Cureus
Part of SPRINGER NATURE

Open Access Case Report

Cardiogenic Shock Secondary to Rituximab Administration: A Case Report

Dina Farhat [1], Joe Kadou [1], Paul Boulos [1], Raphael Rozenblum [2], Simon Kalisz [2]

1. Emergency Department, Centre Hospitalier Interrégional Edith Cavell, Brussels, BEL 2. Emergency Department, Chirec Delta Hospital, Brussels, BEL

Corresponding author: Simon Kalisz, simon.kalisz@gmail.com

Review began 09/18/2026
Review ended 11/05/2026
Published 11/08/2026

© **Copyright** 2026
Farhat et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.119317

Abstract

Rituximab is a synthetic antibody used in the treatment of B cell-mediated autoimmune diseases, including immune thrombotic thrombocytopenic purpura. Although generally well tolerated, it may be associated with adverse effects, ranging from infusion-related reactions to rare but severe delayed complications. We report the case of a 64-year-old woman with a history of systemic lupus erythematosus and immune thrombotic thrombocytopenia who developed cardiogenic shock following rituximab reintroduction. The patient presented five days after infusion with asthenia, dyspnea, and chest pain, preceded by arthralgia. Initial cardiac evaluation revealed severe left ventricular systolic dysfunction with diffuse hypokinesis. The patient required inotropic and vasopressor support for cardiogenic shock. Subsequently, she developed a macular rash and persistent polyarthralgia, consistent with a serum sickness-like reaction. This case suggests a diagnosis of rituximab-induced serum sickness associated with non-ischemic cardiomyopathy leading to cardiogenic shock. While cardiac adverse events related to rituximab are uncommon, they may include acute coronary syndromes, arrhythmias, and cardiomyopathy. Delayed presentations, although rare, should be recognized.

Categories: Cardiology, Emergency Medicine, Internal Medicine
Keywords: cardiogenic shock, rituximab-induced serum sickness, rituximab therapy, secondary effect, serum sickness-like reaction

Introduction

Rituximab is the first monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of several B cell-mediated autoimmune diseases [1]. It works by targeting and eliminating CD20-positive B lymphocytes. Its approved indications are non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, and pemphigus vulgaris [2]. Beyond these approved indications, rituximab is widely used off-label, with a substantial body of supporting evidence, in systemic lupus erythematosus (SLE), multiple sclerosis, and immune thrombotic thrombocytopenic purpura (iTTP) [1,3]. In iTTP, the 2025 focused update of the International Society on Thrombosis and Haemostasis (ISTH) guidelines recommends rituximab in the acute phase in addition to therapeutic plasma exchange and corticosteroids, and conditionally recommends preemptive rituximab in patients in clinical remission with persistently low ADAMTS13 activity to prevent relapse [4]. As the use of rituximab keeps expanding across specialties, clinicians in acute care settings are increasingly likely to encounter its rare complications.

Rituximab is associated with a wide range of adverse effects, and two hypersensitivity phenotypes should be distinguished. Infusion-related reactions are the most frequent; they typically occur during or within hours of the first infusion and are mediated by cytokine release, complement activation, and mast cell degranulation associated with B cell lysis [5]. Their manifestations range from fever, chills, rigors, rash, pruritus, nausea, and headache to, in severe forms, hypotension, bronchospasm, angioedema, hypoxia, and anaphylaxis [5]. Other well-described adverse effects include hypogammaglobulinemia, late-onset neutropenia, and infections [6].

Rituximab-induced serum sickness (RISS) is a distinct, delayed, type III hypersensitivity reaction mediated by immune complexes formed between rituximab and host anti-drug antibodies. It occurs seven to 21 days after exposure, and earlier after re-exposure, and is characterized by the classical triad of fever, rash, and arthralgia or arthritis, sometimes accompanied by myalgia, malaise, lymphadenopathy, and purpura [7,8]. Its incidence is difficult to estimate; a systematic review identified 33 cases up to 2015, and a more recent analysis of 39 reported cases found a median age of 33 years with a clear female predominance (71.8%) [7,8]. Cardiac involvement in RISS is exceptional and remains poorly characterized: cardiogenic shock following rituximab has only been described in isolated case reports, and whether cardiac dysfunction in this setting results from serum sickness itself or from a distinct rituximab-associated cardiotoxicity is unknown [9-11].

We report the case of a 64-year-old woman with iTTP who developed cardiogenic shock seven days after the second infusion of a second rituximab cycle, in association with a serum sickness-like reaction. Our aim is to

describe the clinical presentation, the diagnostic work-up that excluded the main alternative causes, and the level of causal inference that can reasonably be drawn from a single observation.

Case Presentation

We present the case of a 64-year-old female with a history of iTTP who presented to the emergency department in January 2026 with acute chest pain, respiratory distress, and profound asthenia.

Prior medical history included systemic lupus erythematosus with articular and renal involvement in 1989, successfully treated with cyclophosphamide and corticosteroids, with no relapse reported since. Sjögren's syndrome was diagnosed in 2002. There was no personal history of cardiovascular disease, although a left bundle branch block (LBBB) had been documented on a previous electrocardiogram (ECG), and no self-report of prior or current consumption of illicit substances, alcohol, or tobacco products. No additional medication was reported.

iTTP was diagnosed in 2015 in the setting of severe thrombocytopenia (platelet count, 10×10^{9}/L) and biochemical evidence of hemolysis (LDH, 1324 U/L), with a hemoglobin level of 12.4 g/dL. ADAMTS13 activity was markedly reduced at 11% at diagnosis. Schistocyte quantification was not available, and an ADAMTS13 inhibitor was not assessed. The patient was initially treated with methylprednisolone (1 mg/kg/day), resulting in stabilization of ADAMTS13 activity at approximately 23%. However, ADAMTS13 activity subsequently decreased to 10%, prompting therapeutic plasma exchange, which was performed from May to July 2015. Following plasma exchange, the patient achieved clinical and biological stabilization.

During subsequent follow-up, ADAMTS13 activity was monitored approximately every six months and remained relatively stable, ranging between 30% and 33%. No further clinical deterioration requiring additional treatment was documented during this period. In 2024, however, ADAMTS13 activity decreased again to 12%, despite the previous long-term stabilization. This biological relapse prompted the initiation of rituximab in May 2024, at a dose of 375 mg/m² once weekly for four consecutive weeks. The treatment was well tolerated, with no adverse reactions. Following rituximab treatment, ADAMTS13 activity increased and stabilized at approximately 46.6%, as measured by chromogenic ELISA (laboratory reference range >50%).

