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GOLIMUMAB-ASSOCIATED MYOCARDITIS WITH PROGRESSIVE EOSINOPHILIA AFTER ROUTE SWITCH IN RHEUMATOID ARTHRITIS

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ABSTRACT

Introduction: Tumour necrosis factor-alpha (TNF-α) inhibitors are cornerstone therapies in rheumatoid arthritis (RA) and generally reduce cardiovascular events. Drug-induced myocarditis associated with TNF-α inhibitors is not well-established in pharmacovigilance databases.

Case description: A 51-year-old male with seropositive RA receiving intravenous golimumab presented with acute chest pain, dyspnoea, and left arm numbness without viral prodrome. He had been switched from subcutaneous to intravenous golimumab 6 months prior, producing a 14-fold increase in peak serum concentration. High-sensitivity troponin I peaked at 32,419 ng/l with mildly reduced left ventricular ejection fraction (45–49%) and global hypokinesis. Coronary angiography revealed non-obstructive arteries. Comprehensive viral serology was negative for acute infection. Inflammatory markers were normal. Progressive eosinophilia developed during hospitalization (0.12 → 0.54 $\times 10^3$/µl). Cardiac magnetic resonance imaging was unavailable at our institution. Despite not initiating prescribed sacubitril/valsartan (continuing only metoprolol), repeat echocardiography at 4 weeks demonstrated complete normalization of left ventricular function; coinciding with near-complete drug elimination. Golimumab was permanently discontinued.

Conclusion: This case meets criteria for clinically suspected myocarditis per the 2024 American College of Cardiology Expert Consensus Decision Pathway. The absence of viral prodrome, negative viral serology, progressive eosinophilia, normal inflammatory markers, and complete functional recovery paralleling drug elimination support drug-induced hypersensitivity myocarditis. Causality assessment yields "probable" by both the World Health Organization - Uppsala Monitoring Centre system and the Naranjo algorithm (score 6 to 8). This case contributes to the limited literature on TNF-α inhibitor cardiotoxicity and emphasizes the need for continued pharmacovigilance.

KEYWORDS

Golimumab, myocarditis, rheumatoid arthritis, TNF-α inhibitors, eosinophilic myocarditis

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LEARNING POINTS

- Tumour necrosis factor-alpha inhibitor–associated myocarditis is exceptionally rare; clinicians should consider this diagnosis in patients presenting with acute troponinemia and non-obstructive coronary arteries while receiving biologic therapy.
- Switching from subcutaneous to intravenous golimumab produces an approximately 14-fold increase in peak serum concentration (C_{max} 44.4 vs. 3.2 μg/ml), which may theoretically contribute to immune sensitization and delayed hypersensitivity myocarditis.
- Progressive peripheral eosinophilia in the setting of acute myocardial injury without viral prodrome should raise suspicion for drug-induced hypersensitivity myocarditis, even when the offending agent was administered weeks prior.

INTRODUCTION

Rheumatoid arthritis (RA) confers a 1.5- to 2-fold increased cardiovascular risk compared with the general population. Tumour necrosis factor-alpha (TNF-α) inhibitors generally reduce major adverse cardiovascular events (RR 0.60, 95% CI 0.40–0.89); however, rare paradoxical immune-mediated cardiotoxic effects have been documented[1]. A systematic analysis of the World Health Organization (WHO) pharmacovigilance database identified 62 drugs associated with myocarditis, but TNF-α inhibitors were not among them[2]. Similarly, neither the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database nor a recent global analysis of the top 10 drugs most frequently associated with myocarditis identified TNF-α inhibitors[3].

We report clinically suspected myocarditis temporally associated with intravenous golimumab in a patient with seropositive RA, notable for a recent subcutaneous-to-intravenous route switch producing a 14-fold increase in peak drug exposure, progressive eosinophilia, and complete functional recovery paralleling drug elimination.

CASE DESCRIPTION

A 51-year-old male with seropositive RA (anti- cyclic citrullinated peptide, CCP, 82 units), hypertension, and obesity (body mass index 38.4 kg/m^2) presented with sudden-onset severe substernal chest tightness (8/10) radiating to the left arm, with dyspnoea and numbness after swimming. He denied fever, prodromal illness, or recent infection.

