

Acute hypercapnic respiratory failure in thyroid storm and the role of plasma exchange

Thyroid storm is a life-threatening condition due to excessive release of thyroid hormone. Cardiovascular, gastrointestinal and neurological manifestations have been described.¹ Acute respiratory failure as the initial presentation of a thyrotoxic crisis may occur due to pre-existing cardiopulmonary disease. Management is supportive, with medications aimed at inhibiting synthesis and release of thyroid hormone. In this article, we discuss a patient with thyroid storm who presented with decompensated hypercapnic respiratory failure.

Case presentation. A 61-year-old man presented to the emergency department for severe respiratory distress of acute onset. He was a chronic smoker with known Graves' disease, for which he had defaulted follow-up. He had no prior history of chronic lung disease. On arrival, his temperature was 36.6°C, blood pressure 142/86mmHg, heart rate 226 beats/min, respiratory rate 28 breaths/min and oxygen saturation 96% on room air. Physical examination was significant for tachypnoea, respiratory distress, confusion, exophthalmos, a diffuse goitre, proximal weakness and hand tremors. Lungs were clear without wheeze. Arterial blood gas done on 4L/min nasal oxygen showed pH of 7.23, partial pressure of carbon dioxide (PaCO₂) 57mmHg, partial pressure of oxygen (PaO₂) 201.1mmHg, base excess -4.9mmol/L and bicarbonate 20.1mmol/L. Lactate was 4.4mmol/L. He was presumptively treated for exacerbation of chronic obstructive pulmonary disease (COPD) with bronchodilators and non-invasive ventilation (NIV). However, he did not tolerate NIV—repeat blood gas showed pH of 7.112, PaCO₂ 75.9mmHg and PaO₂ 145.8mmHg on expiratory positive airway pressure (EPAP) 5cmH₂O, inspiratory positive airway pressure (IPAP) 20cmH₂O and fraction of inspired oxygen (FiO₂) 0.5. He was intubated for worsening hypercapnic respiratory failure and was admitted to the intensive care unit.

Laboratory tests revealed thyrotoxicosis, mixed respiratory and metabolic acidosis, and raised transaminases (Table 1). Electrocardiogram showed atrial fibrillation with rapid ventricular response. Chest X-ray showed clear lung fields. COVID-19 polymerase chain reaction test result was negative. Further history was notable for weight loss, heat intolerance, diarrhoea and painful eyes over the past 6 months, with tremors and palpitations noted over the past few weeks. His

lactic acidosis resolved following intravenous hydration. However, he remained persistently hypercapnic. Capnography and ventilator mechanics were not suggestive of bronchospasm. He was diagnosed with thyroid storm following a Burch-Wartofsky Point Scale score of 95 points. He was commenced on intravenous hydrocortisone 100mg 4 times a day, oral cholestyramine 4g 3 times a day, and Lugol's iodine and lithium 400mg 2 times a day. Liver transaminases continued to rise on day 2 of admission to levels exceeding 10 times upper limit of normal (Table 1), for which autoimmune and infective studies returned unyielding. With elevated bilirubin levels, there was concern for impending acute liver failure and therefore, conventional anti-thyroid medications were contraindicated. With multiple organ involvement, he was deemed to require urgent control of thyrotoxicosis. Hence, decision was made for initiation of therapeutic plasma exchange (TPE) as a bridge to emergency thyroidectomy. He underwent 2 cycles of TPE through a right femoral venous catheter on days 2 and 3 of admission. Fresh frozen plasma (FFP) was used as exchange fluid, with 1 plasma volume exchanged per session. There was marked clinical and biochemical improvement. He was extubated and his liver transaminases normalised. His therapeutic options were reconsidered, and he was started on carbimazole 10mg every morning. He tolerated treatment, allowing thyroidectomy to be deferred pending further evaluation. At this time of writing, he has been scheduled for spirometry to exclude COPD.

