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Antithrombotic Strategy Considerations for Warm Antibody Autoimmune Hemolytic Anemia Associated with Acute Ischemic Stroke

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Abstract

Objective

This study aimed to investigate the clinical characteristics and antithrombotic strategies in patients with warm autoimmune hemolytic anemia (wAIHA) and acute ischemic stroke (AIS), to provide insights into the management of this rare clinical scenario.

Methods

We retrospectively analyzed clinical data (laboratory parameters, imaging findings, treatment, and outcomes) of five patients with wAIHA-associated AIS and performed a narrative literature review on thrombotic risk and its management.

Results

The five patients (median age 66 years, range 64–73) presented with neurological deficits as their initial manifestation,with a median diagnostic delay of 3 days. On admission, they exhibited evidence of active hemolysis: median hemoglobin 59 (29–84) g/L, reticulocyte count 242 (30.5–302)×10^9/L, indirect bilirubin 35.3 (19.2–45.9) μmol/L, and lactate dehydrogenase 528 (262–889) U/L. Direct antiglobulin test was positive in five patients (IgG alone in two, IgG and C3d in three), and indirect antiglobulin test was positive in four. Antinuclear antibody was positive in all cases, while antiphospholipid antibodies were detected in one. Brain magnetic resonance imaging revealed multifocal acute infarcts predominantly involving the posterior circulation, without large vessel stenosis. All patients received antiplatelet therapy combined with glucocorticoids, statins, and neuroprotective agents; adjunctive therapies included blood transfusions, intravenous immunoglobulin, immunosuppressants, or rituximab in select cases. Two patients developed recurrent thrombotic events during active hemolysis with suboptimal control: one developed massive pulmonary embolism and deep vein thrombosis two months later but recovered after ECMO, thrombectomy, and anticoagulation; the other developed disseminated intravascular coagulation and improved after switching from antiplatelet to anticoagulant therapy.

Conclusion

The hemolysis-driven coagulation cascade in wAIHA-associated AIS highlights the importance of effective hemolysis control in this setting. Our observations suggest that recurrent thrombotic events may occur despite antiplatelet therapy during active hemolysis, supporting the need for prospective studies evaluating the potential role of anticoagulation in selected patients—a scenario for which high-quality evidence is currently lacking.

Key Points

- wAIHA-associated AIS often presents with neurological deficits as the initial manifestation, delaying diagnosis of underlying hemolysis.
- Antiplatelet monotherapy may be insufficient; anticoagulation during acute hemolysis may confer greater benefit.
- Hemolysis control is the cornerstone of thromboprophylaxis; early hematology-neurology collaboration is essential.

Introduction

Autoimmune hemolytic anemia (AIHA) is a rare acquired hemolytic disorder caused by immune dysregulation, in which autoantibodies mediate red blood cell (RBC) destruction that outpaces bone marrow compensatory capacity[1–3]. It has an annual incidence of 1.0–3.0 per 100,000 population[4]. AIHA is categorized as primary (idiopathic) or secondary to other autoimmune disorders or lymphoproliferative diseases. According to the thermal optimum of antibody-RBC binding, it is further classified into warm AIHA (wAIHA), cold AIHA (cAIHA), and mixed AIHA(mAIHA)[1–3].

Patients with AIHA carry a markedly elevated risk of thrombotic complications, with reported incidence rates ranging from 11% to 29.6%, particularly for venous thromboembolism (VTE) during the acute phase of hemolysis[5–17]. The underlying prothrombotic mechanism is multifactorial, driven by hemolysis through free heme release, phosphatidylserine exposure, tissue factor upregulation, platelet activation, microparticle release, and nitric oxide scavenging, with complement activation and inflammation further amplifying hypercoagulability[18–20]. While the VTE risk is well recognized, arterial thrombotic events (ATE)—including acute ischemic stroke (AIS)—are less frequent and mechanistically less defined, though plausibly linked to hemolysis-driven hypercoagulability. Clinically, AIHA-associated AIS often presents with acute neurological deficits, leading clinicians to prioritize emergency stroke management while overlooking the underlying hemolytic etiology, frequently resulting in delayed or missed AIHA diagnosis. Unlike atherosclerotic cerebral infarction, which is characterized by intracranial and anterior circulation artery stenosis (particularly in Chinese populations)[21], AIHA-associated AIS appears to be primarily driven by hemolysis-induced coagulation cascade activation and often presents as multifocal small vessel infarcts without large artery stenosis on neuroimaging, a pattern that may have therapeutic implications. Therefore, effective control of hemolysis represents the cornerstone of both thromboprophylaxis and disease management, as it directly targets the primary driver of hypercoagulability in this population.

Currently, no established consensus or clinical guideline exists regarding antithrombotic therapy for AIHA-associated AIS. In routine practice, antithrombotic regimens are largely extrapolated from secondary prevention for atherosclerotic cerebral infarction, with antiplatelet therapy as the mainstay—especially when AIHA diagnosis is delayed[22]. Whether antiplatelet monotherapy can sufficiently mitigates thrombotic risk in this specific patient population thus remains poorly defined. Against this backdrop, we present clinical data and therapeutic outcomes of five patients with wAIHA-associated AIS, together with a

focused literature review. We propose hypothesis- generating, mechanism-directed antithrombotic strategies that question whether antiplatelet therapy alone suffices and whether anticoagulation may offer additional benefit in selected patients during active hemolysis, with the aim of informing clinical reasoning in this rare but high-risk scenario.

Materials and methods

Patients

We retrospectively enrolled five patients diagnosed with wAIHA-associated AIS. Among them, three cases were identified from a cohort of 58 patients with wAIHA treated at Wuhan Hospital of Traditional Chinese and Western Medicine between January 2019 and December 2025; the remaining two cases were identified at other tertiary hospitals. AIHA was diagnosed based on a positive direct antiglobulin test (DAT) plus evidence of hemolysis (anemia, decreased haptoglobin, and elevated lactate dehydrogenase (LDH) and/or bilirubin)[1, 2]. AIS was confirmed by diffusion- weighted imaging (DWI) of brain magnetic resonance imaging (MRI) showing acute infarcts consistent with clinical symptoms. This retrospective study was approved by the Ethics Committee of Wuhan Hospital of Traditional Chinese and Western Medicine (Approval No.: XS-2025111). The requirement for written informed consent was waived due to the retrospective nature of the study.

Clinical parameters

We analyzed baseline clinical data for all enrolled patients. The assessment included: (1) demographics and medical history; (2) clinical presentation, encompassing initial symptoms, disease course, thrombotic events, and treatment regimens; and (3) Laboratory workup, including complete blood count, biochemical panels, LDH, coagulation profiles, D-dimer, DAT, indirect antiglobulin test (IAT), and a comprehensive autoimmune screening panel. The autoimmune screening consisted of antinuclear antibody (ANA) profile with 18 specificities (anti-dsDNA, anti-SSA, anti-SSB, anti-Jo-1, anti-Sm, anti-nRNP, anti-Scl-70, anti-CENP-B, anti-histone, anti- nucleosome, anti-P0, anti-RO52, anti-PM-Scl, anti-PCNA, anti-AMA, anti-Ku, anti-Mi-2, and anti- MCV antibodies), antineutrophil cytoplasmic antibody (ANCA), complement levels (C3 and C4), and immunoglobulins (IgG, IgA, IgM). Antiphospholipid antibodies (aPL), including anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (aβ2GPI), as well as lupus anticoagulant (LA), were also evaluated in all patients. All thrombotic events were objectively confirmed by imaging studies, such as Doppler ultrasonography, contrast-enhanced computed tomography, or MRI.

Treatment and outcome assessment

The treatment options considered for AIHA were: (1) steroids, either alone or with intravenous immunoglobulin (IVIG); (2) immunosuppressant drugs; (3) rituximab (RTX), administered either at 375mg/m^2 weekly for 4 weeks or at the fixed low dose of 100mg weekly for 4 weeks; and (4) splenectomy[1, 2]. Other interventions, including transfusions, plasma exchange, and erythropoietin administration, were also recorded. Treatment response was categorized as: complete response (CR) (hemoglobin > 120 g/L and normalization of all hemolytic markers), partial response (PR) (hemoglobin > 100 g/L or an increase of at least 20 g/L, with no transfusion requirement). AIS was managed according to the AHA/ASA guidelines, including antiplatelet therapy, statin therapy, neuroprotective agents as adjunctive treatment, and standard blood pressure and glucose control[22].

