Title	Macrotroponin as a cause of falsely elevated cardiac troponin in systemic sclerosis
Authors	Tio, Sherdya;Zia, Fatima;Joyce, Caroline Martha;Halsall, David J.;Ryan, John
Publication date	2025-09-17
Original Citation	Tio, S., Zia, F., Joyce, C.M., Halsall, D.J. and Ryan, J. (2025) 'Macrotroponin as a cause of falsely elevated cardiac troponin in systemic sclerosis', BMJ Case Reports, 18(9), e266536 (7pp). https://doi.org/10.1136/bcr-2025-266536
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://casereports.bmj.com/content/18/9/e266536 - 10.1136/bcr-2025-266536
Rights	© 2025, BMJ Publishing Group Ltd. This article has been accepted for publication in BMJ Case Reports 2025, following peer review, and the Version of Record can be accessed online at: https://doi.org/10.1136/bcr-2025-266536. Reuse of this manuscript version (excluding any databases, tables, diagrams, photographs and other images or illustrative material included where a another copyright owner is identified) is permitted strictly pursuant to the terms of the Creative Commons Attribution-Non Commercial 4.0 International (CC-BY-NC 4.0) http://creativecommons.org - ttps://creativecommons.org/licenses/by-nc/4.0/
Download date	2026-08-05 19:54:43
Item downloaded from	https://hdl.handle.net/10468/17890

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

BMJ Case Reports

TITLE OF CASE

Macrotroponin as a cause of falsely elevated Cardiac Troponin in Systemic Sclerosis

SUMMARY

This case report discusses a patient in his late 30s with recent diagnosis of systemic sclerosis (SSc) who presented with persistently elevated cardiac troponin (cTn) levels, raising concerns for cardiac involvement. Despite elevated troponin-I (cTnI) and troponin-T (cTnT), clinical investigations, including echocardiogram and cardiac MRI, were unremarkable. The persistence of elevated troponin without corresponding clinical evidence prompted further investigation, leading to the identification of macrotroponin as the cause. This case emphasizes the importance of recognising macrotroponin as an interferent in patients with unexplained raised troponin levels to avoid unnecessary cardiac interventions.

BACKGROUND

Systemic sclerosis (SSc) is a complex autoimmune disease with multiorgan involvement. The prevalence of cardiac involvement in SSc is high, but often subclinical and diagnosed late, which significantly increases morbidity and mortality in SSc patients(1).

cTn is a biomarker released in response to myocardial injury, irrespective of the underlying cause. There are 2 primary types of cTn differentiated by markers I and T. cTnI is exclusive expressed in cardiac muscle, making it highly specific for detecting cardiac injury. cTnT is predominantly found in the heart but is also present in limited quantity in other muscle tissues. Notably, the cTnT form found in the cardiac muscle has unique structural configuration that further enhance its utility in diagnosing cardiac-specific damage.

The finding of a raised troponin level is concerning, especially in younger patients. However, a persistently raised cardiac troponin in the absence of diagnostic clinical symptoms and signs should raise the suspicion of a false positive result. A false positive result could be generated in the cTn immunoassay by the presence of interfering substances (i.e. heterophilic or human anti-mouse antibodies, or macrotroponin). Macrotroponin is a high molecular weight complex of troponin and immunoglobulin(2), which is not biologically active, but its presence interferes with assays used to measure cTn, typically causing a falsely elevated result. Macrohormone and macroenzyme complexes have been described for a wide range of frequently measured biomarkers including peptide hormones and cardiac biomarkers such as Creatine Kinase (3).

The exact prevalence of macrotroponin interference in immunoassays is unknown. This case raises awareness of the potential presence of macrotroponin as a cause of unexpectedly elevated troponin levels that do not align with the clinical presentation.

CASE PRESENTATION

A man in his 30s was referred to our specialist rheumatology unit following persistently elevated cardiac troponin levels and markedly reduced exercise tolerance. He was recently diagnosed with anti-Scl70 positive diffuse systemic sclerosis, presenting with worsening skin tightness. The diagnosis was based on the 2013 ACR/EULAR Classification criteria (4) with a total score of 15 points. Physical examination revealed sclerodactyly of the fingers, skin tightening extending proximal to bilateral elbow, Raynaud's phenomenon, normal cardiac auscultation with no murmurs or gallop, clear lung fields without crepitations and oxygen saturation of 98% on room air at rest.