Discussion. The pathophysiology of hypercapnic respiratory failure in thyroid storm has been rarely discussed in existing literature. At steady state, the volume of carbon dioxide (CO₂) eliminated per minute is equal to that produced by the body. This relationship is illustrated by the equation: $VA = K \times VCO_2 / PaCO_2$, where VA represents alveolar ventilation, K represents a constant (0.863), and VCO₂ represents CO₂ production.²

In thyrotoxicosis, muscle mass and strength may be decreased by approximately 20% and 40%, respectively.³ It is theorised that thyrotoxic myopathy arises from damage to the motor end plates.⁴ Functional weakness of the diaphragm has also been described in active Graves' disease.⁵ As weak muscles require more energy relative to their maximum energy consumption to achieve a set amount of work, the balance between

Table 1. Serial laboratory values of a patient with thyroid storm who received plasmapheresis on days 2 and 3 of admission

Serial laboratory values / Day	Admission	Day 1	Day 2 #1 TPE	Day 3 SBT #2 TPE	Day 4	Day 5	Day 6 carbamazole 10mg OM started	Day 19	Reference values
Full blood count									
Haemoglobin (g/dL)	13.4			10.9	10.2	10.6	10.7		11.5–15
TW (10 ⁹ /L)	13.4			19.8	20.8	18.1	11.4		4.0–10.0
Platelets (10 ⁹ /L)	280			152	146	164	188		150–450
Thyroid function									
Free triiodothyronine (pmol/L)	32.8		25.4	9.7	7.9	5.3	7.1	6.3	3.2–5.3
Free thyroxine (pmol/L)	69.7		51.7	53.0	35.2	35.4	29.4	12.7	10.0–20.0
TSH (mU/L)	<0.010					<0.010		<0.010	0.400–4.00
Liver function									
Total protein (g/L)	57		53	54	51	50	47	69	62–82
Albumin (g/L)	34		31	31	30	28	27	39	37–51
Total bilirubin (µmoles/L)	56		46	33	28	40	40	22	5.0–30.0
Alkaline phosphatase (U/L)	198		186	129	88	107	98	163	32–103
ALT (U/L)	617		784	614	217	137	80	24	10–55
AST (U/L)	851		1088	470	95	40	46	26	10–45
Arterial blood gas									
pH	7.112	7.274	7.361	7.402	Extubated				7.35–7.45
PaCO ₂ (mmHg)	75.9	62.5	51.8	50.7					38.9
PaO ₂ (mmHg)	145.8	102.2	93.1	70.2					69.3
Base excess (mmol/L)	-7.2	0.4	2.5	5.2					
Renal panel									
Urea (mmol/L)	6.4	9.3	12.2	14.6	14.4	11.1	7.4		2.8–7.7
Sodium (mmol/L)	140	146	147	148	147	147	142		135–145
Potassium (mmol/L)	5.2	4.1	3.4	4.2	4.2	38	3.6		3.5–5.3
Chloride (mmol/L)	103	103	109	111	109	110	108		96–108
Bicarbonate (mmol/L)	20.9	25.1	29.8	31.8	34.0	32.4	27.0		19–31
Creatinine (µmol/L)	50	71	71	49	37	37	33		65–125
Lactate (mmol/L)	6.7	3.2	1.8						0.50–2.20

ALT: alanine transaminase; AST: aspartate transaminase; OM: every morning; SBT: spontaneous breathing trial; TPE: therapeutic plasma exchange; TSH: thyroid stimulating hormone; TW: total white cell count

energy demand and supply weighs in favour of the former, resulting in fatigue. When fatigued, respiratory muscles fail to generate adequate mean tidal pressures, with resultant decreases in both tidal volumes and minute ventilation, reducing the ventilatory capacity of the respiration system (reduced VA). Other causes of respiratory muscle weakness in thyroid storm include rhabdomyolysis and thyrotoxic periodic paralysis—the latter encountered more frequently in Asian population. A normal creatine kinase level and absence of hypokalaemia suggest against these 2 causes in our patient. As a metabolic end product, CO₂ production increases in thyrotoxic states. Increased CO₂ production gives rise to excessive ventilatory demand (increased VCO₂) which, in the setting of compromised ventilatory capacity, can result in acute hypercapnic respiratory failure.

