Unusual association of diseases/symptoms

A patient with isolated adrenocorticotropin deficiency presenting with repetitive oesophageal ulcer and stenosis

Hiroyuki Tamiya, Akihisa Ishikawa, Shinya Mano, Toshiro Kamoshida, Shinji Hirai, Noriko Chikatsu, Yuji Oka

Department of Internal Medicine, Hitachi General Hospital, Hitachi, Ibaraki, Japan

Correspondence to Hiroyuki Tamiya, tamiatky@gmail.com

Summary

Isolated adrenocorticotrophic hormone (ACTH) deficiency (IAD) is a potentially fatal condition that is difficult to diagnose. The authors diagnosed IAD in a patient who presented with recurrent oesophageal ulceration resulting in oesophageal stenosis. The recurrent oesophageal ulcers were due to frequent nausea and vomiting that were the presenting digestive symptoms of adrenal insufficiency. Severe hypoglycaemia during this patient's course suggested the diagnosis of adrenal insufficiency. This case is educational because digestive symptoms are the most common symptoms in patients with adrenal insufficiency, but the diagnosis of adrenal insufficiency in such patients is not easy.

BACKGROUND

Isolated adrenocorticotrophic hormone (ACTH) deficiency (IAD) is a potentially fatal condition that is difficult to diagnose. It was thought to be very rare, but reported cases of IAD have been increasing recently.¹⁻³ IAD mostly affects middle-aged males and is often

underdiagnosed. Diagnosis usually follows manifestation of adrenal insufficiency under stress, but is hindered by the complete lack of specific symptoms and paucity of measurable signs. We report a patient with IAD who presented with recurrent oesophageal ulceration and stenosis.

Figure 1 Ulcer (A), (B), (C) and stenosis (D) of the oesophagus revealed by upper gastrointestinal endoscopy.

Table 1 Laboratory data on admission and basal endocrinological data obtained before cortisol replacement.

		Range	Unit
WBC	11.5	4.0–8.0	$\times 10^3/\mu\text{l}$
St	3	2–13	%
Seg	63	38–65	%
Eos	6	2–5	%
Mono	3	2–8	%
Bas	0	0–7	%
Lym	3.4	26–47	%
Hb	9.3	14–17	g/dl
Hct	29.7	39.8–51.8	%
Plt	1.84	1.40–3.50	$\times 10^6/\mu\text{l}$
MCV	85.8	82.7–101.6	fL
TP	6.7	6.3–7.8	g/dl
Alb	3.9	3.7–4.9	g/dl
T-Bil	0.9	0.2–1.0	mg/dl
BUN	12.8	9–21	mg/dl
Cre	0.7	0.6–1.1	mg/dl
AST	42	11–45	IU/l
ALT	17	6–43	IU/l
LDH	214	120–245	IU/l
γ GTP	12	10–50	IU/l
ALP	117	80–260	IU/l
Amy	192	60–200	IU/l
CK	366	57–197	IU/l
Na	137	135–149	mEq/l
K	4.3	3.5–4.9	mEq/l
Cl	99	96–108	mEq/l
Ca	9.6	8.5–10.5	mg/dl
IP	4.2	2.5–4.5	mg/dl
T-Cho	135	130–220	mg/dl
TG	92	50–150	mg/dl
CRP	9.49	<0.3	mg/dl
PT	15.8	11–13	s
APTT	33.8	27–40	s
CEA	1.3	<5	ng/ml
SCC	1.9	<2.0	ng/ml
Glu	20	70–110	mg/dl
HbA1c	4.5	4.3–5.8	%
TSH	1.58	0.34–3.5	$\mu\text{U/ml}$
ft4	1.48	0.9–1.8	ng/dl
ft3	2.7	2.0–4.0	pg/ml
ACTH	<1.0	4.4–52	pg/ml
Cortisol	<2.0	2.7–15.5	mg/dl
GH	0.14	<0.17	ng/ml
IGF1	77	68–216	ng/ml
LH	5.50	1.6–9.5	mIU/ml
FSH	8.37	1.2–15	mIU/ml
PRL	19.3	1.2–15	ng/ml
Test	5.61	3–10.5	ng/ml
NSB	7	<8	%
FIRI	5	1.7–10.4	$\mu\text{U/ml}$
TIRI	8	5–15	$\mu\text{U/ml}$

ACTH, adrenocorticotrophic hormone; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Amy, amylase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; Bas, basophil; BUN, blood urea nitrogen; Ca, calcium; CEA, carcinoembryonic antigen; CK, creatine kinase; Cl, chloride; Cre, creatinine; CRP, C reactive protein; Eos, eosinophil; FIRI, free immunoreactive insulin; FSH, follicle stimulating hormone; ft4, free thyroxine; ft3, free triiodothyronine; GTP, γ -glutamyl transpeptidase; GH, growth hormone; Glu, glucose; Hb, haemoglobin; HbA1c, haemoglobin A1c; Hct, haematocrit; IGF1, insulin-like growth factor-I; IP, inorganic phosphorus; K, potassium; LDH, lactate dehydrogenase; LH, luteinising hormone; Lym, lymphocyte; MCV, mean corpuscular volume; Mono, monocyte; Na, sodium; NSB, non-specific binding; Plt, platelet count; PRL, prolactin; Seg, segment; PT, prothrombin time; SCC, squamous cell carcinoma; St, stab; TP, total protein; T-Bil, total bilirubin; T-Cho, total cholesterol; Test, testosterone; TIRI, total immunoreactive insulin; TG, triglyceride; TSH, thyroid stimulating hormone; WBC, white blood cell.

