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Atypical Presentation of Adrenocortical Insufficiency with Anorexia and Jaundice

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Xiang-Xing Li
ABCEF 1 Jie Liu
ABDE 1 You-Lian Chen
BDE 1 Guang-Jian Chen
BDE 1 Zhen-Yu Wang
BDF 1 Jun-Jun Zhu
ABCDEF 2 Yun-Wei Guo
ABCDEFG 1,2 Xiu-Qing Wei

1 Department of Gastroenterology, Yuedong Hospital of the Third Affiliated Hospital of Sun Yat-sen University, Meizhou, Guangdong, P.R. China
2 Department of Gastroenterology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P.R. China

Corresponding Authors: Xiu-Qing Wei, e-mail: wei-xiuqing@163.com, Yun-Wei Guo, e-mail: guoyw@mail.sysu.edu.cn, Jie Liu, e-mail: 1315071368@qq.com, You-Lian Chen, Purity666@163.com

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Patient: Female, 65
Final Diagnosis: Adrenocortical insufficiency
Symptoms: Anorexia and jaundice
Medication: Glucocorticoid replacement
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Challenging differential diagnosis

Background: Adrenal insufficiency is mainly due to insufficient adrenal corticosteroid hormones secretion by the adrenal cortex, which leads to clinical manifestations such as weakness, weight loss, hyperpigmentation, hypotension, and vomiting. However, the clinical manifestations of adrenocortical insufficiency may be atypical: anorexia, ascites, impaired liver function, and alacrima have been reported. Jaundice and anorexia presenting together in the same patient as the main symptoms are rare.

Case Report: We present a rare case of a 65-year-old woman diagnosed as having adrenocortical insufficiency with chief complaints of anorexia and jaundice. The patient had a history of hiatus hernia and gastroesophageal reflux disease, which can easily lead to a misdiagnosis in clinical practice, which is what happened with this patient at the beginning in our hospital and in the other hospitals that treated her previously. Hiatus hernia was considered the mostly likely cause of her vomiting, and a laparotomy was done to repair the hernia at the local hospital. However, there was no improvement. After regular glucocorticoid replacement, the patient's symptoms all soon disappeared.

Conclusions: Adrenal insufficiency can atypically present as anorexia and jaundice. In order to avoid misdiagnosis, physicians should pay attention to these atypical symptoms.

MeSH Keywords: Adrenal Insufficiency • Anorexia • Jaundice

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Background

Adrenocortical insufficiency, including primary or secondary adrenocortical insufficiency, is caused by a decrease in production of adrenal corticosteroids. Primary adrenocortical insufficiency, also known as Addison's disease, is due to deficiency or defect of the adrenal gland cortex, leading to decreased production of glucocorticoid, mineral corticoid, androgen, with elevated adrenocorticotropic hormone**,** and serum renin level [1,2]. Secondary adrenal insufficiency is adrenal hypofunction due to a lack of production of corticotrophin-releasing hormone by the hypothalamus and lack of adrenocorticotropic hormone production by the pituitary gland. It is mainly caused by inflammation of the hypothalamus, cancer, or vascular lesion. It can also be caused by a negative feedback inhibition of the hypothalamus and the pituitary gland due to long-term use of corticosteroid. The common clinical symptoms of adrenocortical insufficiency include fatigue, weight loss, arthralgia, back pain, darkening of the skin, hypotension, nausea, vomiting, hyponatremia, and psychological disturbances like depression, apathism, and even coma [1]. The clinical manifestations of adrenocortical insufficiency may be atypical; anorexia [3], ascites [4], impaired liver function [5,6], and alacrima [7] have been reported. However, there have been no case reports of anorexia and jaundice together caused by adrenocortical insufficiency in the same patient.

