

Transfusion double whammy? Adrenaline-takotsubo-anaphylaxis-Kounis complex post transfusion?

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Abstract

Background and Objectives: The adrenaline-takotsubo-anaphylaxis-Kounis, or the ATTACK complex, where there are clinical and pathophysiological overlaps between takotsubo and Kounis syndromes, in which histaminergic, adrenergic and other mediators may play roles, was recently described. The objective of this report was to describe three cases where the ATTACK complex was suspected to have occurred after transfusion.

Materials and Methods: Three cases were recently reported to the New Zealand Blood Service haemovigilance programme that appeared to have features in common suggestive of the ATTACK complex.

Results: All three patients had had a blood component transfused, an initial severe allergic reaction, treatment with adrenaline or a congener, subsequent acute left ventricular failure or transfusion-associated circulatory overload, and features suggestive of takotsubo cardiomyopathy.

Conclusions: Although rarely described, transfusion-associated ATTACK complex may be occurring more often than believed. Circumstances during a transfusion may predispose to it. It should be suspected if the sequence of events described above occur. Its characteristics need to be better understood. Risk factors for it may be modifiable.

KEYWORDS

ATAK complex, Kounis syndrome, takotsubo syndrome, transfusions

Highlights

- Transfusion-related severe allergic reactions may quickly develop into transfusion-associated circulatory overload in some patients.
- The features are suggestive of the recently described adrenaline-takotsubo-anaphylaxis-Kounis or ATTACK complex.

INTRODUCTION

Three patients with common features showed a rare sequence of transfusion-associated adverse reactions (henceforth, reactions or reaction). Initially, all had respiratory and other features suggesting severe allergic reactions. They were treated as such. Shortly afterwards, the nature of the reactions changed to resemble transfusion-associated circulatory overload (TACO). None fitted a recognized reaction category.^{1, 2}

CASE 1

A 71-year-old female with platelet count less than $10 \times 10^9/L$ (probable immune thrombocytopenic purpura) received an ABO-identical, non-pathogen-reduced, 7-day-old unit of pooled platelets in platelet additive solution. Pre-transfusion temperature (T) was 36.3°C, heart rate (HR) 96 beats/min, blood pressure (BP) 138/82 mmHg, respiratory rate (RR) 17/min and peripheral oxygen saturation (SpO₂) 97%

on room air (RA). After 230 ml of transfusion, she developed breathlessness, restlessness, extensive skin rash, chills, rigours, hypotension (BP = 78/62 mmHg), tachycardia (HR = 103 beats/min), tachypnoea (RR = 29/min) and hypoxia (SpO₂ = 95% on O₂ at 6 L/min). She was given metaraminol for the hypotension. Shortly afterwards, her observations were T = 36°C, HR = 145 beats/min, BP = 201/148 mmHg, RR = 31/min and SpO₂ = 90% on RA. The electrocardiogram (ECG) showed segment elevation in the anterior leads, and troponin T and B-natriuretic peptide (BNP) were elevated (510 ng/L and 953 pg/ml, respectively). Chest X-ray (CXR) taken 30 min post the event showed no pulmonary oedema. A chest CT scan taken 6 h post the event showed bilateral apical and lower lobe ground-glass attenuation, suggesting haemorrhage or oedema. Trans-thoracic echocardiography 9 h after the event was suggestive of a new takotsubo cardiomyopathy with an estimated left ventricular (LV) ejection fraction (EF) of 40%–45% (Figure 1). CT coronary angiography 10 days post the event showed normal coronary arteries.

CASE 2

An 89-year-old female presented with breathlessness of short duration. Initial observations were T = 36.2°C, HR = 89 beats/min, BP = 180/65 mmHg, RR = 23/min and SpO₂ = 100% on RA. CXR taken shortly after admission showed clear lungs, normal cardiac size and no pleural effusions. Baseline blood results were consistent with iron-deficiency anaemia (haemoglobin 76 g/L, mean corpuscular volume 80 fl, mean corpuscular haemoglobin 24 pg, serum ferritin 14 µg/L and transferrin saturation 4%). She was admitted for an elective red blood cell (RBC) transfusion. She also had type 2 diabetes mellitus (T2DM), hypertension, hyperlipidaemia, osteoarthritis, gout, cataracts and glaucoma.