Statistical analysis

Statistical analyses were performed using GraphPad Prism 8.0. For the cohort of 58 patients with wAIHA, continuous variables are expressed as median with range, and categorical variables as frequencies and percentages. Comparisons between patients with and without thrombotic events were made using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, given the relatively small sample size. The five patients with wAIHA- associated AIS were analyzed descriptively as a case series; no comparative statistics were applied to this subgroup due to the limited number of cases (n = 5). A two-tailed p-value < 0.05 was considered statistically significant for the cohort analysis.

Results

1. **Detailed diagnostic and therapeutic profiles of 5 patients with wAIHA-associated AIS**

Case 1

A 65-year-old female with a 16-year history of wAIHA (maintained on prednisone 5–10 mg daily) presented on April 23, 2023 with dizziness and unsteady gait for 3 days. Admission hemoglobin (HGB)84 g/L, LDH 262 U/L, Ret% 10.06%. DAT was positive for IgG, and IAT was positive. ANA was positive at 1:320 with anti-SSA antibodies. LA and aPL were negative. Brain DWI revealed an acute small infarct in the left cerebellar hemisphere, multiple small infarcts in the bilateral centrum semiovale and frontotemporoparietal lobes; Magnetic resonance angiography (MRA) revealed intracranial atherosclerosis without evidence of large vessel occlusion or significant stenosis. She was diagnosed with primary wAIHA and AIS (NIHSS 0). She received prednisone 15 mg daily, cyclosporine A 50 mg twice daily, atorvastatin, clopidogrel, and neuroprotective agents, and improved after 9 days. She was subsequently maintained on long-term therapy with prednisone, Cyclosporin A(CSA), clopidogrel, and atorvastatin. Two months later, HGB rose to 107 g/L (PR). At last follow-up (January 2026), HGB was 131 g/L (CR) with no recurrent thrombosis.

Case 2

A 64-year-old female with no significant past medical history presented on December 13, 2023 with dizziness and unsteady gait for 10 hours. Admission HGB 69 g/L, LDH 282 U/L, Ret% 4.69%. DAT was positive for IgG and C3, while IAT was negative. ANA was positive at 1:320. LA and aPL were negative. Brain DWI revealed an acute right cerebellar infarct and a right frontal ischemic focus; MRA showed no abnormalities. She was diagnosed with primary wAIHA and AIS (NIHSS 0). She received methylprednisolone 40 mg daily, mycophenolate mofetil (MMF) 0.25 g twice daily, atorvastatin, clopidogrel, and neuroprotective agents, and improved after 15 days. However, hemolysis remained poorly controlled, with HGB only 86 g/L at two months. On February 15, 2024, she was readmitted with chest pain and dyspnea for three days, and experienced one syncopal episode. Echocardiography showed marked right ventricular enlargement, severe tricuspid regurgitation, and moderate pulmonary hypertension. Lower extremity venous ultrasound revealed right lower extremity thrombosis involving the popliteal, posterior tibial, peroneal, and calf intermuscular veins. Pulmonary computed tomography angiography (CTA) demonstrated multiple pulmonary emboli. She was diagnosed with massive pulmonary embolism (PE), Deep vein thrombosis (DVT), wAIHA, and recovering cerebral infarction. She received extracorporeal membrane oxygenation (ECMO), mechanical thrombectomy, low-molecular-weight heparin (LMWH), and methylprednisolone 40 mg, with gradual recovery. By May 24, 2024, DVT had resolved and HGB rose to 98 g/L (PR). She continued on steroids, MMF and Rivaroxaban, with HGB levels (80–100 g/L) but hemolysis remained suboptimally controlled; no higher-intensity therapy was given. At last follow-up (January 26, 2026), HGB was 83 g/L (PR), with no further thrombotic events.

Case 3

A 70-year-old male with a history of hypertension and gastric ulcer presented on May 7, 2024 with dizziness, unsteady gait, and limb numbness for 3 months, worsening over 3 days. Three months prior, he had been evaluated at another hospital where HGB was 67 g/L, and his symptoms improved after symptomatic treatment. Over the recent 3 days, his symptoms worsened. Admission HGB 54 g/L, LDH 528 U/L, Ret% 23.07%. DAT was positive for IgG, and IAT was positive. ANA was positive at 1:320. LA and aPL were negative. Brain DWI revealed acute left temporo-occipital infarct; multiple infarcts in the left cerebellum, corpus callosum, bilateral basal ganglia, and frontal lobe, some with encephalomalacia; MRA revealed intracranial atherosclerosis without evidence of large vessel occlusion or significant stenosis. He was diagnosed with primary wAIHA, AIS (NIHSS 2), and hypertension. He received dexamethasone 10 mg daily, atorvastatin, clopidogrel, RBC transfusions, and neuroprotective agents, and improved after 16 days. Two months later, HGB rose to 130 g/L (CR). At last follow-up (June 13, 2025), HGB was 124 g/L (CR), with no further thrombotic events.

Case 4

A 66-year-old male with a history of well-controlled hypertension was admitted on May 10, 2024, with cognitive impairment for 1 day. Admission HGB 59 g/L, LDH 636 U/L, Ret% 12.4%. DAT was positive for IgG and C3, and IAT was positive. ANA was positive at 1:320. LA and aPL were negative. Brain DWI revealed acute infarct in the left temporoparieto-occipital lobe; MRA revealed intracranial atherosclerosis without evidence of large vessel occlusion or significant stenosis. He was diagnosed with primary wAIHA, AIS (NIHSS 5), hypertension, and reactive thrombocytosis. He received dexamethasone 10 mg daily, atorvastatin, aspirin, and neuroprotective agents, and improved after 22 days. Hemolysis control achieved CR. At last follow-up (May 28, 2025), HGB was 137 g/L (CR), with no further thrombotic events.

Case 5

A 73-year-old female with a 1-year history of wAIHA (maintained on prednisone 5 mg daily) presented on December 5, 2025 with dizziness, fatigue, and slurred speech for 3 days. Admission HGB 29 g/L, LDH 889 U/L, Ret% 7.04%. DAT was positive for IgG and C3, and IAT was positive. ANA was positive at 1:1000, with anti-SSA and anti-RO52 antibodies.LA was positive, with aCL and aβ2GPI titers at 210.1 CU and 142.5 CU, respectively. Brain DWI revealed acute infarcts in the bilateral frontal and parietal lobes, periventricular regions, and basal ganglia. MRA revealed intracranial atherosclerosis without evidence of large vessel occlusion or significant stenosis. She was diagnosed with wAIHA, AIS (NIHSS 1), antiphospholipid syndrome (APS), and hypertension. She received dexamethasone 15 mg daily, IVIG 20 g for 3 days, CSA 75mg twice daily, atorvastatin, clopidogrel, neuroprotective agents, and RBC transfusions. After 4 days, HGB rose to 69 g/L, but PLT progressively decreased to 27 × 10^9/L. Coagulation profile: D-dimer 8.95 mg/L, Fibrinogen degradation products (FDP) 29.5 μg/mL, Fibrinogen (FBG) 1.67 g/L. ISTH score was 5, and disseminated intravascular coagulation (DIC) was diagnosed. Antiplatelet therapy was discontinued and switched to enoxaparin, initially at 2000 IU q12h, which was gradually increased to the therapeutic dose as platelet counts recovered. With the addition of anticoagulation to her ongoing immunosuppressive regimen, her HGB rose to 91 g/L and PLT increased to 167 × 10^9/L one week later, with resolution of DIC and achievement of PR of hemolysis. She was discharged on a tapering regimen of methylprednisolone, CSA 75 mg twice daily, RTX 100 mg weekly for 4 doses, and rivaroxaban. At last follow-up (February 9, 2026), HGB was 130 g/L (CR), aCL was 71.9 CU, aβ2GPI was 50.6 CU, with no further thrombotic events. The detailed treatment course and dynamic changes of key laboratory parameters in Case 5 are presented in Fig. 1.