Although he did not report typical cardiac symptoms such as chest pain or shortness of breath, his consistently elevated troponin level and decline in exercise ability, raised concerns of potential cardiac involvement, especially given his previously high-performance level of physical fitness as a block layer. His medical history was otherwise unremarkable, aside from being a heavy smoker.

INVESTIGATIONS

On initial presentation, routine biochemistry results revealed persistently elevated cardiac high sensitivity (hs) troponin-I levels, ranging from 500–800 ng/L **(Figure 1)**, 99th percentile cut-off is 19.8 ng/L, and a cardiac hs troponin-T levels of 169 ng/L, 99th percentile cut-off is 14 ng/L. Troponin levels above the 99th percentile cut-off are indicative of myocardial injury. These elevated troponin levels raised concerns about possible myocardial injury, particularly myocarditis, given the patient's systemic sclerosis. His other routine bloods including serum NT-ProBNP and inflammatory markers were normal.

Given the patient's presenting history of decreased exercise tolerance and well-established association between diffuse SSc and significantly increased risk of interstitial lung disease (ILD), comprehensive pulmonary investigations were essential (5). Chest radiography showed no interstitial markings, and high-resolution computed tomography (HRCT) demonstrated no evidence of ILD. Complete pulmonary function tests (PFTs) including diffusing capacity of the lung for carbon monoxide (DLCO), were within normal limits, and right-heart catheterisation excluded pulmonary hypertension. Additional cardiac investigations, including an electrocardiogram (ECG), showed no signs of ischemia or arrhythmia. An echocardiogram and cardiac magnetic resonance imaging (MRI) were performed, both of which demonstrated normal left ventricular function and no evidence of myocarditis, pericarditis, or myocardial fibrosis.

Given the significant discordance between the persistently elevated troponin levels and the lack of clinical findings, an analytical interference was suspected. Biochemical investigations were conducted to explore the presence of macrotroponin. Dilution studies performed on serum samples showed non-linear dilution, raising suspicion of an interferent. Following polyethylene glycol (PEG) precipitation to remove immunoglobulins from the serum, only 10% of the Troponin immunoreactivity remained, supporting the presence of an immunoglobulin based interferent (6). Gel filtration chromatography (GFC) confirmed the presence of approximately 65% high molecular mass troponin immunoreactivity (macrotroponin) **(Figure 2)**.

DIFFERENTIAL DIAGNOSIS

Cardiac involvement is a common complication in SSc, occurring in about 15% of the cases, and usually detected in later stages, resulting in high morbidity and mortality(7). The elevated troponin levels in this case initially raised concerns about potential cardiac injury. Potential causes of cardiac SSc includes both primary causes such as myocarditis, fibrosis vascular abnormalities or inherent cardiomyocyte dysfunction (8), and secondary causes including pulmonary arterial hypertension, interstitial lung disease, or scleroderma renal crisis.

Given the wide range of possibilities, a cardiologist was involved in management of patient's care. Non-invasive investigations including serial echocardiogram and cardiac MRI were reassuringly normal. Despite the elevated cTn levels, the patient exhibited no cardiac symptoms. The discrepancies between laboratory findings and clinical presentation raised the possibility of a non-pathological cause for the troponin elevation, leading us to collaborate with our clinical biochemist to conduct additional testing to determine the cause.

We considered that the elevated troponin could be a false positive result due to analytical interference. Laboratory investigations were performed and supported the presence of an interferent. Dilution studies and PEG precipitation supported the presence of macrotroponin, which was confirmed by GFC. This is a complex of troponin bound to immunoglobulin, which causes artificially high levels of troponin in blood tests but is not indicative of acute myocardial injury (9).

TREATMENT

Once macrotroponin was identified as the cause of the elevated troponin levels, no additional invasive cardiac investigation was deemed necessary. No treatment is required to treat macrotroponin. Patient received standard immunosuppressive therapy according to EULAR recommendations for SSc, comprising of Rituximab and Mycophenolate (10). We noticed a slight decrease in cTnI on 15th July 2023 as demonstrated **(Figure 1)** after patient received immunosuppressant treatment.

OUTCOME AND FOLLOW-UP

The patient remained stable throughout follow-up, without signs of cardiac involvement and stable troponin concentrations No clinical or radiographic evidence of progression was observed over a follow-up period of 12 months. Specifically, there was no worsening of skin fibrosis, cardiac and pulmonary function. There was no emergence of new clinical manifestations indicative of SSc progression.

