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Complement-Mediated Autoimmune Hemolytic Anemia as the Initial Presentation of Renal Cell Carcinoma: A Case Report

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***Abstract*: Autoimmune hemolytic anemia (AIHA) is a rare hematological disorder that may occur as a primary condition or secondary to underlying diseases including malignancies. Although AIHA is commonly associated with lymphoproliferative disorders, association with solid tumors such as renal cell carcinoma (RCC) remains uncommon. We report a 67-year-old gentleman who presented with symptomatic anemia and laboratory evidence of complement-mediated hemolysis. Direct antiglobulin testing demonstrated anti-IgG positivity and strong C3d positivity suggestive of complement-mediated AIHA. Clinical examination revealed a ballotable left-sided abdominal mass. Imaging demonstrated a left renal mass with central necrosis and para-aortic lymphadenopathy highly suggestive of RCC. The patient demonstrated favorable hematological response following corticosteroid therapy and transfusion support. This case highlights the importance of evaluating for underlying malignancy in patients presenting with unexplained hemolysis.**

***Keywords*: Autoimmune hemolytic anemia, Renal cell carcinoma, Cold agglutinin disease, Paraneoplastic syndrome, Complement-mediated hemolysis.**

1. Introduction

Autoimmune hemolytic anemia (AIHA) is an uncommon disorder characterized by premature destruction of erythrocytes due to autoantibody-mediated hemolysis. AIHA may occur as a primary condition or secondary to infections, autoimmune diseases, medications, and malignancies [1], [2]. It is broadly classified into warm, cold, and mixed subtypes based on the thermal reactivity and immunological characteristics of the antibodies involved [3].

Complement-mediated or cold-type AIHA is more frequently associated with secondary causes, particularly infections and lymphoproliferative disorders [3], [4]. Association with solid tumors is considerably less common, although paraneoplastic AIHA has been reported in renal malignancies including RCC [5], [6]. RCC is recognized for its wide range of paraneoplastic manifestations including anemia, hypercalcemia, hepatic dysfunction, cachexia, and less commonly immune-mediated hematological complications [7].

We report a case of complement-mediated AIHA presenting as the initial manifestation of RCC with para-aortic lymphadenopathy, highlighting the importance of systematic evaluation in patients presenting with unexplained hemolysis.

2. Case Presentation

A 67-year-old Malay gentleman with underlying hypertension and diabetes mellitus, as well as a history of treated latent tuberculosis, presented with a two-week history of lethargy, reduced effort tolerance, palpitations, and intermittent dizziness. There was no history of melena, hematochezia, or overt gastrointestinal bleeding. The patient reported passing dark stools attributed to ongoing hematinic therapy. He had a previous history of anemia of unclear etiology. His father had a history of colorectal carcinoma.

On examination, the patient appeared pale but was hemodynamically stable. Blood pressure was 132/69 mmHg, pulse rate 120 beats per minute, temperature 36.8°C, and oxygen saturation 98% on room air. Cardiovascular and respiratory examinations were unremarkable. Abdominal examination revealed a soft, non-tender abdomen with a ballotable mass in the left hypochondriac region suggestive of retroperitoneal origin. No peripheral lymphadenopathy was noted.

Initial laboratory investigations demonstrated severe anemia with hemoglobin of 6.2 g/dL on 25 March 2026, with nadir hemoglobin of 5.1 g/dL. Direct antiglobulin test was strongly positive (3+) with anti-IgG 1+ and anti-C3d 4+, suggestive of complement-mediated hemolysis. Peripheral blood film findings were suggestive of cold autoimmune hemolytic anemia with reactive thrombocytosis and inflammatory changes.

Total bilirubin was elevated at 61 µmol/L and ferritin was elevated at 1372 µg/L. Tumor markers showed AFP 1.5 ng/mL, CEA 3.8 ng/mL, mildly elevated CA19-9 of 38.6 U/mL, and PSA 0.849 ng/mL within normal range. Infective screening including hepatitis B, hepatitis C, HIV, mycoplasma, and legionella were negative.

The patient was transfused 1 pint packed cells on 27 March 2026 for symptomatic anemia. He received intravenous

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hydrocortisone from 25 March 2026 until 1 April 2026, followed by oral prednisolone 30 mg twice daily. Prednisolone was tapered by 10 mg weekly pending hematology follow-up. Initially, rituximab was considered in the event of steroid failure; however, the patient demonstrated favorable hematological response to corticosteroid therapy.