The etiological work-up included a bone marrow examination, negative rheumatoid factor, anti-CCP, and ANCA antibodies in both 2015 and 2024, a low-titer positive antinuclear antibody (ANA, 1:80), normal serum protein electrophoresis in 2016, and negative hepatitis C virus serology. An ADAMTS13 inhibitor was not assessed at diagnosis.

The patient was then lost to follow-up for several months. In January 2026, she consulted for a follow-up, without any clinical symptoms, and laboratory findings showed reduced ADAMTS13 levels at 6.9%. This situation corresponds to clinical remission with severe ADAMTS13 deficiency rather than to an acute relapse, and preemptive rituximab was therefore prescribed in line with the 2025 ISTH conditional recommendation [4]. Before this second cycle, a cardiac evaluation had been performed a few days before the start of treatment: the 12-lead ECG showed sinus rhythm with a LBBB (QRS duration 156 ms) (Figure *1*), already known since 2024, and transthoracic echocardiography was reported as normal with a normal LVEF and no significant abnormality (images unavailable). The first infusion of the second cycle was given 14 days before the index admission, and the second infusion seven days before admission (Table *1*). Six days after the second infusion, the patient presented to an emergency department with arthralgia. Blood tests and chest radiography (Figure *2*) were within normal limits, and she was discharged with symptomatic treatment.

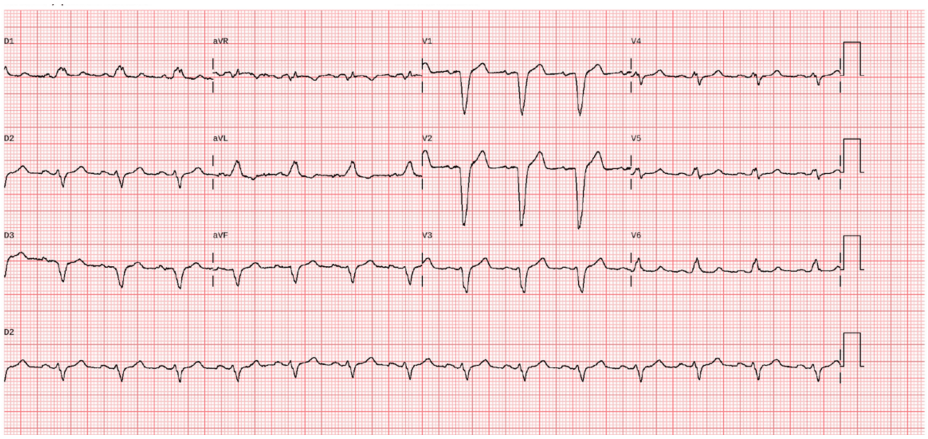


FIGURE 1: ECG at the initial presentation of cardiogenic shock

Sinus rhythm at 87 beats per minute with a complete left bundle branch block (QRS duration 162 ms), unchanged compared with the baseline tracing obtained before the second rituximab cycle. No ST-segment change beyond that expected with left bundle branch block and no arrhythmia.

Time (day 0 = ED admission)	Event
1987	SLE with articular and renal involvement; complete remission after cyclophosphamide and corticosteroids, no subsequent relapse
2002	Sjögren's syndrome
2015	Diagnosis of iTTP; therapeutic plasma exchange + methylprednisolone 1 mg/kg/day
2015-2024	ADAMTS13 activity monitored every six months and maintained at approximately 30–33%, without requiring additional treatment.
2024	Decrease of ADAMTS13 activity → first rituximab cycle (four weekly infusions), well tolerated; ADAMTS13 activity stabilized at 46.6%
2024-2025	Lost to follow-up
Day -14	Hematology visit: asymptomatic, ADAMTS13 activity 6.9% → first infusion of second rituximab cycle
Day -7	Second infusion of second rituximab cycle
Day -1	ED visit for arthralgia: blood tests and chest X-ray unremarkable → discharged with symptomatic treatment
Day 0	ED admission: chest pain, dyspnea, somnolence, shock (BP 92/42 mmHg, CRT >4 s, lactate 3 mmol/L). Point-of-care echocardiography: LVEF 5-10%, VTI 8 cm, $ScvO_2$ 35%. Dobutamine + norepinephrine. CT pulmonary angiography and coronary angiography normal. ICU admission
Day 2	Erythematous macular rash and diffuse arthromyalgia; complement consumption (C3 0.76 g/L, C4 0.04 g/L); no fever → serum sickness-like reaction; further rituximab doses withheld; IV methylprednisolone 80 mg/day
Day 3	Complete weaning of inotropic and vasopressor support (72 hours after admission)
Day 5	Cardiac MRI (LGE, T1/T2 mapping): no myocardial tissue abnormality, no evidence of acute myocarditis or Takotsubo syndrome
Day 8	Bedside echocardiography: LVEF 40-50%, persistent diffuse hypokinesis; discharge home on oral corticosteroids
Day 21	Outpatient echocardiography: LVEF 45%, septal dyskinesia, grade I diastolic dysfunction without elevated filling pressures; ADAMTS13 activity 41.6%; corticosteroids continued for four weeks after discharge

TABLE 1: Chronology of events.

BP, blood pressure; CRT, capillary refill time; ED, emergency department; ICU, intensive care unit; iTTP, immune thrombotic thrombocytopenic purpura; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; $ScvO_2$, central venous oxygen saturation; SLE, systemic lupus erythematosus; VTI, velocity time integral