This case highlights how early identification of macrotroponin can prevent expensive medical investigations and unnecessary treatments thereby reducing the risk of adverse side effects from medications that would not address the underlying issue.

DISCUSSION

Macrotroponin, a high-molecular-weight complex of troponin and immunoglobulin, can interfere with troponin assays, leading to false positives results. This phenomenon complicates clinical decision-making in systemic sclerosis, as elevated troponin typically suggests myocardial injury. Being aware of the existence of macrotroponin is crucial to appropriate clinical management.

The pathogenesis of macrotroponin is not fully understood, but the formation of immunoglobulin-bound troponin complexes has been linked to chronic inflammation and autoimmune diseases like systemic sclerosis(11).The presence of macrotroponin was found to be associated with favourable long-term all cause and cardiovascular mortality outcomes in patients with elevated troponin(12).

Similar published cases have described the detection of macrotroponin in autoimmune diseases, reinforcing the importance of interdisciplinary collaboration between clinicians and laboratory specialists to prevent overtreatment in cases of falsely elevated troponin(13). Whilst GFC is not widely available more accessible methods such as method comparison, dilution, and immunodepletion using PEG or Protein G/A have all been used to successfully expose this type of interference (6, 14).

Analytical interference by macromolecular complexes is not limited cardiac biomarkers. Similar interference phenomena have been extensively documented in immunoassays, most notably prolactin and thyroid stimulating hormone (TSH), where macroprolactin and macro-TSH complexes can lead to persistent false elevations and diagnostic confusion unless specifically investigated (15, 16). Additionally, macroenzymes such as macroamylase and macro-creatine kinase (macro-CK type 1 and 2) are recognised causes of misleading biochemical results, further complicating the interpretation of laboratory assays (17-19). Awareness of these phenomena is essential, underscoring the importance of clinical insight and active collaboration between clinician and laboratory specialists when unexpected findings are encountered.

LEARNING POINTS/TAKE HOME MESSAGES

- The exact prevalence of macrotroponin is still unknown. This case intends to raise awareness of the possibility of macrotroponin interference in unexpected high troponin results.
- Macrotroponin can cause false-positive troponin elevations in systemic sclerosis, which may mimic cardiac injury. Recognising macrotroponin avoids unnecessary investigations and treatments.
- Biochemical investigations, such as dilution studies, immunosubtraction and gel filtration chromatography can be used to confirm the presence of macrotroponin and prevent misdiagnosis. Communicating and collaboration with laboratory experts to initiate further studies in suspected cases is recommended.
- The presence of macrotroponin should always be interpretated in conjunction with clinical presentation and symptoms, emphasizing the importance of clinical judgement. Laboratory tests alone should not drive decision-making, clinical context remains paramount. A multidisciplinary approach is critical in distinguishing true cardiac involvement from potential assay interference.

