CASE REPORT

Myxoedema coma in the setting of hyperglycaemic hyperosmolar state

Alexander Spyridoulas,¹ Muhammad Shakeel Riaz²¹Anaesthesia and Intensive Care, Tameside Hospital NHS Foundation Trust, Lancashire, UK²Anaesthesia and Critical Care, Tameside Hospital NHS Foundation Trust, Lancashire, UK**Correspondence to**Dr Alexander Spyridoulas;
aspyridoulas@doctors.org.uk

Accepted 18 December 2015

SUMMARY

Decompensated hypothyroidism is a rare endocrine emergency but a differential that should be considered in patients presenting critically unwell with systemic illness. We report a case of myxoedema coma in a woman presenting with respiratory failure, hypotension, hypothermia and a reduced level of consciousness, all of which are poor prognostic features in decompensated hypothyroidism. The patient was admitted to critical care for mechanical ventilation and cardiovascular support and treated with a combination of insulin, liothyronine and levothyroxine, making a good recovery. We wanted to highlight this case of myxoedema coma occurring in the context of a hyperglycaemic hyperosmolar state (HHS), as the former condition is normally associated with hypoglycaemia, hyponatraemia and hypo-osmolality. Decompensated hypothyroidism should be considered in presentations of HHS as well as with other metabolic derangements, as delays in thyroid hormone replacement are associated with poorer outcomes. It has multisystem effects challenging its recognition and we discuss potential complications and their management.

BACKGROUND

A high index of suspicion is required for myxoedema coma in patients presenting with a reduced level of consciousness who have a history of hypothyroidism, thyroidectomy, radio-iodine therapy or an adjustment or discontinuation of thyroid medications. It can be the first presentation of hypothyroidism, however, it most commonly presents during winter months in elderly women who have a known history of hypothyroidism and have developed a concurrent illness. It may be misdiagnosed as the precipitating condition that led to the decompensation of hypothyroidism, which may include sepsis, cardiac failure, myocardial infarction, cerebrovascular accident, anaesthetic, sedative or antidepressant drug use or metabolic and electrolyte disorders.¹ It may also be associated with conditions such as diabetes mellitus, Addison's disease, pernicious anaemia and hypopituitarism, which should also be excluded.

CASE PRESENTATION

A 54-year-old Caucasian woman was brought to the emergency department resuscitation, with respiratory failure, hypotension and a reduced level of consciousness. She had a history of anorexia, malaise and increasing lethargy without any seizure activity. Medical history included hypertension, stroke with residual left-sided weakness, type 2 diabetes, hypothyroidism, hypercholesterolaemia and

depression. She did not work and lived at home with her husband.

On assessment, the patient had a body mass index of 39 kg/m² and a respiratory rate of 8 breaths/min and oxygen saturations of 94% on 15 L/min oxygen. Her heart rate was 50 bpm with a blood pressure of 84/52 mm Hg. She was unresponsive with a Glasgow Coma Scale (GCS) of 6/15 and a tympanic temperature of 32°C. On examination, she had a swollen facial appearance, dry mucous membranes and non-pitting oedema in her limbs. Auscultation revealed reduced basal air entry and no cardiac murmurs were elicited. Arterial blood gas analysis showed hypoxaemia with a metabolic alkalosis and blood glucose of 33 mmol/L. Urinalysis was negative for ketones.

The patient was intubated and mechanically ventilated for respiratory failure and airway protection. She was resuscitated with intravenous 0.9% saline and treated with a bolus of intravenous liothyronine 62.5 µg, based on the suspected diagnosis of myxoedema coma. She was also given stress dose steroids as intravenous hydrocortisone 100 mg for any associated adrenal insufficiency that may have been contributing to her critical illness. She was started on an insulin infusion and rewarming measures with a forced air warming blanket were taken for her hypothermia. Blood and urine cultures were taken and she was started on empirical broad-spectrum piperacillin and tazobactam, according to local guidelines, as it was also considered that severe sepsis may have been a precipitating cause. She was taken for a brain CT due to her history of stroke, however, this did not reveal any new acute changes. She was then subsequently transferred to critical care for ventilation and ongoing treatment.