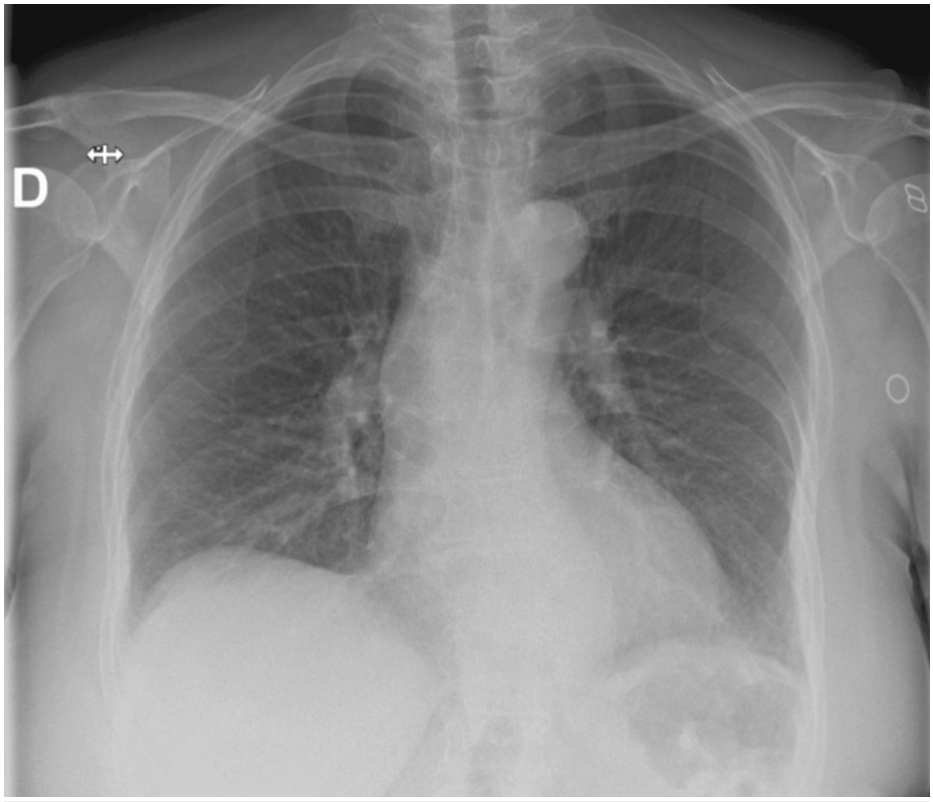


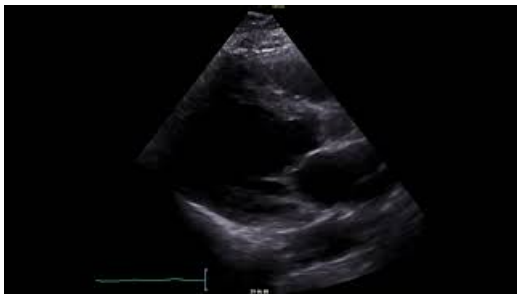
FIGURE 2: Chest X-ray

Normal cardiac silhouette, no pulmonary congestion, pleural effusion, or parenchymal consolidation.

On the following day, the patient was admitted to our emergency department with acute chest pain, dyspnea, profound asthenia, and headache. History taking was made difficult by somnolence present on arrival.

On admission, temperature was 36.2°C, blood pressure 92/42 mmHg (mean arterial pressure approximately 59 mmHg), heart rate 82 beats per minute, respiratory rate 28 breaths per minute, and peripheral oxygen saturation 90% on room air. The patient was cyanotic, tachypneic, and bradypsychic, without lateralizing neurological signs. Heart sounds were regular without murmur, lung auscultation was unremarkable, and the abdomen was soft and non-tender. Bilateral lower-limb edema was present and capillary refill time exceeded four seconds. There was no peripheral lymphadenopathy. The combination of hypotension, altered mental status, cyanosis, prolonged capillary refill time, and hyperlactatemia (3 mmol/L on venous blood gas) met clinical criteria for shock, corresponding to Society for Cardiovascular Angiography and Interventions (SCAI) stage C once the need for pharmacological support became evident [12].

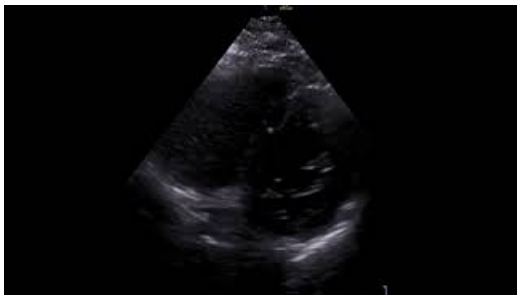
A 12-lead ECG showed the previously described left bundle branch block and was unchanged compared to previous investigations (QRS duration 162 ms). Point-of-care transthoracic echocardiography revealed severe left ventricular systolic dysfunction with a visually estimated LVEF of 5-10%, diffuse left ventricular hypokinesis, and septal akinesis (Videos *1*-*2*). The sub-aortic velocity time integral (VTI) was 8 cm (normal range 18-22 cm), indicating a markedly reduced stroke volume (Figure *3*). Central venous oxygen saturation ($ScvO_2$) was 35%, confirming inadequate oxygen delivery and pointing to a low-output rather than a distributive mechanism despite the marked inflammatory syndrome.



VIDEO 1: Transthoracic cardiac echography - parasternal long-axis view

Transthoracic echocardiography in the parasternal long-axis view showing severe left ventricular systolic dysfunction, with an estimated LVEF of 5-10%, diffuse left ventricular hypokinesis, and septal akinesis.

View video here: https://www.youtube.com/watch?v=rHjhbtsEPNA



VIDEO 2: Transthoracic cardiac echography - parasternal short-axis view

Transthoracic echocardiography in the parasternal short-axis view showing severe left ventricular systolic dysfunction, with an estimated LVEF of 5-10%, diffuse left ventricular hypokinesis, and septal akinesis.

View video here: https://www.youtube.com/watch?v=yCX29d11A_I

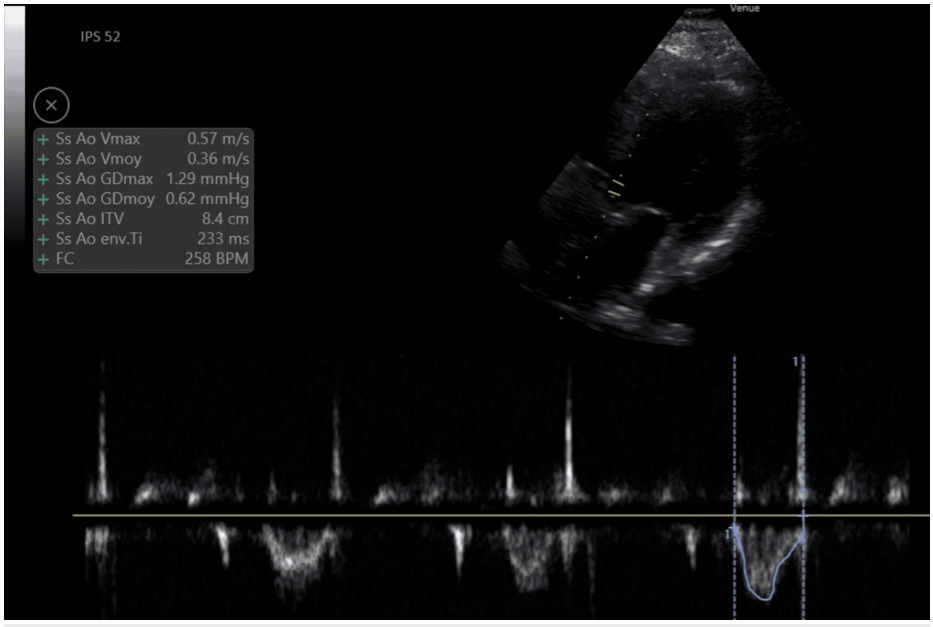


FIGURE 3: Transthoracic echocardiography, apical five-chamber view, pulsed-wave Doppler of the left ventricular outflow tract (day 0).

