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CASE REPORT

More, less or both?

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SUMMARY

A 67-year-old Caucasian woman with no prior medical history was admitted to our hospital with complaints of generalised weakness, nausea, diarrhoea and weight loss. The patient suffered from tachycardia and hypotension. Blood tests revealed Graves' thyrotoxicosis and the patient was treated accordingly. However, patient's health continued to decline rapidly and further tests revealed a concomitant Addisonian crisis. Additional treatment with corticosteroids led to a full recovery. It is well known that autoimmune endocrine disorders tend to cluster. However, the presentation is usually sequential in time. This case reports the highly rare simultaneous presentation of Addison's disease and Graves' thyrotoxicosis. It also provides several suggestions to help establish the diagnoses.

BACKGROUND

Autoimmune endocrine disorders occur frequently in the general population and tend to cluster. This clustering is usually sequential in time although simultaneous presentations do occur in rare cases. These presentations often pose a challenge to the clinician and a delay in treatment is common.

The simultaneous presentation of two autoimmune endocrine disorders that we present in our case is extremely rare and difficult to diagnose. We aim to increase the knowledge of all physicians on the presentation of autoimmune endocrine disorders and also provide several suggestions, which can help in timely recognition and treatment of these disorders.

CASE PRESENTATION

A 67-year-old Caucasian woman presented to the emergency room of our hospital with complaints of generalised weakness, nausea, diarrhoea and weight loss. The patient had visited her general practitioner several times in the previous months with complaints of fatigue and generalised weakness. During her recent trip through Africa, she was hospitalised in Morocco and treated for a presumed bacterial enterocolitis, for which she received intravenous fluids and a course of azithromycin. However, the symptoms recurred directly after discharge.

At presentation in our hospital, we saw a weakened but not acutely ill woman. The patient was well orientated in time, place and person. The patient had a blood pressure of 85/49 mm Hg, pulse rate of 120 beats/min and a temperature of 37.4°C. Examination of heart, lungs and abdomen revealed no abnormalities. No hyperpigmentation

of the skin or mucous membranes was found after thorough examination; there was no bulging of the eyes or lid lag. We did not detect any myxoedema. Neurological investigation was without abnormalities and no signs of myopathy were observed.

INVESTIGATIONS

Blood tests at presentation showed a C reactive protein (CRP) of 3 mg/L (range: <8 mg/L), erythrocyte sedimentation rate (ESR) 25 mm/hour (range: <30 mm/hour), haemoglobin 13.2 g/dL (range: 12–18 g/dL), white cell count $6.4 \times 10^9/L$ (range: $4.5 - 11 \times 10^9/L$), sodium 132 mmol/L (range: 136–146 mmol/L), potassium 4.1 mmol/L (range: 3.6–4.8 mmol/L), creatinine 29 $\mu\text{mol/L}$ (range: 49–90 $\mu\text{mol/L}$), urea nitrogen 8.7 mmol/L (range: 3.0–7.5 mmol/L), thyroid-stimulating hormone (TSH) <0.05 mU/L (range: 0.3–4.5 mU/L), free thyroxine (T4) 79.3 pmol/L (range: 12–22 pmol/L), TSH-receptor antibodies positive (4.7 IU/L, range: <1.1 IU/L) and no signs of inflammation.

Blood cultures were negative, and blood tests 3 days later, taken before administration of fludrocortisone/hydrocortisone and before aggressive fluid resuscitation, showed an autoimmune-mediated hypocortisolism and hypoadosteronism, with blood cortisol <30 nmol/L (range: 150–600 nmol/L), aldosterone <0.03 nmol/L (range: 0.03–0.35 nmol/L) and positive adrenal cortex antibodies (NOVA Lite Adrenal IFA Slides; Inova Diagnostics, San Diego, California, USA). Erroneously, we did not measure adrenocorticotrophic hormone (ACTH) levels before starting treatment, making a reliable measurement afterwards impossible. Furthermore, stool samples were negative for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridium difficile* and other infectious micro-organisms.

DIFFERENTIAL DIAGNOSIS

The combination of tachycardia, negative blood cultures and failure to respond to intravenous fluids for hypovolaemia warranted further investigations. At initial presentation, we considered a septic shock. However, there were no signs of inflammation. We also considered a hypovolaemic shock due to ongoing diarrhoea. However, the patient did not respond to intravenous fluids. Infectious colitis and inflammatory bowel disease were also briefly considered; however, stool samples were negative and there was a normal CRP and ESR. Ischaemic colitis could also have been possible; however, the chronicity of the presentation and the normal laboratory findings made this unlikely. Pulmonary embolism was also considered, but the clinical presentation did not fit with this diagnosis.



