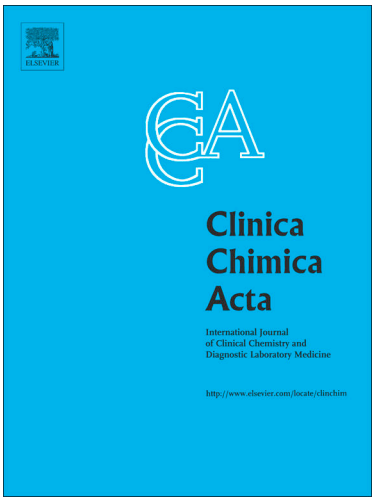
Journal Pre-proofs



Case report

A colossal, enigmatic, and long-lasting high-sensitivity cardiac troponin T elevation

Matthieu Deltombe, Arnaud Nevraumont, Jean-Louis Bayart, Anne-Catherine Pouleur, Laura Labriola, Damien Gruson

PII: S0009-8981(21)00219-9
DOI: https://doi.org/10.1016/j.cca.2021.06.018
Reference: CCA 16634

To appear in: *Clinica Chimica Acta*

Received Date: 2 April 2021
Revised Date: 9 June 2021
Accepted Date: 9 June 2021

Please cite this article as: M. Deltombe, A. Nevraumont, J-L. Bayart, A-C. Pouleur, L. Labriola, D. Gruson, A colossal, enigmatic, and long-lasting high-sensitivity cardiac troponin T elevation, *Clinica Chimica Acta* (2021), doi: https://doi.org/10.1016/j.cca.2021.06.018

Article Title

A colossal, enigmatic, and long-lasting high-sensitivity cardiac troponin T elevation.

Authors

Matthieu Deltombe[1], Arnaud Nevraumont [1], Jean-Louis Bayart [5], Anne-Catherine Pouleur[3], Laura Labriola[4], Damien Gruson[1,2]

Affiliations

1. *Department of Clinical Biochemistry, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.*

2. *Pôle de recherche en Endocrinologie, Diabète et Nutrition, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium.*

3. Department of Cardiology,, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

4. Department of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

5. Department of Clinical Biochemistry, Cliniques Saint-Pierre, Ottignies, Belgium.

Corresponding author(s)

Matthieu Deltombe (matthieu.deltombe@uclouvain.be)

Abstract

This case describes the incidental finding of a massive and persistent elevation of troponin T in a patient with end-stage renal disease. This high troponin T value was not consistent with the patient's clinical condition and the laboratory was called in to investigate this discrepancy. After exclusion of analytical interference and discovery of a discordance between troponin T and troponin I, a clinical investigation including cardiac and whole-body magnetic resonance imaging was performed. Magnetic resonance imaging results allowed us to exclude a cardiac origin of troponin elevation but revealed a skeletal muscle pathology. This case constitutes the first description of high-sensitivity cardiac troponin T elevation due to musculoskeletal pathology without cardiac involvement in a patient with end-stage renal disease.

Keywords

Troponin T, Troponin I, Interference, Discrepancy, Skeletal muscle

Ethics Statement

Informed consent was obtained.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have or could be perceived to have influenced the work reported in this article.

Highlights:

1. **Troponin I should be tested in case of doubtful elevation of troponin T.**
2. **Causes of immunoassay interferences must be excluded.**
3. **If there is no obvious muscular pathology, complete cardiac check-up must be carried out.**
4. **Non-cardiac causes can lead to very high levels of troponin T.**

1. Introduction:

Cardiac troponin (cTn) measurement has significant value in the diagnosis of acute coronary syndrome **[1]**. However, this assay, which targets cardio-specific troponin isoforms, can be improved. Indeed, all immunoassays may be the target of analytical interferences that lead to falsely elevated or decreased results depending on the origin of the interference **[2],[3]**. In this case report, we describe a case of an end-stage renal failure patient with a large elevation of highly sensitive cardiac troponin T (hsTnT) not related to cardiac muscle injury.