RBC transfusion (ABO-identical, 20-day-old) started 8 h post presentation. Pre-transfusion observations were T = 36.7°C, HR = 88 beats/min, BP = 210/75 mmHg, RR = 28/min and SpO₂ = 93% on RA. After 40 min and 57 ml of the transfusion, she became breathless, tachypnoeic, wheezy, desaturated, hypotensive (systolic BP = 60–70 mmHg) and febrile (T = 38.5°C), but there was no skin rash.

Adrenaline (1 mg im × 2), hydrocortisone 100 mg and fluids intravenously (iv) were given for anaphylaxis. CXR taken 30 min post the event showed small volume lungs, bilateral, confluent air-space opacities consistent with acute LV failure but no cardiomegaly. During pre-intubation laryngoscopy, foamy material, but no oedema, was seen in the oropharynx. CXR taken in the intensive care unit (ICU) 90 min later showed bilateral, extensive and confluent opacities. She was given esmolol 20 mg iv (because HR = 130 beats/min and BP = 210/130 mmHg), became hypotensive, and was given further adrenaline. In the ICU, she needed circulatory support with noradrenaline and vasopressin, and piperacillin + tazobactam for persistent fever. Clinical and radiological improvement started within 24 h. The next day, she was

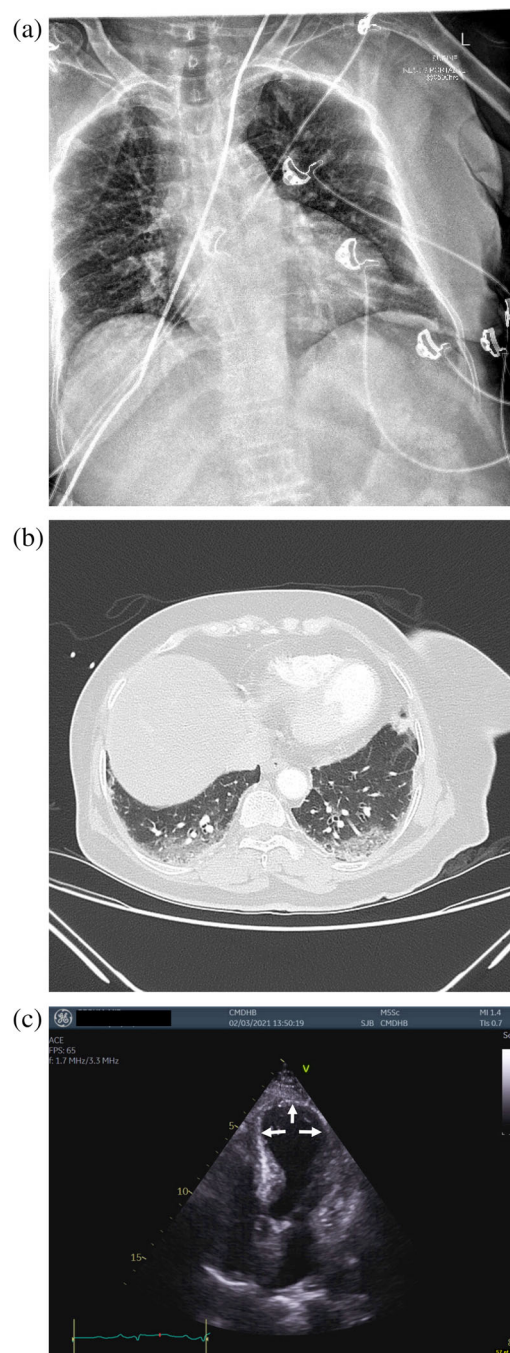


FIGURE 1 Case 1 (a) Chest X-ray taken 30 min after the initial allergic reaction. The lung fields are clear, and there is nothing to suggest pulmonary oedema. (b) Contrast-enhanced chest CT taken 6 h after the initial reaction, showing ground-glass attenuation in both lower lobes with nodular foci. The overall appearance, taken in context, is suggestive of pulmonary oedema or haemorrhage. (c) Transthoracic echocardiogram, apical four-chamber view, 9 h after the event, suggestive of regional wall motion abnormalities (left ventricular apical hypo-/dys-kinesia and basal hyper-kinesia), leading to the 'takotsubo' (octopus pot) appearance (arrows)

extubated, but she still needed intermittent respiratory support following discharge to the ward.

