EJCRIM
European Journal of Case Reports in Internal Medicine

TRIPLE-POSITIVE ANTIPHOSPHOLIPID SYNDROME WITH SPLENIC INFARCTION TRIGGERED BY TOCILIZUMAB WITHDRAWAL IN A HIGH-TITER ACPA-POSITIVE RHEUMATOID ARTHRITIS PATIENT: AN UNMASKING STORM OF POLYAUTOIMMUNITY

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Received: 07/06/2026
Accepted: 17/07/2026
Published: 21/10/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for the anonymous publication of his medical history and clinical documentation.
Declaration of generative AI and AI-assisted technologies in the manuscript preparation process: Notebook LM was used to generate Figure 2. The corresponding author reviewed and verified the AI-assisted output for accuracy and took full responsibility for it.
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How to cite this article: Coviello FE, Rotondo C, D'Onofrio F, Barile R, Cantatore FP, Corrado A. Triple-positive antiphospholipid syndrome with splenic infarction triggered by tocilizumab withdrawal in a high-titer ACPA-positive rheumatoid arthritis patient: an unmasking storm of polyautoimmunity. EJCRIM 2026;13:doi:10.12890/2026_007169

ABSTRACT

Introduction: We describe the occurrence of an uncommon thrombotic event, namely splenic infarction, as the onset of antiphospholipid syndrome (APS) after temporary suspension of anti-IL-6 treatment in a patient with rheumatoid arthritis (RA).

Case description: A 53-year-old patient with anti-citrullinated protein antibody (ACPA) and rheumatoid factor-positive RA, previously showing transient positivity for immunoglobulin (Ig)G anticardiolipin antibodies and lupus anticoagulant (LAC), refractory to multiple biological disease-modifying anti-rheumatic drugs (DMARDs), anti-tumour necrosis factor (TNF)-α agents, and rituximab, had been treated with tocilizumab since 2013 with good clinical response. After temporary suspension of tocilizumab for minor orthopaedic surgery complicated by skin abscess, he developed acute abdominal pain and computed tomography evidence of splenic infarction. Laboratory evaluation revealed elevated inflammatory markers and triple positivity for LAC, aCL IgG, and aB2GPI IgG, leading to the diagnosis of APS. Treatment with warfarin, methotrexate, and baricitinib resulted in stable disease control without recurrent thrombotic events.

Conclusion: Clinical stability in RA is a delicate balance between control of inflammation and avoidance of medication toxicity, especially in patients with high thrombotic risk and previous antiphospholipid positivity. Temporary withdrawal of biologic therapy may induce immunological rebound and thrombotic complications. This case highlights the importance of thrombotic risk stratification and multidisciplinary management when biologic therapies are suspended.

KEYWORDS

Rheumatoid arthritis, splenic infarction, antiphospholipid syndrome, tocilizumab, anti-TNF, pathogenesis

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Tocilizumab may act as a suppressor of autoreactive B-cell clones producing antiphospholipid antibodies.
- A high anti-citrullinated protein antibody (ACPA) titer may be associated with an increased risk of developing autoantibody storm with possible prothrombotic complications in rheumatoid arthritis, such as antiphospholipid syndrome.
- In case of surgical interventions in patients with rheumatoid arthritis treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) it is important to evaluate the stratification of thrombotic risk with multidisciplinary discussion before suspending therapy.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thromboembolic events associated with antiphospholipid antibodies. The 2023 American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) classification criteria emphasize the integration of autoimmune serology and clinical manifestations, requiring at least one laboratory and one clinical criterion for diagnosis[1]. APS may occur as a primary disorder or secondary to autoimmune diseases such as rheumatoid arthritis (RA), where prevalence ranges from 5% to 75%[2]. Previous reports described APS onset after anti-tumour necrosis factor (TNF)-α therapy, suggesting that biologic agents may promote autoantibody formation or thrombosis in predisposed patients[3]. Arterial thrombosis is one of the main manifestations of APS and often involves unusual anatomical locations. Hepatic thrombosis is the most common gastrointestinal macrovascular involvement and splenic infarction is rare; therefore, it may represent the first clinical sign of APS[4]. We report a case of APS presenting as splenic infarction after temporary suspension of tocilizumab in a multifailure RA patient previously exposed to anti-TNF-α agents and rituximab.

