A Case of Autoimmune Polyglandular Syndrome Type 2 Presenting as Dyspnea

Anton Moshynskyy, Keren-happuch Ho, Gudrun Caspar-Bell

College of Medicine, University of Saskatchewan, Regina, SK, Canada

Corresponding Author: Anton Moshynskyy: aim695@mail.usask.ca

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Abstract
We will discuss the case of a 17-year-old male who initially presented to care with shortness of breath on exertion. His symptoms progressed over 7 months to include general weakness, anorexia, and malaise. He presented again to care with tachycardia and hypotension. A combination of dermatological manifestations of autoimmune disease, extensive family history of autoimmune disease, and electrolyte abnormalities prompted a bedside thyroid ultrasound, which led to investigation for thyroid disease. Hormone and antibody testing confirmed the diagnosis of autoimmune polyglandular syndrome type 2 (APS2), and he was successfully treated with levothyroxine, hydrocortisone, and fludrocortisone replacement. We present a case of APS2 in an unusual patient population, with a seldom reported initial manifestation. We will discuss diagnostic clues, investigations, management, and further monitoring of APS2.

Resume
Nous aborderons le cas d’un adolescent de 17 ans qui a d’abord consulté pour un essoufflement à l’effort. Ses symptômes ont évolué sur une période de sept mois et comprennent une faiblesse générale, une anorexie et un malaise. Puis, il a consulté de nouveau pour une tachycardie et une hypotension. Une combinaison de signes dermatologiques de maladie auto-immune, d’antécédents familiaux importants de maladie auto-immune et d’anomalies électrolytiques a conduit à la réalisation d’une échographie de la thyroïde au chevet du patient, ce qui a mené à la recherche d’une maladie thyroïdienne. Le dosage des hormones et le dépistage d’anticorps ont confirmé le diagnostic de polyendocrinopathie auto-immune de type 2 (PEA2), et il a été traité avec succès par la lévothyroxine, l’hydrocortisone et la fludrocortisone de remplacement. Nous présentons un cas de PEA2 chez une population de patients inhabituelle, une manifestation initiale y étant rarement rapportée. Nous aborderons les pistes de diagnostic, les examens, la prise en charge et la surveillance accrue de la PEA2.
Introduction

Autoimmune Polyglandular Syndrome Type 2 (APS2) is characterized by primary adrenal insufficiency and either type 1 diabetes mellitus or autoimmune thyroiditis.1,2 It was first described by Schmidt in 1926. There is primarily a polygenic inheritance pattern.3,4

The prevalence of APS2 is reported as 1.5–5 per 100,000.2,5,6 The typical patient with APS2 is a middle-aged female; however, a high index of suspicion in all patients with signs and symptoms of multiple autoimmune endocrinopathies should prompt testing.

APS2 is associated with other autoimmune conditions such as pernicious anemia, alopecia areata, alopecia universalis, vitiligo, autoimmune hepatitis, celiac disease, and primary gonadal failure.3,7–9 Alopecia universalis in particular is seen in only 1–4% of APS2.8

Cases of APS2 are characterized by multiple presentations to care before a diagnosis is made and delay in treatment as patients tend to present with non-specific symptoms, including fatigue, weight loss, and anorexia.9–18 Comorbid diseases further complicate accurate diagnosis.

We describe the case of a 17-year-old patient with APS2 presenting with dyspnea as the chief complaint.