He had been switched from subcutaneous golimumab (Simponi) 50 mg monthly to intravenous golimumab (Simponi Aria) 2 mg/kg every 8 weeks approximately 6 months prior due to insurance reasons, receiving approximately 4 infusions. The last infusion was 4 weeks before presentation. Intravenous golimumab achieves a maximum serum concentration (C_{max}) of 44.4 ± 11.3 μg/ml; approximately 14-fold higher than subcutaneous (C_{max} 3.2 ± 1.4 μg/ml)[4]. Given a terminal half-life of ~14 days, approximately 25% of peak concentration remained at presentation. Concomitant medications included methotrexate 15 mg weekly (stable long-term), amlodipine, valsartan, and escitalopram 5 mg. RA was in clinical remission (C-reactive protein 5 mg/l, erythrocyte sedimentation rate 2 mm/hr).

On examination, he was hemodynamically stable and afebrile. Electrocardiogram showed sinus bradycardia without ST changes *(Fig. 1)*. Serial high-sensitivity troponin I: 30 → 32,419 → 11,326 → 7,866 ng/l (reference < 54). creatine kinase 428 U/l; creatine kinase-myocardial band 44.8 ng/ml. B-type natriuretic peptide was normal. Antinuclear antibody was negative. Absolute eosinophil count rose progressively: 0.12 → 0.27 → 0.45 → 0.54 ×10^3/μl (4.5-fold increase) *(Table 1)*.

Comprehensive viral serology was negative for acute infection: parvovirus B19 IgM negative (IgG positive); Epstein-Barr virus viral capsid antigen (VCA) IgM negative, VCA IgG positive, Epstein-Barr nuclear antigen (EBNA) IgG negative (reference ≥22 U/ml); consistent with past infection with absent EBNA seroconversion, a variant in 5–10% of previously infected individuals; cytomegalovirus IgM negative; human herpesvirus-6 IgM negative (IgG positive); enterovirus ribonucleic acid polymerase chain reaction (PCR) negative; severe acute respiratory syndrome coronavirus 2) antigen negative *(Table 1)*.

Echocardiography showed left ventricular ejection fraction (LVEF) 45–49% with global hypokinesis, no regional wall motion abnormalities *(Fig. 2)*. Coronary angiography: non-obstructive arteries *(Fig. 3)*. Computed tomography pulmonary angiography: no embolism. Cardiac magnetic resonance imaging (MRI) was unavailable at our institution.

Chest pain resolved within 24 hours with supportive care. Golimumab was permanently discontinued. The patient was

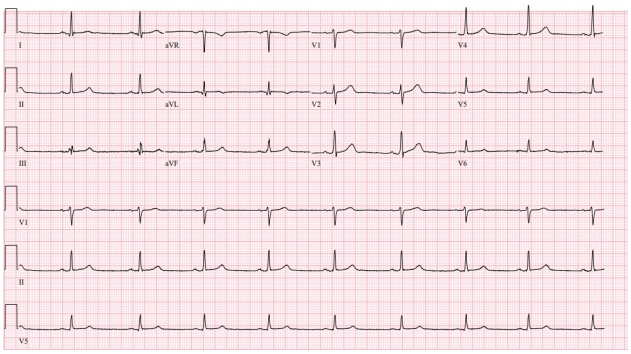


Figure 1. *Electrocardiogram at presentation showing sinus bradycardia without ST-segment changes or ischemic findings.*

discharged on day 3 on metoprolol and sacubitril/valsartan. At 4-week follow-up, despite not initiating sacubitril/valsartan, repeat echocardiography demonstrated complete normalization of LVEF, coinciding with near-complete golimumab elimination (~8 weeks post-last infusion, ~6% residual C_{max}). A patient timeline is presented in *Table 1*.

DISCUSSION

This case meets criteria for clinically suspected myocarditis per the 2024 ACC Expert Consensus Decision Pathway, based on compatible symptoms, elevated biomarkers, and new LV dysfunction without an alternative diagnosis[5]. It also meets Brighton Collaboration Level 2 (probable) criteria, based on compatible symptoms with at least one abnormal diagnostic test (elevated cardiac biomarkers and abnormal echocardiography) in the absence of an alternative diagnosis.

