Anamnesis of rare severe decompensated hypothyroid emergency management-myxedema crisis

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ABSTRACT

Background: Myxedema crisis is a rare decompensated hypothyroid clinical condition with high mortality if remains unrecognized.

Case presentation: We report a case of 36-year old male with a 3 week history of difficulty in breathing and facial puffiness. Periorbital edema, very dry skin, and non-pitting edema of legs was noticed on clinical examination. The patient was commenced on oral thyroxine for abnormal thyroid functions but deteriorated over the next few days. A diagnosis of myxedema crisis was made and was treated with a loading dose of oral thyroxine followed by maintenance dose along with intravenous steroids and intravenous antibiotics. Thyroxine dose was adjusted with serial thyroid functions on alternate days to confirm absorption. The patient clinically improved as thyroid functions advanced toward normalization.

Conclusion: Myxedema crisis remains poorly recognized condition due to extremely rare endocrine emergency. Under circumstances where intravenous hormone not available, oral thyroxine with daily or alternate day thyroid hormone level to confirm absorption and to adjust dose is equally effective way of management. Patient must be considered for an adrenal insufficiency unless proven otherwise.

Keywords: Case report, myxoedema crisis, thyroxine, steroids, antibiotics, adrenal insufficiency.

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Back ground

Myxedema crisis is an exceptionally rare endocrine emergency especially in western countries due to the widespread availability of screening tests for thyroid dysfunctions and even diagnosed at the subclinical stage [1]. The incidence of the myxedema crisis is approximately 1.08 cases per million people per year in Japan and 0.22 in Europe; however, no such data are available from Gulf Cooperation Council countries [2]. Hypothyroidism is fourfold more common in women than men. Despite the best possible care, the mortality rates may be as high as 25%-60% [3]. The term myxedema coma is a misnomer as most patients neither exhibit nonpitting edema nor coma, rather its cardinal manifestation is an altered mental status [4,5]. As thyroid hormone is vital to maintain normal body functions at both genetic and cellular levels. However pathophysiological substrate lies in the decreased intracellular T3 levels which lead to hypothermia and cardiac decompensation. Compensating mechanisms such as moderate diastolic hypertension, chronic peripheral vasoconstriction, and decreased blood volume get activated in chronic hypothyroidism. At this stage, any form of stress would end up breaking this fragile equilibrium of compensatory mechanisms [6].

Case Presentation

A 39-year-old male presented with 3 weeks history of dizziness, lethargy, facial swelling, and shortness of breath. There was no significant past medical history including illicit drug use. He was a smoker and apart from constipation he denied any systemic symptoms. He denied any drug or food allergies. On physical examination, he had facial puffiness, falling asleep with snoring otherwise oriented and arousable. He was afebrile, with a blood pressure of 100/70 mmHg, pulse rate of 70/minute regular, random blood sugar of 6.5 mmol/l, and room air oxygen saturation were 96%. Chest and cardiovascular examinations were normal. The abdomen was soft with significant protuberance. Neurological examination was unremarkable except for diminished ankle reflexes. A general physical examination showed dry skin with nonpitting edema of all four limbs (Figure 1).

Lab results showed hyponatremia with raised creatinine and liver enzymes. WBC was raised with both neutrophilia and eosinophilia (Figure 2).

A low voltage ECG with normal sinus rhythm (Figure 3).