Case Report

A 65-year-old woman was admitted to our hospital because of nausea, vomiting, fatigue, anorexia, and food avoidance during the past 6 months. Vomiting mostly ensued after meals, and the vomitus was fresh gastric contents, with no foul-smelling or coffee-ground-like substances. She went to a local hospital and had regular work-ups done. Complete blood count showed increased white blood cell of 15.5×10^9/L (normal range: $3.5–9.5\times10^9$/L), with a neutrophil percentage of 73.9% (normal range: 40–75%). Serum level of potassium was 2.79 mmol/L (normal range: 3.5–5.3 mmol/L), and bicarbonate 27.3 mmol/L (normal range: 20.2–29.2 mmol/L). Antibiotics, potassium, and fluid were given before she was discharged on relief of symptoms. She had several nocturnal episodes of delirium and cognitive disorder during her first hospitalization. Information on the diagnosis and treatment were not available to us. However, 2 months after discharge, her vomiting recurred, along with fatigue and anorexia. The patient was seen at another local hospital, where an upper-gastrointestinal endoscopy was performed, suggesting esophageal hiatus hernia, reflux esophagitis, and chronic gastritis. Hiatus hernia was considered the mostly likely cause of her vomiting, and a laparotomy was done to repair the hernia. As soon as she went back on oral feedings after surgery, she noticed no improvement with the vomiting after meals, and retching developed between meals. Two weeks before the current admission, her family observed yellow coloration of her sclera and skin, as well as a darkened color of urine and intermittent difficulty in facial recognition of family members. Mild to moderate pitting edema below the level of both ankles was also noticed. She was again sent to a local hospital, where blood tests were done, revealing that serum levels of total bilirubin and direct bilirubin were elevated, at 193.2 μmol/L (normal range: 4.0–23.9 μmol/L) and 119.1 μmol/L (normal range: 0–6.8 μmol/L), respectively, and serum albumin was 29.7g/L (normal range: 36.0–51.0g/L). Symptomatic treatment of jaundice and glycyrrhizin was not effective and the patient was referred to our department (Department of Gastroenterology, the Third Affiliated Hospital of Sun Yat-sen University). The patient's family members reported that she had a duodenal polyp removed endoscopically 6 years ago and had been diagnosed with primary hypertension 6 months ago. She was diagnosed as having scapulohumeral periarthritis in a local clinic about 3 years ago. Irregular steroid (20–40 mg prednisone per day) was given by the doctor first and then mainly by herself for more than 2 years.

Prednisone was withdrawn about 6 months ago, but this was not reported to us at the beginning. There was no thyroid disorder, autoimmune disease, or other prolonged illness such as hepatitis or liver cirrhosis. Her 5 children were healthy and there was no known family history of cancer or liver disease. She denied consumption of cigarettes and alcohol, as well as use of illicit drugs.

On physical examination of the patient, vital signs were normal except for a blood pressure of 167/85 mmHg. She was awake but quite disoriented. There was significant oligotrichosis in several areas of the body surface, including eyebrows and armpits, which was ignored at the beginning. Skin and sclera was moderately jaundiced and symmetrical pitting edema was noticed from the ankles downward. No hyperpigmentation of skin creases, nipples, or cheek mucosa was seen.

She underwent extensive evaluations for the underlying cause of gastrointestinal symptoms and signs. Disorder of multiple electrolytes was noted, with a serum potassium level of 3.04 mmol/L (normal range: 3.5–5.3 mmol/L), sodium 110 mmol/L (normal range: 137–147 mmol/L), and chloride 92 mmol/L (normal range: 99.0–110.0 mmol/L). Liver enzymes were significantly elevated, with a glutamic-oxaloacetic transaminase of 174 U/L (normal range: 13–35 U/L) and a glutamic-pyruvic transaminase of 89 U/L (normal range: 3–35 U/L). Total bilirubin and direct bilirubin were 163.90 μmol/L (normal range: 4.0–23.9 μmol/L) and 117.90 μmol/L (normal range: 0–6.8 μmol/L), respectively. Tests for hepatitis virus A, B, C, D, and E were negative. Serum level of copper was slightly lower