2. Case description:

Following his usual hemodialysis session, a 68-year-old patient was referred to the cardiovascular intensive care unit (CICU) of our hospital after the fortuitous discovery of a significant increase in hsTnT. The patient only complained of a slight worsening of his chronic dyspnea but reported no chest pain or heart palpitations. His relevant medical history included type 1 diabetes and an IgG4-related disease complicated by interstitial nephritis, interstitial lung damage, pancreatitis, and infiltrations of the cavernous sinus and orbit, which was diagnosed ten years prior to the current admission and was managed by methylprednisolone and rituximab. Additionally, the patient had a reactivation of a hepatitis B virus infection (with positive hepatitis B surface antigen) six months after the last dose of rituximab and two months prior to this hospitalization. On arrival in the CICU, his hsTnT value was 3398 ng/L (age-adjusted institutional range: <30 ng/L), corresponding to a 113-fold increase compared to the upper limit of normal. Both creatine kinase (CK) and CK-MB were also markedly increased with concentrations of 1379 U/L (reference interval, 20-200 U/L) and 54,93 µg/L (reference interval, <6,22 µg/L), respectively. Other pertinent laboratory findings are listed in **Table 1**. Following these findings, an electrocardiography (ECG) was obtained, which did not show any pattern compatible with an acute coronary event. An echocardiography and a coronarography were also pursued and showed a normal left ventricular function and no significant coronary artery disease. As a result of the discrepancy

between the subsequent examinations and the extremely high increase in the hsTnT, assay interference was suspected.

3. Discussion:

3.1 Laboratory investigation:

After a macroscopic examination of the blood sample, a rerun of the previous blood sample and a control run on another blood sample confirmed the rise in the patient's hsTnT. A frozen sample of heparinized plasma was sent to two other clinical laboratories using two different troponin immunoassays (detailed in **Table 2**). Surprisingly, the first laboratory reported a normal hsTnI value of 25,5 ng/L (Abbott Architect STAT; reference interval, <26 ng/L), and the second laboratory reported a slightly increased hsTnI value of 12 ng/L (Ortho Vitros; reference interval, <12 ng/). Both results suggested the likelihood of analytical interference on the hsTnT assay performed in our hospital. In the meantime, interferences related to hemolysis, fibrinogen and rheumatoid factor were excluded. The serial dilution of the sample was linear, and the presence of macrotroponin T was excluded after the precipitation of the sample with PEG-6000. Further analysis using VeraTest Biotin™ and VeraPrep Biotin™ enabled us to rule out biotin interference in the sample. No heterophilic antibodies were detected using a heterophilic blocking tube (Scantibodies®). An additional frozen sample sent to the manufacturer (Roche Diagnostics) for further investigations confirmed the elevation of hsTnT, but this did not uncover any interferences using size exclusion chromatography. Therefore, investigations in our laboratory did not allow us to address any previously described analytical interference. However, even more surprisingly, the kinetics of the patient's hsTnT, CK and CK-MB showed no significant decreases over the six months of follow-up (**Table 2**).

3.2. Cardiac magnetic resonance imaging:

To confirm the absence of the involvement of the cardiac muscle in the patient's hsTnT and because the patient's condition could not justify the performance of an endomyocardial biopsy, it was decided to perform cardiac magnetic resonance imaging (cMRI). A first cMRI was performed shortly after admission and showed generalized myocardial edema suggesting acute myocardial injury but no evidence of myocardial necrosis. Five months later, as the cardiac enzymes were still as high as at admission, a second cMRI was performed. The second cMRI did not show any edema, necrosis or sequelae of myocarditis. In addition, no perfusion

abnormalities were detected, and both ventricles were of normal size with a preserved systolic function. According to these results, cardiac injury explaining this elevated hsTnT value was unlikely. It is indeed difficult to conceive that such a marked increase in troponin could be the result of a cardiac microlesion that would be too small to be detected by magnetic resonance. It should be noted that the edema documented in the first cardiac RMI could have been due to cardiac injury caused by COVID-19, without overt myocarditis **[4]**. However, this diagnosis was excluded by a negative RT-qPCR result on two nasopharyngeal swabs performed 3 days apart during hospitalization, and by periodic monthly serologic testing performed from April 2020 in the haemodialysis unit. This also points the value of repeating an examination in case of doubt.

