CASE REPORT

Addison's disease in a patient with hypothyroidism: autoimmune polyglandular syndrome type 2

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SUMMARY

A 57-year-old Caucasian woman with known autoimmune hypothyroidism diagnosed in 2006 presented to hospital with flu-like symptoms and circulatory collapse. She reported weight loss and gradual increase in her skin pigmentation over a 1-year period. Aggressive fluid resuscitation was instituted. Hormonal tests showed primary adrenal insufficiency. Appropriate steroid replacement was started with rapid clinical response. Subsequent antibody tests confirmed the diagnosis of autoimmune polyglandular type 2 (Schmidt's) syndrome. The adrenal crisis had been precipitated by influenza virus type B infection.

BACKGROUND

Diagnosis of autoimmune polyglandular syndromes (APS) is often difficult due to the non-specific and insidious nature of symptoms and clinical signs. Stressful insults such as infection, surgery or other trauma may precipitate catastrophic collapse in affected individuals. Accurate and timely diagnosis with subsequent appropriate hormone replacement therapy is often life-saving.

CASE PRESENTATION

A 57-year-old Caucasian woman was referred to hospital by her general practitioner with a 2-day history of flu-like symptoms, tachycardia and hypotension. The symptoms included malaise, headache, vomiting, appetite loss, dizziness as well as neck and joint pain. She had a history of hypothyroidism and was on adequate levothyroxine replacement.

In addition to her acute symptoms, the patient reported 20 kg of weight loss, lethargy, skin darkening (figure 1) and intermittent abdominal pain over 12 months preceding the acute presentation.

She appeared unwell, was mildly tender in the periumbilical region of the abdomen and had hyperpigmented palmar creases.

Blood tests showed hyponatremia with sodium at 128 mmol/L (reference range 135–145 mmol/L), normal potassium at 3.9 mmol/L (reference range 3.5–5.2 mmol/L), elevated urea at 8.9 mmol/L (reference range 2.9–7.7 mmol/L), increased creatinine at 99 µmol/L (reference range 45–90 µmol/L) and decreased estimated glomerular filtration rate 55 mL/min (appropriate >60 mL/min). C reactive protein (CRP) was elevated at 24 mg/L (reference range 0–8 mg/L) and the morning cortisol was low at 147 nmol/L (reference range 200–700 nmol/L). The baseline adrenocorticotrophic hormone (ACTH) was markedly elevated at 220 pmol/L (reference range 2–11 pmol/L). A short Synacthen test was

performed; baseline cortisol was 123 nmol/L, with a muted response to 132 and 143 nmol/L at 30 min and 60 min, respectively, poststimulation with 250 µg of Synacthen (normal incremental response should be greater than 200 nmol/L with respect to the baseline value).

Her plasma renin activity (PRA) was elevated at 12 ng/mL/h (reference range 0.5–5 ng/mL/h).

Adrenal autoimmunity was positive; this was shown by indirect immunofluorescence, 1:10 dilution, using a Euroimmun mosaic kit with monkey adrenal gland substrate able to demonstrate antibodies to the adrenal enzymes 21-hydroxylase, 17-hydroxylase and side-chain cleavage.

Human leukocyte antigen (HLA) typing using Luminex technology demonstrated HLA-DRB1*03.

Nasopharyngeal swabs had been sent as the patient had presented during the influenza season; real-time PCR tests were positive for influenza virus type B RNA.

Chest X-ray and abdominal X-ray showed no acute pathology.

The patient was diagnosed with Addison's disease in crisis, which was most likely precipitated by influenza type B infection. There was no other obvious source of infection.

Acute treatment included intravenous hydrocortisone with aggressive fluid resuscitation in the form of normal saline. She was subsequently switched to oral hydrocortisone. Mineralocorticoid replacement with fludrocortisone was also started.

She was discharged home with sick day advice to double up her hydrocortisone dose when unwell. She was also advised to obtain a medical alert emblem depicting that she had APS type 2 (APS2) and was on steroid replacement. She was issued

Figure 1 Pigmented skin of the patient (right) compared to her daughter's skin (left).

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Table 1 Comparing of the main features of different APS**Main features of autoimmune polyglandular syndromes**

APS Type 1/APECED	2 of 3 present from: mucocutaneous candidiasis Hypoparathyroidism Addison's disease
APS type 2/Schmidt's syndrome	Addison's disease AND Autoimmune thyroid disease AND/OR Type 1 diabetes mellitus
APS type 3/thyrogastic syndrome	Autoimmune thyroid disease AND Other autoimmune disease (EXCLUDING Addison's disease)
APS type 4	Combinations of autoimmune disease not fitting into the previous categories
IPEX/XLAAD/XPID	Immune dysfunction, diarrhoea and polyendocrinopathies, commonly type 1 diabetes mellitus

APECED, autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyglandular syndrome; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X linked; XLAAD, X linked autoimmunity-allergic dysregulation syndrome; XPID; X linked polyendocrinopathy immune dysfunction and diarrhea.

with a prescription for an ampoule of 100 mg hydrocortisone to be administered via the intramuscular route in case of an Addisonian crisis prior to getting to hospital; her partner was educated on how to reconstitute and administer the parenteral hydrocortisone.