REFERENCES

1. Jones XM, Bottini N, Boin F, Marbán E. Cardiac involvement in systemic sclerosis: A critical review of knowledge gaps and opportunities. J Scleroderma Relat Disord. 2025:23971983241313096.
2. Remaley AT, Wilding P. Macroenzymes: biochemical characterization, clinical significance, and laboratory detection. Clin Chem. 1989;35(12):2261-70.
3. Dedeene L, Stockman M, Steels S, Vermeersch P, Frans G. Detection of macroenzymes: establishing upper reference limits for eight enzymes after polyethylene glycol precipitation. Biochem Med (Zagreb). 2023;33(1):010705.
4. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-47.
5. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020;8(3):304-20.
6. Lam L, Kyle C. Practical approaches to the detection of macrotroponin. Ann Clin Biochem. 2024;61(2):122-32.
7. Desai CS, Lee DC, Shah SJ. Systemic sclerosis and the heart: current diagnosis and management. Curr Opin Rheumatol. 2011;23(6):545-54.
8. Nadel A, Nadel M, Taborska N, Stępień B, Gajdecki J, Brzezińska O, et al. Heart involvement in patients with systemic sclerosis—what have we learned about it in the last 5 years. Rheumatology International. 2024;44(10):1823-36.
9. Michielsen EC, Bisschops PG, Janssen MJ. False positive troponin result caused by a true macrotroponin. Clin Chem Lab Med. 2011;49(5):923-5.
10. Del Galdo F, Lescoat A, Conaghan PG, Bertoldo E, Čolić J, Santiago T, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Annals of the Rheumatic Diseases. 2024:ard-2024-226430.
11. Salaun E, Drory S, Coté MA, Tremblay V, Bédard E, Steinberg C, et al. Role of Antitroponin Antibodies and Macrotroponin in the Clinical Interpretation of Cardiac Troponin. J Am Heart Assoc. 2024;13(12):e035128.
12. Lam L, Ha L, Gladding P, Tse R, Kyle C. Effect of macrotroponin on the utility of cardiac troponin I as a prognostic biomarker for long term total and cardiovascular disease mortality. Pathology. 2021;53(7):860-6.
13. Nardi-Agmon I, Di Meo A, Lam L, Kyle C, Abdel-Qadir H, Amir E, et al. Circulating Macrotroponin Complexes and Their Impact on Cardiac Troponin Measurements: Potential Implications for Cardio-Oncology. JACC CardioOncol. 2024;6(4):608-11.
14. Desaegher A, Marin V, Beauvieux M-C, Colombiès B, Lauga M, Alloug S, et al.
15. Fahie-Wilson M, Smith TP. Determination of prolactin: the macroprolactin problem. Best Pract Res Clin Endocrinol Metab. 2013;27(5):725-42.
16. Chiardi I, Rotondi M, Cantù M, Keller F, Trimboli P. Macro-TSH: An Uncommon Explanation for Persistent TSH Elevation That Thyroidologists Have to Keep in Mind. J Pers Med. 2023;13(10).
17. Aljuani F, Tournadre A, Cecchetti S, Soubrier M, Dubost JJ. Macro-creatine kinase: a neglected cause of elevated creatine kinase. Internal Medicine Journal. 2015;45(4):457-9.
18. Axinte CI, Alexa T, Cracana I, Alexa ID. Macro-creatine kinase syndrome as an underdiagnosed cause of ck-mb increase in the absence of myocardial infarction: two case reports. Rev Med Chir Soc Med Nat Iasi. 2012;116(4):1033-8.
19. Čásenská J, Franeková J, Mačinga P, Jabor A. Significant elevations of serum amylase caused by macroamylase: Case reports and detection possibilities. J Clin Lab Anal. 2023;37(5):e24859.

FIGURE

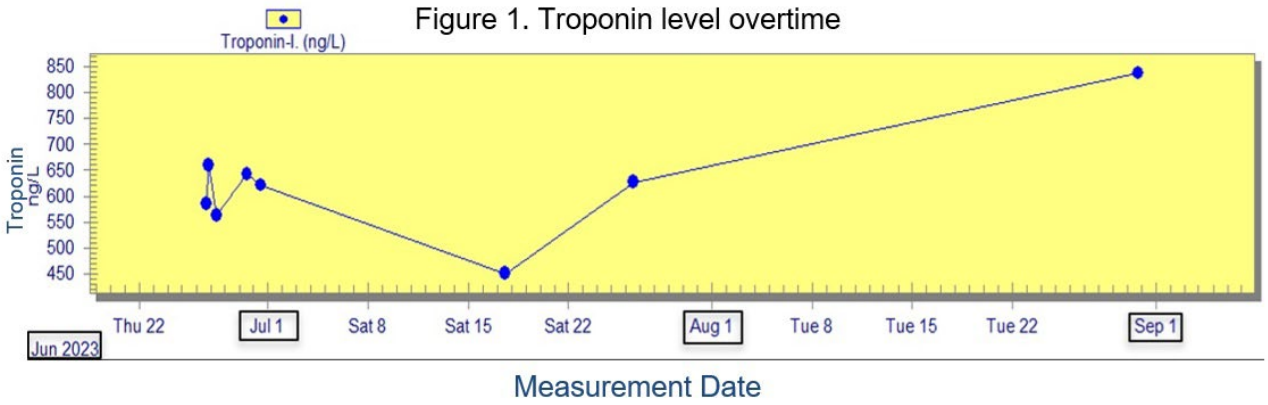

Figure 1: Graph showed troponin levels over time from June 2023 to September 2023