INVESTIGATIONS

Thyroid function tests confirmed the suspected diagnosis of severe hypothyroidism resulting in myxoedema coma, with a free T₄ of <2.0 pmol/L (range 7–17) and thyroid-stimulating hormone (TSH) of >100 mU/L (range 0.4–4.5). Results from the patient's initial investigations after admission showed a white cell count of 12.4×10⁹/L, C reactive protein of 7 mg/L and lactate of 4.5 mmol/L. Sodium was 140 mmol/L, potassium 3.3 mmol/L, urea 8.0 µmol/L and creatinine 122 µmol/L, with a serum osmolality of 346 mOsm/kg. Blood gas analysis showed pH 7.47, pO₂ 8.9 kPa, pCO₂ 6.7 kPa, bicarbonate 30.3 mmol/L, base excess +6 mmol/L. The haemoglobin, platelets and prothrombin time were within the normal range and the patient's

CrossMark

To cite: Spyridoulas A, Riaz MS. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213411

liver function tests, cardiac troponins and corrected calcium were also normal.

DIFFERENTIAL DIAGNOSIS

The initial clinical impression for the patient's reduced level of consciousness in the emergency department was thought to be respiratory failure, hypotension and hypothermia, in addition to a hyperglycaemic state. Differentials included severe decompensated hypothyroidism considering her medical history and myxoedematous appearance, sepsis and cerebrovascular accident.

TREATMENT

The patient had a total intravenous fluid infusion of 6 L of crystalloids, using 0.9% saline and Hartmann's solution over the first 24 h of admission, in order to achieve euvolaemia, guided by central venous pressure, systolic pressure variation on intra-arterial blood pressure waveform and urine output. She required norepinephrine to support her blood pressure but remained cardiovascularly stable after initial resuscitation. Synchronised intermittent mandatory ventilation was achieved in keeping with a normal respiratory compliance.

Ongoing treatment involved intravenous hydrocortisone 100 mg three times per day and continued thyroid hormone replacement with intravenous liothyronine 20 µg two times per day and levothyroxine 100 µg once daily via nasogastric tube. Free T₄ increased to 8.4 pmol/L and TSH decreased to 4.7 mU/L over the subsequent 6 days, approaching normality. The patient was maintained on a nasogastric feed, which she was absorbing with minimal aspirates, and also required additional intravenous potassium supplementation via a central line. Other biochemical parameters also normalised during this time. Her septic screen was negative and antibiotic therapy was discontinued. A cortisol level checked on day 2 was >1660 nmol/L.

She was extubated uneventfully after 5 days to a GCS of 14, returning to her baseline level of cognition according to her family. Her husband confirmed that she had been taking her medication regularly at home, including her metformin and levothyroxine, leading up to her presentation to hospital without any recent dose changes.

OUTCOME AND FOLLOW-UP

The patient was discharged from intensive care after 7 days and remained in hospital for a further 3 weeks. Thyroid hormone treatment was subsequently titrated down as her thyroid levels normalised, after which she was managed on thyroxine therapy alone, and steroids were discontinued. She required physiotherapy input to return her mobility to baseline level of function and had a slow improvement in her other clinical symptoms such as anorexia.

