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THYROID STORM IN THE SHADOWS OF MULTIPLE ENDOCRINE NEOPLASIA (MEN) 2A: A CASE OF OVERLAPPING ENDOCRINE EMERGENCIES

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ABSTRACT

Thyroid storm is observed in patients with untreated Graves' disease, typically triggered by stressors such as acute illness or recent surgery. This case presents a female with acute metabolic encephalopathy initially attributed to drug overdose and septic shock, later diagnosed with thyroid storm. Despite clinical stabilisation, the patient developed resistant hypertension and elevated metanephrine levels, raising suspicion for phaeochromocytoma and potential multiple endocrine neoplasia (MEN) 2A. This case highlights the importance of considering syndromic and autoimmune associations in complex endocrine presentations.

KEYWORDS

Thyroid storm, phaeochromocytoma, MEN 2A, acute metabolic encephalopathy

LEARNING POINTS

- Thyroid storm should be considered when there is a rising temperature and increasing agitation despite appropriate treatment.
- If hypertension persists after the fever of thyroid storm was managed with propylthiouracil and iodine an additional diagnosis, such as phaeochromocytoma, should be considered.
- We found no published reports on MEDLINE linking Graves' disease or thyroid storm with MEN 2A to help guide our management.

INTRODUCTION/BACKGROUND

Thyroid storm is a rare and life-threatening manifestation of thyrotoxicosis. It is characterised by hypertension, tachycardia, hyperthermia, tremors and other multiorgan manifestations. MEN 2A is an autosomal dominant genetic disorder characterised by medullary thyroid carcinoma, primary hyperparathyroidism and phaeochromocytoma. Although no reports link Graves' disease or thyroid storm

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with MEN 2A, we present a unique case of thyrotoxicosis from new-onset Graves' disease with high suspicion for MEN 2A.

CASE DESCRIPTION

A 42-year-old female with mild asthma presented to the emergency department with altered mental status secondary to opioid and cocaine overdose. She was intubated for acute hypoxic respiratory failure and admitted to the ICU. Initial vital signs were as follows: temperature 37.8°C, pulse 108 bpm, respiratory rate 26 breaths per minute, blood pressure 84/53 mmHg and SpO_2 86% on high-flow nasal cannula. On examination, she was obtunded, unable to follow commands and her Glasgow Coma Scale was 3. Other significant examination findings included constricted pupils and severe respiratory distress. Laboratory results showed a white blood cell count of 5.6 $\times 10^3$/µl, potassium 2.6 mmol/l, lactate 5.2 mmol/l, alanine aminotransferase 36 U/l, aspartate aminotransferase 63 U/l, alkaline phosphatase 275 U/l. Urine toxicology was positive for fentanyl.

On the first day of ICU admission, the patient was diagnosed with septic shock secondary to influenza B infection, complicated by superimposed methicillin-sensitive Staphylococcus aureus pneumonia. She received IV fluids, vasopressors, oseltamivir, vancomycin and piperacillin-tazobactam. Vasopressors were removed within 24 hours.

On day 2, she developed hypertension (150–160/50–60 mmHg) and tachycardia (heart rate 110–120s), managed with IV labetalol. Suspected opioid and cocaine withdrawal was managed using the Clinical Opiate Withdrawal Scale protocol and methadone. Despite the infection being resolved, she had persistent fevers up to 39.4°C; investigation revealed a thyroid stimulating hormone level of <0.015 mIU/l and a free T4 level >6.99 ng/dl. She scored 80 points on the Burch-Wartofsky Point Scale (BWPS) and TS1 on Akamizu diagnostic criteria, which strongly suggested thyroid storm, prompting an endocrinology consultation.

On day 4, the patient started methimazole, propranolol and hydrocortisone. Pharmacy was consulted the same day, and the patient was initiated on an oral solution of potassium iodide administered via the orogastric tube. Her thyroid stimulating immunoglobulin was 373% and the thyrotropin receptor antibody was 31 IU/l, confirming the diagnosis of Graves' disease; her thyroglobulin antibody was 9 IU/ml. The thyroid ultrasound revealed a left-sided nodule with a thyroid imaging reporting and data system category 4, indicating moderate suspicion for malignancy. To manage her hypertension, she was started on losartan and amlodipine, along with labetalol as needed.