- **2.Clinical characteristics of the 5 patients with wAIHA complicated by AIS**
- At our institution, 14 of 58 wAIHA patients (24.14%) experienced 19 thrombotic events during the acute hemolytic phase, including 10 DVT, 4 PE, 3 AIS, and 1 each of DIC and lower extremity arterial embolism. Thrombotic events were associated with lower HGB, higher LDH, advanced age, and need for RBC transfusions (detailed in Table 1), findings broadly consistent with our previous report[16]. Prophylactic anticoagulation was administered to 6 patients before thrombotic events: 1 in the thrombotic group (for atrial fibrillation) and 5 in the non-thrombotic group (3 for SLE, 2 for APS). Among the 14 patients who developed thrombotic events, 11 received therapeutic anticoagulation after the event—including 1 patient who had been on prophylactic anticoagulation for atrial fibrillation but still developed thrombosis. The remaining 3 patients in the thrombotic group received antiplatelet therapy alone for AIS; among them, one subsequently developed PE and DVT and was switched to anticoagulation. Notably, none of the 5 patients who received prophylactic anticoagulation in the non-thrombotic group developed thrombosis during follow-up. However, given the small number of patients and heterogeneous indications for anticoagulation, this descriptive observation should not be interpreted as evidence of prophylactic efficacy. To expand the case series for detailed analysis, we included two additional patients with wAIHA-associated AIS from other tertiary hospitals, bringing the total to five cases. Their clinical characteristics are summarized in Table 2.

- **2.1 Baseline characteristics.** Among the five patients, there were two males and three females, with a median age of 66 years (range, 64–73 years). None of the five patients had a documented history of atrial fibrillation or other major cardioembolic sources. Four patients (80%) had primary wAIHA, and one (20%) had secondary wAIHA associated with APS. Two patients had a documented history of AIHA (Case 1 for 16 years, Case 5 for 1 year), both maintained on low-dose prednisone. Systematic evaluation to exclude underlying lymphoproliferative disorders was performed in all patients. None presented with B symptoms (fever, night sweats, or weight loss). Chest and abdominal computed tomography revealed no lymphadenopathy or hepatosplenomegaly, and peripheral blood smears showed no atypical lymphocytes. Bone marrow aspiration and biopsy were performed in Cases 1 and 2, both showing trilineage hematopoiesis without morphologic abnormalities or aberrant antigen expression on cytomorphology and flow cytometry. In the remaining three patients, bone marrow biopsy was not performed due to advanced age, favorable response to immunosuppressive therapy, and absence of clinical, laboratory, or imaging features suggestive of an underlying lymphoproliferative disorder.
- **2.2 Presenting department and diagnostic delay.** All five patients initially presented with AIS. Four were admitted to neurology and one to the Emergency Intensive Care Unit (EICU). Among the three with newly diagnosed AIHA, diagnosis was delayed by 2, 3, and 10 days, respectively. None of the five patients presented within the time window for intravenous thrombolysis.
- **2.3 Laboratory findings.** Admission data showed active hemolysis: median HGB 59 g/L (range, 29–84 g/L), LDH 528 U/L (range, 262–889 U/L), and Ret% 10.06% (range, 4.69%–23.07%). DAT was positive in all patients, with IgG alone in two patients and both IgG and C3d in three patients. ANA was positive in all; LA and aPL were positive in one patient (who also developed DIC).
- **2.4 Neuroimaging findings.** All five patients exhibited multifocal acute ischemic infarcts on brain MRI, with a distribution predominantly involving the posterior circulation, whereas MRA showed no evidence of significant large artery stenosis or occlusion. Representative brain MRI findings of wAIHA-associated AIS are shown in Fig. 2.

Table 1
Characteristics associated with thrombosis in 58 patients with wAIHA

	All patients (N = 58)	**wAIHA/TE (N = 14)**	**wAIHA/NO (N = 44)**	**P Value**
Baseline Characteristics				
Age, median (range)	62(14–83)	69(41–82)	59(14–83)	0.026
Male/Female	17/41	4/10	13/31	0.944
Follow-up duration (months), median(range)	18(0.5–233)	17.5(0.5, 48)	20.5(2, 233)	0.250
Primary/Secondary	23/35	10/4	19/25	0.330
ANA positive/cases tested	54/58	14/14	40/44	0.242
aPL positive/cases tested	16/38	2/10	14/28	0.099
Padua high risk(N)	9	3	6	0.483
DAT				0.790
IgG+C3d	35	8	27	
IgG	17	5	12	
C3d	6	1	5	
Laboratory Parameters at Hemolytic Peak				
Hemoglobin (g/L)	65.91 ± 23.04	53.57 ± 18.02	70.00 ± 23.12	0.020
Platelets(^10^9/L)	148.5(16–736)	175(42–736)	160(16–357)	0.214
Reticulocyte (%)	13.63 ± 10.58	12.93 ± 9.61	13.83 ± 10.96	0.815
Reticulocyte count(^10^9/L)	216.4 ± 131.7	172.3 ± 121.8	230.7 ± 128.8	0.154
Total bilirubin (umol/L)	45.48 ± 36.53	50.29 ± 35.47	43.95 ± 37.13	0.576
LDH(U/L)	461.5(150–4254)	605(282–4254)	398.5(150–1594)	0.014
PT(s)	13.23 ± 2.93	13.80 ± 4.78	13.03 ± 1.90	0.843
APTT(s)	35.35 ± 11.40	34.59 ± 16.53	35.63 ± 9.10	0.772
D-dimer(mg/L)	2.14 ± 1.97	2.70 ± 1.13	1.95 ± 2.17	0.240
Treatment				
Methylprednisolone(N)	57(98.28%)	14	43	0.569
Methylprednisolone(mg/d)	53.45 ± 24.06	59.80 ± 25.43	48.60 ± 22.56	0.167
Rituximab(N)	17(29.31%)	4	13	0.944
Cyclosporine(N)	14(24.14%)	3	11	0.786
Tacrolimus(N)	1(1.72%)	0	1	0.241
Mycophenolate mofetil(N)	3(5.17%)	1	2	0.702
Cyclophosphamide(N)	4(6.90%)	0	4	0.563
Therapeutic plasma exchange(N)	11(18.97%)	5	6	0.067
RBC transfusion(N)	19(32.76%)	9	10	0.004
Intravenous immunoglobulin(N)	13(22.41%)	2	11	0.489
Anticoagulation(N)	17(29.31%)	12	5	< 0.001
Prophylactic anticoagulation(N)	6(10.34%)	1	5	0.652

Abbreviations: wAIHA/TE: wAIHA with thrombotic events, **wAIHA/NO**: wAIHA without thrombotic events, **LDH**: Lactate dehydrogenase, **PT**: Prothrombin time, **APTT**: activated partial thromboplastin time, **ANA**: antinuclear antibodies, **aPL**: antiphospholipid antibodies, **DAT**: direct antiglobulin test.

Table 2
Clinical characteristics of 5 patients with wAIHA-associated acute ischemic stroke

Admission time	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**
	2023/4/24	**2023/12/13**	**2024/5/7**	**2024/5/10**	**2025/12/5**
Diagnosis of wAIHA	Admission	3 days later	2 days later	10 days later	Admission
Age/Gender	65/female	64/female	70/male	66/male	73/female
Medical history	AIHA 16 years	No	Hypertension, Gastric ulcer	Hypertension	AIHA 1 years
HGB (g/L)	84	69	54	59	29
Reticulocyte count (10^9/L)	242	30.5	302	220	157
Reticulocyte%	10.06%	4.69%	23.07%	12.40%	7.04%
LDH (U/L)	262	282	528	636	889
TBIL(μmol/L)	41.8	26.7	54.1	37.5	67.1
IBIL (μmol/L)	35.3	19.2	45.9	23	40.4
LDL-C(mmol/L)	2.07	1.74	3.39	2.94	2.32
DAT	IgG	IgG+C3	IgG	IgG+C3	IgG+C3
IAT	Postive	Postive	Postive	Postive	Postive
ENA	ANA 1:320 SSA(+)	ANA 1:320	ANA 1:320	ANA 1:320	ANA 1:1000 SSA(+) RO-52□+□
LA	Negative	Negative	Negative	Negative	Postive
aPL	Negative	Negative	Negative	Negative	Postive
D-dimer(mg/L)	0.27	0.53	1.67	1.01	4.91
Padua score	2	2	3	2	5
Initial antithrombotic	APT	APT	APT	APT	APT
AIHA treatment	Pred 15mg qd CSA 75 mg q12h	MP 40mg qd MMF 0.25g q12h	Dex 10mg qd RBC transfusion	Dex 10mg qd	Dex 15mg qd IVIG 20g × 3d CSA 75mg q12h RTX 100mg qw RBC transfusion
Thrombotic events	No	PE and DVT LMWH	No	No	DIC LMWH
Hospital days	8 days	15days	16 days	25 days	12 days
Last follow-up HGB(g/L)	2026/01/25 131g/L	2026.01.26 83g/L	2025.06.13 124g/L	2025.05.28 137g/L	2026/02/09 130g/L