The patient was followed up in clinic and had further screening for autoimmune disease including antiglutamic acid decarboxylase, anti-insulinoma antigen 2 (IA-2), antinuclear, antithyroid peroxidase (TPO), antithyroglobulin (Tg), antigastric parietal, antimitochondrial and antismooth muscle antibodies. These results were all negative except for positive anti-TPO and anti-Tg antibodies, in keeping with the patient's known autoimmune hypothyroidism.

DISCUSSION

This patient presented with both acute and chronic symptoms consistent with Addison's disease. Her history of significant weight loss, chronic fatigue, abdominal pain and darkening of the skin indicated that adrenal insufficiency had been present for some time. Autoimmune adrenal insufficiency is generally an insidious process with first the zona glomerulosa being affected, which may cause low serum aldosterone and increased PRA, followed later by zona fasciculata involvement with subsequent decrease in serum cortisol levels and increased ACTH, with hypocortisolism symptoms ensuing sometimes years after the beginning of the process.¹ The zona reticularis may also be affected, which can cause adrenal androgen deficiency;² however, this was not a feature in our patient. Infection, such as the influenza type B seen in this patient, is a common precipitant of adrenal crisis³ and patients often present with vomiting, abdominal pain and signs of shock. There was no other obvious source of infection in this patient, but the CRP of more than 20 mg/L suggests the possibility of a concomitant infection and/or inflammatory process at the time of presentation. The low cortisol in the context of acute illness was very suggestive of adrenal insufficiency, and the corresponding elevated ACTH and suboptimal cortisol response to ACTH after the short Synacthen test clinched the diagnosis. Positive adrenal antibodies confirmed an autoimmune cause for the adrenal insufficiency.

Autoimmunity is the most common cause of primary adrenal insufficiency in the developed world.

Autoimmune polyglandular syndrome type 2

APS2 is characterised by primary adrenal insufficiency associated with autoimmune thyroid disease and/or type 1 diabetes mellitus. When thyroid disease is associated with APS2, 50% of the time this is Graves' disease and 50% will be either Hashimoto's or atrophic thyroiditis.⁴ APS2 is a rare condition, with an incidence of 1–2/100 000/year.⁵ In addition to adrenal insufficiency, autoimmune thyroid disease occurs in 70% of APS2 cases, type 1 diabetes mellitus occurs in 50% and gonadal failure occurs in 5–50%.⁴ APS2 is a condition of adult onset, generally presenting in the third to fourth decade.^{5–7} Our patient's presentation with adrenal insufficiency at the age of 57 years was thus unusual and it is likely that her adrenal autoimmunity had been present for a considerable duration prior to development of clinical adrenal insufficiency. The clinical features of hypoadrenocorticism do not begin to appear until at least 90% of the glandular tissue has been destroyed.

There is a complex genetic basis for APS2 with association of certain HLA alleles and several patterns of inheritance including autosomal recessive, autosomal dominant and polygenic.⁷

Other autoimmune conditions are associated with variable frequency. These include pernicious anaemia, coeliac disease, hypogonadism, vitiligo, immune gastritis, parathyroid disease, myasthenia gravis, Sjögren's syndrome, rheumatoid arthritis and alopecia areata.^{4–6–7} The order of onset of autoimmune conditions is variable, with adrenal insufficiency presenting first in 50% of cases and following a diagnosis of thyroid disease or type 1 diabetes mellitus in 20% of cases.⁴ Management of APS2 involves screening for and treatment of related autoimmune conditions. Screening should be repeated at regular intervals as autoantibodies can develop at any time. Consideration should also be given for screening first-degree relatives of affected individuals. Screening for autoimmune conditions includes functional screening and screening for specific autoantibodies.⁶

Other APS

APS2 is the most common of several described APS.^{5–7} APS1, also called APECED (autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy) is characterised by chronic mucocutaneous candidiasis, hypoparathyroidism and Addison's disease.^{4–7} Ectodermal dystrophy also occurs, manifesting as nail, teeth and skin problems.^{4–8} It is a disease of juvenile onset caused by a monogenetic mutation of the autoimmune regulatory gene which plays a role in T-cell development.^{4–7}

APS3 is characterised by thyroid autoimmune disease with other autoimmune diseases excluding Addison's disease.⁹

APS4 describes combinations of autoimmune diseases that do not fit into the previously described APS groups.⁹

Immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) is another APS which has been described, and is rarer than both APS1 and APS2.^{7–10} IPEX is an acronym for immune dysfunction, polyendocrinopathies, enteropathy, X linked.^{7–10} Like APS1, this syndrome is related to a single mutation of the FOXP3 gene on the X chromosome.^{7–10} Typically, this syndrome presents shortly after birth with a phenotype of dermatitis, enteropathy and endocrinopathies.⁷ Type 1 diabetes mellitus and autoimmune thyroid disease are the most commonly occurring endocrinopathies seen in the IPEX

syndrome,^{7 11} and depending on which of these are present, IPEX may fit under the classification of APS3 or APS4.

Learning points

- ▶ Autoimmune polyglandular syndrome type 2 (APS2) is characterised by primary adrenal insufficiency associated with autoimmune thyroid disease and/or type 1 diabetes mellitus.
- ▶ APS2 is a condition of adult onset, generally presenting in the third to fourth decade.
- ▶ Management of APS2 involves screening for and treatment of related autoimmune conditions.
- ▶ Prompt diagnosis and treatment is potentially life-saving.

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Competing interests None declared.

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