CASE DESCRIPTION

A 53-year-old man with type II diabetes mellitus was diagnosed with RA in 2003, which began with polyarthritis involving wrists, elbows, ankles, and small hand joints, associated with rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) positivity. Initial therapy with methotrexate at 15 mg/week, due to scarce

	Infliximab			Tocilizumab			Tocilizumab discontinuation	Normal value
	27/05/08	17/12/09	16/03/11	01/10/13	26/11/14	12/10/16	04/09/18	-
DAS28-ERS	5.2	2.3	3.2	2.4	2	2.45	4.03	-
ERS (mm/h)	30	20	9	9	3	2	65	<20
CRP (mg/dl)	1.53	2.2	6	2.28	1.16	2.6	16.9	<0.5
aCL IgM (U/ml)	-	-	-	1.1	-	-	5	<40
aCL IgG (U/ml)	-	-	-	27.3	-	-	121.2	<40
aβ2GPI IgM (U/ml)	-	-	-	0.1	-	-	5	<7
aβ2GPI IgG (U/ml)	-	-	-	5.5	-	-	81.8	<7
LAC	-	-	-	1.92	-	-	+++	<1.3
ACPA (U/ml)	-	-	-	-	-	-	1000	<20
RF (UI/ml)	93	-	-	-	-	-	87	<14

Table 1. *Variation of parameters between the three phases of the clinical history of the patient.*
Abbreviations: DAS28-ERS, disease activity score in 28 joints using erythrocyte sedimentation rate; ERS, erythrocyte sedimentation rate; CRP, C-reactive protein; aCL IgM, anticardiolipin immunoglobulin M antibodies; aCL IgG, anticardiolipin immunoglobulin G antibodies; aβ2GPI IgM, anti-beta-2 glycoprotein I immunoglobulin M antibodies; aβ2GPI IgG, anti-beta-2 glycoprotein I immunoglobulin G antibodies; LAC, lupus anticoagulant; ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.

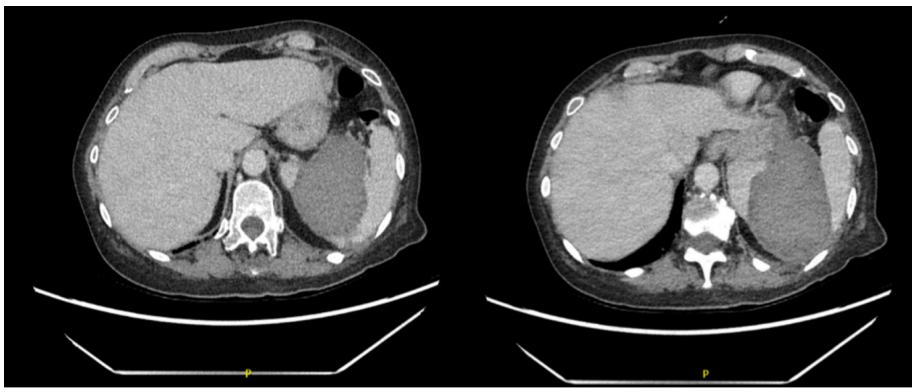


Figure 1. Abdominal contrast-enhanced computed tomography scan: left panel and right panel show hypodense areas coming from the hilar region of the spleen in subsequent slices of portal venous phase imaging.



Figure 2. Longitudinal clinical progression and biomarkers trend.
Abbreviations: DAS28-VES, Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate; ERS: erythrocyte sedimentation rate; CRP, C-reactive protein; aCL IgG, anticardiolipin immunoglobulin G antibodies; LAC, lupus anticoagulant; ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.

benefit, was combined with infliximab in 2006 and then, in 2011, with rituximab, due to RA disease flare, and discontinued after 2 years due to poor response. In 2013 laboratory tests showed weak positivity for lupus anticoagulant (LAC) and immunoglobulin (Ig)G anticardiolipin antibodies (aCL IgG), while subsequent controls were negative. From January 2013 the patient received tocilizumab 8 mg/kg monthly combined with methotrexate, with good clinical response. Tocilizumab was interrupted from March to June 2018 for minor orthopaedic procedures, including surgical treatment of tenosynovitis and elbow bursectomy complicated by skin abscess. During this period, the patient continued only methotrexate therapy. In August 2018, he developed sudden right hypochondrial pain. Abdominal computed tomography (CT) scan demonstrated a hypodense splenic lesion compatible with splenic infarction *(Fig. 1)*. Laboratory findings showed D-dimer 2264 ng/ml (<500), fibrinogen 612 mg/dl (>400), and C-reactive protein (CRP) 16.9 mg/dl (<0.2), supporting an ischemic process. Rheumatologic evaluation demonstrated triple positivity for APS laboratory criteria (LAC, aCL IgG, anti-beta-2glycoproteinI (aB2GPI) IgG) associated with the arterial thrombotic event, leading to APS diagnosis. At hospitalization, disease activity score (DAS28) was 4.03; RF and ACPA were markedly elevated, antinuclear antibodies (ANA) showed a low-titer granular pattern, while platelet count and complement fractions were normal *(Table 1)*. The patient was discharged on methotrexate, baricitinib 4 mg/day, and warfarin with an international normalized ratio target range of 2.5–3.5. Steroid therapy was gradually tapered and discontinued in 2020. During follow-up, no recurrent thrombotic events occurred while anticoagulation was maintained *(Fig. 2)*.