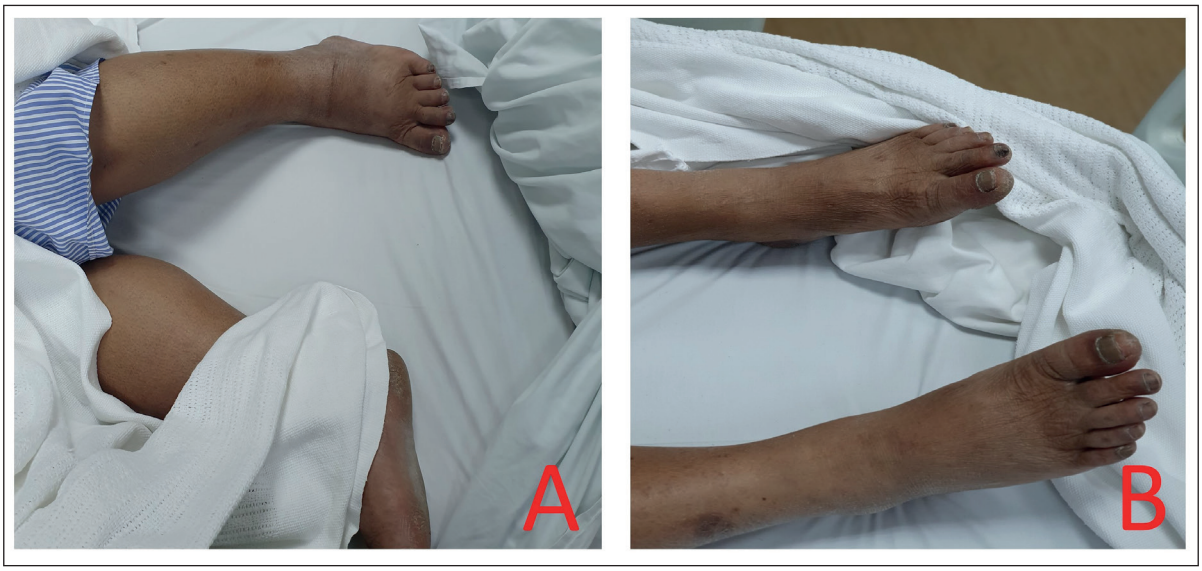

Figure 1. *(A). Nonpitting oedema. (B). Post treatment resolution of oedema.*

	On admission	On Discharge
Na	134	142
AST	168	24
ALT	54.4	45.7
T. Cholesterol	10.5	6.1
CK	1219	190
Eosinophil	1.19	0.02
Creatinine	143	96

Figure 2. *Biochemical parameters pre and post treatment.*

Chest X-ray was unremarkable. Urine showed leukocytes with one plus protein. Lipid profile showed mixed hyperlipidemia with a total cholesterol level of 10.5 mmol/l and triglycerides of 4.7 mmol/l. Thyroid functions were in keeping with severe hypothyroidism. A CT brain was done for a recent history of falls which showed frontoparietal extracranial hematoma.

The initial treatment was aimed at treating suspected sepsis with broad-spectrum antibiotics and oral thyroxine 100 mcg daily. However, the patient gradually deteriorated over the next 5 days with increased drowsiness and a reduction in oxygen saturation to 77%. Arterial blood gas analysis revealed decompensated type 2 respiratory failure. The patient was reviewed by the intensive care team and strong suspicion of severe myxedema was raised based on all available parameters. The patient was immediately commenced on non-invasive respiratory support and an urgent endocrine review was requested. After an endocrine review, a confirmed diagnosis of myxedema crisis was considered based on clinical features (facial puffiness, stupor and obtunded senses, nonpitting edema, bradycardia, hypoxia, low voltage ECG) as well as biochemical parameters (hyponatremia, type 2 respiratory failure, decreased GFR and very abnormal thyroid