3.3. Whole body magnetic resonance imaging:

Shortly after the second cMRI, we decided to perform whole-body magnetic resonance imaging (WB-MRI) to investigate subclinical skeletal muscle injuries. WB-MRI showed atrophic myopathy predominating in the left thigh and arch muscles. In addition, mild edema was visible in the right vastus lateralis, right adductor and right semimembranosus without substantial atrophy. These findings may result from subclinical myopathy and are consistent with the elevation of CK and CK-MB in our patient.

3.4. Causes of discrepancies between hs-cTnT and hs-cTnI:

3.4.1. Isolated elevation of hs-cTnT in end stage renal disease:

Elevation of hsTnT with normal hsTnI in patients with end-stage renal disease (ESRD) has been described for a long time, and three major causes have been proposed **[5]**. The first hypothesis is the possibility of cross-reactivity with skeletal muscle proteins, the second hypothesis is related to the gene expression of cardiac troponin T in skeletal muscle, and the third hypothesis is the existence of minimal cardiac damage. More recently, Mingels *et al* **[6]** demonstrated via gel filtration chromatography that elevated cTnT formed in ESRD patients are linked to small N- and C-terminal truncated cTnT forms that are different from those observed in cases of acute myocardial damage. The physiopathology regarding the accumulation of these fragments remains unclear. However, it is interesting to note that these fragments, of approximately 14-18 kD, are also found in healthy runners after running a marathon, and, in these runners, troponin T values exceed the diagnostic threshold, which is consistent with an acute event **[7]**.

However, to the best of our knowledge, isolated ESRD cases with high hsTnT such high values have never been described. Although ESRD may have contributed to this elevation, it is unlikely in our case.

3.4.2. Cross-reactivity with skeletal muscle or re-expressed cTnT released from diseased skeletal muscle:

Because of this persistent elevation of hsTnT, CK-MB and CK without any deterioration of the cardiovascular condition and a normal cMRI, the hypothesis of skeletal muscle pathology was investigated, despite no muscular complaints from the patient. In addition, it is increasingly reported that a significant number of patients suffering from various neuromuscular pathologies present with isolated elevations of cTnT without elevations of cTnI and without clinical evidence of myocardial injury **[8-10]**. This has also been documented in large cohorts of patients with neuromuscular diseases **[11]**. The origin of cTnT elevations is debated in patients with neuromuscular pathologies. Indeed, several hypotheses have been suggested, such as the re-expression of cardiac isotypes by skeletal muscle, a cross-reaction or a systemic reaction that may involve cardiac muscle. In addition, Jaffe *et al* **[12]** reported the detection of a 39,5 kD protein by western blot on four samples obtained from patients with various skeletal muscle diseases. This 39,5 kD protein is recognized by the two antibodies (capture and detection) used in the hsTnT assay. Troponin elevations secondary to skeletal muscle diseases are described to be rare, but they have no changing patterns and are not apt to confound the diagnosis of myocardial infarction **[12]**. Finally, a biological investigation for autoimmune myositis was also carried out in this patient and turned out to be negative (**Table 1**).

4. Conclusion:

By combining laboratory, clinical and imaging findings, our main hypothesis was that the vast and long-lasting troponin release was originating from skeletal muscle in our patient. It is now well accepted that the performances of the different high sensitivity troponin assay techniques are equal, and there is not one superior troponin assay for the diagnosis of acute myocardial infarction **[13]**. However, this case reminds us once again of the importance of developing new assays targeting epitopes that will no longer cross-react with proteins other than those of cardiac muscle. We consider that in cases of clinicobiological discrepancies affecting troponin T and where there is no confirmation of skeletal

muscle involvement, a troponin I assay should be obtained as a first-line option to avoid costly and potentially invasive additional diagnostics procedures. Such cases should also be investigated at the laboratory level to exclude the main causes of analytical interference and at a clinical level by magnetic resonance to rule out cardiac or skeletal muscle damage that could explain those elevations of cTnT. This clinical case is, to the best of our knowledge, the first description of high- and long-lasting T troponinemia obtained with a new generation assay in a patient with end-stage renal failure without cardiac muscle involvement confirmed by cMRi and WB-MRI.