TPE as a treatment modality in thyroid storm was first described by Ashkar in 1970.⁶ Its use has been reported in patients who had contraindications for or were refractory to conventional medical therapy. Thyroid-binding globulin and bound thyroid hormones are removed with plasma during TPE. FFP contains albumin, which contributes new binding sites for circulating thyroid hormone.⁷ In recent literature, TPE has been described in clinical settings, including methimazole-induced agranulocytosis,⁸ preparation for surgery, postoperative thyroid storm, and type II amiodarone-induced thyrotoxicosis.⁹ TPE remains at Grade 2C for treatment of thyroid storm according to the American Society for Apheresis.¹⁰ Given sparsity of data, knowledge gaps still exist regarding optimal timing and frequency of TPE in the management of thyroid storm.

In conclusion, our case highlights that acute hypercapnic respiratory failure can be the initial presentation of untreated thyrotoxicosis even in the absence of known lung disease. As such occurrences are rare, initial misdiagnosis is possible. Prompt recognition and differentiation from more frequently encountered aetiologies of respiratory failure are important given the unique management of thyroid storm. Furthermore, unlike prior case reports, early use of TPE in our patient ultimately obviated the need for emergency thyroidectomy. We hope that our case contributes to the growing pool of clinical evidence supporting TPE as

a potentially life-saving modality for thyroid storm patients who are not candidates for conventional treatment.

REFERENCES

1. Spitzweg C, Reincke M, Gärtner R. Schilddrüsennotfälle: Thyreotoxische Krise und Myxödemkoma. [Thyroid emergencies: Thyroid storm and myxedema coma]. *Internist (Berl)* 2017; 58:1011-9.
2. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl* 2003;47:3s-14s.
3. Nørrelund H, Hove KY, Brems-Dalgaard E, et al. Muscle mass and function in thyrotoxic patients before and during medical treatment. *Clin Endocrinol (Oxf)* 1999;51:693-9.
4. Kazakov VM. Terminal intramuscular motor innervation and motor end-plates in thyrotoxic myopathy. *Neuromuscul Disord* 1992;2:343-9.
5. Goswami R, Guleria R, Gupta AK, et al. Prevalence of diaphragmatic muscle weakness and dyspnoea in Graves' disease and their reversibility with carbimazole therapy. *Eur J Endocrinol* 2002;147:299-303.
6. Ashkar FS, Katims RB, Smoak WM 3rd, et al. Thyroid storm treatment with blood exchange and plasmapheresis. *JAMA* 1970;214:1275-79.
7. Carhill A, Gutierrez A, Lakhia R, et al. Surviving the storm: two cases of thyroid storm successfully treated with plasmapheresis. *BMJ Case Rep* 2012;2012:bcr2012006696.
8. Vyas AA, Vyas P, Fillipon NL, et al. Successful treatment of thyroid storm with plasmapheresis in a patient with methimazole-induced agranulocytosis. *Endocr Pract* 2010;16:673-6.
9. Diamond TH, Rajagopal R, Ganda K, et al. Plasmapheresis as a potential treatment option for amiodarone-induced thyrotoxicosis. *Intern Med J* 2004;34:369-71.
10. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher* 2016; 31:149-62.

Denise Ann Tsang ¹MBBS (Singapore),

Yi Hern Tan ²MRCP (Edinburgh)

¹ Department of Internal Medicine, Singapore General Hospital, Singapore

² Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore

Correspondence: Department of Internal Medicine, Singapore General Hospital, Academia, 20 College Road Singapore 169856.
Email: denise.tsang@mohh.com.sg