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CASE REPORT

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Recurrent Wunderlich syndrome in systemic lupus erythematosus: a case report

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Abstract

Background Wunderlich syndrome (WS) is a rare condition characterized by spontaneous renal hemorrhage in the absence of obvious trauma or iatrogenic injury. Given that most WS cases are life-threatening and require prompt intervention, timely identification and resolution are essential. Patients with connective tissue diseases (CTDs) account for a small proportion of reported WS cases; however, owing to the specific pathogenic mechanisms and treatments associated with CTDs, these patients exhibit distinctive pathological traits and clinical features in WS.

Case presentation We present the identification and treatment process of WS in a patient with systemic lupus erythematosus. This patient suffered from sudden abdominal pain and a drastic decline in hemoglobin level accompanied by confusion of consciousness. After the abdominal computerized tomography scan revealed the presence of a renal hematoma, transcatheter arterial embolization was performed on her. Unexpectedly, three days later, the patient had severe anemia and consciousness disorders again. Highly suspecting renal rebleeding, we performed a repeated angiography for the patient. After confirming the bleeding, embolization was carried out again. The renal bleeding stopped, and the patient's hemoglobin level gradually stabilized. Regrettably, this patient ultimately died due to multiple systemic infections.

Conclusions WS that occurs in CTDs can evolve into critical and severe conditions. Infection, immune complex deposition, thrombocytopenia, abnormal coagulation function, complement activation, autoantibodies production, and glucocorticoid treatment in patients with CTDs are potentially linked to the development of WS. The treatment strategies for WS should be guided by hemodynamic status.

Keywords Wunderlich syndrome, Spontaneous renal hemorrhage, Connective tissue disease, Systemic lupus erythematosus, Transcatheter arterial embolization

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Background

In 1856, Wunderlich reported a syndrome of spontaneous renal hemorrhage in the absence of evident trauma or iatrogenic injury, subsequently designating this condition as Wunderlich syndrome (WS). The lesions typically occur in the subcapsular area and perirenal space of the kidney [1]. The characteristic clinical manifestations of WS include acute lumbar-abdominal pain, abdominal mass, and hypovolemic shock, which can rapidly progress to critical or even fatal consequences [2, 3]. However, in some patients with WS, symptoms such as abdominal pain or hematuria, are non-specific and need to be accurately identified by clinicians [4]. Among the reported cases of WS, neoplastic or vascular disease are the most prevalent [5, 6], and infections, urinary calculi, and other diseases can also occur [7–10]. While the overall proportion of WS patients with connective tissue diseases (CTDs) is relatively low, early screening in clinical practice is essential because of the inherent risk associated with WS. Herein, we report a case of systemic lupus erythematosus (SLE) complicated by WS, detailing the clinical features of this patient, and examining potential causative factors of CTDs-induced WS.

Case presentation

A 75-year-old female patient presented to our hospital with a two-year history of intermittent bilateral leg weakness. The patient had previously been diagnosed with SLE and lupus nephritis (LN) at a tertiary hospital and was admitted for further treatment due to a poor response to corticosteroids (10 mg/day), mycophenolate mofetil (1 g/day), and belimumab (10 mg/kg). The patient has not received any oral anticoagulants or antiplatelet agents.

Physical examination revealed a few moist rales in the lungs, weakened muscle strength in both lower extremities (approximately grade 2), and a slightly pale face without rashes. Superficial lymph nodes were not enlarged, the abdomen was soft without tenderness or rebound tenderness, and no enlargement of the liver or spleen was palpable. There was no percussion pain in the renal area. Muscle strength in both upper extremities was normal, with no muscle tenderness. Physiological reflexes were present, and no pathological signs were elicited.