Systematic exclusion of alternative diagnoses strengthens the case. Viral myocarditis was excluded by absent prodromal symptoms, negative IgM serology for all cardiotropic viruses, and negative enterovirus PCR. Myocardial infarction with non-obstructive coronary arteries is excluded when myocarditis is identified as the

Timepoint	Event	Key data
Month −6	Switch from SC golimumab (Simponi 50 mg monthly) to IV golimumab (Simponi Aria 2 mg/kg q8 weeks) for insurance reasons	C_{max} increase: 3.2 → 44.4 µg/ml (~14-fold)
Months −6 to 0	~4 IV golimumab infusions administered.	RA in clinical remission (CRP 5 mg/l, ESR 2 mm/hr)
Week −4	Last IV golimumab infusion (2 mg/kg)	Estimated C_{max} 44.4 ± 11.3 µg/ml
Day 0	Symptom onset: acute substernal chest pain (8/10), dyspnoea, left arm numbness after swimming; ED presentation	Initial hs-TnI 30 ng/l (ref <54); ECG: sinus bradycardia, no ST changes; BP 180/95, HR 55, afebrile
Day 0 + 8 hours	Peak troponin, echocardiography performed	hs-TnI 32,419 ng/l; LVEF 45–49%, global hypokinesis; BNP 15 pg/ml (normal); AEC 0.12 ×10³/µl
Day 1	Coronary angiography, chest pain resolved	Non-obstructive coronary arteries; hs-TnI 11,326 ng/l (declining); AEC 0.27 ×10³/µl
Day 2	Continued clinical improvement; viral serology results	All viral IgM negative (Parvo B19, EBV, CMV, HHV-6); enterovirus PCR negative; SARS-CoV-2 negative; AEC 0.45 ×10³/µl
Day 3 (Discharge)	Discharge; golimumab permanently discontinued	hs-TnI 7,866 ng/l; AEC 0.54 ×10³/µl (4.5-fold rise); discharged on metoprolol + sacubitril/valsartan
Week +4 (8 weeks post-last infusion)	Cardiology follow-up; repeat echocardiography	Complete normalization of LVEF; resolution of global hypokinesis; patient had not initiated sacubitril/valsartan (on metoprolol only); estimated residual golimumab ~6% of C_{max} (~2.7 µg/ml)

Table 1. Patient timeline: clinical course from SC-to-IV golimumab switch through follow-up.

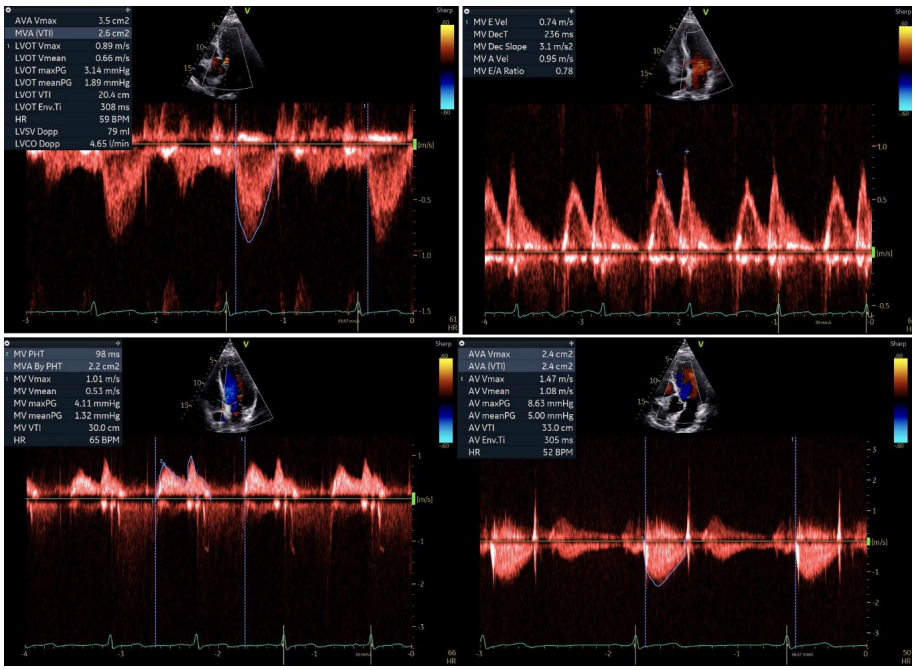


Figure 2. Transthoracic echocardiography demonstrating mildly reduced left ventricular ejection fraction (45–49%) with global hypokinesis.