CASE PRESENTATION

A 67-year-old male was admitted to our hospital in October 2007 complaining of nausea, vomiting, haematemesis and tarry black stool after eating a Chinese meal and drinking an alcoholic beverage. He had a medical history of duodenal ulcer in 2005. He had been treated with thyroid hormone (synthetic thyroxine 50 $\mu\text{g/day}$) for hypothyroidism (serum thyroid stimulating hormone (TSH) level was elevated to 5.3 $\mu\text{U/ml}$; free T4 level was 1.08) since December 2004. He had experienced frequent cold sweats since 2003, and he gradually felt worse after he started thyroxine. One week prior to admission, he started to experience nausea after meals. Endoscopic examination revealed a haemorrhaging oesophageal ulcer (figure 1A,B), and haemostasis was performed with endoscopic guidance. In January 2008, he was admitted to our hospital again – complaining of difficulty in swallowing, nausea, vomiting and tarry stool (figure 1C). Despite careful examination, the cause of repetitive nausea and vomiting was not determined. Oesophageal ulcers were treated with a proton-pump inhibitor (PPI). In March 2008, he re-visited our hospital complaining loss of appetite, frequent vomiting and difficulty in swallowing. Endoscopic examination revealed circumferential stenosis of the oesophagus and balloon dilatation was performed (figure 1D).

In May 2008, he was re-admitted to our hospital by ambulance complaining of high fever and nausea. He had been smoking 10 cigarettes a day for 40 years. He had consumed alcohol, Japanese *sake*, 40 g/day from the age of 20–56, until he suffered from duodenal ulcer, consumed 20 g three times a week from the age of 57–65. After first admission to our hospital in March 2008, he stopped drinking alcohol. He was 153.0 cm tall, and his body weight was 48.2 kg, representing a 12-kg reduction in body weight over the previous 7 months. Vital signs were blood pressure 130/76 mm Hg, pulse rate 100/min and body temperature 38.6°C. On physical examination, no abnormal findings were seen on head, neck, chest and abdominal examination. His periphery was very cold, and he was shivering.

Laboratory data revealed a slight leucocytosis with a non-suppressed eosinophil count (white blood cell 11 500 cells/ μl with 6% eosinophils) and severe hypoglycaemia (glucose 20 mg/dl; table 1). Chest CT revealed thickening of the oesophageal wall and pleural fluid. Upper gastrointestinal endoscopy revealed circumferential stenosis of the oesophagus and a hiatal hernia. Balloon dilatation of the oesophagus alleviated difficulty in swallowing. However, the patient experienced hypoglycaemic attacks even following food intake and glucose administration was necessary to prevent severe hypoglycaemic episodes. The differential diagnosis of hypoglycaemia included hypothyroidism, insulinoma, hepatic failure, renal failure, hormone producing tumour including insulin-like growth factor-II producing tumour, impaired glucose tolerance, gastrectomy and insulin antibody syndrome. He had no history of operation, and liver enzymes and creatinine levels were normal. No tumour was seen in the abdomen, including pancreas on abdominal ultrasonography or enhanced abdominal CT. On focused repeat physical examination, loss of physiological skin pigmentation such as nipple and pubic area pigmentation was identified. This phenotype

Figure 2 Midsagittal view of the pituitary gland on T1-weighted MR image. The pituitary gland was slightly atrophic.

Figure 3 Results of combined (corticotropin-releasing hormone, thyrotropin releasing hormone, luteinising hormone releasing hormone and growth hormone-releasing hormone) loading test.

suggested the existence of central hypocortisolism as a cause of the hypoglycaemia. Serum ACTH and cortisol levels were undetectable, and urinary cortisol excretion was below 11.5 mg/day (table 1). Serum TSH, thyroid

hormones, growth hormone (GH), insulin-like growth factor-I, gonadotropins and testosterone were normal. Brain MRI scan of the pituitary showed a slightly atrophic pituitary gland (figure 2). Combined corticotropin-releasing

Figure 4 Hypothesis of the pathophysiology of this case.

hormone, growth hormone-releasing hormone, luteinising hormone releasing hormone, thyrotropin releasing hormone loading test revealed no response in ACTH and cortisol, but normal response in GH, follicle stimulating hormone, luteinising hormone, TSH and prolactin (figure 3). Antipituitary and anti-thyroid peroxidase antibody antibodies were negative.

