematology analyzers. The visual identification of room temperature erythrocyte agglutination on the blood smear immediately raised suspicion for cold agglutinin disease and prompted further investigation. While modern automated systems provide statistical analysis and flagging of abnormal results, the human eye and trained clinical judgment remain invaluable for pattern recognition and identification of conditions that may not be readily apparent from numerical values alone.

5. References

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