Q#	Question	Answer	Score	Rationale
1	Are there previous conclusive reports on this reaction?	Yes (debatable)	+1 or 0	Rare pharmacovigilance signals for TNF-α inhibitors and myocarditis exist in WHO VigiBase and FAERS databases, though TNF-α inhibitors are not among the top drug classes
2	Did the adverse event appear after the suspected drug was administered?	Yes	+2	Myocarditis occurred 4 weeks after the last IV golimumab infusion, during active drug exposure (~25% Cmax remaining given t½ ~14 days)
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1	Complete normalization of LVEF at 4 weeks post-presentation, coinciding with near-complete drug elimination (~6% residual Cmax at ~8 weeks post-last infusion)
4	Did the adverse reaction reappear when the drug was readministered?	Do not know	0	Rechallenge is contraindicated and was not performed
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	No	+2	Systematic exclusion performed: negative viral serology/PCR, no viral prodrome, non-obstructive coronaries, no regional wall motion abnormalities (excludes Takotsubo), normal CRP/ESR (excludes active RA myocarditis), negative ANA
6	Did the reaction reappear when a placebo was given?	Do not know	0	Not applicable to this clinical setting
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	Do not know	0	No established toxic concentration threshold exists for golimumab-induced myocarditis; serum drug levels were not measured
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Yes (debatable)	+1 or 0	The SC → IV route switch constituted a de facto dose escalation with a 14-fold increase in Cmax (44.4 vs. 3.2 µg/ml); no cardiac events occurred during prior SC therapy at lower peak exposure
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0	No prior cardiac events on SC golimumab or any other TNF-α inhibitor
10	Was the adverse event confirmed by any objective evidence?	Yes	+1	Confirmed by hs-troponin I (peak 32,419 ng/l), echocardiography (LVEF 45–49%, global hypokinesis), and coronary angiography (non-obstructive arteries)
	TOTAL SCORE		**8 or 6**	**Interpretation: probable (score 5–8)**

Table 2. *Naranjo adverse drug reaction probability scale: itemized scoring for golimumab-associated myocarditis.*

Scoring interpretation: ≤0 = doubtful; 1–4 = possible; 5–8 = probable; ≥9 = definite.

Abbreviations: C_{max}, maximum serum concentration; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FAERS, FDA Adverse Event Reporting System; hs-troponin I, high-sensitivity troponin I; IV, intravenous; LVEF, left ventricular ejection fraction; RA, rheumatoid arthritis; SC, subcutaneous; t½, terminal half-life; WHO, World Health Organization.

underlying cause. Takotsubo syndrome requires regional wall motion abnormalities (typically apical ballooning), not the global hypokinesis observed here. RA-associated myocarditis is unlikely given completely normal inflammatory markers in quiescent disease.

Several features support drug-induced hypersensitivity myocarditis. The progressive 4.5-fold rise in eosinophils is characteristic of drug hypersensitivity; a 2026 multicentre registry of 156 biopsy-proven eosinophilic myocarditis cases reported peripheral eosinophilia in only 57.4% (median 630/µl), with hypersensitivity forms accounting for 14.1%[6]. The 14-fold C_{max} increase from route switch could theoretically have contributed to cumulative immune sensitization[4]. Although the 4-week latency exceeds the median time-to-onset of 15 days (IQR 10–23) for drug-induced myocarditis,[2] significant drug levels (~25% C_{max}) remained at symptom onset[2]. Complete LVEF normalization paralleled drug elimination despite incomplete heart failure therapy, consistent with a self-limited drug-mediated process.