Case

A 17-year-old male presented to his family physician with increasing shortness of breath on exertion and weakness. His shortness of breath was thought to be due to painless thyroiditis and he was treated with a trial of propranolol. At the time, his medical history included depression and anxiety treated with citalopram, recurrent pneumonia, and vitiligo. Three weeks later, he presented to the emergency department with nausea and vomiting. On review of systems, he was found to have had general weakness, anorexia, and malaise for the 7 months prior to presenting to care. He also endorsed difficulty performing instrumental activities of daily living. There were no risk factors for tuberculosis and he had no travel history or symptoms suggestive of fungal infection. He did not report any symptoms of polyuria, polydipsia, polyphagia, or vision blurriness. There was a family history of autoimmune hypothyroidism, celiac disease, and vitiligo. On physical exam, he was alert and awake, but weak. He had areas of vitiligo and diffuse patches of skin darkening, not restricted to classically affected areas such as skinfolds. He had a blood pressure of 79/31 mmHg, heart rate of 110 beats per minute, oxygen saturation of 95% on room air, and was afebrile. He had no peripheral edema and his jugular venous pressure was flat, with an otherwise unremarkable cardiorespiratory exam. His abdomen was soft and nontender. There were no focal neurological findings. His ECG showed sinus tachycardia.

Notable laboratory values included sodium of 120 mmol/L, potassium of 5.0 mmol/L, chloride of 87 mmol/L, an elevated TSH of 17.21 mIU/L, a normal T4 of 14.5 pmol/L, and random blood glucose of 4.4 mmol/L (normal). His HIV test was negative. Three weeks prior to his presentation to the emergency department, a workup showed subclinical hypothyroidism. Beside, ultrasound showed heterogeneous thyroid parenchyma suggestive of Hashimoto’s thyroiditis and further bloodwork showed elevated anti-thyroid peroxidase antibody levels. He was diagnosed with adrenal insufficiency by an ACTH stimulation test during his hospital stay, which showed a cortisol of 29.0 nmol/L at 0 min, a cortisol of 31.9 nmol/L at 30 min, and a cortisol of 32 nmol/L at 60 min.

A clinical picture of Hashimoto’s thyroiditis, primary adrenal insufficiency, and vitiligo are all autoimmune in nature. He was treated for adrenal insufficiency with Hydrocortisone 20 mg once in the morning and 10 mg at 13:00, and Fludrocortisone 0.05 mg twice per day, and for hypothyroidism with Levothyroxine 50 mcg once daily. At a clinic follow-up 2 years later, he endorsed painless hair loss in multiple areas. His clinical status has otherwise been stable and without evidence of primary hypogonadism, pernicious anemia, or autoimmune hepatitis.

Discussion

Diagnosis is often delayed, in part because the symptoms are often vague and nonspecific until more serious manifestations such as adrenal insufficiency develop. Diagnosis is also complicated by the fact that the three primary manifestations, adrenal insufficiency, type 1 diabetes mellitus, and autoimmune thyroid disease, rarely present simultaneously.19 As symptoms are often nonspecific, one must maintain suspicion for an autoimmune endocrinopathy if basic investigations do not yield a satisfying result and symptoms persist. This is particularly true when minor components of APS2, such as those listed in Table 1, or family history of autoimmune disease are present.5

When assessing a hypotensive patient, it is important to first rule out life-threatening causes of hypotension and shock. The different types of shock include the general
adrenal reserve. Adrenal insufficiency should therefore be ruled out and treated prior to thyroid hormone replacement.

When APS2 is clinically suspected, testing should include autoantibodies to 21-hydroxylase, glutamic acid decarboxylase, insulin-associated antigen, cytoplasmic islet cell antibodies, thyroperoxidase antibodies, TSH-receptor antibodies, thyroglobulin antibodies, and tissue transglutaminase antibodies. This is especially true when Addison’s disease is the initial presentation; however, when the initial presentation is autoimmune thyroid disease or type 1 diabetes, screening for Addison’s disease is less useful.

Antibodies to 21-hydroxylase are useful because they are a marker that can be used to identify individuals at risk of progression to clinical adrenal insufficiency. It is proposed that an ACTH stimulation test is sufficient for diagnosis of autoimmune adrenal insufficiency in patients with other autoimmune endocrinopathies. The utility of adrenal antibodies is the ability to suggest a latent component of autoimmune adrenal disease, and suggests it may be beneficial to monitor for progression to overt disease with annual morning cortisol and ACTH stimulation test.