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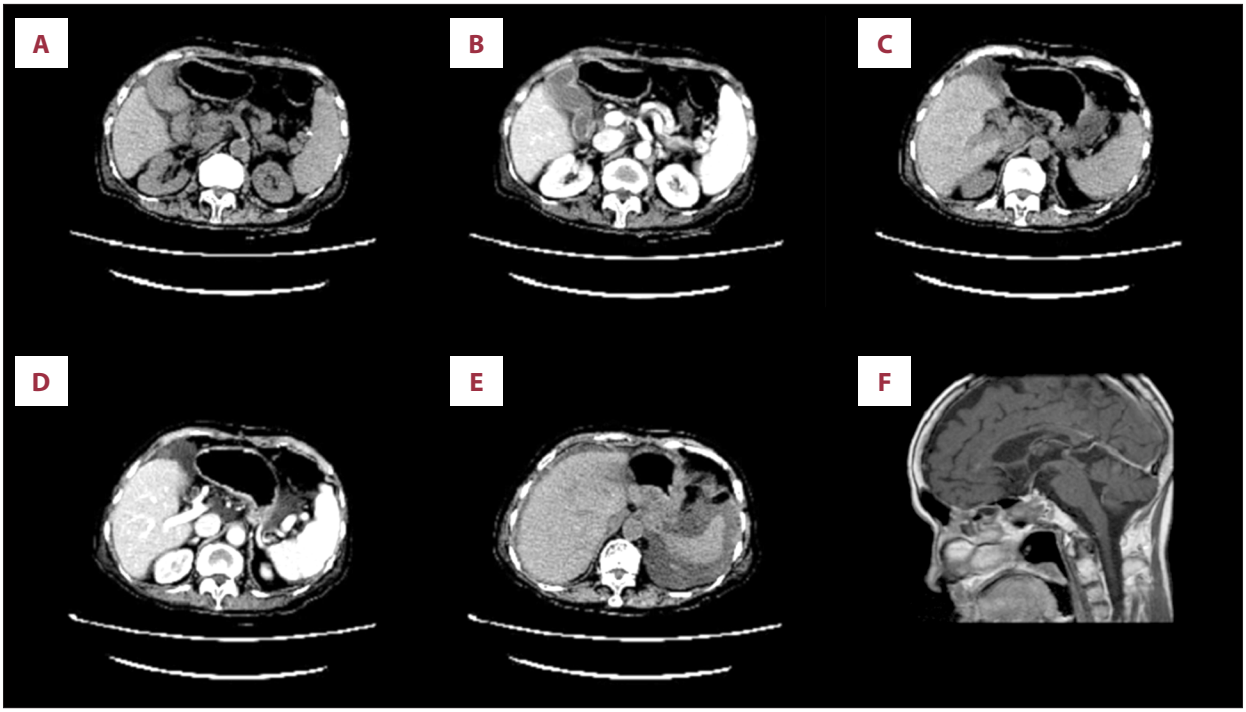

Figure 1. Computerized tomography images indicated normal adrenal glands (**A–D**) and ascites (**E**), and magnetic resonance imaging indicated a normal pituitary (**F**). (**A**) Plain abdominal computerized tomography (CT) scan; (**B**) The arterial phase; (**C**) Plain CT scan; (**D**) The arterial phase; (**E**) Plain CT scan; (**F**) T1 plain MRI scan of the pituitary gland.

than normal, serum levels of ceruloplasmin was normal, and ophthalmologic examination showed no evidence of K-F ring. Antibodies suggestive of autoimmune liver diseases were also negative. Taking her previous treatments at local hospitals into account, drug-induced liver injury was considered as one of the possible diagnoses, nor could we rule out cholestasis related to long-term use of parenteral nutrition. Reduced glutathione and transmetil were used to treat liver injury and cholestasis. Prokinetic drugs were given to relieve the symptoms of vomiting and anorexia. Electrolytes, albumin, and fluid were intravenously administered as needed.

She received 2 units of packed red blood cells after a routine blood test showed a hemoglobin level of 77 g/L (normal range: 115–150 g/L), and her body temperature rose to 38.5°C during the transfusion, which was considered a transfusion reaction. Dexamethasone was intravenously administered with a dose of 6 mg, which brought her temperature down to normal. Much to our surprise, shortly after this single injection of corticosteroids, remarkable improvement of symptoms, including vomiting, fatigue, and anorexia, was reported by the patient. This instant effect of dexamethasone suggested that her original symptoms might have resulted from depletion of endogenous glucocorticoid. She eventually remembered taking corticosteroids as anti-inflammatory agents for her intermittent attacks of joint pain. Further work-ups were done to testy our hypothesis of iatrogenic adrenal insufficiency. Serum was repeatedly tested for cortisol level at midnight (76.67 nmol/L, normal range: 85.3–459.6 nmol/L nmol/L), at 8 am (42.12 nmol/L, normal range: 118.6–618 nmol/L), and at 4 pm (74.23 nmol/L, normal range: 85.3–459.6 nmol/L), and adrenocorticotropic hormone was very low (1.23 pmol/L, normal range: <10.2 pmol/L). Hormones on other pituitary axes were also tested. Thyroid-stimulating hormone, triiodothyronine, and tetraiodothyronine were within normal ranges, as were growth hormone, gonadotropin-releasing hormone, follicle-stimulating hormone, and luteinizing hormone. Computed tomography (CT) of the adrenal glands showed no significant deviation from normal (Figure 1A–1D). Abdominal CT showed ascites (Figure 1E). MRI showed a normal pituitary gland (Figure 1F). However, the liver biopsy only showed minimal inflammation of the liver (Figure 2A–2C).

We therefore confirmed the diagnosis of iatrogenic adrenal insufficiency and immediately initiated corticosteroids replacement therapy, using 20 mg of intravenous hydrocortisone at 8 am and 10 mg at 4 pm for 5 days. The patient's symptoms continued to improve, and by the time the treatment was switched to 4 mg of oral methylprednisolone at 8 am plus 2 mg at 4 pm, her appetite had fully recovered. She was eating a normal amount of food, without nausea or vomiting after or between meals. Jaundice was relieved and bilateral edema of the lower limbs disappeared. Total bilirubin and direct bilirubin fell to 20.5 μmol/L and 12.1 μmol/L, respectively. Hypokalemia,

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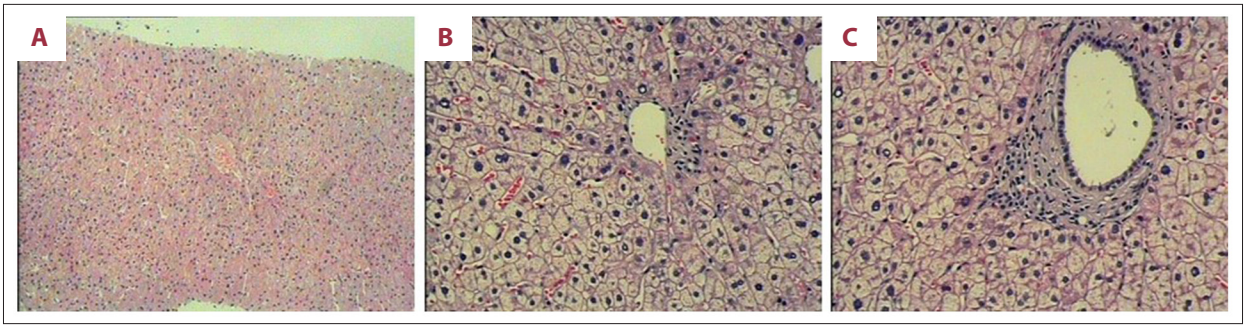

Figure 2. Liver biopsy only showed minimal inflammation (**A–C**). (**A**) HE stain ×100; (**B**) HE stain ×400; (**C**) HE stain ×400.

hyponatremia, and hypochloremia were also sustainably corrected. After more than 1-year follow-up, she remains healthy on hormone replacement therapy.