DISCUSSION

Myxoedema coma is a presentation of decompensated severe hypothyroidism with hypotension, hypothermia and reduced level of consciousness or coma. It is a rare endocrine emergency with an incidence of 0.22/million/year. It requires rapid diagnosis and treatment to improve outcomes, and is associated with multiorgan failure with a reported mortality of 25–60%.^{2–4}

Poor prognostic factors associated with myxoedema coma include older age, requirement for mechanical ventilation, bradycardia of <44 bpm, persistent hypotension, hypothermia of <34°C, reduced level of consciousness, delayed treatment, APACHE II >20, and associations with sepsis and myocardial infarction. Treatment defaulters are also likely to have more severe hypothyroidism with higher mortality rates compared to

de novo presentations, however, the aetiology of hypothyroidism has not been shown to influence outcomes. The Sequential Organ Failure Assessment has also been shown to be effective in predicting mortality.^{5 6}

Respiratory failure in severe hypothyroidism is caused by reduced sensitivity to hypoxia and hypercapnia with diminished central respiratory drive and hypoventilation, which is also contributed to by skeletal muscle weakness, reduced ATP production and decreased nerve conduction speed.⁷ As a result, respiratory compliance is reduced and patients may require mechanical ventilation.⁸ The patient's respiratory failure in this case likely resulted from a combination of diminished central drive with muscular weakness, and reduced chest wall compliance related to her obesity, as gas exchange rapidly improved after instituting intermittent supportive mechanical ventilation. This patient had a grade 1 laryngoscopy; however, intubation may also be difficult due to weight gain, mucopolysaccharide infiltration of the laryngopharynx and vocal cord oedema, which may itself cause airway obstruction.^{9 10}

Severe hypothyroidism also impairs myocardial contractility, reducing stroke volume and cardiac output, and it may present with bradycardia, atrioventricular conduction blockade and shock. Pericardial effusions can occur, and the ECG may feature a low voltage waveform with QT interval prolongation and flattened T waves.

It is rare for patients to present in a comatose state even in profound hypothyroidism, and they are more likely to have fluctuating cognition and hypoactive delirium than an altered level of consciousness. Cerebellar signs such as ataxia and delayed tendon reflexes may also be present, and seizures can occur that are also contributed to by coexisting hypoxia, hypercapnia, hypoglycaemia and hyponatraemia.¹¹ In the case described, the respiratory failure and hyperglycaemic state will have contributed to a depressed level of consciousness.

Severe decompensated hypothyroidism is typically associated with hypoglycaemia, hypo-osmolality and hyponatraemia due to increased antidiuretic hormone production secondary to reduced cardiac output, and reduced renal plasma flow and glomerular filtration rate, which may increase total body water.^{12 13} This patient, however, had marked hyperglycaemia causing a hyperosmolar state with a normal plasma sodium concentration and no significant blood ketones, which is typical of hyperglycaemic hyperosmolar state (HHS). HHS characteristically features severe dehydration, hyperglycaemia (>30 mmol/L) without significant ketonaemia (<3 mmol/L) or acidosis, and has a high osmolality over 320 mOsmol/kg. It carries a higher mortality than diabetic ketoacidosis and generally affects older patients with diabetes.

We did not identify any precipitating source such as infection, myocardial infarction, stroke, trauma or surgical stress that may have caused it in this case. In addition, this patient had not altered or started taking any new medications that may have affected her blood glucose levels. It is likely that decompensation of her hypothyroidism and resulting stress response caused an acute reduction in the insulin level of this diabetic patient, precipitating a HHS. Decompensation of her hypothyroidism may have initially been related to undertreatment, and this subsequently deteriorated faster as HHS progressed over a number of days prior to her presentation with critical illness.