Upon admission, laboratory tests (Table 1) showed an increased white blood cell (WBC) count, mild anemia, normal liver function, decreased serum albumin levels, mildly elevated pancreatic enzymes, and normal coagulation function. Renal function was markedly impaired, with elevated serum creatinine, reduced estimated glomerular filtration rate (eGFR), and significant proteinuria. Autoimmune-related tests revealed positive anti-Sm antibodies and antinuclear antibodies, negative anti-double-stranded DNA antibodies, elevated immunoglobulin G/A/M levels, significantly decreased complement levels, and negative antiphospholipid antibodies. Infection-related tests confirmed *Staphylococcus aureus* infection via sputum culture, while influenza, Legionella pneumophila, adenovirus, and respiratory syncytial virus infections were ruled out. These results affirmed that the patient met the Systemic Lupus International Collaborating Clinics (SLICC) criteria (Table 1).

Simultaneously, comprehensive imaging evaluations were performed (Table 2). An initial electrocardiogram suggested the possibility of a minor myocardial infarction; however, upon re-evaluation several hours later, only tachycardia and ventricular premature beats were observed. Echocardiography revealed no structural cardiac abnormalities. A chest computed tomography (CT) scan revealed signs of interstitial lung disease. Abdominal CT scan demonstrated marked peritoneal and abdominal wall edema with ascites. Color Doppler ultrasound of the lower extremities revealed no vascular inflammation or embolism.

Two days after admission, the patient developed acute abdominal pain, a sudden drop in blood pressure, a rapid decrease in hemoglobin from 75 to 42 g/L, a decline in platelets from 96 to 70 ($\times 10^9$/L), and altered mental status. Renal function deteriorated, with elevated serum creatinine and decreased eGFR (Table 1). An emergency abdominal CT scan revealed a large hematoma in the left posterior kidney, with the largest measurement being 63 × 42 mm (Fig. 1). Owing to the patient's hemodynamic instability, we promptly consulted the Departments of Imaging and Urology for urgent evaluation. Angiography and transcatheter arterial embolization (TAE) were chosen to investigate and control the bleeding source. Under local anesthesia, right femoral artery puncture and catheterization using the *Seldinger* technique were performed. Contrast agent administration revealed point-like extravasation at the distal branch of the left upper pole renal artery, confirming a rupture and hemorrhage. Gelatin sponge particles (150–350 μm) and coils were used for embolization. Post-embolization angiography confirmed cessation of hemorrhagic signs.

Subsequently, we prudently adjusted the patient's oral medications to avoid exacerbating renal damage. Enteral nutrition support was provided due to the patient's inability to eat normally, and intestinal flora regulation was enhanced to prevent complications such as diarrhea. Urine output was monitored, and diuretics were administered appropriately to maintain fluid and electrolyte balance. Antibacterial and prophylactic antifungal treatments were actively administered. These interventions effectively stabilized the patient's condition.

Unfortunately, three days after TAE, the patient experienced recurrent mental confusion and a rapid decrease in hemoglobin levels. Coagulation function tests revealed