Abbreviations: AIHA: Autoimmune Hemolytic Anemia; **HGB**: Hemoglobin; **LDH**: Lactate dehydrogenase; **TBIL**: Total bilirubin; **IBIL**: Indirect bilirubin; **LDL-C**: Low-density lipoprotein cholesterol; **DAT**: Direct antiglobulin test; **IAT**: Indirect antiglobulin test; **ENA**: Extractable nuclear antigen panel; **LA**: Lupus anticoagulant; **aPL**: Antiphospholipid antibody; **APT**: Antiplatelet therapy; **Pred**: Prednisone; **MP**: Methylprednisolone; **RTX**: Rituximab; **Dex**: Dexamethasone; **MMF**: Mycophenolate mofetil; **CSA**: Cyclosporine; **RBC**: red blood cells; **LMWH**: Low molecular weight heparin; **DVT**: Deep venous thrombosis; **PE**: Pulmonary embolism; **DIC**: disseminated intravascular coagulation.

- **2.5 Stroke etiology classification.** All patients underwent standard etiologic workup for AIS, including electrocardiography, transthoracic echocardiography, cervical vascular ultrasonography, and brain MRI with MRA and DWI. These investigations systematically excluded atrial fibrillation, valvular heart disease, significant atherosclerotic stenosis, and other major cardioembolic sources. Based on these findings and the neuroimaging features of multifocal small-vessel infarcts without large artery stenosis, the stroke mechanism was classified according to the TOAST criteria as stroke of other determined etiology, which may be most reasonably attributable to AIHA-associated hypercoagulability during active hemolysis.
- **2.6 Antithrombotic treatment and outcomes.** All five patients initially received antiplatelet therapy. Among them, Case 2 developed massive PE and DVT two months later, surviving after ECMO, mechanical thrombectomy, and LMWH. Case 5 developed DIC on day 4; antiplatelet therapy was switched to LMWH. Median hospital stay was 16 days (range, 9–22 days), and median follow-up duration was 8 months (range, 2–34 months). All five patients survived with no further thrombotic events during the follow-up period, with four achieving CR and one achieving PR.
- **3. Narrative literature review of thrombotic risk and clinical characteristics in AIHA patients.**
- To further elucidate the incidence, risk factors, and current status of antithrombotic management in AIHA, we searched the PubMed database and identified 16 clinical studies reporting thrombotic events,comprising 2,328 patients. Key data are summarized in Table 3.

- **3.1 Incidence of thrombotic events.** Across the 16 studies, the overall incidence of thrombotic events ranged from 11% to 29.6% (most studies reporting approximately 20%–25%), with VTE predominating—particularly DVT and PE[5–17]. The incidence of ATE was relatively lower, ranging from 1.7% to 9.5%, mainly comprising AIS, transient ischemic attack (TIA), and myocardial infarction[7–9, 11, 13, 15, 16, 23, 24]. Among studies reporting ATE, the incidence of AIS ranged from 0.7% to 9.5%[7–9, 11, 13, 15, 16, 23, 24]. In a cold agglutinin disease registry (n = 608), Broome et al. reported a cerebral embolism rate of 14.0% (85/608)[17]. Seven studies reported thrombotic-related deaths, primarily attributed to PE, myocardial infarction, and cerebral infarction[7–9, 13–16].
- **3.2 Risk factors for thrombosis.** Multiple studies consistently demonstrated that thrombotic events in AIHA patients are closely associated with the degree of hemolytic activity. Identified risk factors included severe anemia, markedly elevated LDH, intravascular hemolysis, need for RBC transfusion or plasma exchange, and infection[8–10, 13, 15, 16]. Splenectomy was also identified as a risk factor in some studies[9, 15, 25]. Several studies found no association with aPL, LA, or Padua score, suggesting a distinct mechanism with limited overlap with traditional risk factors for thrombosis[8–10, 13, 16, 23, 25].
- **3.3 Current status of antithrombotic therapy.** The role of prophylactic anticoagulation in AIHA patients remains uncertain,though accumulating observational data suggest a potential benefit. Hendrick et al. reported 36 acute hemolytic exacerbations in 28 patients: VTE occurred in 5 of 15 exacerbations without prophylaxis, compared with only 1 of 21 exacerbations with prophylaxis[7]. Lecouffe et al. found that among 40 wAIHA patients, 5 who received prophylaxis for conventional indications (2 APS, 2 mechanical heart valves, 1 atrial fibrillation) had no thrombotic events, whereas 8 of the remaining 35 without prophylaxis developed VTE[10]. Schär et al. observed that among 77 patients, 2 of 10 receiving prophylaxis for atrial fibrillation developed thrombosis, compared with 18 of 67 without prophylaxis[14]. In a prospective 2020–2021 follow-up of 174 patients, PE occurred in 5 of 16 patients with acute hemolysis and LDH ≥ 1.5×ULN who did not receive prophylaxis, whereas no thrombotic complications were observed in the 17 patients who received prophylactic anticoagulation ($p = 0.01$)[13]. Collectively, these data suggest that prophylactic anticoagulation may reduce thrombotic risk during acute hemolysis, although the evidence remains predominantly observational and requires prospective validation. Current guidelines (BJH 2017; AIHA Consensus 2020; NEJM 2021) recommend thromboprophylaxis with LMWH or direct oral anticoagulants for hospitalized AIHA patients with acute exacerbations, active hemolysis, splenectomy, or additional risk factors (prior thrombotic events, limited mobility, inherited thrombophilia, advanced age, or active malignancy)[1–3]. For AIHA patients who develop VTE, anticoagulation should be continued for at least 3 months or until complete recanalization[26].

Table 3
Summary of thrombotic risk and clinical characteristics in patients with wAIHA.