The sub-aortic velocity time integral measures 8 cm (normal 18-22 cm), indicating a severely reduced stroke volume and confirming a low-output state.

Laboratory evaluation (Table *2*) revealed high-sensitivity troponin levels increasing from 10 ng/L at baseline to 19 ng/L at H+2, followed by a peak of 69 ng/L on day 2 and a subsequent decrease to 7 ng/L on day 3. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was also elevated at 467 pg/mL on admission (reference value <125 pg/mL). C-reactive protein was 144 mg/L with neutrophilic leukocytosis (12.8 $\times 10^3/mm^3$, neutrophils 11.81 $\times 10^3/mm^3$) and lymphopenia (0.67 $\times 10^3/mm^3$); procalcitonin was 0.02 µg/L. There was no evidence of active thrombotic microangiopathy: platelet count 149 $\times 10^3/mm^3$, hemoglobin 14.2 g/dL, lactate dehydrogenase 198 U/L, and total bilirubin 1.2 mg/dL. A peripheral blood smear for schistocytes and a contemporaneous ADAMTS13 activity were not obtained at admission; the last available ADAMTS13 activity, measured 14 days earlier, was 6.9%. Complement testing showed consumption of both

C3 (0.76 g/L; reference [0.8-1.64]) and C4 (0.04 g/L; reference [0.1-0.4]), a profile consistent with classical pathway activation by circulating immune complexes; CH50, erythrocyte sedimentation rate, anti-double-stranded DNA antibodies, and anti-rituximab antibodies were not measured. Eosinophil count was 0.04 $\times 10^3/mm^3$. Liver tests showed mildly elevated transaminases (AST 87 U/L, ALT 68 U/L) with normal gamma-glutamyl transferase and alkaline phosphatase, and creatinine was 1.19 mg/dL (estimated glomerular filtration rate 46 mL/min/1.73 m^2).

Category	Parameter	Result	Unit	Reference range
Hematology	Hemoglobin	14.2	g/dL	11.7-16.0
	Hematocrit	41.1	%	
	Platelets	149	$\times 10^3/mm^3$	150-400
	White blood cells	12.8 ↑	$\times 10^3/mm^3$	4.5-11.0
	Neutrophils	11.81 (92.3%) ↑	$\times 10^3/mm^3$	
	Lymphocytes	0.67 ↓	$\times 10^3/mm^3$	
	Eosinophils	0.04	$\times 10^3/mm^3$	
Hemolysis	Haptoglobin	1.3	g/L	
	Lactate dehydrogenase	198	U/L	
	Total / direct bilirubin	1.2 / 0.8 ↑	mg/dL	
Hemostasis	Prothrombin time (Quick)	>100	%	
	INR	0.9	—	
	aPTT	27.0	s	
	Fibrinogen	544 ↑	mg/dL	
	D-dimer	1.5 ↑	µg/mL	<0.5
Biochemistry	Sodium / potassium / chloride	135 / 3.6 / 97	mmol/L	
	Bicarbonate	22	mmol/L	
	Glucose	166 ↑	mg/dL	
	Urea / creatinine	50 ↑ / 1.19 ↑	mg/dL	0.50-0.90 (creatinine)
	eGFR (MDRD)	46 ↓	mL/min/1.73 m^2	
Liver	AST / ALT	87 / 68 ↑	U/L	
	Gamma-GT / alkaline phosphatase	36 / 77	U/L	
Cardiac markers	Creatine kinase	27	U/L	
	hs-Troponin T (H0 / H+2)	10 / 19	ng/L	<14
	hs-Troponin T peak	69	ng/L	
	NT-proBNP	467 ↑	pg/mL	<125
Inflammation	C-reactive protein	144 ↑	mg/L	<5
	Procalcitonin	0.02	µg/L	
Complement	C3	0.76 ↓	g/L	0,8-1.64
	C4	0.04 ↓	g/L	0,1-0,4
Venous blood gas	pH / pCO_2 / HCO_3^-	7.30 / 53 / 26	— / mmHg / mmol/L	
	Lactate	3	mmol/L	<1.39
Microbiology	Blood cultures	Negative	—	
Hemodynamics	$ScvO_2$	35 ↓	%	

TABLE 2: Laboratory results on admission

↑ above / ↓ below reference range. ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; hs, high-sensitivity; INR, international normalized ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; $ScvO_2$, central venous oxygen saturation.

Computed tomography pulmonary angiography showed no pulmonary embolism, no deep infectious focus, and no other acute thoracic abnormality (Figure *4*). Coronary angiography demonstrated right coronary dominance with angiographically normal coronary arteries and no obstructive lesion (Figure *5*).

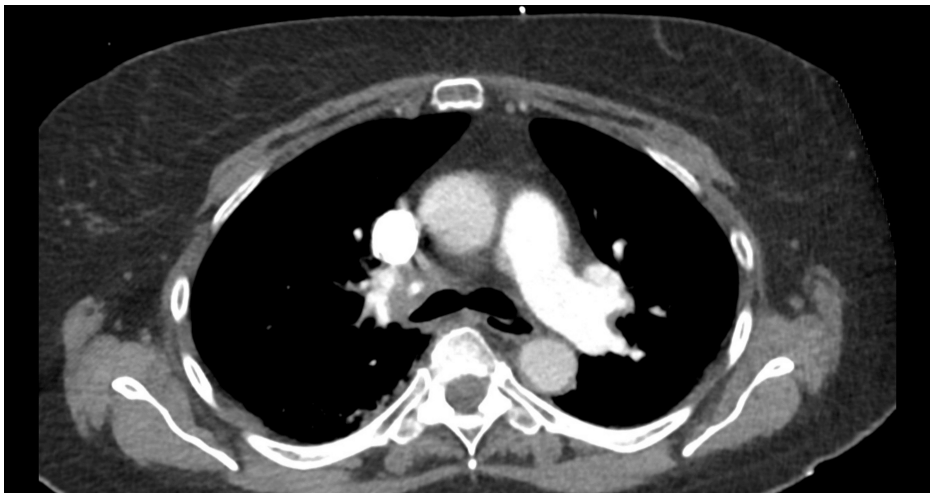


FIGURE 4: Computed tomography pulmonary angiography, axial view at the level of the pulmonary arteries (day 0)

Normal opacification of the pulmonary arteries without filling defect, excluding pulmonary embolism; no pleural effusion, consolidation or deep infectious focus.