Serologic anomalies suggestive of a haemolytic transfusion reaction and evidence of bacterial contamination of the transfusion were absent. Patient blood cultures were negative. There was evidence of stage 2 acute kidney injury, likely secondary to hypoperfusion (serum creatinine 90 $\mu\text{mol/L}$ at admission rising to 160 $\mu\text{mol/L}$ 2 days later). Troponin T rose from 28 ng/L on admission to 243 and 1139 ng/L at 3 and 11 h post the event, respectively, with no cardiac ischaemia symptoms or new ECG changes (there was evidence of a chronic left bundle branch block). This was considered to be consistent with type 2 NSTEMI. Trans-thoracic echocardiography 18 h post the event showed moderate left atrial dilatation and global LV impairment with estimated LVEF of 35%–40%, significant mitral regurgitation, and mild aortic stenosis and tricuspid regurgitation. N-terminal pro-BNP at admission was 507 pmol/L (suggesting heart failure). No post-event result was available.

CASE 3

A 42-year-old male with spondylodiscitis, myositis, gluteus maximus abscesses, end-stage renal failure (ESRF), anaemia secondary to ESRF, T2DM, peripheral neuropathy, chronic diarrhoea, gout, hyper- and dys-lipidaemia, cardiomyopathy and raised BMI with a baseline haemoglobin of 69 g/L was receiving an ABO-identical, 20-day-old RBC transfusion. Pre-transfusion observations were $T = 36.2^\circ\text{C}$, $HR = 81/\text{min}$, $BP = 108 \text{ beats}/42 \text{ mmHg}$, $RR = 18/\text{min}$ and $SpO_2 = 99\%$ on RA. After about 1 h and 246 ml of the transfusion, he developed a choking sensation in the throat (but not shortness of breath initially) and abdominal and left-sided chest pain, and he became anxious, restless and nauseous. Later, he developed extensive flushing, dyspnoea, increased work of breathing, bilateral wheezes, chills and rigours. He had no skin rash or oro-pharyngeal or peripheral oedema. At this point his observations were $T = 37.9^\circ\text{C}$, $RR = 25/\text{min}$, $SpO_2 = 79\%$ (RA), $HR = 108 \text{ beats}/\text{min}$ and $BP = 158/60 \text{ mmHg}$. He was given 0.5 mg adrenaline im, 5 mg salbutamol nebulized, 10 mg loratadine orally and 100 mg hydrocortisone iv for anaphylaxis. ECG was normal. CXR taken 50 min post the event showed a new atelectatic band in the left mid-zone and prominent pulmonary arteries with upper lobe redistribution, but no air-space shadowing, pleural effusions or cardiomegaly. The next day he was found to have bilateral basal chest crepitations. Echocardiography was not done.

DISCUSSION

Our cases suggest that initial severe allergic reactions can sometimes quickly change to TACO and may be examples of the recently described adrenaline-takotsubo-anaphylaxis-Kounis (ATAK) complex.

Takotsubo syndrome (TS) is a well-recognized cause of acute reversible heart failure often precipitated by 'stressors' such as sudden BP drops, asthma attacks, medical procedures, pain, surprises and so on. It is especially common in post-menopausal women. The defining feature is regional ventricular dysfunction, causing characteristic

echocardiographic abnormalities. Atherosclerotic coronary artery disease is absent, but ECG and biochemical features often suggest cardiac ischaemia. Symptoms include chest pain, breathlessness, dizziness and other features of heart failure.³

Catecholamines (e.g., noradrenaline) and stress-related neuropeptide Y are believed to play central roles in TS causing not only cardio-inhibitory effects but also acute microvascular dysfunction.³ Interestingly, asthma exacerbation, especially after treatment (short-acting β_2 adrenergic receptor agonist, adrenaline and intubation), is well described as a TS trigger.^{4, 5}

Kounis syndrome (KS) is an acute coronary syndrome precipitated by severe allergic events. In KS, it is postulated that mast cell mediators such as histamine, platelet-activating factor, cytokines, and so on cause coronary artery spasm, atheromatous plaque rupture or coronary artery stent thrombosis. Many drugs, foods, and so on—although not yet blood or its derivatives—have been implicated. Clinical, biochemical, ECG and angiographic features overlap allergic reactions and cardiac ischaemia.⁶

Lately, the ATAK complex, which overlaps TS and KS, has been described. Exogenous adrenaline may also play a role.⁷ Recent reports include a female aged 60 years receiving gelofusine who became breathless and sweaty and received adrenaline; a male aged 48 years in Addisonian crisis treated with steroids and noradrenaline; and a 44-year-old anaesthetised female who received adrenaline for peri-anaesthesia anaphylaxis.^{8–10}