We managed this patient's fluid resuscitation using 0.9% saline and Hartmann's solution, avoiding hypotonic fluids. Considering that her metabolic parameters are likely to have deteriorated over a few days, we did not want to correct the plasma osmolality too rapidly, which may have caused cerebral

oedema. We also monitored the plasma osmolality daily to ensure it was gradually normalising, and to guide fluid replacement. HHS requires intravenous fluid replacement of 100–200 mls/kg with 0.9% sodium chloride to replace fluid and electrolyte losses. Although we started an insulin infusion after admission to critical care, in HHS, the blood glucose concentration will normally decrease with fluid replacement alone, and intravenous insulin should only be started once blood glucose levels plateau or if there is significant concurrent ketosis present.¹⁴ Starting insulin before adequate fluid resuscitation may actually worsen shock as a further decrease in plasma osmolality may cause fluid to move out of the vascular compartment into the intracellular volume, and our patient may not have required as much vasopressor had we delayed starting insulin. It is therefore recommended that plasma glucose decrease at a rate of 4–6 mmols/h, aiming to achieve a target blood glucose level of 10–15 mmol/L with a normalisation of biochemistry by 72 h.¹⁴ This prevents rapid changes in osmolality, which can be harmful.

Severe hypothyroidism is also associated with a reduced basal metabolic rate and impaired thermoregulation. Mucopolysaccharide infiltration and oedema of the gastrointestinal tract can cause gastric atony and paralytic ileus affecting enteral feeding and medication absorption, however, we managed this by the use of prokinetics, finding minimal aspirates via the nasogastric tube.

Patients are also reported to have a higher risk of bleeding due to coagulopathy relating to a reduction in factors V, VII, VIII, IX and X, with acquired von Willebrands syndrome.¹⁵ There is also a reduced cell-mediated immune response and an increased risk of severe infection. Investigations will show decreased plasma triiodothyronine and thyroxine concentrations, and raised TSH levels in primary hypothyroidism, and low/normal levels in secondary hypothyroidism.

There is varying opinion on thyroid hormone replacement strategy in managing myxoedema coma due to the lack of clinical studies available on the treatment of acute decompensated hypothyroidism. Both T₄ and T₃ are available parenterally and via the nasogastric route in those with coma, although the route of administration has not been shown to have an influence on outcome if the patient is absorbing via the gastrointestinal tract.^{5 16} Administration is a balance between increasing thyroid levels quickly against the risk of precipitating arrhythmias or myocardial ischaemia. This patient was managed in conjunction with the endocrinology team and was treated with a bolus dose of liothyronine followed by a combination of normal doses of both agents, which was tolerated well and provided a swift clinical response.

The use of combination therapy avoids larger doses of a single hormone, which is more likely to cause cardiac stress. T₃ also has the advantage of having a faster onset of action compared to T₄. It crosses the blood–brain barrier more readily, improving cognitive symptoms, and its supplementation is beneficial in hypothyroidism and systemic illness where there is a reduced rate of peripheral conversion of T₄ to T₃.¹ The use of T₃ hormone, however, has previously been reported to increase the risk of developing arrhythmias and to have a higher mortality rate.⁴ T₃ has been used safely in cardiac patients with congestive heart failure and in those undergoing coronary artery bypass surgery.^{17 18} The risk of complications is increased in elderly patients or those with cardiac comorbidities or instability and when higher doses of T₃ are administered (more than 75 µg/day).¹ T₄ monotherapy can be used with a loading dose of 200–500 µg, allowing a slower peripheral conversion to T₃

and a steady increase in thyroid levels. Thyroxine is recommended as first-line treatment in such patients, and the addition of T₃ should be considered on an individual basis in younger patients and in those without cardiovascular complications. As thyroid levels increase, bradycardia and hypotension will be corrected; thermoregulation is also restored and metabolic derangements should normalise.

Steroid replacement should also be administered to patients presenting with myxoedema coma as they may have concurrent hypoadrenalism, and thyroxine administration can increase the metabolism of cortisol causing a relative adrenal insufficiency.

This patient had a successful outcome despite a number of poor prognostic factors. Early recognition of decompensated hypothyroidism, management in critical care and timely initiation of thyroid hormone treatment, we believe were vital in achieving a positive outcome. The HHS was also recognised and treated, contributing to a prompt recovery for the patient.