Table 1 Laboratory test indicators of the patient

Indicators	Baseline	First WS	First TAE	Second WS	Second TAE	Normal range	SLICC criteria
White blood cell (*10^9/L)	9.9	6.92	12.37	14.07	12.5	3.5–9.5	
Red blood cell (*10^12/L)	2.41	1.38	1.64	1.1	2.62	3.80–5.10	
Lymphocyte (*10^9/L)	0.66	0.31	0.68	0.28	0.12	1.1–3.2	
Lymphocyte (%)	7.2	4.5	5.5	2	1	20.0–50.0	
Hemoglobin (g/L)	75	42	50	35	81	115.0-150.0	
Platelet (*10^9/L)	96	70	82	111	114	125.0-350.0	Clinical criteria
Neutrophils (*10^9/L)	7.8	6.39	10.91	13.17	12.16	1.8–6.3	
Neutrophils (%)	85.3	92.3	88.2	93.6	97.2	40.0–75.0	
Total protein (g/L)	47.6	38.4		44.8	48.3	66.0–87.0	
Albumin (g/L)	32.8	24.7		30.4	31.7	40.0–55.0	
Globulin (g/L)	14.8	13.7		14.4	16.6	20–35	
ALT (U/L)	10	9		13	14	7–40	
AST (U/L)	20	15		24	20	13–35	
LDH (U/L)	300	200		380	371	120–250	
Creatinine (μmol/L)	225	260		509	415	45–84	
eGFR (ml/min/1.73m^2)	17.9	15.7		6.7	8.5	> 90	
KDIGO classification	CKD G4	AKI Stage 1		AKI Stage 2			
Urea (mmol/L)	14.1	14.3		24.2	24.7	3.1–8.8	
Uric acid (μmol/L)	434	446		517	463	142.8-339.2	
Cholesterol (mmol/L)	3.17	2.21		3.06	3.16	< 5.18	
Total bilirubin (μmol/L)	8.2	6.6		8.6	10.7	≤ 23	
APTT (s)	40.1		45.9		39.5	29.0–42.0	
Thrombin time (s)	18.9		19.2		17.9	<21.0	
Prothrombin activity (%)	106		90		117	80.0-135.0	
Prothrombin time (s)	12.9		13.8		12.4	11.5–14.5	
Fibrinogen (g/L)	2.4		1.81		2.17	2.00–4.00	
D-D dimer (μg/mL FEU)	2.08		1.96		2.38	< 0.5	
FDP (μg/mL)					10	< 5.0	
Amylopsin (U/L)	55					15–53	
Pancreatic lipase (IU/L)	67.7					13–60	
NT-proBNP (pg/mL)	2417	2873				< 738	
Troponin I (μg/L)	28.1					≤ 15.6	
Complement 3 (g/L)	0.64	0.74				0.8–1.8	Immunology criteria
Complement 4 (g/L)	0.17	0.21				0.1–0.4	Immunology criteria
IgA (g/L)	0.59	0.34				0.7-4.0	
IgG (g/L)	1.74	4.11				7.0–16.0	
IgM (g/L)	0.25	0.17				0.4–2.3	
C-reactive protein (mg/L)	6.19	24.1				0–10.0	
IL-10 (pg/ml)	5.9					0.1-5.0	
IL-2 (pg/ml)	1.39					0.1–4.1	
IL-4 (pg/ml)	1.23					0.1–3.2	
IL-6 (pg/ml)	5.3					0.1–2.9	
IFN-r (pg/ml)	1.78					0.1–18.0	
TNF-α (pg/ml)	1.1					0.1–23	
ACA	negative					negative	
LAC	negative					negative	
GM/G test	negative					negative	
Coomb's test	negative					negative	
Urine protein	3+					negative	Clinical criteria
ANA	1:320 nucleolar type					negative	Immunology criteria
Anti-dsDNA	negative					negative	
Anti-Sm	positive					negative	Immunology criteria
Anti-RO52	positive					negative	

Table 1 (continued)

Indicators	Baseline	First WS	First TAE	Second WS	Second TAE	Normal range	SLICC criteria
Anti-CCP (RU/ml)	< 2.00					0–20	
AKA	negative					negative	
ASO (IU/ml)	2.75					0-250	
RF (IU/ml)	16					0–30	
ANCA	negative					negative	

ALT: Alanine aminotransferase, KDIGO: Kidney Disease: Improving Global Outcomes, CKD: Chronic kidney disease, AKI: Acute kidney injury, AST: Aspartate aminotransferase, LDH: Lactic dehydrogenase, eGFR: estimated glomerularfiltrationrate, UA: Uric acid, CRP: C-reactive protein, APTT: Activated partial thromboplastin time, FDP: Fibrinogen degradation products, ACA: Anticardiolipin antibody, LAC: Lupus anticoagulant, RSV: Respiratory syncytial virus, CCP: Cyclic citrullinated peptide antibody, AKA: Anti-keratin antibody, ASO: Antistreptolysin, RF: Rheumatoid arthritis, ANA: Antinuclear antibodies, dsDNA: Double-stranded deoxyribonucleic acid, ANCA: Anti-neutrophil cytoplasmic antibodies, SLICC: Systemic Lupus International Collaborating Clinics