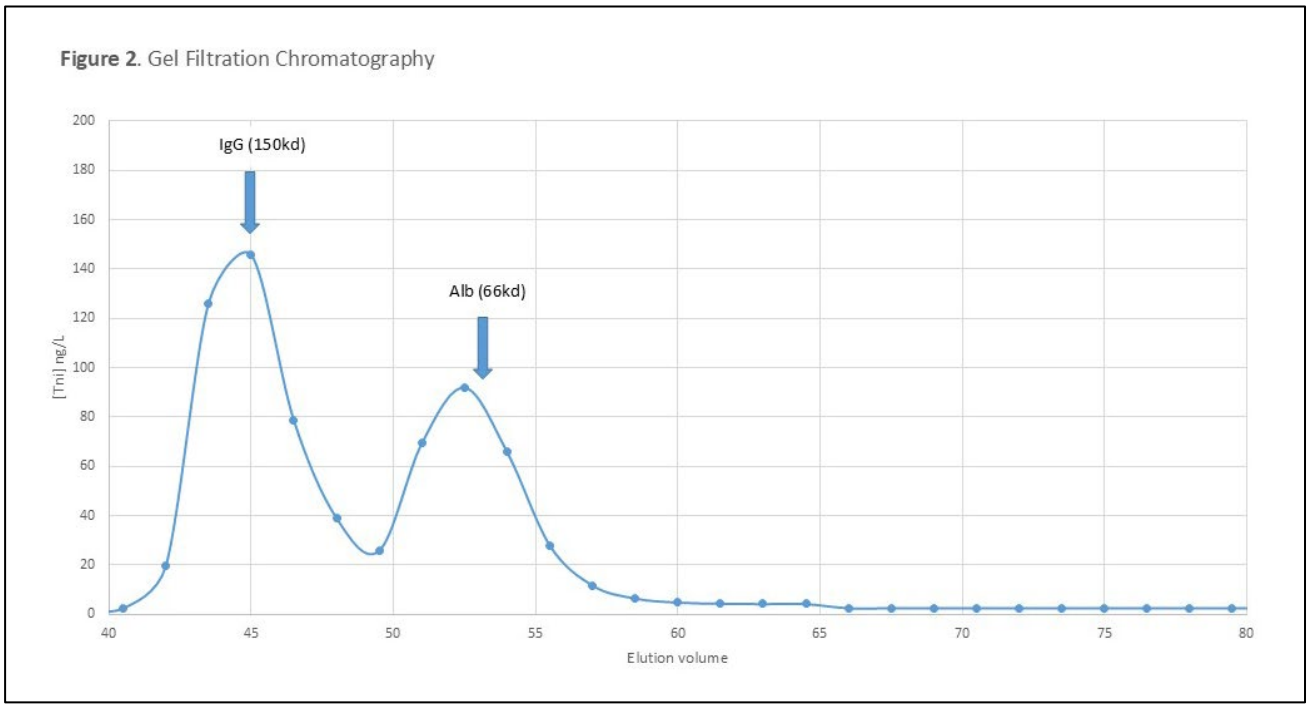

Figure 2: Gel Filtration Chromatography shows two peaks of immunoreactive troponin, the first (macrotroponin) co-elutes with Immunoglobulin (~ 150 kDa) and the second prior to albumin (66 kDa). The ratio of high to low molecular weight (MWt) TnI immmunoreactivity is ~ 65%

PATIENT'S PERSPECTIVE

When I was told that I needed to be admitted to the hospital for further investigation of my heart, it came as a shock. A blood test had shown elevated levels that suggested possible heart injury. At that time, I had just been diagnosed with systemic sclerosis; a condition I had never heard of before. I was already overwhelmed by this unexpected diagnosis, and now I faced the possibility of heart issues. Additionally, the treatment I'd started could impact our plans for a family, something my wife and I have been hoping for. This added another layer of complexity and worry, making me feel as if life had thrown us into the deep end. I'm still trying to process what this all means for our future.

Although I generally felt well, aside from fatigue and low energy, I had no chest pain or breathlessness, so I hadn't expected anything to be wrong with my heart. What bothered me more were my tight skin and freezing cold hands. Initially, I resisted the idea of hospital admission since I didn't feel very sick, but being told it was necessary to investigate my heart made me anxious. Anything involving the heart seemed serious.

During my week-long stay under the rheumatology team, I underwent numerous tests and was seen by a heart specialist. When most of the tests came back normal, apart from the blood test, I felt reassured but also curious about what was happening. I was informed that some of my blood samples would be sent to the United Kingdom for further analysis. Eventually, I learned that there was a presence of large molecules causing false positives in my bloodwork. With a normal echocardiogram and cardiac MRI, the specialists were not concerned about heart involvement and did not recommend further investigations at this time. I was advised, however, that I would need routine monitoring due to my systemic sclerosis.

Hearing this news was a huge relief for me and my wife.

INTELLECTUAL PROPERTY RIGHTS ASSIGNMENT OR LICENCE STATEMENT

Date: 8th July 2024