By day 6, her free T4 levels began to decline with her fever improving, though she continued to have occasional but less frequent episodes of low-grade fever *(Fig. 1)*. However, her hypertension persisted requiring addition of chlorthalidone, and hydralazine was added to her regimen. Concurrently, the patient developed tachypnoea and diffuse bilateral wheezing; a repeat chest X-ray was clear, raising concern for an asthma exacerbation, possibly precipitated by propranolol. Propranolol was replaced with carvedilol, resulting in resolution of her wheezing and tachypnoea. By day 8, her free T4 levels had normalised to 1.15 ng/dl. However, her blood pressure remained elevated at 150–160/70–80 despite aggressive antihypertensive therapy, which included losartan 100 mg daily, carvedilol 25 mg twice daily, amlodipine 10 mg daily, chlorthalidone 50 mg daily, nifedipine 60 mg daily and labetalol as needed.

On day 9, the patient was successfully extubated. Her potassium iodide was discontinued, and steroid taper was started. Persistent hypertension without tachycardia prompted evaluation for secondary causes. Her renin-aldosterone ratio was unremarkable. However, 24-hour urine collection revealed total metanephrines of 1,689 mcg/24 hrs, fractionated metanephrines of 257 µg/24 hours, and normetanephrine levels of 1,200 µg/24 hours; parathyroid hormone was mildly elevated at 60 pg/ml. She was transferred to the inpatient unit with outpatient plans for CT abdomen/pelvis, PET scan, thyroid nodule biopsy and genetic testing.

DISCUSSION

Thyroid storm is a rare, life-threatening endocrinological emergency, triggered in patients with untreated Graves' disease during acute stress. Mortality can reach up to 25% if left untreated[1]. The precise pathophysiology of thyroid storm remains incompletely understood; however, it is thought to result from a surge of free T3 and T4 levels[2].

Diagnosis can be delayed due to symptoms overlapping with other critical conditions, as seen in our patient who had multifactorial encephalopathy. Diagnosis relies on a combination of clinical features and laboratory tests demonstrating suppressed thyroid stimulating hormone with elevated free T4 and/or T3, along with other diagnostic tools such as the BWPS score and Akamizu diagnostic criteria. Burch and Wartofsky developed a points system to help distinguish thyroid storm from severe thyrotoxicosis

Figure 1. Daily body temperature trends throughout the hospital corse.

by scoring dysfunction in four major systems, with scores ≥45 indicating high suspicion; the system is sensitive but not highly specific[3]. In 2012, Akamizu et al. established diagnostic criteria for thyroid storm based on Japanese surveys, defining 'definite' cases as elevated free thyroid hormones with central nervous system symptoms and at least one non-central nervous system symptom[3]. Other useful diagnostic workup consists of elevated thyroid stimulating immunoglobulin/thyroid stimulating hormone receptor antibody, which can help identify underlying Graves' disease along with thyroid ultrasound.

Management involves a comprehensive approach with identification and treatment of precipitating factors. Our patient had multiple triggers: overdose, infection and unrecognised Graves' disease. Haemodynamic stabilisation is a critical initial step, followed by targeted pharmacologic therapy. This includes the use of thionamides (e.g. propylthiouracil or methimazole) followed by iodine administration. Glucocorticoids are also employed to reduce peripheral conversion of T4 to T3, and to address potential relative adrenal insufficiency. Beta blockers are recommended to mitigate the effects of sympathetic overactivity; however, agent selection must be individualised based on comorbid conditions. In this case, propranolol-induced asthma exacerbation necessitated a switch to carvedilol, a cardio selective beta-blocker with a more favourable respiratory profile.

Resistant hypertension refers to persistently elevated blood pressure despite using three different antihypertensive drugs, including a diuretic, at maximum tolerated doses. Our patient had persistent hypertension on six antihypertensive medications despite resolution of thyrotoxicosis and opioid withdrawal, prompting evaluation for secondary causes of hypertension. Her markedly elevated 24-hour urine metanephrines are highly sensitive for detecting phaeochromocytoma.

The possibility of autoimmune polyglandular disease should be considered when multiple endocrine abnormalities are present. In this case, resistant hypertension prompted concern for phaeochromocytoma, a catecholamine-secreting tumour that may occur as part of a syndromic disorder such as MEN 2A. The diagnosis of MEN 2A is further supported by the co-occurrence of a thyroid nodule with features suspicious for malignancy, elevated parathyroid hormone levels and biochemical evidence of phaeochromocytoma, fulfilling the classical triad of medullary thyroid carcinoma, primary hyperparathyroidism and phaeochromocytoma. Although rare, case reports have suggested a potential link between MEN 2A and autoimmune phenomena, raising the hypothesis that germline RET proto-oncogene mutations may affect immune tolerance and predispose to autoimmune disorders[5]. These findings underscore the need to consider both hereditary neoplastic syndromes and immune-mediated processes in the comprehensive evaluation of complex endocrine presentations.

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