Table 2 The imaging examinations of the patient

System	Manifestations
Cardiac	Electrocardiogram: Premature ventricular beat, sinus tachycardia. Echocardiogram: No obvious abnormalities were found in the morphology, structure of the heart and the activity of the valves
Respiratory	Chest CT: Pleural effusion, atelectasis, emphysema, interstitial pneumonia
Peritoneal	Abdominal CT: Peritoneal and mesenteric thickening and edema, abdominal effusion, extensive subcutaneous edema in the abdominal wall and lumbar and dorsal regions, and soft tissue edema anterior to the sacrum
Hepatic	Abdominal CT: Multiple cysts in the liver, gallbladder calculi
Renal	Ultrasonography: Renal cyst
Neurological	Cranial CT: Lacunar cerebral infarction, cerebral atrophy, cerebral atherosclerosis
Vessel of lower limb	Ultrasonography: The common femoral vein, deep femoral vein, superficial femoral vein, popliteal vein and their tributaries all show no abnormalities

CT: Computed tomography

decreased coagulation factors II, XII, XIII and X. The patient's renal function deteriorated acutely, with creatinine levels rising more than twofold the baseline level and eGFR dropping to 6.7 ml/min/1.73m^2 (Table 1). After evaluation by the intensive care unit and the Department of Urology, a second angiography was performed, revealing another rupture and hemorrhage from a branch of the left renal artery. Reapplication of gelatin sponge embolization controlled the bleeding. Thereafter, the patient showed no further WS symptoms. Regrettably, approximately two months later, the patient succumbed to multiple systemic infections and severe immune disorders.

Discussion and conclusions

Although the occurrence of WS is usually accompanied by the progression of the primary disease, reports indicate that WS may present as the initial symptom in many cases. WS has been reported as the first symptom in patients with leukemia [11], SLE [12–14], antiphospholipid syndrome (APS) [15], polyarteritis nodosa [16], cancer [17], and factor VII-deficient hemophilia [4]. With the advent of advanced treatment modalities in recent years, WS has also frequently been reported during hemodialysis treatment [18] or after kidney transplantation [19]. Current research on CTDs-associated WS remains limited. Based on existing case reports, the clinical characteristics of WS vary across different CTDs. Case studies involving ANCA-associated vasculitis (AAV) ($n = 15$) suggest that WS typically occurs in the early stage of the disease and correlates with disease activity, with renal artery aneurysm rupture being the principal cause [20]. A single-center report and systematic review ($n = 1640$) revealed that a shorter disease course, significantly elevated inflammatory markers (WBC and ESR), decreased hemoglobin, reduced albumin, and deteriorated renal function are associated with the occurrence of WS [21]. A 21-year retrospective study indicated that patients with AAV in the early stages (≤ 3 months) and those with higher disease activity are more likely to develop WS [22]. Furthermore, in patients with Sjogren syndrome complicated by cryoglobulinemia, WS manifests with symptoms such as high fever, pulmonary edema, and abdominal pain, often progressing rapidly to renal failure necessitating hemodialysis [23]. WS in AAV patients generally exhibits milder symptoms [24], whereas WS in patients with SLE undergoing hemodialysis tends to be more severe [25]. However, further research is needed to verify these conclusions.