Our patients showed initial features of significant allergic reactions. One had extensive rashes; another, significant hypotension; the third, bilateral wheezes and a choking sensation. Two patients received RBC and one patient received platelets. Two received adrenaline, and the third metaraminol (a direct α -1 and an indirect β -1 adrenoceptor agonist). CXR in all was consistent with TACO. In one, there was also echo evidence of TS. In another, echocardiography was done 18 h post the event and global LV impairment was seen. In the third, echocardiography was not done. Early echocardiography is recommended because changes can be transient. Mitral regurgitation (as seen in one) is known in TS, and CXR may show features of pulmonary oedema, cardiomegaly and upper lobe diversion (as seen in all our patients).^{11, 12}

We came across one other similar transfusion-associated case. A 48-year-old female developed acute reversible heart failure with TS features and urticaria while receiving platelets. Adrenaline was not given. The authors suggested combined histaminergic and (endogenous) adrenergic elements, causing the cardiac effects.¹³

In conclusion, some transfused patients, some or all of the following may occur together (the 'perfect storm'):

1. Borderline cardiac function
2. Catecholamine release (secondary to stress of the underlying disorder, the transfusion or the reaction to it)
3. Histamine release (in allergic reactions)
4. Treatment with adrenaline
5. Volume overload.

This may cause the ATAK complex and TACO. An epidemiological study on KS-associated TS suggests that older people, females, non-

Whites, hypertensives and the dys-lipidaemics may be at risk.¹⁴ Although rarely described in transfused patients, they may be at particular risk. Transfusion-associated ATAK complex (TAAC) should be considered in patients with the following sequence: severe allergic reactions, treatment with adrenaline or congener and TACO. TAAC may be occurring more often than is known. Its incidence, pathophysiology, transfusion correlates and clinical course need to be better understood.

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Krishna G. Badami conceived, wrote, reviewed, made changes to, and approved the final version of the paper.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. International Society of Blood Transfusion. Working party on Haemovigilance. Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions.
2. Kopko PM, editor. Transfusion reactions. 5th ed. Bethesda: AABB Press; 2021.
3. de Chazal HM, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1955–71.
4. Saito N, Suzuki M, Ishii S, Morino E, Takasaki J, Naka G, et al. Asthmatic attack complicated with Takotsubo cardiomyopathy after frequent inhalation of inhaled corticosteroids/long-acting beta2-adrenoceptor agonists. *Intern Med*. 2016;55:1615–20.
5. Pontillo D, Patruno N, Stefanoni R. The tako-tsubo syndrome and bronchial asthma: the chicken or the egg dilemma. *J Cardiovasc Med*. 2011;12:149.
6. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med*. 2016;54:1545–59.
7. Kounis NG. Attack the ATAK: “ὅς ὁ θεὸς συνέζευξε, ἄνθρωπος μὴ χωρίζετω” (ous o theos synezeuxe anthropos me horizeto) “what therefore god hath joined together, let not man put asunder”. *Int J Cardiol*. 2016;203:960–1.
8. Marganato D, Abete R, Di Giovine G, Delfino P, Massimiliano G, Mazzetti S, et al. Takotsubo cardiomyopathy associated with Kounis syndrome: a clinical case of the “ATAK complex”. *J Cardiol Cases*. 2019;20:52–6.
9. Singh G, Manickam A, Sethuraman M, Rathod RC. Takotsubo cardiomyopathy in a patient with pituitary adenoma and secondary adrenal insufficiency. *Indian J Crit Care Med*. 2015;19:731–4.
10. Alshaeri T, Gupta DE, Nagabhushana AN. Peri-anesthesia anaphylaxis (PAA): we still have not started post-PAA testing for inciting anesthesia-related allergens. *Middle East J Anaesthesiol*. 2016;23:465–9.
11. Izumo M, Akashi YJ. Role of echocardiography for Takotsubo cardiomyopathy: clinical and prognostic implications. *Cardiovasc Diagn Ther*. 2018;8:90–100.
12. Rahman A, Liu D. Broken heart syndrome a case study <https://www.racgp.org.au/download/documents/AFP/2012/JanFeb/201201rahman.pdf>. Accessed 03 Dec 2021.
13. Zhou JQ, Choe E, Ang L, Schnittger I, Rockson SG, Tremmel JA, et al. Stress-induced cardiomyopathy associated with a transfusion reaction: a case of potential crosstalk between the histaminic and adrenergic systems. *Exp Clin Cardiol*. 2011;16:30–2.
14. Desai R, Singh S, Kounis NG, Sachdeva R, Kumar G. Epidemiology of Takotsubo syndrome associated with Kounis syndrome in the United States. *Int J Cardiol*. 2020;310:32.

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