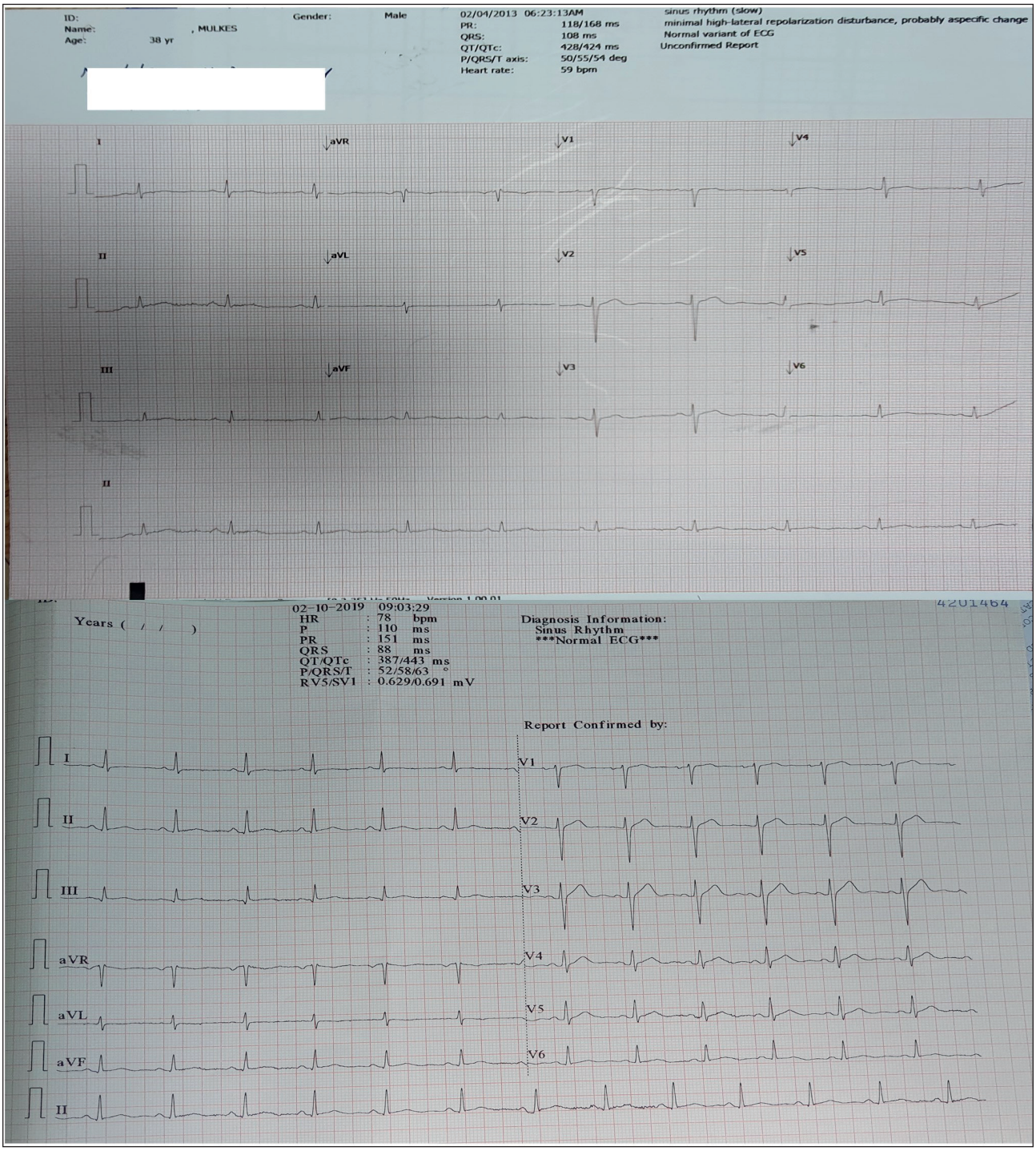

Figure 3. *(A). Pre-treatment. (B). Post- treatment.*

functions). A raised eosinophil was observed likely related to adrenal insufficiency.

An oral loading dose of 400 µg of thyroxine followed by a maintenance dose as per body weight was administered due to the unavailability of intravenous preparation. Later on, maintenance thyroxine dose as per body weight (1.6 µg/kg) was adjusted as per FT4 and TSH levels which were done on alternate days to confirm absorption (Figure 4).

Daily weight recording showed an approximately 10 kg weight loss on normalization of thyroid functions. He was also started on intravenous hydrocortisone along with antibiotics. The patient was gradually weaned off from non-invasive ventilation on a resolution of type two respiratory failure. He became more alert with reduced daytime somnolence and snoring. Edema subsided along with the normalization of hyponatremia, dyslipidemia, raised creatinine kinase, and hepatic transaminitis. A short Synacthen test was done with results in keeping with adrenal insufficiency. He was discharged on a daily oral thyroxine 200 µg along with a daily 5 mg prednisolone with advice to repeat the short Synacthen Test on follow-up.