The occurrence of WS involves several pathological mechanisms. Spontaneous renal rupture can be divided into three types according to the lesion site: renal parenchyma, the renal tubular system, and renal vascular rupture. In tumors, inflammation, vascular disease, calculus, and renal pelvic disease, the presence of renal parenchymal damage, renal vascular embolism, local renal venous pressure increase, and hydronephrosis can lead to bleeding [26, 27]. Figure 2 illustrates how the pathological features of CTDs may directly contribute

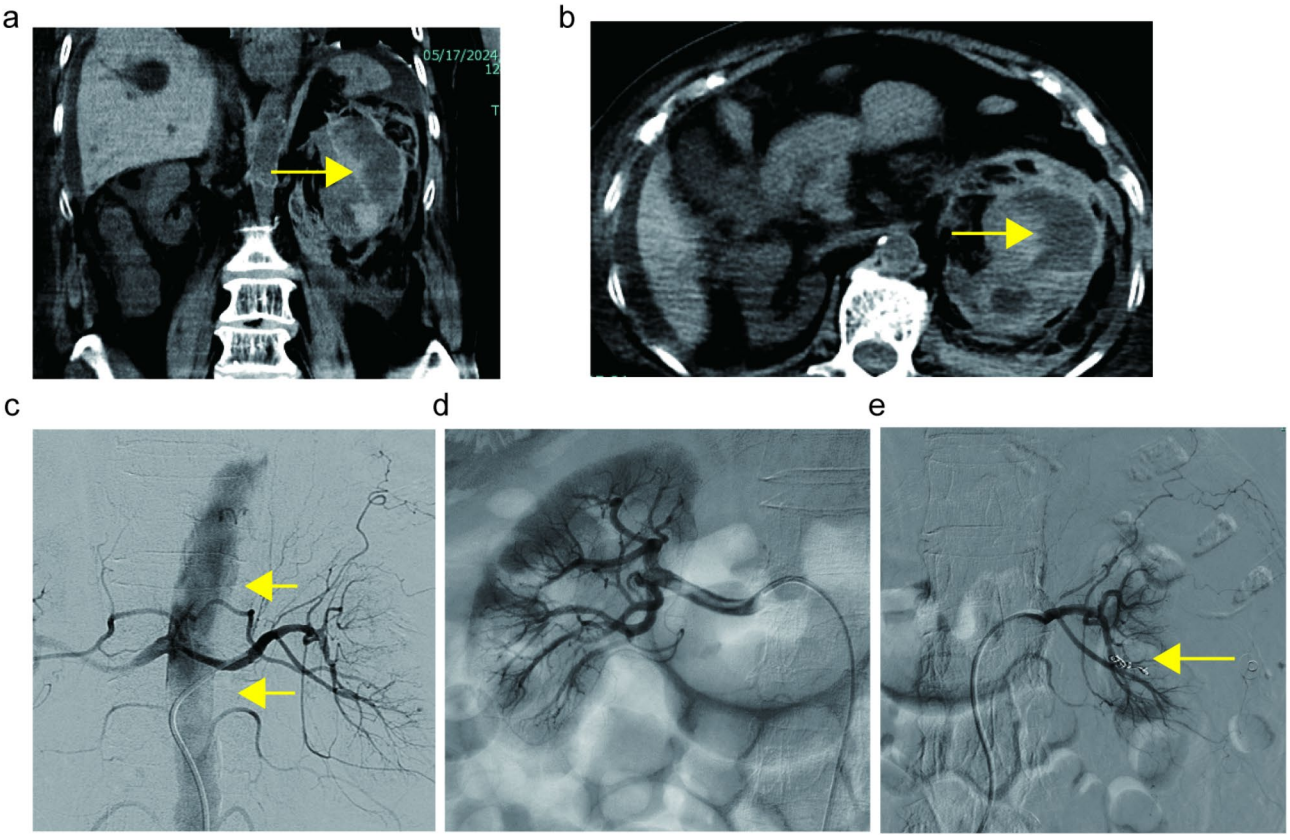

Fig. 1 WS occurring in systemic lupus erythematosus
A 75-year-old female patient presented to our hospital with a two-year history of intermittent bilateral leg weakness. Two days after admission, the patient presented with acute abdominal pain, shock, a significant decrease in hemoglobin levels, and alterations in mental status. An abdominal CT scan revealed a large hematoma in the left kidney compressing the renal parenchyma (yellow arrow), with an overall size of 63×42 mm (**a-b**). Emergency angiography was promptly performed, revealing a rupture of a branch of the left renal artery (yellow arrow) (**c**), whereas the right renal artery remained intact (**d**). The offending vessel was embolized with thread rings and gelatin sponges (yellow arrow), effectively preventing the extravasation of contrast agent (**e**)