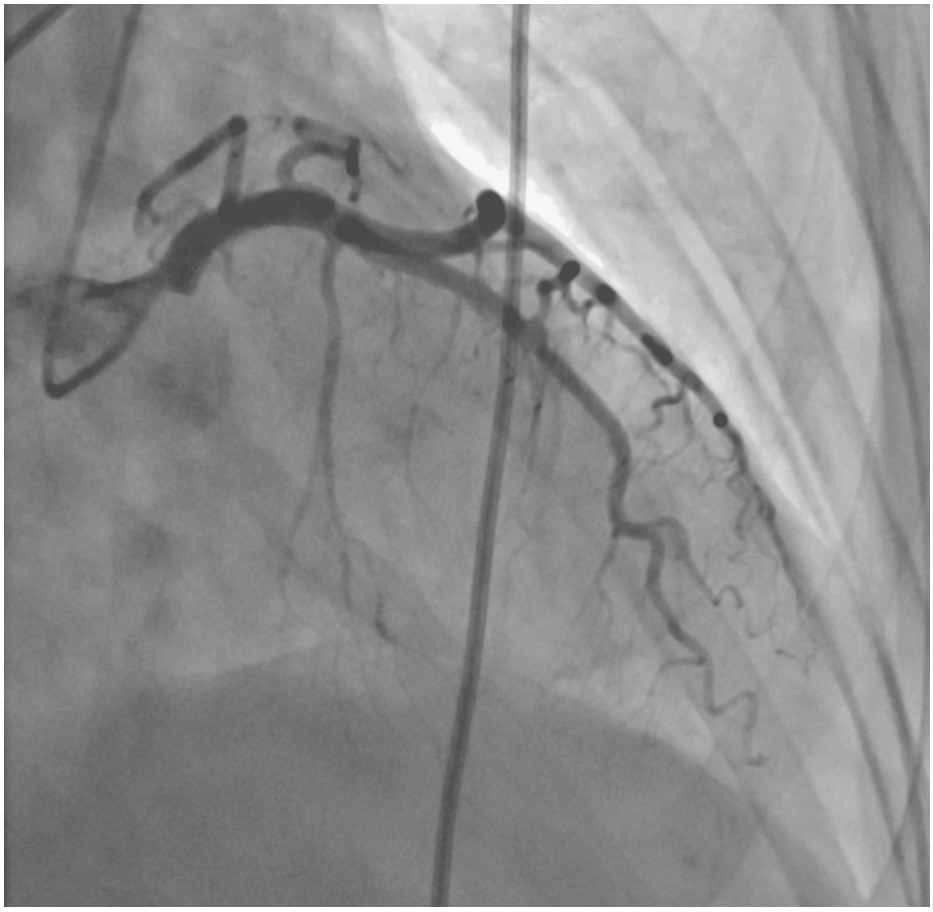


FIGURE 5: Coronary angiography (day 0)

Right-dominant coronary circulation with angiographically normal coronary arteries and no obstructive lesion, excluding an ischemic cause of the acute left ventricular dysfunction.

Hemodynamic support was started immediately with dobutamine titrated to 10 µg/kg/min, combined transiently with norepinephrine (maximum 0.8 µg/kg/min) to maintain an adequate mean arterial pressure, and the patient was transferred to the intensive care unit.

On day 2, an erythematous macular rash appeared on the trunk and all four limbs, sparing the face, with a predominantly periarticular distribution, together with persistent diffuse arthromyalgia and worsening lower-limb edema. Oral examination showed no aphthous lesions. The patient remained afebrile. This association, occurring one week after a rituximab infusion and accompanied by complement consumption, was considered consistent with a serum sickness-like reaction to rituximab, despite the absence of fever. Further rituximab doses were withheld, and the drug was considered permanently contraindicated. Intravenous methylprednisolone 80 mg/day was started and continued orally for four weeks after discharge.

Inotropic and vasopressor requirements decreased progressively and were completely weaned 72 hours after admission. A bedside echocardiography on day 8 (five days after weaning) showed partial recovery of left ventricular systolic function with an LVEF estimated at 40-50% and persistent diffuse hypokinesis. Cardiac magnetic resonance (CMR) imaging was performed using SSFP sequences in axial, short-axis, horizontal long-axis, and vertical long-axis views. Left ventricular ejection fraction was 45%, with an end-diastolic volume of 160 mL (72 mL/m^2), an end-systolic volume of 88 mL (39 mL/m^2), and a cardiac output of 5 L/min. There was no left ventricular dilatation or myocardial hypertrophy.

T1 imaging showed no abnormal myocardial T1 relaxation time. T2-weighted STIR sequences showed no evidence of myocardial edema. First-pass perfusion sequences showed no perfusion abnormality. Cine imaging demonstrated normal and concentric wall motion suggestive of takotsubo syndrome. Late gadolinium enhancement imaging showed no abnormal enhancement. No pericardial or pleural effusion was observed. Gadobutrol (Gadovist®, 0.15 mmol/kg) was used for contrast-enhanced imaging. The updated Lake Louise criteria for acute myocarditis [13] were therefore not met, with the caveat that the study was performed five days after symptom onset and under corticosteroid therapy.

The patient was discharged home on day 8 in a stable clinical condition with cardiology and hematology follow-up. At three weeks, outpatient transthoracic echocardiography showed an LVEF of 45% with septal dyskinesia and grade I diastolic dysfunction without elevated filling pressures. ADAMTS13 activity had risen to 41.6%.

Discussion

We report a 64-year-old woman with iTTP in clinical remission who developed cardiogenic shock seven days after the second infusion of a second rituximab cycle, together with a rash, arthromyalgia, and complement consumption. Two levels of inference must be kept separate. First, the clinical and biological picture (delayed onset after re-exposure, rash, arthralgia, hypocomplementemia, exclusion of infection) supports a probable rituximab-associated systemic hypersensitivity reaction of the serum sickness type. Second, the patient developed a severe, acute, non-ischemic left ventricular dysfunction temporally associated with rituximab, which largely recovered after drug withdrawal and corticosteroid therapy. The available data establish a strong temporal and clinical association between these two events, but they do not demonstrate that serum sickness itself caused the cardiomyopathy; the mechanistic link remains a hypothesis.

The initial presentation, with hypotension at 92/42 mmHg, cyanosis, capillary refill time >4 seconds, and somnolence, required immediate recognition of shock without an obvious etiology. Point-of-care echocardiography redirected the diagnosis by demonstrating a major systolic dysfunction and a sub-aortic VTI of 8 cm, and the $ScvO_2$ of 35% confirmed inadequate oxygen delivery, favoring a low-output mechanism over a distributive one despite a marked inflammatory syndrome. This distinction had direct consequences: inotropic support rather than fluid loading, and no empirical antibiotics once the infectious work-up (apyrexia, procalcitonin 0.02 µg/L, negative blood cultures, no focus on CT) was negative.