DISCUSSION

APS accounts for approximately 5.6% of splenic infarction cases[5], and its coexistence with RA is plausible[2]. However, splenic infarction as the first clinical manifestation of APS during immunosuppressive treatment remains uncommon. This case highlights important aspects of RA management, including molecular immunology, pharmacologic modulation of autoimmunity, and thrombotic risk assessment. Tocilizumab may have acted as a suppressor of autoreactive B-cell clones producing antiphospholipid antibodies (aPLs). Its discontinuation induced a marked serological rebound, progressing from isolated transient positivity to persistent triple positivity, suggesting a central role of interleukin (IL)-6 in controlling

pathogenic autoantibody production. High ACPA titers may also have contributed to the prothrombotic state. ACPAs are associated with severe RA, extra-articular manifestations, and accelerated atherosclerosis[6]. Recent evidence indicates that ACPAs activate macrophages and neutrophils through neutrophil extracellular trap formation, promoting endothelial dysfunction and thrombosis[7]. In this setting, ACPAs may have provided a pro-inflammatory scaffold favouring antiphospholipid-mediated thrombosis and splenic infarction[8]. The clinical course supports the "Two-Hit" hypothesis of APS. The first hit consisted of biologic withdrawal, leading to increased CRP and fibrinogen and creating a hyper-reactive vascular environment. The second hit was represented by surgical stress and bacterial superinfection, which probably triggered massive aPL production and thrombosis[9]. The absence of hypocomplementemia and thrombocytopenia excluded rheumatoid vasculitis or catastrophic APS, supporting a primary arterial thrombotic event. This case suggests that even isolated previous aPL positivity should not be underestimated in RA patients with high ACPA titers before biologic discontinuation. Suspension of tocilizumab for more than 3 months likely resulted in complete IL-6 inhibition washout[10]. These findings raise questions regarding the necessity of prolonged biologic withdrawal before minor surgery and emphasize the importance of thrombotic risk profiling in patients with previous aPL positivity. Monitoring inflammatory markers such as CRP and erythrocyte sedimentation rate during biologic suspension and minimizing withdrawal time, also through multidisciplinary consultation, may help reduce thrombotic complications. Finally, despite the patient's "B-cell oriented" immunologic profile and the previous limited efficacy of rituximab, baricitinib was introduced after anticoagulation because of patient preference for oral therapy. No recurrent thrombosis occurred, suggesting that Janus kinase inhibitors may be a safe therapeutic option in selected patients when associated with adequate anticoagulation and careful monitoring.

REFERENCES

1. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol. 2023;75(10):1687-1702. doi: 10.1002/art.42624.
2. Grygiel-Górniak B, Mazurkiewicz Ł. Positive antiphospholipid antibodies: observation or treatment? J Thromb Thrombolysis. 2023;56(2):301-314. doi: 10.1007/s11239-023-02834-6.
3. Vaz JL, Fernandes V, Nogueira F, Arnóbio A, Levy RA. Infliximab-induced autoantibodies: a multicenter study. Clin Rheumatol. 2016;35(2):325-32. doi: 10.1007/s10067-015-3140-6.
4. Hadfield MJ, Thumar JR. Antiphospholipid Syndrome Presenting With Splenic Infarct. J Clin Rheumatol. 2021;27(1):e19. doi: 10.1097/RHU.0000000000001207.
5. Wand O, Tayer-Shifman OE, Khoury S, Hershko AY. A practical approach to infarction of the spleen as a rare manifestation of multiple common diseases. Ann Med. 2018;50(6):494-500. doi: 10.1080/07853890.2018.1492148.
6. Jeleniewicz R, Majdan M, Targońska-Stępniak B, Dryglewska M. Prevalence of antiphospholipid antibodies in rheumatoid arthritis patients and relationship with disease activity. Pol Arch Med Wewn. 2012;122(10):480-6. doi: 10.20452/pamw.1415.
7. Wu S, Peng W, Liang X, Wang W. Anti-citrullinated protein antibodies are associated with neutrophil extracellular trap formation in rheumatoid arthritis. J Clin Lab Anal. 2021;35(3):e23662. doi: 10.1002/jcla.23662.
8. Duarte JH. Connective tissue diseases: Neutrophil extracellular traps--a mechanism of thrombosis in patients with antiphospholipid syndrome? Nat Rev Rheumatol. 2015;11(8):444. doi: 10.1038/nrrheum.2015.96.
9. Amital H, Govoni M, Maya R, Meroni PL, Ori B, Shoenfeld Y, et al. Role of infectious agents in systemic rheumatic diseases. Clin Exp Rheumatol. 2008;26(1 Suppl 48):S27-32.
10. Mancuso F, Angelini J, Zabotti A, Russiani F, Baraldo M, Quartuccio L, et al. Perioperative Management of Biologic and Targeted Synthetic DMARDs in Orthopedic Surgery: Balancing Infection Risk and Disease Control. Microorganisms. 2026;14(2):398. doi: 10.3390/microorganisms14020398.