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We strongly suspected a thyrotoxicosis at initial presentation, which was confirmed. However, the patient did not respond to the treatment and became increasingly ill in the following 2 days. Further blood test showed hypocortisolism and hypoaldosteronism, in a state of hypotension, with positive adrenal cortex antibodies, confirming the diagnosis of Addison's disease. However, ACTH measurements were unfortunately not performed prior to starting treatment.

TREATMENT

Initially, we started treatment with intravenous fluids and empirically ceftriaxone. Blood cultures proved negative and blood test confirmed the diagnosis of Graves' disease. We therefore stopped ceftriaxone and started treatment with high-dose propylthiouracil and propranolol.

However, the patient became increasingly ill and suffered from tachycardia, vomiting, hypotension and developed a fever (40.5°C). Blood test confirmed our suspicion of an Addisonian crisis, and treatment was started with hydrocortisone and fludrocortisone.

OUTCOME AND FOLLOW-UP

After treatment was started with hydrocortisone and fludrocortisone, the patient initially continued to deteriorate clinically, but showed a positive response after a few hours. The lack of initial improvement was probably due to the concurrent thyrotoxicosis. She was briefly admitted to the medium care unit for close observation. In the following 5 days, the patient started to respond to the therapy and her free T4 levels started to drop from 79.3 to 31.5 pmol/L (range: 12–22 pmol/L). She returned to the internal medicine ward and was discharged briefly thereafter and returned to her home country in good health.

DISCUSSION

This case discusses the simultaneous presentation of Addison's disease and Graves' thyrotoxicosis (figure 1).

Clustering of autoimmune endocrine diseases is well known, as is the case in Whitaker and Schmidt syndrome, also known as polyglandular syndrome type I and II.¹ Relatively common is the combination of hypothyroidism and Addison's disease that may present itself as part of polyglandular syndrome type I. However, the combination of Graves' and Addison's disease, as in our patient, is extremely rare.²



Figure 1 An artistic impression of Dr Thomas Addison and Dr Robert James Graves.

To the best of our knowledge only three cases are known in the literature, which describe the simultaneous presentation of Addison's disease and Graves' thyrotoxicosis.^{3–5} The clinical presentation was highly variable in all these cases. One case presented with a vasovagal episode and extensive vitiligo.³ Another case presented with general weakness and skin pigmentation that started several months ago. In both cases, the diagnosis of Addison's disease was made prior to diagnosing a thyrotoxicosis. In a third case report, the patient presented with headache, paresthesia, heat intolerance, general weakness and vomiting. The diagnosis of Graves' disease was established prior to diagnosing an Addisonian crisis.

One may speculate that the simultaneous presentation in our patient can be explained by the thyrotoxicosis unmasking a latent Addison's disease, since thyroid hormone can increase the metabolism of cortisol.⁶

Some clues in our case deserve special mentioning. First, we were puzzled by the patient's normokalaemia despite having Addison's disease. However, a recent study shows that hyperkalaemia is not universal in patients diagnosed with Addison's disease.⁷ It is also possible that potassium was lower than expected due to sustained gastrointestinal losses. Another explanation is that thyrotoxicosis may lower potassium levels, possibly by affecting the Na/K ATPase activity.⁸ It is therefore possible for thyrotoxicosis to mask hyperkalaemia as is seen normally in Addison's disease.

Second, the low serum creatinine drew our attention, especially in the presence of hypovolaemia and a normal muscle mass. An explanation for this might be long-standing Addison's disease, which can decrease muscle mass due to myopathy. However, thyrotoxicosis itself is associated with a low serum creatinine due to an increase in GFR and decrease in muscle mass.⁹ Since urea nitrogen is usually elevated in thyrotoxicosis, a raised urea/

Patient's perspective

When I was admitted to the hospital I realised that something was seriously wrong. I had been sick before, but never like this. I couldn't even walk properly any more!

During my stay at the hospital I felt somewhat delirious at first. I could not completely process what was going on, but remember that the doctors took a lot of blood for tests. I gave in to the circumstances and was hoping that they could find something in my blood to treat and hopefully cure.