Study	Design	Patients	AIHA type	Prior AT	TE		VTE	ATE	aPL	Padua score	Prothrombo Factors/ Other notab results
					Patients (N)	AT					
Kokori et al., 2000	Single-center retrospective	41	wAIHA 41(100%) (secondary to SLE)	NA	10 patients (24.4%)	NA	NA	NA	NC	NA	AIHA is an independen factor for thrombosis
Pullakart et al., 2002	Multicenter prospective	30	NA	2 TAC	8 patients (27%)	NA	7 DVT, 4 PE, 1 PVT	NA	NC	NA	TE associat LA, Active hemolysis
Hendrick et al., 2003	Single-center retrospective	28	wAIHA 23(82.1%) cAIHA 5(17.9%)	NA	6 patients (21.4%)	NA	6 VTE (4PE)	1 ACI, 1 MI (7.1%)	NC	NA	VTE occurr of 15 exace without pro but in only 21 in which prophylaxis given.
Bongarzoni et al., 2005	Single-center retrospective	21	NA	NA	1 patients (4.8%)	NA	0	2 TIA (9.5%)	NC	NA	Primary AIH coexists wi positive aPl
Roumier et al., 2014	Single-center retrospective	60	wAIHA60 (100%)	NA	12 patients (20%)	NA	12 VTE (8PE)	1 ACI (1.7%)	NC	NA	TE associat severe aner
Barcellini et al., 2014	Multicenter retrospective	307	wAIHA 183(59.6%) cAIHA 84(27.4%%)	NA	33 patients (11%)	NA	11 PE, 13 DVT, 5 ST	3 ACI, 2 TIA, 3 MI (2.6%)	NC	NA	TE associat severe aner higher LDH splenectom
Lecouffe-Desprets et al., 2015	Single-center retrospective	40	wAIHA 40(100%)	5 TAC (2APS, 2MHV,1AF) without TE	8 patients (20%)	NA	4DVT, 8PE	NA	NC	NC	VTE associ with severe
Barcellini et al., 2018	Multicenter retrospective	378	wAIHA 225(59.5%) cAIHA 107(28.3%)	NA	58 patients (15.3%)	NA	NA	NA	NA	NA	NA
Audia et al., 2018	Single-center retrospective	48	wAIHA 48(100%)	NA	11 patients (23%)	2 TAC	10 DVT, 6 PE	2 ACI (4.2%)	NC	NC	TE associat Active hem
Broome et al., 2020	Multicenter retrospective (population-based registry)	608	CAD(100%)	170TAC, 34APT	180 patients (29.6%)	NA	19 DVT, 30 PE, 12 ST, 57 other VTE	85 ACI, 34 MI, 13 other arterial thrombos,	NA	NA	NA
Fattizzo et al., 2022	Multicenter retrospective	287	wAIHA 141(49.1%) cAIHA 103(35.9%)	0TAC	33 patients (11.4%)	29TAC, 4APT	13 PE,8 DVT, 1 PVT, 1 SVT, 1 STP, 2 CRT	2ACI,3 MI (1.7%)	NC	NC	TE associat intravascul hemolysis, transfusion infections, multitreatm
	Multicenter prospective	In a prospective 2020–2021 follow-up of 174 patients, 70 acute hemolytic episodes occurred in 45 patients. Among these 45 ≥ 1.5×ULN; 17 received anticoagulant prophylaxis (no thrombotic complications), whereas 5 PE occurred in the remaining 16									
Higuchi et al., 2022	Single-center retrospective	47	wAIHA 47 (100%)	10 AT	3 patients (6.4%)	1 TAC	0	3 ACI (6.4%)	NA	NA	Infrequent Thrombotic Complicatio Japanese P
Schär DT et al., 2022	Single-center retrospective	77	wAIHA 51(66.2%)	10 TAC	20 patients (26.0%)	18 TAC	NA	NA	NA	NA	prophylacti anticoagula might be

Abbreviations: AIHA: Autoimmune Hemolytic Anemia; wAIHA: warm AIHA; cAIHA: cold AIHA; mAIHA: mixed AIHA; TRD: Thrombosis -related death; SLE: Sys erythematosus; AT: Antithrombotic therapy; TE: Thromboembolic events; VTE: Venous thromboembolism; DVT: Deep venous thrombosis; PE: Pulmonary em throm boembolism; ACI: Acute cerebral infarction; TIA: Transient ischemic attack; DIC: Disseminated intravascular coagulation; CV: Cardiovascular risk; aPL antibody; AF: Atrial fibrillation; MI: Myocardial infarction; LA: Lupus anticoagulant; MHV: Mechanical heart valve; ST: Splanchnic thrombosis; PVT: Portal vein Splenic vein thrombosis; STP: Superficial thrombophlebitis; CRT: Catheter-Related Thrombosis; LLAE:lower limb arterial embolism; NC: No correlation; NA: N Antiplatelet therapy; DAPT: Dual antiplatelet therapy; TAC: Therapeutic Anticoagulation; PAC: Prophylactic Anticoagulation.

Study	Design	Patients	AIHA type	Prior AT	TE		VTE	ATE	aPL	Padua score	Prothrombo Factors/ Other notab results
					Patients (N)	AT					
			cAIHA 13(16.9%)	(for AF, 2 suffered from TE)							considered as the diagı AIHA is cor
Pouchelon C et al., 2022	Multicenter retrospective	62	wAIHA 49(79.0%) cAIHA 8(12.9%)	Systematic thrombo-prophylaxis (ICU patients)	6 patients (9.7%)	NA	6VTE	NA	NA	NA	Optimizing thromboprc strategies i critically pa with AIHA
L. C. Esteves et al., 2025	Multicenter retrospective	88	wAIHA 72(81.8%) cAIHA 16(18.2%)	18 APT, 2 DAPT, 7TAC	22 patients (25.0%)	NA	16 patients (18.2%) 19 VTE	7 patients 11 ATE (3 MI, 6 ACI, 2 LLAE (8.0%)	NC	Padua associated with VTE	VTE associ with primar wAIHA, splenectom VTE history associated age ≥ 80 an CV risk.
Xiong, J et al., 2026	Single-center retrospective	32	wAIHA 32(100%)	1 TAC (for AF)	8 patients (25.0%)	6TAC, 2APT	5DVT,3PE	2 ACI, 1 LLAE (9.4%)	NC	NC	TE associat severe aner higher LDH plasma exc

Abbreviations: AIHA: Autoimmune Hemolytic Anemia; wAIHA: warm AIHA; cAIHA: cold AIHA; mAIHA: mixed AIHA; TRD: Thrombosis -related death; SLE: Sys erythematosus; AT: Antithrombotic therapy; TE: Thromboembolic events; VTE: Venous thromboembolism; DVT: Deep venous thrombosis; PE: Pulmonary em throm boembolism; ACI: Acute cerebral infarction; TIA: Transient ischemic attack; DIC: Disseminated intravascular coagulation; CV: Cardiovascular risk; aPL antibody; AF: Atrial fibrillation; MI: Myocardial infarction; LA: Lupus anticoagulant; MHV: Mechanical heart valve; ST: Splanchnic thrombosis; PVT: Portal veir Splenic vein thrombosis; STP: Superficial thrombophlebitis; CRT: Catheter-Related Thrombosis; LLAE:lower limb arterial embolism; NC: No correlation; NA: N Antiplatelet therapy; DAPT: Dual antiplatelet therapy; TAC: Therapeutic Anticoagulation; PAC: Prophylactic Anticoagulation.

Discussion

- AIHA-associated AIS is a rare clinical entity, and no consensus currently exists regarding optimal antithrombotic strategies. In this series of five patients, all presented with AIS as the initial manifestation, delaying AIHA diagnosis by a median of 3 days. All received antiplatelet therapy during the acute phase, yet one developed massive PE and another developed DIC. These observations reveal two underappreciated issues: First, the initial neurological workup, constrained by specialty-specific priorities, may delay the diagnosis and treatment of underlying AIHA. Second, the current stroke-specific approach of antiplatelet monotherapy may be insufficient in the setting of AIHA-associated AIS and may not fully prevent recurrent thrombotic events.
- The thrombotic mechanism in AIHA is fundamentally distinct from atherosclerotic stroke. Hemolysis itself drives thrombosis through multiple pathways, including free heme released from damaged erythrocytes[19, 27], nitric oxide scavenging by cell-free hemoglobin[27, 28], phosphatidylserine exposure[29, 30], RBC-derived microparticles[31–33], and complement activation[9, 34]. The key pathways linking hemolysis to hypercoagulability and thrombotic complications are summarized schematically in Fig. 3. Consistent with this pathophysiological mechanism, brain MRA of all five patients revealed no significant large-vessel stenosis or occlusion, with imaging findings predominantly characterized by multifocal small-vessel infarcts involving the posterior circulation. Such a pattern may be hypothetically explained by hemodynamic factors. Lower blood flow velocities in the vertebrobasilar system and poorer collateral reserve could make this territory more vulnerable to microembolic showering[35, 36]. Notably, the observed pattern stands in stark contrast to the typical atherosclerotic profile in Chinese patients with ischemic stroke, in which intracranial and anterior circulation arteries are susceptible to stenosis[21]. These observations collectively support that AIHA-associated AIS is more closely related to hemolysis-driven microvascular thrombosis than to large artery atherothrombotic stenosis or occlusion—a distinction with important therapeutic implications. Specifically, conventional antiplatelet therapy, which primarily targets platelet aggregation at sites of vascular injury, may not fully address the distinct pathophysiology of hemolysis-driven microvascular thrombosis.
- Large-scale registry data have unequivocally confirmed a significantly elevated thrombotic risk in AIHA, particularly within the first year after diagnosis[37, 38]. A binational prospective study from Denmark and France (5,994 AIHA patients vs. 81,525 controls) demonstrated a 2.29-fold increased risk of stroke(95% CI: 1.77–2.97, $p < 10^{-9}$)[39]. Overall thrombotic event rates range from 11% to 29.6%, with VTE predominating. ATE occur in 1.7%–9.5% of patients, mainly ischemic stroke, TIA, and myocardial infarction, with cerebral infarction accounting for 0.7%–9.5%. Despite this well-documented risk, current guideline recommendations are based predominantly on observational studies and focus primarily on VTE, leaving a critical evidence gap for AIS. Of note, the only ongoing prospective randomized controlled trial evaluating prophylactic anticoagulation in AIHA (NCT05089227) is currently recruiting. Its results may help establish evidence-based guidelines. Consequently, in the absence of specific guidance, current management largely extrapolates from atherosclerotic stroke pathways—predominantly antiplatelet therapy. Our case series challenges this extrapolation, as two patients developed life-threatening thrombosis while on antiplatelet agents, highlighting the importance of considering AIHA-specific factors in future guideline development.
- Beyond the mechanistic distinction, our case series highlights a critical clinical issue: patients typically present to neurology departments, where focus on acute stroke management often overlooks underlying hemolytic anemia, leading to delayed AIHA diagnosis—even in patients with known AIHA. This "neurology-over-hematology" bias may miss the optimal window for disease control. Based on our observations, we propose a hypothesis-generating