Regarding causality, the WHO - Uppsala Monitoring Centre system classifies this as "probable/likely" based on temporal relationship, exclusion of alternatives, and positive dechallenge. The Naranjo algorithm yields a score of 6 to 8 (probable) *(Table 2)*[7]. Question 1 was scored "yes" (+1) because rare pharmacovigilance signals for TNF-α inhibitors and myocarditis exist in WHO and FAERS databases[2,3]. Question 8 was scored "yes" (+1) because the subcutaneous-to-intravenous route switch produced a 14-fold C_{max} increase, constituting a de facto dose escalation[4]. Both systems concordantly classify this case as "probable".

Concomitant methotrexate (stable long-term, continued without recurrence; negative dechallenge) and escitalopram (not identified among drugs associated with

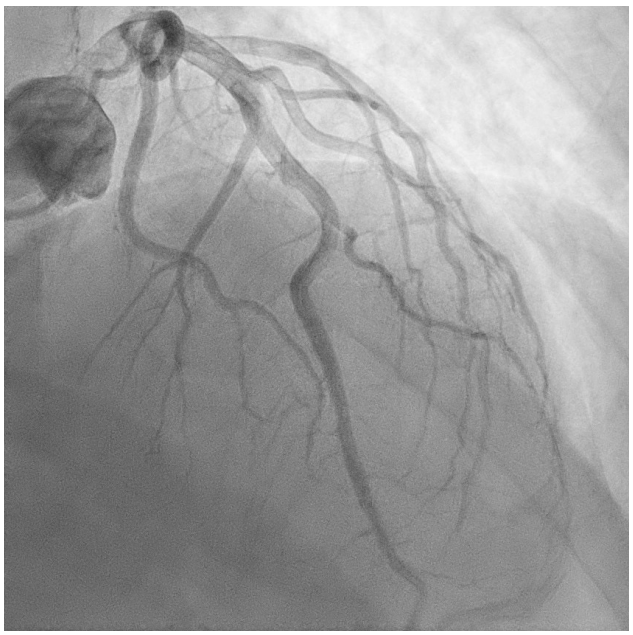


Figure 3. Coronary angiography demonstrates non-obstructive coronary arteries.

myocarditis in pharmacovigilance analyses, continued without recurrence) are unlikely causative agents[1,3].

It is important to note that anti-TNF agents like infliximab have been used to treat certain types of myocarditis. They have been used as a third-line treatment for refractory sarcoidosis and as an option for myocarditis caused by immune checkpoint inhibitors. However, recent guidelines have moved away from using infliximab for immune checkpoint inhibitor (ICI)-myocarditis. The 2025 ACC Concise Clinical Guidance suggests avoiding infliximab because it may worsen heart failure[8]. The 2026 International Cardio-Oncology Society Position Statement also notes that infliximab is linked to higher rates of cardiovascular death[9]. This apparent paradox, that a TNF-α inhibitor could both treat and cause myocarditis, is explained by fundamentally different immunopathological mechanisms. In cardiac sarcoidosis and ICI-myocarditis, TNF-α is a key mediator of the pathological granulomatous or T-cell–mediated inflammatory response, and its inhibition targets the disease mechanism directly. In contrast, the myocarditis in our case is attributed to a drug hypersensitivity reaction to golimumab itself, as evidenced by progressive eosinophilia, absence of viral prodrome, and complete resolution paralleling drug elimination. Preclinical data support this complexity: Rolski et al. demonstrated that TNF-α has a dual, context-dependent role in myocarditis; promoting disease initiation through endothelial activation while simultaneously protecting against disease exacerbation through activation-induced cell death of heart-reactive T cells[10]. Therefore, the therapeutic immunosuppressive properties of anti-TNF agents in granulomatous myocarditis do not preclude their capacity to trigger hypersensitivity-mediated myocardial injury through an entirely distinct immunological pathway.

The primary limitation is the absence of cardiac MRI, which was unavailable at our institution. Endomyocardial biopsy was appropriately deferred by guidelines given hemodynamic stability[5]. Additional limitations include inability to rechallenge (contraindicated) and potential false-negative viral testing. Additionally, the FDA label cautions that the safety of switching between golimumab formulations has not been established, underscoring the clinical significance of this case.

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