Days	1st	7th	8th	10th	12th	14th	17th	20th	26nd
FT4	0.5	7.1	8.8	15.3		13.3	16.5	21.7	25.9
TSH	100	100	100	43.4		47.2	64	26.8	10.7
Thyroxine	100	400	200	200	150	200	250		

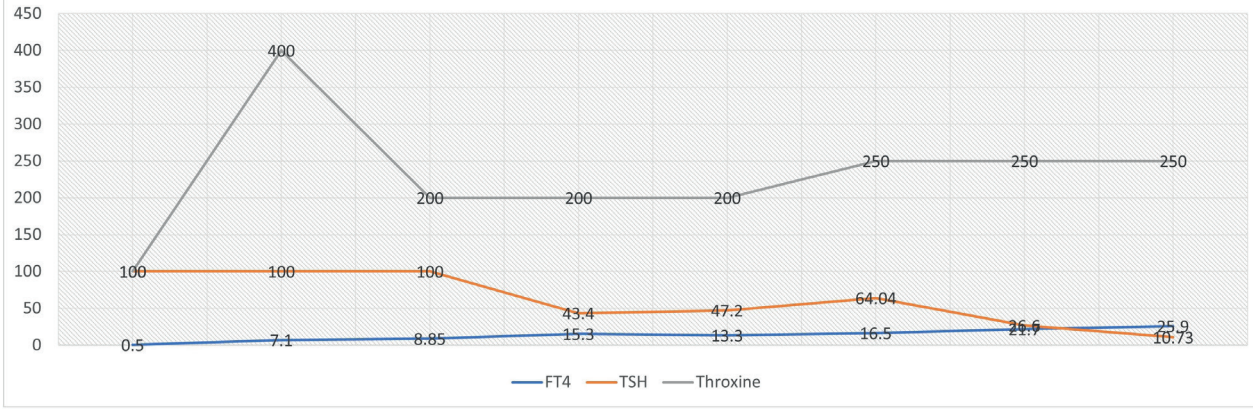

Figure 4. *TSH and FT4 response to adjustment of thyroxine.*

Table 1. *Physical findings in myxoedema crisis.*

Altered mental state
Alopecia
Cardiovascular: Raised diastolic blood pressure at early stage , hypotension at late stage, bradycardia
Delayed reflex relaxation
Dry cool doughy skin
Decreased gut motility and abdominal distension, paralytic ileus, faecal impaction, megacolon
Hypothermia
Hyperventilation
Non pitting oedema
Myxoedema face: Generalised swelling, macroglossia, ptosis, periorbital oedema, coarse sparse hair

Discussion

Myxedema crisis can be a result of any cause of hypothyroidism, e.g., autoimmune thyroiditis, post-radioactive iodine, and thyroidectomy. It can also be secondary to pituitary failure or related to drugs such as lithium or amiodarone toxicity. In severe long-standing hypothyroidism, multiple organ systems and metabolic pathways of the body slow down [4].

Approximately 80% of myxedema cases occur in females. Mortality rates can be more than 50% if the disease is not promptly diagnosed and treated. Even with timely medical intervention, mortality rates are as high as 25% [3]. There are three key features of the myxedema crisis. The first one is an altered mental state which can be initially somnolence and lethargy for months that can further progress to a comatose stage via stupor. The second is defective thermoregulation. Fever may be absent despite infection. Third is precipitating factors [7] (Table 1).

Low intracellular T3 is the basic underlying pathology that causes hypothermia and reduced cardiac contractility. Hypothermia is a strong predictor of mortality. The body tries to compensate through neurovascular adaptations including chronic peripheral vasoconstriction, mild diastolic hypertension, and diminished blood volume. Another consequence is a decreased metabolism of drugs leading to overdosing on medications particularly sedatives, hypnotics, and anesthetic agents which can precipitate a myxedema crisis. Decreased gluconeogenesis, precipitating factors like sepsis, and concomitant adrenal insufficiency may contribute to hypoglycemia. In addition to the generalized depression of cerebral function, hyponatremia, hypoglycemia, hypoxemia, and reduced cerebral blood flow can precipitate focal or generalized seizures and deterioration in consciousness level [1,3].