conceptual framework for the multidisciplinary management of suspected wAIHA-associated AIS. Step 1 (Screening): In AIS patients with unexplained anemia, particularly those lacking traditional atherosclerotic risk factors, clinicians should suspect underlying AIHA and order a hemolysis workup (DAT, LDH, haptoglobin, reticulocyte count). Step 2 (Diagnosis & Collaboration): Once AIHA is confirmed, early collaboration between neurology and hematology should be established. Step 3 (Hemolysis Control): Early, high-intensity anti-hemolytic therapy should be initiated to achieve rapid and effective control of hemolysis. Step 4 (Thrombolysis Decision & Antithrombotic Strategy): For patients presenting within the thrombolytic time window, the decision to administer intravenous thrombolysis should follow standard stroke guidelines and should not be withheld solely because of a diagnosis of AIHA[22]. However, the presence of active hemolysis, which may be accompanied by thrombocytopenia, coagulopathy, or rapidly evolving laboratory abnormalities, may increase bleeding risk and should be carefully evaluated before thrombolysis. For patients who do not receive thrombolysis or after the 24-hour post-thrombolysis safety window, antithrombotic therapy should be guided by hemolytic activity: anticoagulation may be considered for patients with active hemolysis and no overt bleeding risk, whereas antiplatelet therapy may suffice for those in remission[1, 3, 18, 22]. We emphasize that this framework derives from a small retrospective case series and a narrative literature review, and therefore requires validation in larger prospective cohorts before any clinical adoption can be considered. Antithrombotic decisions should be individualized, and our framework should be viewed as a starting point for discussion and investigation, not as a practice guideline. Incidentally, a recently published case report described a similar approach in an 82-year-old patient with mAIHA complicated by AIS, who received methylprednisolone for hemolysis control combined with enoxaparin and clopidogrel, with favorable outcomes[40].

- However, this study has several limitations, including retrospective design, small sample size, absence of a randomized control group, and relatively short follow-up, which limit the generalizability and extrapolation of our findings to broader patient populations. Additionally, heterogeneity among the original studies included in the literature review precluded a formal pooled analysis. The observed predominance of posterior circulation involvement should also be interpreted with caution, as this finding is derived from a small case series without a control group and requires confirmation in larger cohorts. Despite these limitations, our findings carry direct clinical relevance for wAIHA-associated AIS and lay a foundation for future investigations. Prospective multicenter studies are needed to define optimal management strategies for this high-risk population, particularly to: (1) compare the efficacy and safety of antiplatelet versus anticoagulant therapy in patients with active hemolysis; (2) validate the predictive value of MRA findings (absence of large-vessel stenosis) as a biomarker for hemolysis-driven stroke; and (3) evaluate whether early hematology-neurology collaboration reduces diagnostic delay and improves long-term outcomes.

Abbreviations

- AIHA Autoimmune hemolytic anemia
- RBC Red blood cell
- VTE Venous thromboembolism
- ATE Arterial thrombotic events
- AIS Acute ischemic stroke
- DAT Direct antiglobulin test
- LDH Lactate dehydrogenase
- DWI Diffusion- weighted imaging
- MRI Magnetic resonance imaging
- IAT Indirect antiglobulin test
- ANA Antinuclear antibody
- ANCA Antineutrophil cytoplasmic antibody
- aPL Antiphospholipid antibodies
- aCL Anticardiolipin antibodies
- aβ2GPI Anti-β2-glycoprotein I antibodies
- LA Lupus anticoagulant
- IVIG Intravenous immunoglobulin
- RTX Rituximab
- CR Complete response
- PR Partial response
- HGB Hemoglobin
- MRA Magnetic resonance angiography
- CSA Cyclosporin A
- MMF Mycophenolate mofetil
- CTA Computed tomography angiography
- PE Pulmonary embolism
- DVT Deep vein thrombosis
- ECMO Extracorporeal membrane oxygenation

- LMWH Low-molecular-weight heparin
- APS Antiphospholipid syndrome
- EICU Emergency intensive care unit
- TIA Transient ischemic attack
- FDP Fibrinogen degradation products
- FBG Fibrinogen

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board ([Approval No.: XS-2025111]), and informed consent was waived due to the retrospective design.

Consent for publication

Not applicable.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

F.L. and L.W. designed the research; Y.Z. and X.C.J interpreted the data; L.W. drafted the paper; B.C.H and X.L.Z revised the manuscript.

References

1. Hill QA, Stamps R, Massey E, et al. The diagnosis and management of primary autoimmune haemolytic anaemia[J]. Br J Haematol. 2017;176(3):395–411.
2. Berentsen S, Barcellini W. Autoimmune Hemolytic Anemias[J]. N Engl J Med. 2021;385(15):1407–19.
3. Jager U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting[J]. Blood Rev. 2020;41:100648.
4. Hansen DL, Möller S, Andersen K, et al. Increasing Incidence and Prevalence of Acquired Hemolytic Anemias in Denmark, 1980–2016[J]. Clin Epidemiol. 2020;12:497–508.
5. Kokori SI, Ioannidis JP, Voulgarelis M, et al. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus[J]. Am J Med. 2000;108(3):198–204.
6. Pullarkat V, Ngo M, Iqbal S, et al. Detection of lupus anticoagulant identifies patients with autoimmune haemolytic anaemia at increased risk for venous thromboembolism[J]. Br J Haematol. 2002;118(4):1166–9.
7. Hendrick AM. Auto-immune haemolytic anaemia–a high-risk disorder for thromboembolism?[J]. Hematol (Amsterdam Netherlands). 2003;8(1):53–6.
8. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients[J]. Am J Hematol. 2014;89(9):E150–5.
9. Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients[J]. Blood. 2014;124(19):2930–6.
10. Lecouffe-Desprets M, Neel A, Graveleau J, et al. Venous thromboembolism related to warm autoimmune hemolytic anemia: a case-control study[J]. Autoimmun Rev. 2015;14(11):1023–8.
11. Audia S, Bach B, Samson M, et al. Venous thromboembolic events during warm autoimmune hemolytic anemia[J]. PLoS ONE. 2018;13(11):e207218.
12. Barcellini W, Zaninoni A, Fattizzo B, et al. Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers[J]. Am J Hematol. 2018;93(9):E243–6.
13. Fattizzo B, Bortolotti M, Giannotta JA, et al. Intravascular hemolysis and multitreatment predict thrombosis in patients with autoimmune hemolytic anemia[J]. J Thromb Haemost. 2022;20(8):1852–8.
14. Schar DT, Daskalakis M, Mansouri B, et al. Thromboembolic complications in autoimmune hemolytic anemia: Retrospective study[J]. Eur J Haematol. 2022;108(1):45–51.