to WS. First, diseases such as SLE can induce the formation of immune complexes, triggering pro-inflammatory responses in vascular endothelial cells and altering cell signaling pathways. This leads to the upregulation of molecules including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, IL-8, IL-6, TNF-α and nuclear factor kappa B [28]. Consequently, these changes can result in the obstruction of small vessels or microvessels in the kidney, potentially leading to vascular thrombosis or necrosis [29]. Second, abnormal coagulation is an important pathogenic factor. A perirenal hematoma was confirmed by imaging in a 22-year-old man with severe coagulopathy and subsequent abdominal tenderness and hypotension following a venomous snakebite [30]. Anticardiolipin antibodies and lupus anticoagulants are typically present in most patients with SLE, and hypercoagulability potentially increases the pressure on the blood vessels in the kidneys, causing thrombosis, coagulation dysfunction, and even disseminated intravascular coagulation (DIC) tendency [26, 31, 32]. In the case reported in this article, antiphospholipid antibodies tests were negative, and there was no evidence of thrombotic events. Additionally, the patient had not been administered any anticoagulant orantiplatelet medications. Prior to the onset of WS, the patient did not meet the diagnostic criteria for DIC. Therefore, DIC is unlikely to be the primary cause of WS. Third, SLE can affect the blood system and cause thrombocytopenia, which promotes bleeding [33, 34], this point is manifested in the case we reported. Fourth, ANCAs, autoantibodies associated with vasculitis, target serine protease 3 and myeloperoxidase. Under disease conditions, the binding of neutrophil cytoplasm antigens to ANCAs triggers degranulation and reactive oxygen species generation, leading to local blood vessel damage [35, 36]. Fifth, cytotoxic reactions mediated by either the complement pathway or antibodies can cause sustained or additional damage to vascular endothelial cells [37], as observed in this case. These mechanisms, acting independently or in conjunction with renal system involvement, can induce WS.

The immune status of patients with CTDs can indirectly trigger WS. Renal infection accounts for 5–10%