Discussion

Our patient was diagnosed as having secondary adrenal insufficiency caused by insufficiency of the pituitary gland and the hypothalamus due to drug withdrawal via a negative feedback inhibition of the pituitary gland and the hypothalamus caused by a history of long-term use of corticosteroids for arthralgia, as previously reported in other patients by Nieman et al. [8]. However, since her first symptoms at the onset of the disease were nausea, vomiting, and anorexia, she was misdiagnosed as having only esophageal hiatus hernia. However, esophageal hiatus hernia repair surgery failed to improve the symptoms and cholestasis jaundice appeared later on. To the best of our knowledge, there are no previous reports of a patient with adrenal insufficiency presenting with simultaneous symptoms of anorexia and jaundice.

Anorexia is a severe and potentially life-threatening psychological disorder mostly seen in females with psychological diseases [9,10], impaired liver function [11,12], impaired kidney function, digestive system diseases, and even adrenocortical insufficiency [3]. Adrenocortical insufficiency can lead to decreased glucose, fat, and protein metabolism, and then anorexia. In this case, the laboratory tests showed impaired functioning of the adrenal cortex resulting in decreased production of corticoids. Furthermore, the patient developed ascites and lower-extremity edema, which were due to hypoproteinemia through the malnutrition caused by the chronic anorexia, nausea, and vomiting [4]. Hypokalemia (but not hyperkalemia), hyponatremia, and hypochloremia were seen together, which were caused by metabolic disturbance, vomiting, and insufficient food intake. These made the diagnosis of this case difficult. Corticosteroids are the first-line therapy for anorexia caused by adrenocortical insufficiency, which can also remarkably improve mental state [3], and all these symptoms gradually improved once the primary disease was treated. Thus, we believe that anorexia in this case was due to adrenocortical insufficiency.

Cholestasis is due to either a lesion of the biliary track that leads to obstruction of bile flow, or a lesion of the track affecting the formation, absorption, or secretion of the bile, which leads to accumulation of the bile in the body [13], thereby elevating serum bilirubin, causing yellow coloration of the skin, mucosa, and sclera. It is mostly seen in viral hepatitis, drug-induced hepatitis, biliary calculi, liver cirrhosis, autoimmune diseases, infections, adrenocortical insufficiency, and parenteral nutrition [14–17]. In our patient, the possibility of drug-induced hepatitis as cause of the jaundice was considered but was ruled-out because of the absence of elevated transaminases, hypereosinophilia, absence of suspected drug use, and improvement of symptoms after corticoids were started. On the other hand, our patient had been on long-term parenteral nutrition because of anorexia, which we considered could also be the cause of the jaundice. However, jaundice failed to improve after stopping the parenteral nutrition and this possibility was excluded. Hyperbilirubinemia and jaundice sometimes are seen in chronic adrenal insufficiency [18–22]. In our case, anorexia, jaundice, hypotrichosis, ascites, and lower-extremity edema all developed, serum levels of cortisol and ACTH were low, and the symptoms improved only after introducing corticoids. So, we are sure that the hyperbilirubinemia was due to the decrease in adrenal corticoid secretion, which led to impaired bile flow.

In this case, the patient first present with anorexia, nausea, and vomiting, followed later by jaundice, which can easily be overlooked as being related to adrenal insufficiency. Therefore, physicians must enhance their knowledge of the atypical signs and symptoms of adrenal insufficiency to avoid misdiagnosis.

Conclusions

Adrenal insufficiency is mainly due to insufficient adrenal corticosteroid hormones secretion by the adrenal cortex, which leads to a variety of clinical manifestations, including weakness,

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weight loss, hyperpigmentation, hypotension, and vomiting. However, the clinical manifestations of adrenocortical insufficiency may be atypical; anorexia, ascites, impaired liver function, and alacrima have been reported. Jaundice and anorexia occurring simultaneously as the main symptoms is rare. Anorexia and jaundice can be the main clinical manifestation of adrenal insufficiency. Other symptoms of adrenal insufficiency may be not obvious and may be ignored by gastroenterologists and other physicians. There are no specific pathological findings of the liver in patients with jaundice due to adrenal insufficiency. Physicians must enhance their knowledge of the atypical signs and symptoms of adrenal insufficiency to avoid misdiagnosis.

Conflict of interest

None.

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