When I got admitted to the medium care unit I realised that it might be more serious than I thought at first. I was never at fear of dying but had complete faith in the hospital and its staff. I recovered shortly after my stay at the medium care and left the hospital in good health.

After my admission to the hospital I contacted my general practitioner and she was shocked that I was diagnosed with Addison's disease and a fast working thyroid gland. I had visited her multiple times prior to my travels and hospitalisation with complaints of fatigue and generalised weakness. In hindsight I think she might have missed my condition due to lack of awareness, which she confirmed. I still visit the same medical centre but often choose a colleague of my old general practitioner, since I have lost some faith in her due to what happened. I would advise the medical community to raise awareness among medical professionals and the general community regarding autoimmune diseases, such as Addison's disease. That way the diagnosis can hopefully be confirmed much faster.

Learning points

- ▶ Always keep the possibility of several autoimmune endocrine disorders presenting simultaneously in mind.
- ▶ A raised urea/creatinine ratio may point to the diagnosis of a thyrotoxicosis.
- ▶ Normokalaemia in Addison's disease may be caused by a concomitant thyrotoxicosis.
- ▶ Early recognition and treatment of a patient with simultaneous Addison's disease and Graves' thyrotoxicosis will lead to reduced morbidity and mortality.

creatinine ratio, as was seen in our patient, may point to this diagnosis. Third, the lack of hyperpigmentation was also surprising, but several recent studies show that this is not always present in Addison's disease.^{7 10} The clues in our patient for Addison's disease were weakness, fatigue, gastrointestinal symptoms, hypotension, low sodium, low cortisol, low aldosterone and positive adrenal antibodies. These clues are highly specific for Addison's disease.^{7 10} Finally, we did not perform an ACTH test before starting treatment with hydrocortisone. We had no reasonable doubts with regards to the diagnosis, since we did measure hypocortisolism, hypoadosteronism and positive adrenal antibodies in a state of hypovolaemia, confirming the diagnosis of an 'adrenal hypocortisolism'. It was not possible to measure ACTH as we had already started treatment. However, we do recommend to always include an ACTH measurement, prior to starting treatment with hydrocortisone, as this gives more strength to the diagnosis, since it rules out a possible coexisting pituitary failure. Furthermore, measurement of ACTH is also important in the follow-up of Addison's disease since the value can give suspicion to over-replacement with corticosteroids. We did not perform a follow-up because the patient quickly returned to her home country after being discharged from the hospital.

Our case demonstrates the rare simultaneous presentation of Graves' thyrotoxicosis and Addison's disease. Possible clues for Addison's disease such as hyperkalaemia may be masked by the concomitant thyrotoxicosis. This case shows the importance of always keeping the possibility of another autoimmune endocrine

disorder in mind. It also provides several suggestions that can help the clinician in recognising the simultaneous presentation of a thyrotoxicosis and Addison's disease.

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REFERENCES

- 1 Leshin BYM. Southwestern Internal Medicine Conference : Polyglandular Autoimmune Syndromes. *Am J Med Sci* 1985;290:77–88. Elsevier Masson SAS.
- 2 Boelaert K, Newby PR, Simmonds MJ, *et al*. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010;123:183.e1–183.e9.
- 3 Newrick PG. Addison's disease and thyrotoxicosis presenting simultaneously. *Postgrad Med J* 1984;60:478–9.
- 4 Naqui J. Co-existence of Addison's disease and thyrotoxicosis. *Case reports* 1963:129–30.
- 5 Ganguri M, Abbas J, Zhyzhneyskaya S, *et al*. Simultaneous presentation of Graves' thyrotoxicosis and Addison's disease presenting as incipient adrenal crisis. *Endocr Abstr Poster Present* 2013;31:P96.
- 6 Hoshiro M, Ohno Y, Masaki H, *et al*. Comprehensive study of urinary cortisol metabolites in hyperthyroid and hypothyroid patients. *Clin Endocrinol* 2006;64:37–45.
- 7 Saevik A, Akterman A, Gronning K, *et al*. Clues for early detection of autoimmune Addison's disease – myths and realities. *J Intern Med* 2018;238:1–10.
- 8 Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. *Indian J Endocrinol Metab* 2012;16:204–10.
- 9 Iglesias P, Bajo MA, Selgas R, *et al*. Thyroid dysfunction and kidney disease: An update. *Rev Endocr Metab Disord* 2017;18:131–44.
- 10 Michels A, Michels N. Addison disease: early detection and treatment principles. *Am Fam Physician* 2014;89:563–8.

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