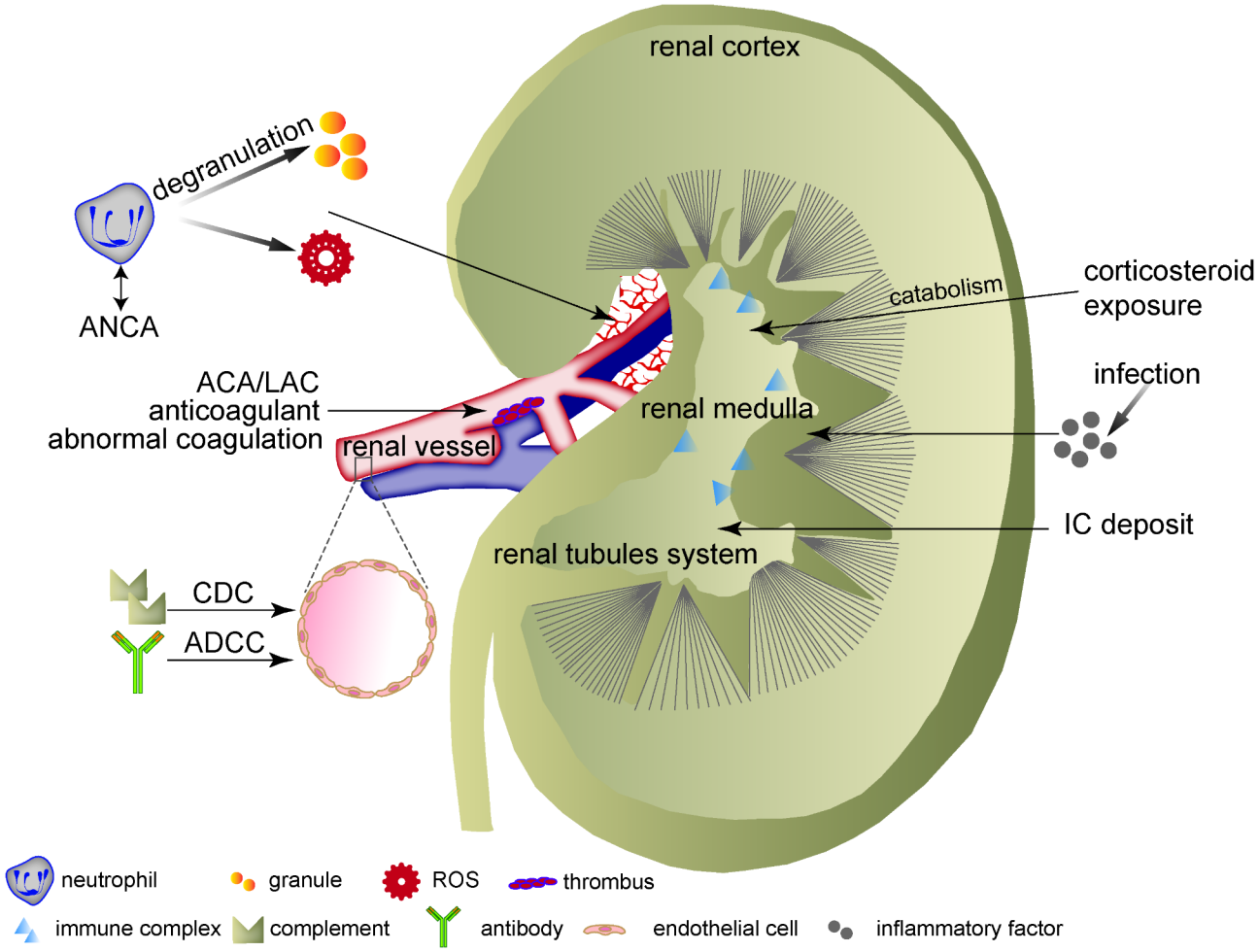

Fig. 2 Possible mechanisms of WS occurrence in patients with CTDs
In cases of abnormal coagulation functions, such as the presence of anticardiolipin antibody (ACA) and lupus anticoagulants (LACs) and the use of anticoagulant medications, a hypercoagulable state results in a marked increase in renal vascular pressure. Immune complexes are deposited within renal tubules and microvessels, potentially leading to vascular embolism or necrosis. The activation of the complement system in patients with CTDs induces a complement-dependent cytotoxic (CDC) effect to attack vascular endothelial cells. Similarly, the existence of autoantibodies mediates an antibody-dependent cell-mediated cytotoxic (ADCC) effect, contributing to renal vascular damage. The ANCA binds to the target antigen of neutrophils, triggering degranulation and the release of granular substances, which, along with reactive oxygen species (ROS) generation, jointly cause local vascular damage. Additionally, the catabolic effect of glucocorticoid treatment on tissues can exacerbate potential renal parenchymal or vascular rupture. Moreover, the dysregulated immune status of CTDs is prone to concurrent multiple infections, releasing inflammatory factors that reach the kidneys through the bloodstream, and providing facilitating conditions for the occurrence of WS