5. References:

[1] K. Thygesen, J.S. Alpert, A.S. Jaffe, B.R. Chaitman, J.J. Bax, D.A. Morrow, H.D. White, E S C Scientific Document Group, Fourth universal definition of myocardial infarction (2018), Eur. Heart J. 40 (2019) 237–269. https://doi.org/10.1093/eurheartj/ehy462.

[2] G. Ward, A. Simpson, L. Boscato, P.E. Hickman, The investigation of interferences in immunoassay., Clin. Biochem. 50 (2017) 1306–1311. https://doi.org/10.1016/j.clinbiochem.2917.08.015.

[3] J. Tate, G. Ward, Interferences in immunoassay., Clin. Biochem. Rev. 25 (2004) 105–120.

[4] T. Kotecha, D.S. Knight, Y. Razvi, K. Kumar, K. Vimalesvaran, G. Thornton, R. Patel, L. Chacko, J.T. Brown, C. Coyle, D. Leith, A. Shetye, B. Ariff, R. Bell, G. Captur, M. Coleman, J. Goldring, D. Gopalan, M. Heightman, T. Hillman, L. Howard, M. Jacobs, P.S. Jeetley, P. Kanagaratnam, O.M. Kon, L.E. Lamb, C.H. Manisty, P. Mathurdas, J. Mayet, R. Negus, N. Patel, I. Pierce, G. Russell, A. Wolff, H. Xue, P. Kellman, J.C. Moon, T.A. Treibel, G.D. Cole, M. Fontana, Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance., Eur. Heart J. 42 (2021) 1866–1878. https://doi.org/10.1093/eurheartj/ehab075.

[5] J. Mair, B. Lindahl, C. Müller, E. Giannitsis, K. Huber, M. Möckel, M. Plebani, K. Thygesen, A.S. Jaffe, What to do when you question cardiac troponin values., Eur. Hear. Journal. Acute Cardiovasc. Care. 7 (2018) 577–586. https://doi.org/10.1177/2048872617708973.

[6] A.M.A. Mingels, E.P.M. Cardinaels, N.J.H. Broers, A. van Sleeuwen, A.S. Streng, M.P. van Dieijen-Visser, J.P. Kooman, O. Bekers, Cardiac Troponin T: Smaller Molecules in Patients with End-Stage Renal Disease than after Onset of Acute Myocardial Infarction., Clin. Chem. 63 (2017) 683–690. https://doi.org/10.1373/clinchem.2016.261644.

[7] W.H.M. Vroemen, S.T.P. Mezger, S. Masotti, A. Clerico, O. Bekers, D. de Boer, A. Mingels, Cardiac Troponin T: Only Small Molecules in Recreational Runners After Marathon Completion., J. Appl. Lab. Med. 3 (2019) 909–911. https://doi.org/10.1373/jalm.2018.027144.

[8] A.S. Jaffe, V.C. Vasile, M. Milone, A.K. Saenger, K.N. Olson, F.S. Apple, Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T., J. Am. Coll. Cardiol. 58 (2011) 1819–1824. https://doi.org/10.1016/j.jacc.2011.08.026.

[9] S.C.A. Wens, G.J. Schaaf, M. Michels, M.E. Kruijshaar, T.J.M. van Gestel, S. In 't Groen, J. Pijnenburg, D.H.W. Dekkers, J.A.A. Demmers, L.B. Verdijk, E. Brusse, R.H.N. van Schaik, A.T. van der Ploeg, P.A. van Doorn, W.W.M.P. Pijnappel, Elevated Plasma Cardiac Troponin T Levels Caused by Skeletal Muscle Damage in Pompe Disease., Circ. Cardiovasc. Genet. 9 (2016) 6–13. https://doi.org/10.1161/CIRCGENETICS.115.001322.

[10] D. Rittoo, A. Jones, B. Lecky, D. Neithercut, Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction., J. Am. Coll. Cardiol. 63 (2014) 2411–2420. https://doi.org/10.1016/j.jacc.2014.03.027.