Cardiovascular manifestations are considered the main cause of mortality in the myxedema crisis [8]. Low intracellular T3 has a negative ionotropic and chronotropic effect on cardiac muscles leading to reduced stroke volume, low cardiac output, bradycardia, and sometimes hypotension [9]. In the decompensated state, low cardiac output and hypotension will result in cardiogenic shock which may not be responsive

Table 2. *Diagnostic scoring system for myxoedema coma.*

Thermoregulatory dysfunction		Cardiovascular dysfunction	
>35°C	0	Bradycardia	
32°C-35°C	10	Absent	0
<32°C	20	50-59	10
Central nervous system effects		40-49	20
Absent	0	<40	30
Somnolent/lethargic	10	Other ECG changes	10
Obtunded	15	Pericardial/pleural effusions	10
Stupor	20	Pulmonary oedema	15
Coma/Seizures	30	Cardiomegaly	15
Gastrointestinal findings		Hypotension (90/60 mmHg)	20
Anorexia/Abdominal pain/constipation	5	Metabolic disturbances	
Decreased intestinal motility	15	Hyponatremia (<135 mEq/l)	10
Paralytic ileus	20	Hypoglycaemia (<60)	10
Precipitating event		Hypoxemia (pO2<88)	10
Absent	0	Hypercapnia (pCO2<50)	10
Present	10	Decrease in GFR	10
Total score			
60/>		Highly suggestive/diagnostic of MC	
25-59		Suggestive of risk for MC	
<25		Unlikely to indicate MC	

ECG: QT prolongation, low voltage complexes, BB block, heart blocks or nonspecific ST-T changes.
Source: Popoveniuc et al. [11].

to vasopressors even with thyroid hormone replacement in the initial stages [8]. In severe cases, pericardial effusion is caused by the accumulation of mucopolysaccharides-rich fluid within the pericardial sac. Congestive cardiac failure is rare in the absence of pre-existing cardiac disease. ECG findings may include bradycardia, varying degrees of blocks, low voltage, nonspecific ST segment changes, flattened or inverted T waves, prolonged QT interval, and ventricular or atrial arrhythmias. Among these patients, plasma volume is decreased with increased capillary permeability resulting in fluid accumulation in tissues and spaces [3]. All of these cardiac changes are reversible with hormone replacement [10].

The main pulmonary effect is hypoventilation due to central ventilatory drive suppression with decreased responsiveness to hypoxia and hypercapnia [4]. Macroglossia or myxedema of the nasopharynx and larynx reduces the effective airway passage. Fluid accumulations and altered vascular permeability lead to pleural effusions and decreased diffusing capacity. Full recovery may take up to 3 to 6 months after hormone replacement therapy [10]. Renal impairment is multifactorial due to poor cardiac output and renal hypoperfusion which leads to reduced glomerular filtration rate, and excess. Rhabdomyolysis secondary to hypothyroid myopathy can cause acute kidney injury [6]. As far as the gastrointestinal

Table 3. *Diagnostic scoring system for myxoedema coma adapted for Chiong et al. [12].*

GLASGOW Coma scale	
0-10	4
11-13	3
14	2
15	0
TSH	
>30	2
15-30	1
Low T4	1
Hypothermia	1
Bradycardia (<60)	1
Precipitating event	1
Recommendation	
Total score	
Category	
Most Likely	8-10
Treat	5-7
Likely	
Treat if there are no Other causes	
Unlikely	
Consider other diagnosis	<5

Source: Chiong et al. [12].

tract is concerned, in myxedema coma, there is mucopolysaccharide infiltration, edema, and neuropathic changes that lead to malabsorption, gastric atony, impaired peristalsis, paralytic ileus, and megacolon. Coagulopathy due to acquiring Von Willebrand syndrome and decreased factors V, VII, VIII, IX, and X can cause gastrointestinal bleeding. An anemic picture can be microcytic secondary to hemorrhage or macrocytic due to B12 deficiency or normocytic normochromic due to decreased oxygen requirement and erythropoietin [3].

There are two diagnostic scoring systems available for myxedema crisis but neither of them is globally validated. The first diagnostic scoring system is based on clinical parameters [11]. A score of 60 or above has a sensitivity of 100% and specificity of 85% while a score between 45 to 59 could be classified as at risk for myxedema coma (Table 2).