of all WS cases [38], and patients with CTDs are susceptible to multiple infections attributed to immune disorders. Inflammatory factors released after infection attack the renal parenchyma or renal vessels through the circulation [1], and significantly increase the risk of WS in patients. This is evident in the case reported here, where the patient had a compromised immune system and was infected with methicillin-resistant *Staphylococcus aureus* (MRSA) at the time of WS onset. Concurrent pulmonary sepsis and active SLE are the main causes leading to acute kidney injury (AKI) and accelerating the progression of LN. In addition, therapeutic drugs for patients with CTDs may promote the occurrence of WS. Glucocorticoids represent the standard treatment for CTDs; however, they negatively influence the healing of connective tissues and muscles [39]. In patients with mild renal parenchymal or vascular disease, the negative effects of glucocorticoid exposure may catalyze the progression and deterioration of WS. Moreover, anticoagulant use is a risk factor for WS [40–42], especially warfarin, the first-line treatment for APS, which is strongly associated with the emergence of WS [43, 44]. Retroperitoneal hematoma caused by branch bleeding of the left renal artery has also been reported in patients with APS taking aspirin [45].

WS is typically diagnosed on the basis of imaging findings, when WS is highly suspected, angiography becomes the preferred approach for precise localization of the bleeding site and simultaneous embolization treatment

at the rupture site [13]. Although the treatment for WS includes conservative treatment and invasive approaches, arterial embolization should be considered as early as possible in all WS patients [46]. TAE is a safe and effective method for controlling spontaneous renal hemorrhage, effectively alleviating symptoms while minimizing the incidence of further hemorrhage and renal atrophy [47].

This report has certain limitations. Firstly, owing to the patient's extremely low eGFR, angiographic examination was not performed to rule out obliterative arteriopathy. Additionally, no pathological samples were obtained from the involved renal vessels and kidney. Limited available literature currently precludes accurate identification of WS-related risk factors for CTDs. However, in prospective studies related to chronic kidney disease (CKD), Peterson et al. proposed that indicators, such as reduced thrombin and elevated fibrin, could predict the risk of spontaneous major bleeding in patients with CKD [48].

In conclusion, WS in CTDs is a rare but potentially life-threatening disorder that can progress rapidly. Early diagnosis and management of WS are crucial for patients with related risk factors. Effective treatment plans should be tailored to the specific disease conditions of each patient. This includes avoiding medications that may exacerbate renal injury, providing enteral nutrition support, maintaining electrolyte balance, selecting anti-infective agents with minimal nephrotoxicity, and implementing preventive measures against fungal infections when necessary. Notably, follow-up imaging is recommended, as the initial perirenal hematoma may mask the underlying cause.

Take-home messages

1. Wunderlich syndrome (WS) is a spontaneous renal hemorrhage condition that can cause critical and severe outcomes.
2. The occurrence of WS in patients with connective tissue diseases is associated with infection, abnormal coagulation function, complement activation, autoantibody generation, and glucocorticoid therapy.
3. In case of hemodynamic disorders, transcatheter arterial embolization should be the preferred treatment modality for WS.
4. In addition to surgical intervention, targeted management strategies for acute kidney injury, such as anti-infection, nutritional support, and maintaining the equilibrium of water and electrolytes, should be concurrently administered to WS patients.

Abbreviations

WS	Wunderlich syndrome
CTDs	Connective tissue diseases
SLE	Systemic lupus erythematosus
LN	Lupus nephritis
WBC	White blood cell
eGFR	Estimated glomerular filtration rate
dsDNA	Double-stranded DNA
CT	Computed tomography
DIC	Disseminated intravascular coagulation
TAE	Transcatheter arterial embolization
ANCA	Antineutrophil cytoplasmic antibody
APS	Antiphospholipid syndrome
CKD	Chronic kidney disease

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Author contributions
LL D conceived and designed the study. YZ Z acquired the data and drafted the manuscript. YZ Z and LL D interpreted the data and revised the manuscript critically. All the authors read and approved the final manuscript.

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Data availability
All the data are presented in this manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The authors declare no competing interests.

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