Learning points

- ▶ Decompensated hypothyroidism is a cause of reduced level of consciousness in patients presenting with hypothermia to the emergency department.
- ▶ Myxoedema coma is associated with multiorgan failure and a high mortality rate that requires early recognition, timely initiation of thyroid hormone replacement and organ support in critical care.
- ▶ Severe hypothyroidism should be considered in patients with a hyperglycaemic hyperosmolar state as well as in its characteristic presentation of hypoglycaemia, hyponatraemia and hypo-osmolality.
- ▶ A hyperglycaemic hyperosmolar state features severe metabolic derangements and its management should involve specialist endocrinologist and critical care teams to guide fluid replacement and correct osmolality, electrolyte and glucose derangements.

Twitter Follow Muhammad Shakeel Riaz at @mshakeelriaz

Contributors AS and MSR were involved in acquisition of information in writing the case report. AS drafted and revised the report and approved the final version to be published, and is accountable for its accuracy. MSR supervised writing the report, revised it and approved the final versions.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Klubo-Gwiedzinska J, Wartofsky L. Myxoedema Coma. In: Wass JAH, Stewart PM. 2011. *Oxford textbook of endocrinology and diabetes*: Oxford, 2011:537–42.
- 2 Salomo LH, Laursen AH, Reiter N, et al. Myxoedema coma: an almost forgotten, yet still existing cause of multiorgan failure. *BMJ Case Rep* 2014;2014:pii: bcr2013203223.
- 3 Jordan RM. Myxedema coma. Pathophysiology, therapy, and factors affecting prognosis. *Med Clin North Am* 1995;79:185–94.
- 4 Yamamoto T, Kukurama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid* 1999;9:1167–74.
- 5 Dutta P, Bhansali A, Masoodi SR, et al. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. *Crit Care* 2008;12:R1.
- 6 Beynon J, Akhtar S, Kearney T. Predictors of outcome in myxoedema coma. *Crit Care* 2008;12:111.
- 7 Mills L, Lim S. Identifying and treating thyroid storm and myxedema coma in the emergency department. *Emerg Med Pract* 2009;11:8.

- 8 Klubo-Gwiedzinska J, Wartofsky L. Thyroid emergencies. *Med Clin N Am* 2012;96:385–403.
- 9 Lee CH, Wira CR. Severe angioedema in myxedema coma: a difficult airway in a rare endocrine emergency. *Am J Emerg Med* 2009;27:1021.
- 10 Sherry KM, Hutchinson IL. Postoperative myxoedma. A report of coma and upper airway obstruction. *Anaesthesia* 1984;39:1112–14.
- 11 Fjølner J, Søndergaard E, Kampmann U, *et al.* *BMJ Case Rep* 2015;2015:pii: bcr2014209071.
- 12 Skowsky WR, Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. *Am J Med* 1978;64:613–21.
- 13 DeRubertis FR Jr, Michelis MF, Bloom ME, *et al.* Impaired water excretion in myxedema. *Am J Med* 1971;51:41–53.
- 14 Scott AR, Joint British Diabetes Societies (JBDS) for Inpatient Care; JBDS hyperosmolar hyperglycaemic guidelines group. Management of the hyperosmolar hyperglycaemic state in adults with diabetes. *Diabet Med* 2015;32:714–24.
- 15 Manfredi E, van Zaane B, Gerdes VE, *et al.* Hypothyroidism and acquired von Willebrand's syndrome: a systematic review. *Haemophilia* 2008;14: 423–33.
- 16 Arlot S, Debussche X, Lalau JD, *et al.* Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. *Intensive Care Med* 1991;17:16–18.
- 17 Hamilton MA, Stevenson LW, Fonarow GC, *et al.* Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. *Am J Cardiol* 1998;81:443–7.
- 18 Güden M, Akpınar B, Saggıbag E, *et al.* Effects of intravenous triiodothyronine during coronary artery bypass surgery. *Asian Cardiovasc Thorac Ann* 2002;10:219–22.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow