# A PATIENT WITH ADDISON'S AND GRAVES' DISEASE AS MANIFESTATION OF AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 2

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***Abstract***

Addison's disease is a rare disease caused by insufficient production of glucocorticoids, mineralocorticoids, and androgens in the adrenal cortex. It occurs more frequently in women between the ages of 30 and 50 years. Approximately two-thirds of patients with Addison's disease may develop other autoimmune disorders such as autoimmune polyglandular syndrome (APS) that could potentially manifest as autoimmune thyroid disease (ATD), autoimmune gastritis, type 1 diabetes mellitus (T1DM), premature ovarian failure (POF), vitiligo, or celiac disease. Here, we reported a case of a 51-year-old woman with complaints of weakness, nausea, vomiting, weight loss, frequent bowel movements, and hyperpigmentation. Laboratory examinations showed a decreased level of morning cortisol, increased adrenocorticotropic hormone (ACTH), increased free thyroxin (FT4), decreased thyroid stimulating hormone (TSH), increased thyrotropin receptor antibody (TRAb), and positive glutamic acid decarboxylase 65 (GAD65). The patient was diagnosed with Addison's disease accompanied with autoimmune thyroid disease-causing Graves' disease and T1DM, leading to APS type 2. After being given steroid, insulin, and anti-thyroid drugs therapy, the patient's condition improved.

***Keyword*****:** Addison's Disease, Graves' Disease, Autoimmune Polyglandular Syndrome Type 2

## *Introduction*

Addison's disease is characterized by the inability of the adrenal cortex to produce sufficient amount of glucocorticoids and/or mineralocorticoids. The estimated annual incidence rate in Europe is 4.4–6.2 cases per 1 million population (1). Patients with Addison's disease may develop other autoimmune disorders such as autoimmune thyroid disease (ATD), type 1 diabetes mellitus (T1DM), autoimmune gastritis, vitiligo, or celiac disease recognized as autoimmune polyglandular syndrome (APS) (2). Chronic deficiency of glucocorticoids and/or mineralocorticoids underlies the clinical symptoms occurring in patients with Addison's disease. Adrenal insufficiency often presents as several conditions including weakness, anorexia, weight loss, dehydration-associated orthostatic hypotension, muscle and abdominal pain, hyperpigmentation, and nausea vomiting in patients (3).

Although uncommon, Addison's disease is potentially fatal and life-threatening given that the hormones produced by the adrenal cortex (glucocorticoids and mineralocorticoids) have central roles in the regulation of energy, electrolytes, and fluid homeostasis. In addition, symptoms in patients are often non-specific, resulting in delayed diagnosis (4). Therefore, establishing accurate diagnosis is critical. Further diagnostic tests such as randomized blood samples to simultaneously evaluate adrenocorticotropic hormone (ACTH) and cortisol levels in patients with signs and symptoms suggestive of Addison's disease are needed to detect glucocorticoid deficiency, which is recognized as the main clinical characteristic. A low cortisol level in serum along with high ACTH is a hallmark of Addison's disease (5).

Addison's disease may also be accompanied by several other autoimmune disorders such as the autoimmune thyroid disorder called Graves' disease and/or T1DM, leading to the development of APS type 2. Although such combination (Addison's and Grave's diseases) is extremely uncommon, diagnosis is prominent since the occurrence

of hypercortisolism together with hyperthyroidism may accelerate the metabolic rate, increasing the risk for adrenal crisis. The aim of this report was to describe and provide information about the combination of Addison's and Graves' diseases in a patient with manifestation of APS type 2.

## *Case report*

A 51-year-old woman presented with complaints of weakness, nausea, and vomiting after each meal 1 week prior to hospital admission. 10 days before hospitalization, the patient's lips, tongue, face, toenails and hands had turned dark. There was also decreased appetite and weight loss (6 kg) in the last 2 months. About 5 years ago, the patient had tanned skin with increased ACTH (up to 4126 pg/mL) and decreased cortisol levels (0.5 µg/dL), for which she received routine treatment with prednisone (once 5 mg/day) in a private hospital. The patient also had T1DM for more than 15 years and received glimepiride (once 2 mg/day) and metformin (3 times 500 mg/day).

On physical examination, there was skin darkening on the face, the upper and lower extremities, and the oral mucosa. The lips and gums were hyperpigmented (Figure 1A-G). The patient was generally weak, but had good consciousness. Blood pressure was 110/80 mmHg, pulse 104 times/min (regular), breathing 20 times/min, and axillary temperature 37°C. Weight was 50 kg, height 155 cm, and body mass index 20.8 kg/m$^2$.

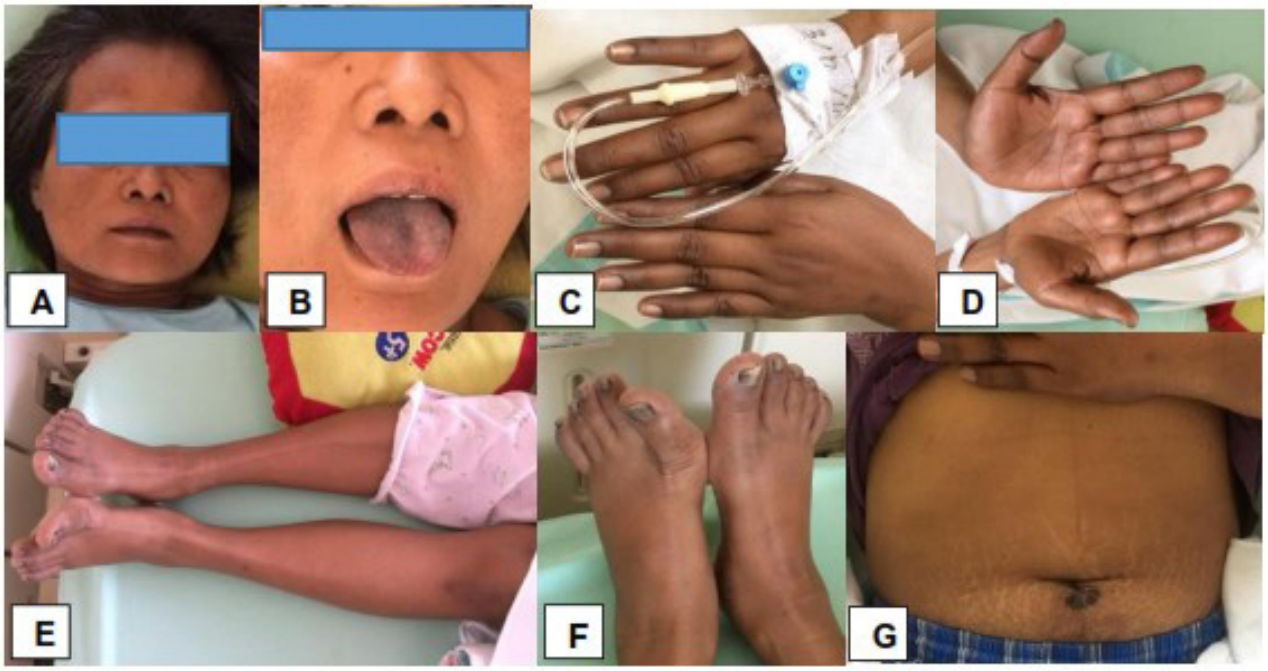


**Figure 1**: Skin darkening in the patient: (A) face (lips); (B) tongue and oral mucosa; (C-D) upper extremities; (E) lower extremities; (F) toenails; and (G) abdomen

Laboratory examination confirmed the clinical suspicion of Addison's disease: ACTH 62.9 pg/mL (normal value < 46 pg/mL), morning serum cortisol 0.50 µg/dL (normal range 4.30–22.40 µg/dL), sodium 128 mmol/L, potassium 4.4 mmol/L. Hyperthyroidism was also indicated: free thyroxin (FT4) 9.85 ng/dl (normal range 0.89–1.76 ng/dL), thyroid stimulating hormone (TSH) 0.024 µIU/mL (normal range 0.55–4.78 µIU/mL), thyrotropin receptor antibody (TRAb) 2.73 IU/L (negative if < 1.75 IU/L), which was associated with Grave's disease. The patient confirmedly suffered from T1DM: random blood sugar 271 mg/dL, HbA1C 10%, and positive anti-glutamic acid decarboxylase 65 (GAD65). The result of a CT-scan of the abdomen with contrast of the adrenal focus revealed an extremely small size of the right and left adrenal glands (right size: body 4.5 mm, limb 2.3 mm; left size: body 4 mm, limb 2.7 mm), suspected as bilateral adrenal gland hypoplasia (Figure 2). The patient was finally diagnosed with Addison's disease accompanied by Graves' disease and T1DM, leading to APS type 2.

We initiated the treatment with hydrocortisone injection (3 times 100 mg/day) and continued by oral administration once the patient's condition had improved. On the 8th day of treatment, the patient complained of chest palpitations, headache, and general weakness. On physical examination, a rapid and irregular pulse was detected and the electrocardiography (ECG) results showed atrial fibrillation (Figure 3A). The patient received thyrozol (2 times 20 mg/day) and propranolol (3 times 20 mg/day). Therapy was then continued with the administration of steroids, insulin, and anti-thyroid drugs. The patient condition improved after undergoing therapy indicated by normal ECG (Figure

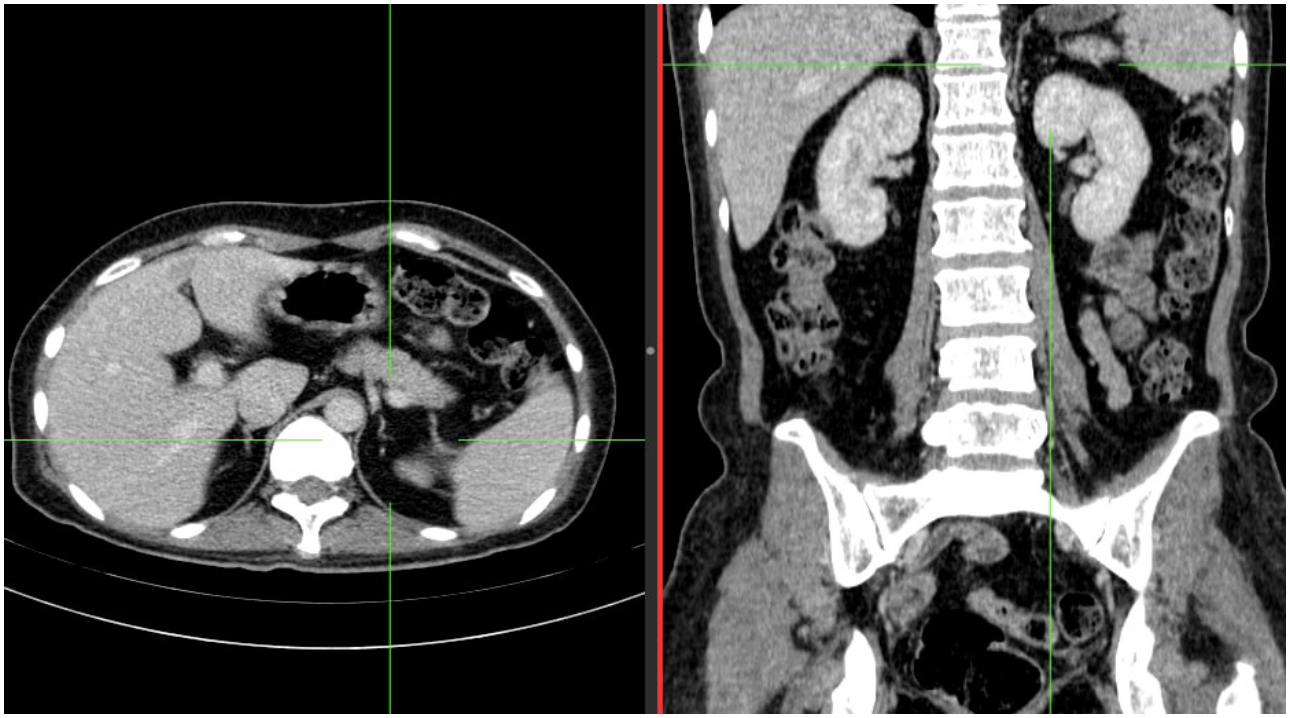

**Figure 2**: Patient CT-scan of the abdomen with contrast showing the adrenal gland

3B) and the patient was discharged. The patient received outpatient treatment with hydrocortisone (3 times 20 mg/day), thyrozol (2 times 20 mg/day), propranolol (3 times 20 mg/day), insulin aspart injection (6 units, subcutaneous, 15 min before meals), and insulin glargine injection (8 units, subcutaneous, night). One month after her initial hospital admission, the patient routinely underwent monthly outpatient control.

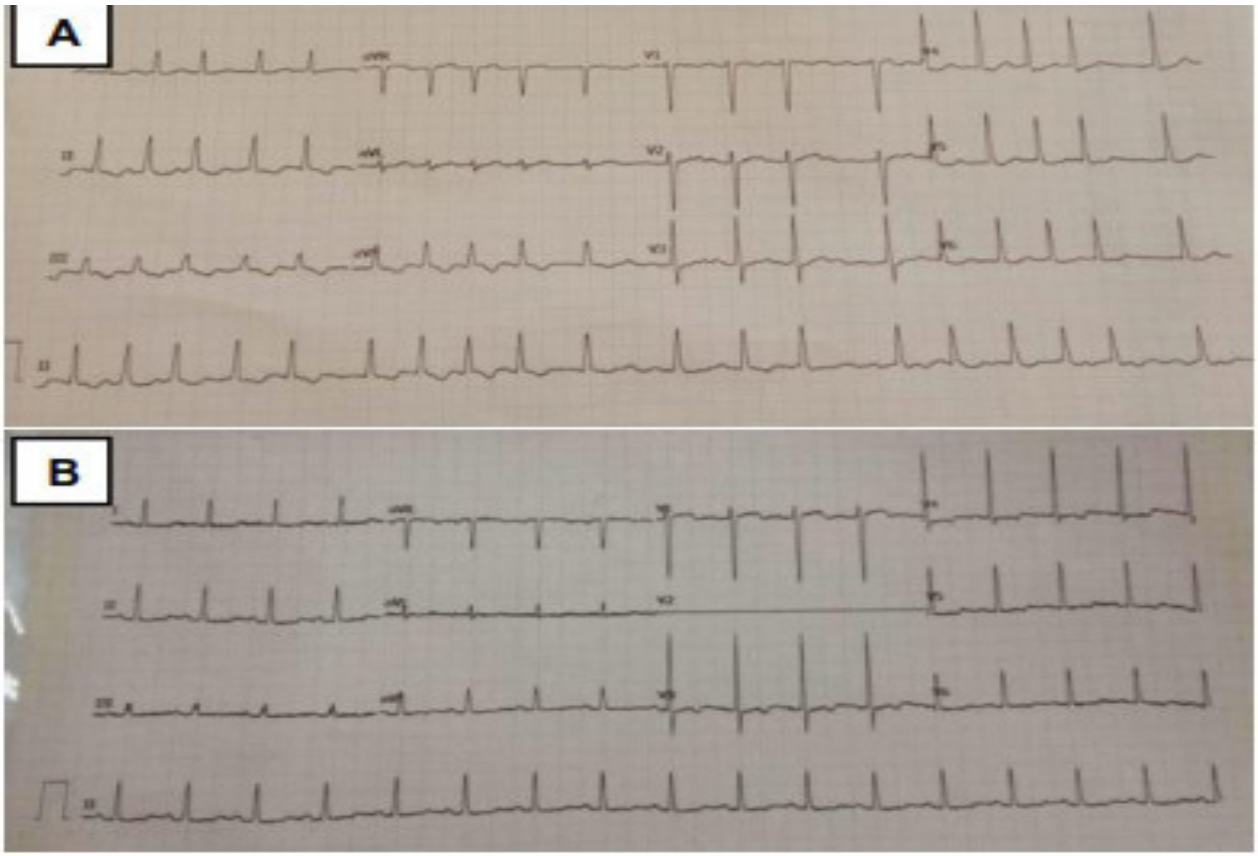


**Figure 3**: ECG indicates the atrial fibrillation (A) before the therapy and the ECG (B) after the therapy

## *Discussion*

We received complaints of body weakness, decreased appetite, weight loss and hyperpigmentation from our patient, clinically suspected of Addison's disease. Although symptoms in patients with this disorder are often non-specific (4), Addison's disease should be suspected in all acutely or chronically ill patients with generalized fatigue or severe weakness and unexplained dehydration, hypotension, weight loss, fever, abdominal pain, and hyperpigmentation.

The results of the laboratory examination showed decreased morning cortisol levels, increased ACTH, and hyponatremia, supporting the diagnosis of Addison's disease in our patient. Hyponatremia, hyperkalemia, and hypoglycemia are the main laboratory characteristics of the disease reflecting glucocorticoid and mineralocorticoid deficiency. The hallmark of Addison's disease is a low serum cortisol concentration in combination with high ACTH. According to generally accepted clinical guidelines, Addison's disease is considered highly probable when cortisol level is < 5 g/dL (138 nmol/L) with concomitant ACTH increasing more than 2-fold beyond the upper limit of the normal range. Further, dynamic testing of adrenocortical function with the corticotropin stimulation test, known as the cosyntropin test, is the best method for the diagnosis or exclusion of Addison's disease (6). However, cosyntropin test was not available in this case.

Autoimmune adrenalitis (80% in Western societies), tuberculosis or other infectious diseases, malignant disease (in about 10% of cases), bilateral adrenalectomy, genetic disease, and adrenal hemorrhage are among several causes of Addison's disease (7). In our patient, the cause of Addison's disease was assumingly associated with autoimmune adrenalitis since the patient had no signs and symptoms of tuberculosis or other infectious diseases, nor was there any adrenal bleeding and genetic disorders. In addition, computed tomography (CT) scan of the patient's abdomen with contrast of adrenal focus revealed a very small size of the right and left adrenal glands with suspicion of bilateral adrenal gland hypoplasia. In patients with autoimmune adrenal disorder, a CT scan usually shows a reduced size adrenal gland. The CT scan showing bleeding, tuberculosis-associated calcifications, or masses in the adrenal glands may appear in Addison's disease with other causes (8).

Autoimmune adrenalitis may also occur in combination with other autoimmune disorders, such as chronic mucocutaneus candidiasis, hypoparathyroidism, thyroid autoimmune disease, T1DM, or other autoimmune diseases, as part of APS (9). To confirm T1DM in our patient, anti-GAD65 test was performed, with confirmation of a positive result. This patient was classified as latent autoimmune diabetes in adults (LADA). The Immunology for Diabetes Society (IDS) has specified three criteria for LADA diagnosis: (1) age greater than 35 years; (2) positive autoantibodies to islet beta cells; and (3) insulin independence for at least the initial 6 months after initial diagnosis (10). The patient met all these criteria. GAD65 autoantibodies can accurately predict the development of autoimmune diabetes (T1DM) in combination with other surrogate humoral biomarkers (11). These results lead to the diagnosis of APS type 2, a rare autoimmune disorder characterized by Addison's disease accompanied by autoimmune thyroid disease (including thyroiditis Hashimoto and Graves' disease) and/or T1DM. In addition, our patient was a middle-aged woman (51 years), the peak incidence AGE of APS type 2. Most patients with APS type 2 are between the ages of 20 and 60 years and women are reportedly affected more often than men (12). In addition, the C-peptide level in our patient was within normal limit, 2.99 ng/mL. In LADA, the destruction of pancreatic beta cells is slow, which causes the patient to still achieve normal glucose with oral hypoglycemic drug supplementation and diet. A study found that LADA patients with positive anti-GAD tend to have low to normal C-peptide levels while patients with negative anti-GAD, the C-peptide levels were found to be normal or elevated (13).

On the 8th day of treatment, the patient complained of chest palpitations, headache, and general weakness. On physical examination, the pulse was rapid and irregular. Laboratory results showed an increase in FT4 (117.6 ng/dL) and a decrease in TSH (< 0.004 μIU/mL). The ECG results indicated atrial fibrillation. Based on these clinical symptoms, physical and supporting examinations, the patient was confirmed to have hyperthyroidism with heart complications, called atrial fibrillation. Clinical manifestations in patients with hyperthyroidism who experience atrial fibrillation include palpitations, angina on exercise, dyspnea, fatigue, syncope, or symptoms of thromboembolism (14). After receiving thyrosol (2 times 20 mg/day) and propranolol (3 times 20 mg/day), our patient's condition improved. Hyperthyroidism in this patient may also affect the severity of adrenal failure and diabetes. Studies have found that hyperthyroidism was associated with subtle impairment of adrenocortical reserve (15, 16). It is also well known that hyperthyroidism may cause an elevated risk of poor glycemic control and severe hyperglycemia (17). A study in Korea assessed the risk of diabetes in patients with hyperthyroidism and found that the hazard ratio for diabetes incidence was 1.18 (18); indicating that the risk of diabetes was significantly higher in patients with long-standing hyperthyroidism such in Graves' disease. This may have been worse during the COVID-19 pandemic (19).

In patients with chronic adrenal insufficiency, appropriate therapy can save lives. Administration of glucocorticoids (20–30 mg hydrocortisone or 25–50 mg cortisone acetate) are required in 2 or 3 daily doses. Administration of glucocorticoids can be carried out in the morning, during the day (about 6-8 h after the first administration), and continued in the evening. Furthermore, providing a patient with a diet rich in sodium is prominent. Administration of glucocorticoids should be doubled or tripled, or possibly by intramuscular or intravenous injection in emergency conditions such as fever, injury, vomiting,

surgical procedures, tooth extraction or in pregnancy (7). In addition, mineralocorticoid supplementation is also required in patients with adrenal insufficiency to maintain sodium, fluid balance and blood pressure. Inadequate mineralocorticoid and/or salt intake is among the most common causes for repeated adrenal crisis. Mineralocorticoid replacement is usually taken as a single dose of 50–200 µg of fludrocortisone. In our case, the patient did not receive fludrocortisone since it is not available in our hospital. In addition, during evaluation at the hospital with the given therapy, the patient's condition improved with stable blood pressure and electrolyte levels.

Monitoring of other autoimmune disorders is important since patients with Addison's disease have a lifelong risk of developing additional autoimmune diseases (12). To reduce mortality and improve quality of life in APS type 2 patients, it is very important to diagnose the disorder early and provide therapy (20). Health monitoring and assessment such as measurement of body weight, blood pressure and serum electrolytes should be done at least once a year. Routine laboratory analyzes should include serum sodium and potassium determinations. Although not recommended for routine monitoring of glucocorticoid replacement, cortisol measurements can be useful to obtain evidence of adequate cortisol uptake. Monitoring of replacement therapy is primarily clinical. A patient with good appetite, stable weight, and ability to perform normal daily activities is the goal of therapy (6).

## *Conclusion*

Patients with Addison's disease often present with non-specific symptoms, resulting in late diagnosis and clinical presentation with a life-threatening adrenal crisis. In this case, we report a 51-year-old woman with complaints of weakness, nausea, vomiting, hyperpigmentation, and weight loss. Our patient was diagnosed with Addison's disease accompanied by autoimmune thyroid disease-causing Graves' disease and T1DM, leading to APS type 2. Appropriate therapy can save lives and avoid adrenal crisis. Monitoring of the patient's complaints and clinical condition, vital signs, weight, and supporting examinations including electrolytes, cortisol, and ACTH levels are needed. The goal of managing patients with Addison's disease is important to ensure a better quality of life as indicated by a good appetite, stable weight, and being able to carry out daily activities.

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## *Competing interests*

The author stated that there is no conflict of interest.

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## *Informed consent*

Written informed consent was obtained from the patient to be included as case-report.

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