The Endocrine Society Clinical Practice Guidelines suggest screening for autoimmune thyroid disease and type 1 diabetes mellitus when patients present with primary adrenal insufficiency. Alopecia areata and vitiligo are autoimmune diseases that may be related to APS2. These guidelines also discuss the utility of genetic counseling as a best practice statement due to the finding of primary adrenal insufficiency in relatives of proband patients.

First-degree relatives should also be screened. Patients with adrenal insufficiency should double or triple glucocorticoid dose during times of illness or stress. Overall management of endocrine organ dysfunction should follow hospital, health region, and national guidelines at the discretion of the physician and are beyond the scope of this report. With respect to long-term follow-up in these patients, it is important to note that other endocrinopathies may develop later in life, up to 22 years after initial presentation.

Table 1. Major and minor conditions associated with autoimmune polyglandular syndrome type 2

<table>
<thead>
<tr>
<th>Associated conditions</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td><strong>Major associated conditions</strong></td>
<td></td>
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<tr>
<td>Autoimmune adrenal disease</td>
<td>18.5–100%</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>65.6–88%</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>23–60.9%</td>
</tr>
<tr>
<td><strong>Minor associated conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
<td>4.5–20%</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>11%</td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td>3.6–10%</td>
</tr>
<tr>
<td>Chronic autoimmune hepatitis</td>
<td>3–4%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0.5–6%</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>1–5%</td>
</tr>
<tr>
<td>Seronegative arthritis</td>
<td>2%</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>3%</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0–2%</td>
</tr>
</tbody>
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categories of septic distributive, nonseptic distributive, cardiogenic, hypovolemic, and obstructive shock. Adrenal insufficiency is classified as nonseptic distributive shock, as are spinal cord trauma, anaphylaxis, toxic shock syndrome, and myxedema coma. Our case is the second to our knowledge which includes dyspnea as the chief complaint on initial presentation of APS2. This highlights the importance of exploring associated symptoms, as initial endocrinopathy presentations can be nonspecific. The diagnostic journey of patients with APS2 may involve psychiatric diagnoses and medications, due, in part, to the often vague presentation of adrenal insufficiency and is concerning because an adrenal crisis can be potentially fatal. Up to 84% of cases of APS2 begin after 20 years of age. The majority of APS2 occurs in middle-aged women. Our case further deviates from the typical presentation in that it was a 17-year-old male who initially presented with dyspnea, general fatigue and malaise, and weakness. A strong suspicion for APS2 in cases of primary adrenal insufficiency, strong family history of autoimmune disease, and bedside ultrasound led to the identification of Hashimoto’s thyroiditis, which was treated.

Certain nonspecific features of the symptoms of hypothyroidism and adrenal insufficiency overlap, such as fatigue, weakness, and hyponatremia. A diagnosis of one of these disease processes should include the evaluation for the other. Thyroid hormone replacement may increase the breakdown of steroid hormones, precipitating adrenal crisis due to impaired adrenal reserve. Adrenal insufficiency should therefore be ruled out and treated prior to thyroid hormone replacement.

When APS2 is clinically suspected, testing should include autoantibodies to 21-hydroxylase, glutamic acid decarboxylase, insulin-associated antigen, cytoplasmic islet cell antibodies, thyroperoxidase antibodies, TSH-receptor antibodies, thyroglobulin antibodies, and tissue transglutaminase antibodies. This is especially true when Addison’s disease is the initial presentation; however, when the initial presentation is autoimmune thyroid disease or type 1 diabetes, screening for Addison’s disease is less useful.

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**Conclusion**

Patients presenting with nonspecific symptoms of adrenal insufficiency and APS2 often spend a long time without a clear diagnosis. Their course is often complicated by comorbid diseases or other endocrinopathies. A complete differential diagnosis for hypotension and shock should include adrenal insufficiency. Our patient’s case illustrates
the difficulties patients experience throughout the course of their disease and the difficulties clinicians can face in diagnosis and treatment. Specifically, a presentation of adrenal insufficiency and vitiligo raised suspicion for a polyglandular autoimmune process.

References