The modest rise in high-sensitivity troponin T (10 then 19 ng/L) with a peak of 69 ng/L on day 3 and the moderately elevated NT-proBNP (467 pg/mL) contrast with the severity of the ventricular dysfunction. The most likely explanations are the very recent onset of the dysfunction, the absence of extensive myocardial necrosis and, for NT-proBNP, sampling before the neurohormonal response had fully developed. Troponin is a marker of myocyte injury rather than of hemodynamic failure and may remain near normal in forms of cardiogenic shock that are not driven by acute myocardial necrosis [14].

iTTP is a rare thrombotic microangiopathy caused by autoantibodies against ADAMTS13, the plasma metalloprotease that cleaves von Willebrand factor [15,16]. Inhibitory antibodies most often target the spacer domain, but non-inhibitory antibodies that accelerate ADAMTS13 clearance also contribute in some patients [16,17]. The resulting accumulation of ultra-large von Willebrand factor multimers causes platelet-rich microthrombi, microangiopathic hemolytic anemia, and ischemic organ injury. Neurological manifestations occur in about 60% of patients, and cardiac involvement, ranging from subtle electrocardiographic changes to acute coronary syndrome and cardiac arrest, is reported in roughly a quarter of patients [15,18]. In a patient with a history of iTTP presenting with acute cardiac dysfunction, TTP-related cardiac injury must therefore be excluded first. In our patient, the absence of thrombocytopenia (149 $\times 10^3/mm^3$), anemia, and elevated lactate dehydrogenase made an active microangiopathic flare very unlikely, although the lack of a peripheral smear and of a contemporaneous ADAMTS13 activity at admission prevents formal exclusion.

Regarding treatment, the 2025 ISTH update maintains therapeutic plasma exchange and corticosteroids as the backbone of acute iTTP management, with rituximab and caplacizumab as adjuncts, and retains a conditional recommendation for preemptive rituximab in patients in clinical remission with low ADAMTS13 activity [4]. Our patient did not receive caplacizumab. The January 2026 episode did not represent an acute relapse: she was asymptomatic with a normal platelet count, and the indication for rituximab was the severe ADAMTS13 deficiency (6.9%) in clinical remission, i.e., preemptive treatment to prevent relapse. Her first rituximab cycle in 2024 had been uneventful.

RISS is a type III hypersensitivity reaction. Anti-rituximab antibodies, favored by the chimeric (murine-human) structure of the molecule, form circulating immune complexes that deposit in tissues, activate the classical complement pathway, and recruit inflammatory cells. Symptoms classically appear one to two weeks after the initial exposure and earlier after re-exposure [7,8]. Published data indicate that RISS most often occurs after the second dose of the first treatment cycle, typically around seven days after infusion [7]. In our patient, symptoms began six to seven days after the second infusion of the second cycle, whereas the first cycle had been well tolerated; the chronology therefore partially matches the literature, the difference being that sensitization presumably occurred during the first cycle and the reaction was triggered by re-exposure.

The classical triad of RISS is fever, rash, and arthralgia or arthritis [7,8]. Two of the three elements were present in our patient (rash and arthromyalgia), but fever was consistently absent (36.2°C on admission and afebrile throughout the stay). Apyrexia does not exclude the diagnosis but does weaken it; it may have been favored by rituximab-induced immunosuppression, reflected by the profound lymphopenia ($0.67 \times 10^3/mm^3$). Because fever was absent, anti-rituximab antibodies were not measured and no histological confirmation was obtained, we prefer the term "serum sickness-like reaction" and regard the diagnosis as clinical and

probable rather than confirmed. Eosinophilia was absent, which argues against a drug reaction with eosinophilia and systemic symptoms (DRESS).

Complement consumption is the main patient-specific biological argument supporting an immune complex-mediated mechanism: the combined decrease in C3 (0.76 g/L) and C4 (0.04 g/L) reflects classical pathway activation, as expected during tissue deposition of immune complexes. This hypocomplementemia must, however, be interpreted with caution in a patient with a history of SLE, since low C3 and C4 are also classical markers of a lupus flare. Several elements argue against a flare: the absence of cytopenia or renal involvement, the absence of cutaneous or articular features typical of lupus, disease quiescence for more than 30 years, and a chronology strictly aligned with the rituximab infusion. Anti-double-stranded DNA antibodies, which were not measured, would have allowed a more formal distinction.

Management of RISS rests primarily on withdrawal of the drug and supportive care. Corticosteroids are frequently used in moderate to severe forms and intravenous methylprednisolone is often reported to be effective, although the evidence is observational and derived from case series; antihistamines may provide symptomatic relief, and mild forms are often self-limited [7,8]. In our patient, the decision to withhold further rituximab doses, combined with corticosteroids, was followed by rapid hemodynamic and functional recovery.

Cardiac adverse events attributed to rituximab are uncommon and heterogeneous. Acute coronary syndromes, Takotsubo syndrome, arrhythmias, and non-ischemic cardiomyopathy have been described in individual case reports, mostly in the hours following an infusion, and occasionally as delayed presentations [19-23]. Arrhythmias have been reported in up to 8% of treated patients and include monomorphic ventricular tachycardia, supraventricular tachycardia, trigeminy and irregular pulse, as well as an isolated fatal infusion reaction secondary to myocardial infarction [22]. Rare cases of cardiogenic shock requiring vasopressor and inotropic support have also been reported: within hours of infusion in a patient treated for refractory TTP [9], 24 hours after infusion in an 81-year-old patient with relapsing ANCA-associated vasculitis, mimicking septic shock [11], and as a delayed presentation [10]. The underlying mechanisms remain incompletely understood.

Two mechanistic hypotheses have been advanced in the literature, and both must be regarded as unproven in humans. First, individual reports of non-ischemic cardiomyopathy after rituximab have described diffuse reticulin fiber deposition in cardiomyocytes together with elevated serum transforming growth factor-β, and it has been suggested that this might reduce myocardial contractility [19,20]. These observations come from single cases and cannot establish a general mechanism of rituximab cardiotoxicity; moreover, a fibrotic process would not readily explain an abrupt fall in LVEF to 5-10% followed by substantial recovery within days, as observed in our patient. Second, by analogy with the tissue injury of serum sickness, immune complex deposition within the myocardium with complement-mediated inflammatory injury has been proposed. In our patient, this hypothesis is supported only indirectly, by the systemic complement consumption and the concomitant rash and arthralgia; there was no endomyocardial biopsy, and CMR did not show inflammation. A transient, functional myocardial depression by cytokines released during the systemic hypersensitivity reaction, akin to that seen in other systemic inflammatory states, is a third possibility compatible with the rapid reversibility, but is equally speculative. We could not identify a series specifically describing myocarditis or cardiomyopathy as a manifestation of RISS; cardiac involvement in RISS therefore rests on isolated observations such as ours and should not be conflated with the broader spectrum of rituximab-associated cardiac events.

The alternative hypotheses were systematically examined. TTP-related cardiac injury was considered unlikely in the absence of any biological stigma of active microangiopathy. Ischemic cardiomyopathy was excluded by normal coronary angiography, an unchanged LBBB and near-normal troponin. Acute myocarditis, viral or lupus-related, was the main alternative given the autoimmune history and the inflammatory syndrome; CMR on day 5 showed no edema or late gadolinium enhancement, the lupus had been quiescent for decades without cytopenia or renal involvement, and troponin was barely elevated. We acknowledge that a CMR performed five days after onset and under corticosteroids does not absolutely exclude a focal or rapidly resolving myocarditis, and that the updated Lake Louise criteria are less sensitive in this setting [13]. Takotsubo syndrome was deemed unlikely because of the diffuse rather than regional wall motion abnormality and the non-contributory CMR. Septic shock was excluded by the persistent apyrexia, normal procalcitonin, negative blood cultures, absence of a focus on CT and the $ScvO_2$ of 35%, which indicates a low-output rather than a distributive state. Pulmonary embolism was excluded by CT pulmonary angiography. Finally, cytokine-mediated cardiotoxicity of the infusion-reaction type typically occurs within minutes to hours of the infusion and is incompatible with a seven-day delay.

The closest previous observation is that of Millward et al., who in 2005 reported cardiogenic shock complicating the first rituximab infusion in a 20-year-old Caucasian woman with refractory TTP [9]. A direct comparison is instructive: Both patients reached a similar nadir of left ventricular function (LVEF 5-10%) and required inotropic support, but the clinical context differed in several respects. In the earlier report, respiratory symptoms began about 6 hours after the infusion, and pulmonary edema, hypoxia, and shock developed within roughly 24 hours, in a patient with active, dialysis-dependent TTP. This timing fits an infusion-related reaction, although the authors did not exclude a contribution from the underlying

microangiopathy, and no coronary evaluation or myocardial tissue was obtained. They proposed acute myocarditis or another immune-mediated mechanism, without confirmation. Her ventricular function normalized within about one week. In contrast, our patient was in clinical remission with no hemolysis or thrombocytopenia, had already tolerated a full four-infusion cycle in 2024, and developed shock seven days after the second infusion of a second cycle, together with rash, arthromyalgia and complement consumption. Normal coronary angiography excluded an ischemic cause, and recovery was slower and incomplete (LVEF 45% at 3 weeks). Taken together, these differences suggest that the two cases may represent distinct phenotypes of rituximab-associated cardiac dysfunction: an early, infusion-related reaction occurring on first exposure during active disease, and a delayed, hypersensitivity-type reaction after re-exposure during remission, possibly immune-complex mediated.

Improvement after drug withdrawal is supportive but does not by itself establish causality: the patient simultaneously received substantial hemodynamic support and corticosteroids, and spontaneous recovery is the rule in several acute cardiomyopathies. No rechallenge was performed, rituximab having been permanently discontinued. To structure the assessment, we applied the Naranjo adverse drug reaction probability scale [24] (Table *3*), which yielded a score in the "probable" range (5-8). The pre-existing LBBB deserves mention as a potential marker of underlying conduction-system or structural disease that a normal baseline LVEF does not exclude; it may have lowered the threshold for decompensation but does not account for an acute fall in LVEF to 5-10% with subsequent recovery.

Naranjo item	Answer	Score
1. Previous conclusive reports on this reaction?	Yes (isolated reports of cardiogenic shock / non-ischemic cardiomyopathy after rituximab)	+1
2. Did the event appear after the suspected drug was administered?	Yes	+2
3. Did the reaction improve when the drug was discontinued or an antagonist given?	Yes (with concomitant corticosteroids and supportive care)	+1
4. Did the reaction reappear when the drug was re-administered?	Not done (rechallenge contraindicated)	0
5. Are there alternative causes that could on their own have caused the reaction?	No (systematic exclusion, Table 3)	+2
6. Did the reaction reappear when a placebo was given?	Not done	0
7. Was the drug detected in blood at toxic concentrations?	Not done	0
8. Was the reaction more severe with increased dose / less severe with decreased dose?	Not assessable	0
9. Did the patient have a similar reaction to the same or similar drug in a previous exposure?	No (first cycle well tolerated)	0
10. Was the adverse event confirmed by objective evidence?	Yes (echocardiography, hemodynamic data, complement consumption)	+1
Total	Probable (5-8)	7

TABLE 3: Naranjo adverse drug reaction probability scale applied to the present case.

Reference: [24]

Several limitations should be acknowledged when interpreting our findings:

First, ADAMTS13 activity was not measured at admission, and a peripheral smear for schistocytes was not performed, so a concomitant microangiopathic relapse could not be formally excluded on specific biological grounds; the absence of thrombocytopenia, anemia, elevated LDH, or reduced haptoglobin nevertheless makes this hypothesis very unlikely.

Second, anti-rituximab antibodies, which would have directly supported a type III hypersensitivity mechanism, were not measured, and CH50 was not obtained. Fever, part of the classical triad, was absent. The diagnosis of serum sickness is therefore clinical and probable, and we use the term "serum sickness-like reaction."

Third, anti-double-stranded DNA antibodies were not measured, so a lupus contribution to the observed hypocomplementemia cannot be formally excluded, although the clinical picture argued against a flare.

Fourth, the concomitant introduction of corticosteroids and hemodynamic support limits the interpretation of drug withdrawal alone in the observed recovery, and no rechallenge was performed.

Fifth, CMR was performed five days after symptom onset and under corticosteroids; a negative study at that time does not absolutely exclude a focal or rapidly resolving myocarditis.

Sixth, no endomyocardial biopsy was performed, as it was not indicated in this context; the proposed mechanisms therefore remain hypotheses.

Seventh, follow-up is limited to three weeks. This is a single, retrospective, single-center observation whose conclusions cannot be generalized.