Table 1
Serial hematological parameters during admission

Date	Hemoglobin (g/dL)	LDH (U/L)	Reticulocyte (%)
25/3/26	6.2	-	-
26/3/26	5.1	828	-
27/3/26	6.0	545	6.75
28/3/26	7.3	737	7.13
29/3/26	7.5	481	8.2
30/3/26	7.1	453	10.8
1/4/26	8.7	567	13.3
3/4/26	8.3	479	7.8
6/4/26	10.2	752	6.5

The patient was advised to avoid cold exposure and arrangements were made for warming of blood products if transfusion became necessary.

Ultrasound abdomen performed on 27 March 2026 demonstrated a lobulated heterogeneously hypoechoic left renal mass suspicious for malignancy with differential diagnosis including non-liquefied abscess. Subsequent CT renal protocol performed on 2 April 2026 demonstrated a left lower pole renal mass with central necrosis and significant para-aortic lymphadenopathy. Additional findings included small indeterminate lung nodules, benign-appearing liver cysts, colonic diverticulosis, and prostatomegaly.

The case was discussed during radiology conference on 6 May 2026. Consensus conclusion was highly suggestive of left RCC, possibly representing infected tumor with metastatic disease involving para-aortic lymph nodes. The patient was planned for left renal mass biopsy followed by referral to the oncology team for further management.

3. Discussion

AIHA is a rare but clinically important condition that may occur either as a primary idiopathic disorder or secondary to underlying disease. Secondary AIHA should always be considered in elderly patients presenting with unexplained hemolysis, particularly when complement-mediated patterns are identified on direct antiglobulin testing [1], [2]. In this case, the presence of strong C3d positivity with relatively weaker IgG positivity suggested complement-mediated hemolysis consistent with cold or mixed-type AIHA.

Cold agglutinin disease is commonly associated with infections such as Mycoplasma pneumoniae and Epstein–Barr virus, as well as lymphoproliferative disorders [3], [4]. Infective screening in this patient was negative, increasing suspicion for malignancy-associated hemolysis. Although AIHA is most frequently associated with hematological malignancies, several reports have demonstrated association with solid tumors including RCC, urothelial carcinoma, ovarian carcinoma, and lung cancer [5], [6].

RCC is well recognized for its diverse paraneoplastic manifestations. Approximately 20–40% of patients develop paraneoplastic syndromes during the course of disease [7]. These manifestations may occur due to ectopic hormone production, cytokine release, immune dysregulation, or tumor-induced autoimmunity. Immune-mediated hematological phenomena such as AIHA are uncommon but clinically significant because they may precede diagnosis of the underlying malignancy.

The pathophysiological mechanism underlying malignancy-associated AIHA remains incompletely understood. Proposed mechanisms include production of tumor-associated autoantibodies, molecular mimicry, dysregulated complement activation, and cross-reactivity between tumor antigens and erythrocyte surface antigens [5], [8]. The strong complement positivity in this patient supports significant complement activation contributing to hemolysis.

This case also emphasizes the importance of detailed clinical examination. The presence of a ballotable abdominal mass prompted early abdominal imaging, ultimately revealing the renal mass and para-aortic lymphadenopathy. The patient demonstrated gradual improvement in hemoglobin following corticosteroid therapy and transfusion support, suggesting steroid-responsive complement-mediated or mixed-type AIHA. Although corticosteroids are generally less effective in pure cold agglutinin disease, partial responsiveness has been reported in mixed or complement-mediated subtypes [2], [3].

Supportive management in cold or complement-mediated AIHA includes avoidance of cold exposure and use of warmed blood products to reduce exacerbation of hemolysis [4]. Rituximab is increasingly used in refractory disease and was considered in this patient if corticosteroid therapy failed [9]. However, escalation was unnecessary due to favorable hematological response.

Definitive management of secondary AIHA ultimately depends on treatment of the underlying malignancy. The patient is currently planned for renal mass biopsy and oncology referral to determine further oncological management.

4. Conclusion

Complement-mediated AIHA may represent the initial manifestation of underlying malignancy. Although rare, RCC should be considered among the differential diagnoses in elderly patients presenting with unexplained hemolysis after exclusion of infective causes. Strong C3d positivity should prompt evaluation for secondary causes including malignancy.

This case highlights the importance of systematic clinical assessment, detailed physical examination, multidisciplinary collaboration, and close hematological monitoring in patients with AIHA. Early recognition of malignancy-associated hemolysis facilitates timely oncological evaluation and appropriate management.

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