15. Esteves LC, Grange L, Gaultier J, et al. Prediction of thrombotic events in patients with autoimmune hemolytic anemia: a multicenter retrospective observational study[J]. J Thromb Thrombolysis. 2025;58(7):945–54.
16. Xiong J, Wan L, Chen H, et al. High thrombotic burden in severe Chinese wAIHA patients: a single-center retrospective study[J]. Thromb J. 2026;24(1):30.
17. Broome CM, Cunningham JM, Mullins M, et al. Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis[J]. Res Pract Thromb Haemost. 2020;4(4):628–35.
18. Capecchi M, Ciavarella A, Artoni A, et al. Thrombotic Complications in Patients with Immune-Mediated Hemolysis[J]. J Clin Med. 2021;10(8):1764.
19. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis[J]. Br J Haematol. 2015;168(2):175–85.
20. Ataga KI. Hypercoagulability and thrombotic complications in hemolytic anemias[J]. Haematologica. 2009;94(11):1481–4.
21. Hua Y, Jia L, Xing Y, et al. Distribution Pattern of Atherosclerotic Stenosis in Chinese Patients with Stroke: A Multicenter Registry Study[J]. Aging disease. 2019;10(1):62–70.
22. Prabhakaran S, Gonzalez NR, Zachrison KS et al. 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association[J]. Stroke, 2026:10–1161.
23. Bongarzoni V, Annino L, Roveda A, et al. Risk of thromboembolism in patients with idiopathic autoimmune hemolytic disease and antiphospholipid antibodies: results from a prospective, case-control study[J]. Haematologica. 2005;90(5):711–3.
24. Higuchi T, Hoshi T, Toriyama M, et al. Infrequent Thrombotic Complications in Japanese Patients with Warm Autoimmune Hemolytic Anemia[J]. Intern Med. 2023;62(10):1441–7.
25. Ho G, Brunson A, Keegan THM, et al. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with autoimmune hemolytic anemia[J]. Blood Cells Mol Dis. 2020;81:102388.
26. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel. Report[J] Chest. 2021;160(6):e545–608.
27. Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease[J]. JAMA. 2005;293(13):1653–62.
28. Villagra J, Shiva S, Hunter LA, et al. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin[J]. Blood. 2007;110(6):2166–72.
29. Zwaal RF, Schroit AJ. Pathophysiologic implications of membrane phospholipid asymmetry in blood cells[J]. Blood. 1997;89(4):1121–32.
30. Camus SM, De Moraes JA, Bonnin P, et al. Circulating cell membrane microparticles transfer heme to endothelial cells and trigger vasoocclusions in sickle cell disease[J]. Blood. 2015;125(24):3805–14.
31. Westerman M, Pizzey A, Hirschman J et al. Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy[J]. Br J Haematol 2008,142(1):126–35.
32. van Beers EJ, Schaap MCL, Berckmans RJ, et al. Circulating erythrocyte-derived microparticles are associated with coagulation activation in sickle cell disease[J]. Haematologica. 2009;94(11):1513–9.
33. Barcellini W, Zaninoni A, Giannotta JA, et al. Circulating extracellular vesicles and cytokines in congenital and acquired hemolytic anemias[J]. Am J Hematol. 2021;96(4):E129–32.
34. Berentsen S. Role of Complement in Autoimmune Hemolytic Anemia[J]. Transfusion medicine and hemotherapy: offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie, 2015,42 (5): 303–10.
35. See AP, Pandey DK, Du X, et al. Optimized Hemodynamic Assessment to Predict Stroke Risk in Vertebrobasilar Disease: Analysis From the VERiTAS Study[J]. J Am Heart Association. 2020;9(12):e16406.
36. Donnan GA. Posterior Circulation Stroke: Advances in Understanding and Management[J]. J stroke. 2021;23(1):144–5.
37. Yusuf HR, Hooper WC, Grosse SD, et al. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees[J]. Thromb Res. 2015;135(1):50–7.
38. Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: A systematic review and meta-analysis[J]. Thromb Res. 2015;136(5):1013–7.
39. Hansen DL, Maquet J, Lafaurie M, et al. Primary autoimmune haemolytic anaemia is associated with increased risk of ischaemic stroke: A binational cohort study from Denmark and France[J]. Br J Haematol. 2024;204(3):1072–81.
40. Wang L, Li H, Zhao H, et al. Mixed-type autoimmune hemolytic anaemia complicated by acute cerebral infarction: a case report[J]. Front Med. 2025;12:1587960.

Figures

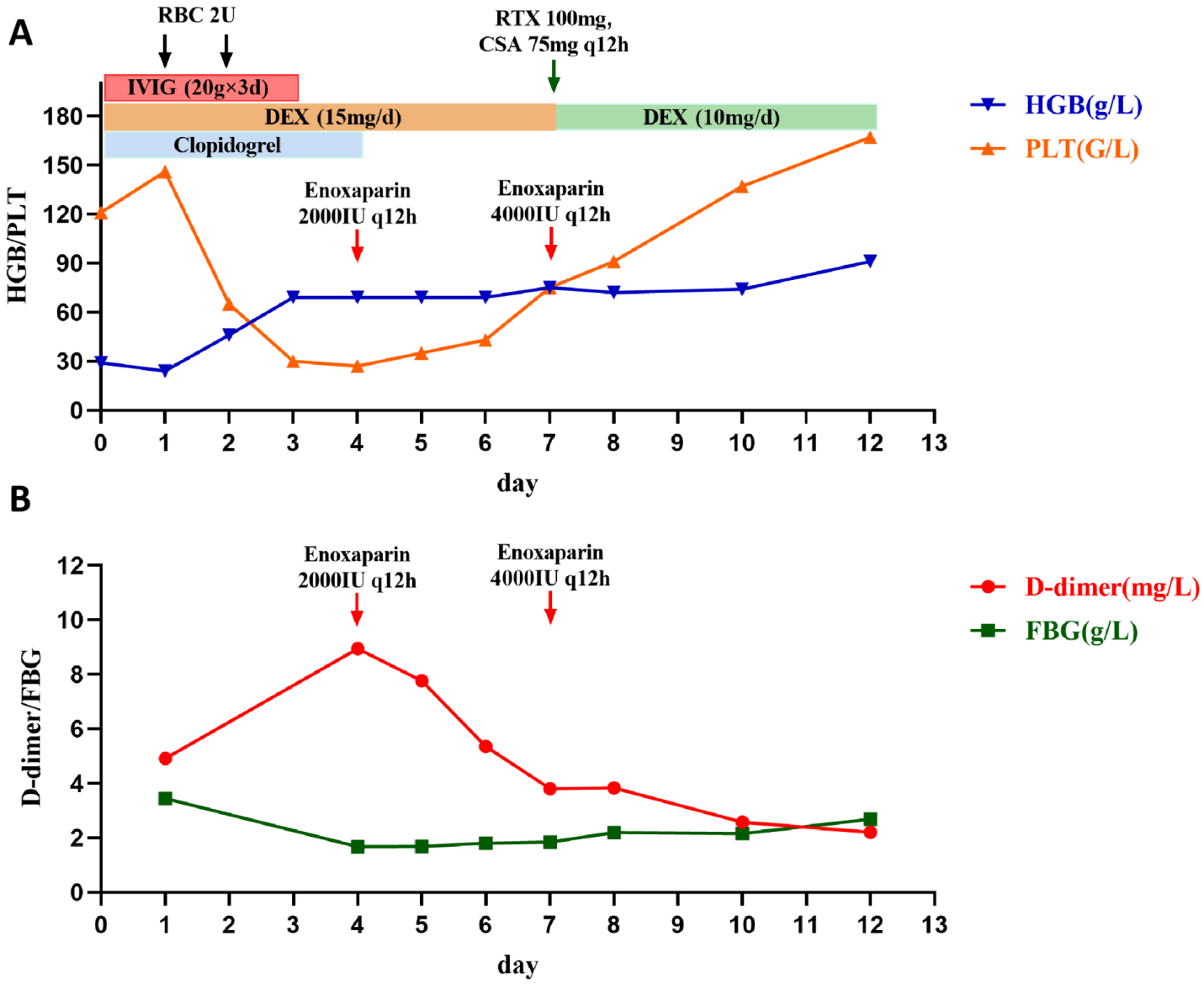


Figure 1

Dynamic changes in key laboratory parameters and treatment timeline in Case 5.