The other scoring system for diagnosis of myxedema coma uses six variables including heart rate, temperature, Glasgow Coma Scale, TSH level, free T4 levels, and precipitating factors with sensitivity and specificity of 80% [12] (Table 3).

The management of myxedema coma/crisis is a real medical emergency as symptomatology overlaps with other critical conditions [13]. Coma, low GCS, and higher APACHE II scores correspond with poor outcomes [3,4,13]. Management should be done in ICU settings and avoid active warming [6]. Initially, there is a poor response to ionotropic support due to decreased sensitivity to alpha and beta-adrenergic stimulation due to a hypothyroid state despite high catecholamine levels [13]. The hypothalamic pituitary adrenal axis is impaired in severe hypothyroidism with a risk of the adrenal crisis on the restoration of normal metabolic rate with exogenous thyroid hormones. Glucocorticoid is indicated empirically at a stress dose prior to starting supplementation of thyroid hormone and should be continued until adrenal insufficiency is ruled out [4-6]. A vigorous search for precipitating factors is mandatory despite the absent signs of infection (like fever, tachycardia, and leukocytosis). Prophylactic antibiotics are indicated until the infection is ruled out [6]. Thyroid hormone replacement recommendations are based on a series of case reports and expert opinions due to the rarity of the disease. The ultimate treatment is synthetic thyroid hormone (L thyroxine) replacement. An initial 300-500 µg loading dose of L thyroxine is suggested with preference to intravenous if possible due to alteration in absorption and urgency of immediate bioavailability. Subsequent doses should be 1.6 µg/kg or 75% of this dose in case of intravenous administration [6,14]. If there is no response in 24 hours, the addition of liothyronine is recommended as a conversion of FT4 to FT3 is suppressed in a myxedema crisis. The lower end of the dosing range is recommended for the elderly and those patients who are at risk of cardiac complications such as myocardial ischemia and arrhythmias. An alternative scheme is an initial intravenous dose of 200-300 µg levothyroxine plus 10-25 µg liothyronine followed by 2.5-10 µg liothyronine every 8 hours depending on the patient's age and presence of cardiovascular risk factors [6]. Upon clinical improvement, liothyronine is discontinued and a daily oral T4 replacement dose is maintained [3,7]. Some advocate combination of liothyronine and levothyroxine to have an earlier beneficial effect on neuropsychiatric symptoms [1]. Arlot and colleagues demonstrated that clinical response in the oral route was prompt even in myxedema ileus [15]. Yamamoto et al. [16] showed an association of increased mortality especially in elderly patients with a high dose of LT4 (>500 µg/day) and LT3 (>75 µg/day) [4,13,10]. In our case, due to the non-availability of intravenous levothyroxine and liothyronine, we used oral levothyroxine at loading dose upon diagnosis followed by maintenance dose as per body weight and monitored blood FT4 and TSH level on the almost alternate day to confirm absorption and to titrate thyroxine dose.

Conclusion

We have presented a rare case of an endocrine emergency that has a high mortality despite early recognition and management. Timely diagnosis of myxedema crisis and prompt management with thyroid hormone and glucocorticoid are vital to achieving a positive outcome. In the absence of intravenous thyroid hormone, oral replacement should be offered with serial thyroid hormone levels to verify absorption and optimize hormone replacement therapy in the future.

What is new?

Myxedema crisis is an extremely rare medical emergency with a spectrum of symptoms that overlap with other common medical emergencies. Any delay in diagnosis can lead to very poor outcomes due to very high mortality. The second issue is the lack of evidence-based management protocols. The authors used an oral route of thyroxine to manage our patient with the help of serial thyroid functions to confirm absorption which was very helpful in the management plan in circumstances where intravenous preparations were not available like ours.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written and informed consent was taken from the patient to publish this case report.

Ethics approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 39 years old
2	**Final diagnosis**	Myxedema crisis
3	**Symptoms**	Facial puffiness, shortness of breath, increased somnolence, drowsiness
4	**Medications**	Levothyroxine, hydrocortisone, antibiotics
5	**Clinical procedure**	A loading dose of thyroxine followed by maintenance dose (1.6 µg/kg), hydrocortisone and antibiotics, short Synacthen test
6	**Specialty**	Endocrinology