Conclusions

We describe a probable rituximab-associated acute non-ischemic cardiomyopathy with cardiogenic shock, occurring seven days after re-exposure in association with a serum sickness-like reaction, in a patient with iTTP in clinical remission. The case demonstrates a strong temporal association between rituximab, a systemic hypersensitivity reaction, and severe, largely reversible left ventricular dysfunction, but it cannot establish that serum sickness caused the cardiomyopathy, and the mechanism remains hypothetical. Its practical messages are nevertheless clear. In a patient recently treated with rituximab, acute cardiac dysfunction or unexplained shock, even without fever and even with a normal baseline cardiac evaluation, should prompt consideration of a drug-related complication alongside the usual causes, and, in iTTP, TTP-related cardiac injury must be excluded first. Point-of-care echocardiography with measurement of the sub-aortic VTI, combined with $ScvO_2$, rapidly identifies a low-output state and redirects management. Complement testing is simple and inexpensive and provides a useful biological argument for an immune complex-mediated mechanism. Patients should be informed of these rare risks and encouraged to report chest pain, dyspnea, or palpitations promptly. Whether a baseline cardiac evaluation before rituximab is useful in selected patients cannot be determined from a single observation and would require dedicated studies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Simon Kalisz, Dina Farhat, Joe Kadou, Paul Boulos, Raphael Rozenblum

Acquisition, analysis, or interpretation of data: Simon Kalisz, Dina Farhat

Drafting of the manuscript: Simon Kalisz, Dina Farhat

Critical review of the manuscript for important intellectual content: Simon Kalisz, Dina Farhat, Joe Kadou, Paul Boulos, Raphael Rozenblum

Supervision: Simon Kalisz

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Mostkowska A, Rousseau G, Raynal NJ: Repurposing of rituximab biosimilars to treat B cell mediated autoimmune diseases. FASEB J. 2024, 38:e23536. 10.1096/fj.202302259RR
2. Rituxan (rituximab) prescribing information. (2021). https://www.gene.com/download/pdf/rituxan_prescribing.pdf.
3. Berghen N, Vulsteke JB, Westhovens R, Lenaerts J, De Langhe E: Rituximab in systemic autoimmune

rheumatic diseases: indications and practical use. Acta Clin Belg. 2019, 74:272-9. 10.1080/17843286.2018.1521904
4. Zheng XL, Al-Housni Z, Cataland SR, et al.: 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2025, 23:3711-32. 10.1016/j.jtha.2025.06.002
5. Paul F, Cartron G: Infusion-related reactions to rituximab: frequency, mechanisms and predictors . Expert Rev Clin Immunol. 2019, 15:383-9. 10.1080/1744666X.2019.1562905
6. Athni TS, Barmettler S: Hypogammaglobulinemia, late-onset neutropenia, and infections following rituximab. Ann Allergy Asthma Immunol. 2023, 130:699-712. 10.1016/j.anai.2023.01.018
7. Karmacharya P, Poudel DR, Pathak R, et al.: Rituximab-induced serum sickness: a systematic review . Semin Arthritis Rheum. 2015, 45:334-40. 10.1016/j.semarthrit.2015.06.014
8. Huang Y, Li W, Wang Y, Liu X, Huang Y: Clinical characteristics, diagnosis, treatment, and prognosis of rituximab-induced serum sickness: a retrospective analysis of 39 reported cases. Front Immunol. 2026, 17:1798283. 10.3389/fimmu.2026.1798283
9. Millward PM, Bandarenko N, Chang PP, Stagg KF, Afenyi-Annan A, Hay SN, Brecher ME: Cardiogenic shock complicates successful treatment of refractory thrombotic thrombocytopenia purpura with rituximab. Transfusion. 2005, 45:1481-6. 10.1111/j.1537-2995.2005.00560.x
10. Thomas A, Delgado D, Gomez M: A rare case of rituximab-induced cardiogenic shock . Chest. 2023, 164:2200-1. 10.1016/j.chest.2023.07.1490
11. Calderón H P, Rojas E C, Apt B W, Castillo O D: Cutaneous myiasis due to Cochliomyia hominivorax associated with seborrheic dermatitis [Article in Spanish]. Rev Med Chil. 2017, 145:250-4. 10.4067/S0034-98872017000200013
12. Baran DA, Grines CL, Bailey S, et al.: SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv. 2019, 94:29-37. 10.1002/ccd.28329
13. Ferreira VM, Schulz-Menger J, Holmvang G, et al.: Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018, 72:3158-76. 10.1016/j.jacc.2018.09.072
14. Jozwiak M, Lim SY, Si X, Monnet X: Biomarkers in cardiogenic shock: old pals, new friends . Ann Intensive Care. 2024, 14:157. 10.1186/s13613-024-01388-x
15. Pishko AM, Li A, Cuker A: Immune thrombotic thrombocytopenic purpura: a review . JAMA. 2025, 334:517-29. 10.1001/jama.2025.3807
16. Papakonstantinou A, Kalmoukos P, Mpalaska A, Koravou EE, Gavriilaki E: ADAMTS13 in the new era of TTP. Int J Mol Sci. 2024, 25: 10.3390/ijms25158137
17. Halkidis K, Zheng XL: ADAMTS13 conformations and mechanism of inhibition in immune thrombotic thrombocytopenic purpura. J Thromb Haemost. 2022, 20:2197-203. 10.1111/jth.15822
18. Fujimura Y: Thrombotic thrombocytopenic purpura . Rinsho Ketsueki. 2012, 53:185-95. 10.11406/rinketsu.53.185
19. Cheungpasitporn W, Kopecky SL, Specks U, Bharucha K, Fervenza FC: Non-ischemic cardiomyopathy after rituximab treatment for membranous nephropathy. J Renal Inj Prev. 2017, 6:18-25. 10.15171/jrip.2017.04
20. Virk J, Notman D, Thohan V: Non-ischemic cardiomyopathy after rituximab treatment for mucous membrane pemphigoid: a case report. Explor Cardiol. 2025, 3:101266. 10.37349/ec.2025.101266
21. Ng KH, Dearden C, Gruber P: Rituximab-induced Takotsubo syndrome: more cardiotoxic than it appears? . BMJ Case Rep. 2015, 2015:10.1136/bcr-2014-208203
22. Patil VB, Lunge SB, Doshi BR: Cardiac side effect of rituximab . Indian J Drugs Dermatol. 2020, 6:49-52. 10.4103/ijdd.ijdd_64_19
23. Ndukwu PO, Patlolla N, Narayanan N, Isar MM: Rituximab-induced acute coronary syndrome. Cureus. 2025, 17:e94202. 10.7759/cureus.94202
24. Naranjo CA, Busto U, Sellers EM, et al.: A method for estimating the probability of adverse drug reactions . Clin Pharmacol Ther. 1981, 30:239-45. 10.1038/clpt.1981.154