This figure illustrates the clinical course of a 73-year-old female patient with wAIHA-associated AIS and antiphospholipid syndrome who developed disseminated intravascular coagulation during active hemolysis. The patient received multiple concurrent interventions, including dexamethasone (DEX), intravenous immunoglobulin (IVIG), rituximab (RTX), cyclosporine (CSA), transfusion support, and later anticoagulation with enoxaparin. Notably, the initiation of anticoagulation coincided with a rapid recovery of platelet count (PLT) and normalization of coagulation parameters (D-dimer and fibrinogen).

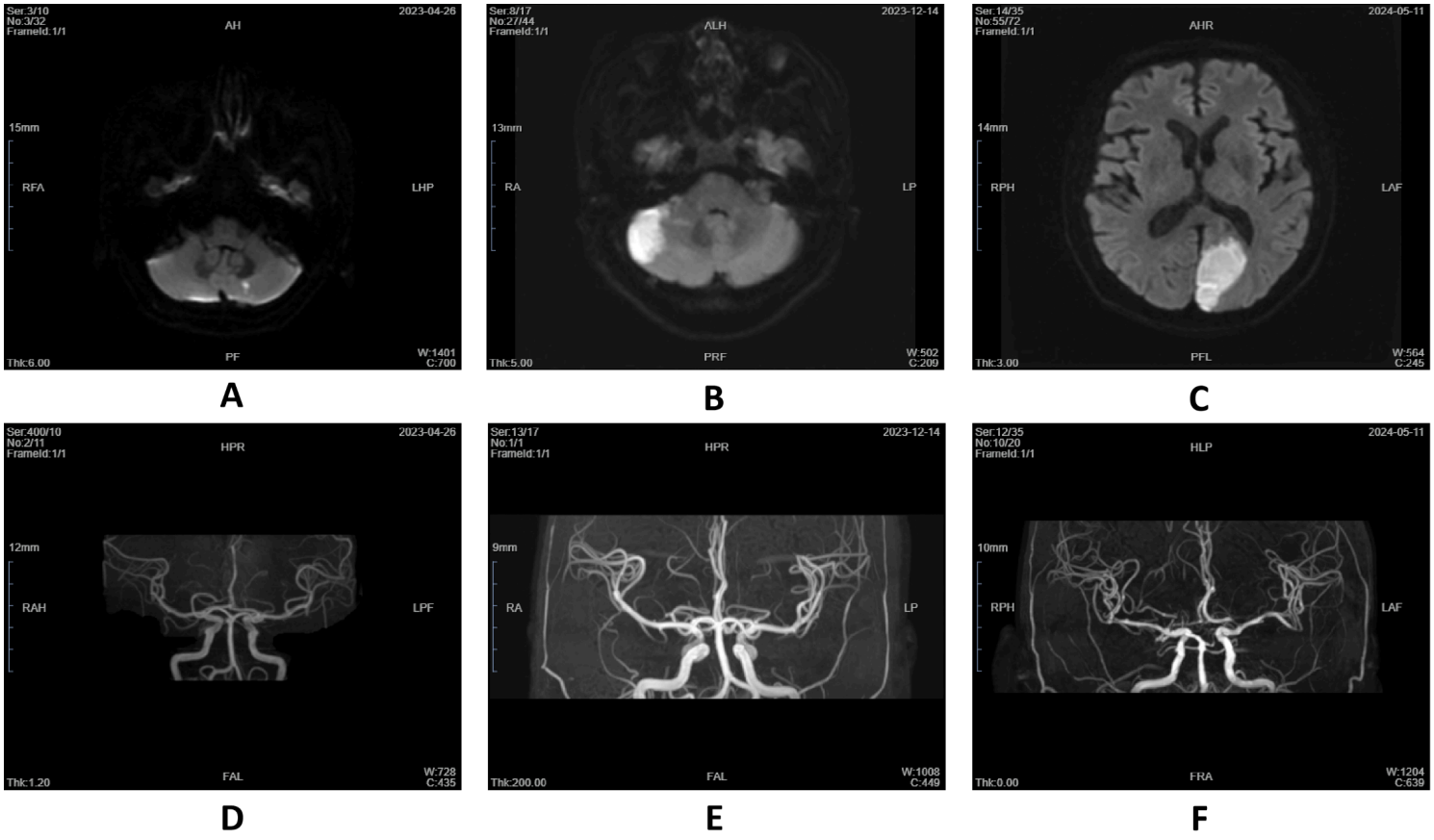


Figure 2

Representative brain MRI findings of wAIHA-associated acute ischemic stroke.

Representative neuroimaging findings from three patients with wAIHA-associated AIS treated at our institution. For each patient, diffusion-weighted imaging (DWI) shows acute infarcts and magnetic resonance angiography (MRA) demonstrates the absence of significant large artery stenosis or occlusion. Case 1: DWI shows an acute small infarct in the left cerebellar hemisphere (A); MRA reveals intracranial atherosclerosis without large vessel stenosis (D). Case 2: DWI reveals an acute right cerebellar infarct (B); MRA shows no abnormalities (E). Case 3: DWI shows acute infarcts in the left temporoparieto-occipital lobe (C); MRA reveals intracranial atherosclerosis without large vessel stenosis (F). The two additional patients from other hospitals showed a consistent imaging pattern (data not shown).

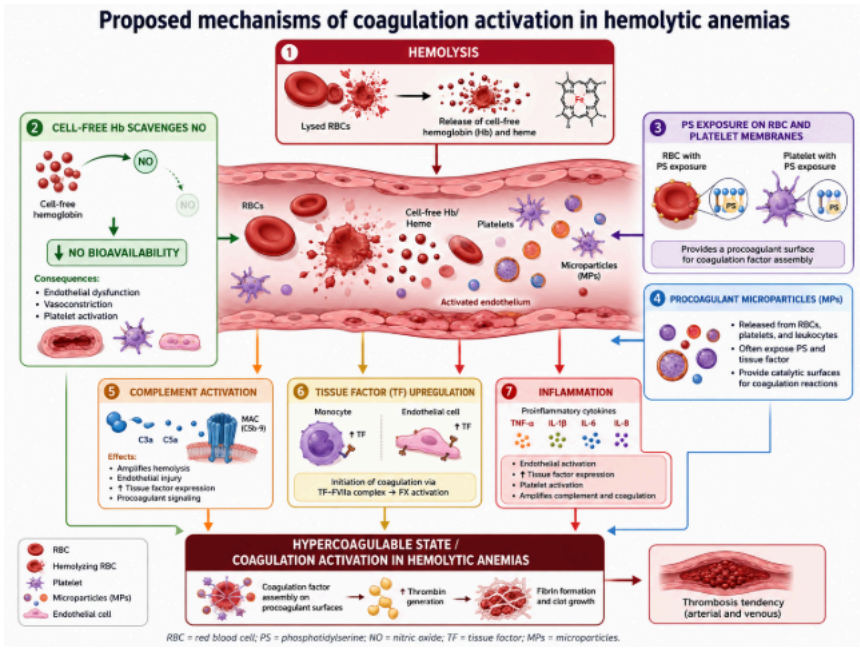


Figure 3

Proposed mechanisms of coagulation activation in hemolytic anemias.

The schematic illustrates the key pathophysiological pathways linking hemolysis to hypercoagulability in hemolytic anemias. Hemolysis of red blood cells (RBC) leads to the release of cell-free hemoglobin and heme, as well as the shedding of procoagulant microparticles (MPs) from activated or damaged cells. The exposure of phosphatidylserine (PS) on the outer leaflet of RBC and platelet membranes provides a catalytic surface for the assembly of coagulation factor complexes, thereby promoting thrombin generation and fibrin formation. Cell-free hemoglobin scavenges nitric oxide (NO), impairing endothelial function and promoting platelet activation and vasoconstriction. Additionally, free heme upregulates tissue factor (TF) expression on endothelial cells and monocytes, further amplifying the coagulation cascade. Complement activation and inflammatory pathways interact with these hemolysis-driven processes through complex crosstalk, collectively establishing a hypercoagulable state that predisposes to both venous and arterial thrombotic events.