OUTCOME AND FOLLOW-UP

The patient was diagnosed with IAD. Cortisol replacement resulted in alleviation of his symptoms with restoration of normoglycaemic condition. Body weight increased to 53 kg (12 kg gain) over 1 year.

DISCUSSION

Caustic, traumatic, irritative, alcoholic, viral, fungal, bacterial, Plummer–Vinson syndrome, collagen disease, oesophageal carcinoma, malignant lymphoma, gastrinoma, eosinophilic, reflux oesophagitis and Mallory–Weiss syndrome were considered in the differential diagnosis of oesophageal ulcer. There was no history of trauma, or ingestion of caustic or irritative substances. Alcohol may play some role, but it's unlikely that alcohol is the main cause of the oesophageal ulcer, because the amount of the alcohol was not so much, and the oesophagitis was recurrent even though he stopped drinking after the first admission, that is, the risk for adverse effects such as tissue damage generally increases following the consumption of more than

2 ounces, 57 g of alcohol.⁴ On serum examination, HIV antibody was negative, and antibodies to cytomegalovirus, herpes simplex virus and Epstein–Barr virus did not reveal an infection pattern. Serum β D-glucan was low (9.8 pg/ml). Repeat biopsy and culture of oesophageal mucosa showed mild *Neisseria*, non-specific inflammation and scarring. No evidence of malignancy, bacterial infection or fungal infection was observed. Tumour markers, including s-IL-2R (762 U/ml) and SCC (1.9 ng/ml) were not elevated. The suspicion of Plummer–Vinson syndrome was low because his anaemia was normocytic. There were no characteristic physical signs of collagen disease; serum immunoglobulin and complement levels were normal; and anti-ribonucleoprotein antibody, anti-neutrophil cytoplasmic antibodies and rheumatoid factor were negative. Gastrin level was only slightly elevated at several points of measurement (100–400 pg/ml) probably due to PPI use. We considered reflux gastritis as a possible cause of the oesophageal ulceration because hyperacidity was suspected based on the history of duodenal ulcers and hiatal hernia. Mallory–Weiss syndrome was considered as another cause of the oesophageal ulcers because he had haematemesis and tarry stool after a meal at the time of his first admission.

In summary, adrenal insufficiency was the likely cause of the nausea and vomiting in this case, with resultant bleeding oesophageal ulcer (Mallory–Weiss syndrome). Complicating factors included hyperacidity, suggested by a history of duodenal ulcer and a hiatal hernia. The

oesophageal ulcer, caused by reflux oesophagitis and Mallory–Weiss syndrome, became chronic, causing oesophageal stenosis. The hypoglycaemia from adrenal insufficiency (which occurs in more than 30% of patients with adrenal insufficiency)³ was worsened by dysphagia from the oesophageal stenosis. In the absence of aggravated hypoglycaemia, adrenal insufficiency would not have been evident (figure 4).

IAD was first reported by Steinberg *et al* in 1954.² It presents with appetite loss, anorexia, general fatigue, unconsciousness, nausea, vomiting, fever and hypoglycaemia. Although IAD has been considered very rare in the past, an increasing number of cases have been reported recently. Over 300 cases of IAD were reported between 1969 and 1994 in Japan, and an increasing number of cases have been reported since then.³ The prevalence of diagnosed cases is 1.91/1 000 000 in the Miyazaki prefecture, 7.3/1 000 000 in Tokushima area and 3.8/1 000 000 in Chuetsu district in Japan.^{5,6} There seems to be a substantial number of undiagnosed patients because clinical diagnosis is made when the patient becomes severely ill due to physical stress.^{7,8} Although nausea and vomiting are the most common symptoms of adrenal insufficiency, seen in more than 90% of patients,^{9,10} IAD patients who present with oesophageal ulcers are very rare.^{11–13} To our knowledge, there is only one case of reported adrenal deficiency resulting in oesophageal ulcer.¹⁴

In this patient, elevation of TSH had been noticed by his home physician in 2005, 3 years before the final diagnosis of IAD which normalised with thyroxine replacement. When the patient received cortisol replacement, TSH normalised, even after thyroxine replacement was stopped. The TSH elevation (compensatory TSH elevation) is one of the comorbidities of IAD seen in 43.8% of patients.¹⁵ Thyroxine replacement may increase the degradation of cortisol, which exacerbates symptoms (figure 4).¹⁶

Learning points

- ▶ Quite a few people are potentially affected by IAD, but adrenal insufficiency is very difficult to diagnose.
- ▶ The most common manifestations of adrenal insufficiency are nausea and vomiting, seen in more than 90% of patients.
- ▶ Nausea and vomiting in a patient generally suggests digestive problems, but adrenal insufficiency, despite its rarity, must be considered in the differential diagnosis of nausea and vomiting, given its lethality.
- ▶ We must consider the possibility of compensatory TSH elevation of hypoadrenalism when TSH elevation is encountered.

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