[11] J. Schmid, L. Liesinger, R. Birner-Gruenberger, T. Stojakovic, H. Scharnagl, B. Dieplinger, M. Asslaber, R. Radl, M. Beer, M. Polacin, J. Mair, D. Szolar, A. Berghold, S. Quasthoff, J.S. Binder, P.P. Rainer, Elevated Cardiac Troponin T in Patients With Skeletal Myopathies., J. Am. Coll. Cardiol. 71 (2018) 1540–1549. https://doi.org/10.1016/j.jacc.2018.01.070.

[12] A.S. Jaffe, F.S. Apple, Science Moves Slowly., J. Am. Coll. Cardiol. 71 (2018) 1550–1552. https://doi.org/10.1016/j.jacc.2018.01.068.

[13] G. Lippi, G. Cervellin, Is one cardiac troponin better than the other?, J. Lab. Precis. Med. Vol 4 (May 2019) J. Lab. Precis. Med. (2019). https://jlpm.amegroups.com/article/view/4994.

Table 1 : Other laboratory findings at admission

Table 1		
Other **laboratory findings at admission**	Reference interval	Results
Haemoglobin	13,3 - 16,7 g/dL	11,2
White blood cells	4,00 - 10,00 x10³/µL	6,87
Neutrophils	1,60 - 7,00 x10³/µL	3,37
Lymphocytes	0,80 - 5,00 x10³/µL	2,35
Platelets	150 - 450 x10³/µL	194
C-reactive protein	<5,0 mg/L	32,1
Sodium	135-145 mmol/L	139
Potassium	3,5 - 5,00 mmol/L	4,29
Creatinine	0,60 - 1,30 mg/dL	4,35
Aspartate transaminase	19 - 48 UI/L	70
Alanine transaminase	10 - 40 UI/L	13
Gamma-glutamyl-transferase	<60 UI/L	11
Bilirubin total	<1,2 mg/dL	0,3
Lipase	13 - 60 UI/L	45
Fibrinogen	150 - 450 mg/dL	370
Covid-19 (PCR)	Detected-Undetected	Undetected
TSH	0,27 - 4,20 mU/L	2,45
IgG4	0,0392 - 0,864 g/L	0,724
Rheumatoid Factor	<14 UI/mL	12
Antinuclear factor (HEP2)	Pos >=1/80	Negative
Anti neutrophil cytoplasmic antibodies (I.F)	Pos >=1/40	Negative
Dot anti ENA Myosite (a) :	Negative	

(a): Targeting J0-1; PI7; PI12; EJ; SRP;Mi2; MDA5; Tif1-gamma; Ro52kD; SAE1/SAE2; NXP2

Table 2

Marker	Reference interval	Date and results					
		Admission	*+ 1 Month*	+ 2 Months	+ 3 Months	+ 4 Months	+ 5 Months
High sensitive cardiac troponin T (Roche diagnostics)	<30 ng/L (a)	3398	4071	4250	5356	4127	3657
Creatine kinase	20 - 200 U/L	1379	2246	2275	2084	1131	1181
CK-MB	<=6,22 µg/L	54,93	135,4	162,5	229,4	163,7	105,6
Lactate dehydrogenase	<=250 UI/L	426	522	525	531	N.A	372

Assay	Upper limit value (ng/L)	Results at admission (ng/L)	Epitopes recognized by antibodies	Biotinylated Antibodies	Detection antibody tag	Limit of detection (ng/L)	%CV at 99th (%)
Elecsys hsTnT, Roche	30 (a)	3398	*Capture: 136-147; Detection: 125-131*	*Yes*	*Ruthenium*	*5*	*<8,0*
Vitros hsTnI, Ortho	12	12	*Capture: 24-40, 41-49; Detection: 87-91*	*No*	*Horse radish peroxydase*	*1*	*<6,5*
Architect STAT hsTnI, Abbott	26	25,5	*Capture: 24-40 Detection: 41-49*	*No*	*Acridinium*	*1,2*	*<6,0*

(a): Age adjusted institutional range for people over 60 years old.