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A case of probable Waterhouse-Friderichsen syndrome due to *Escherichia coli*

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Abstract

Waterhouse-Friderichsen syndrome (WFS) is a rare clinical condition, characterized by adrenal insufficiency and high mortality. We report a case of probable WFS due to *Escherichia coli*. A 70-year-old woman was brought to the emergency room because of fatigue and difficulty breathing. The patient reported severe pain in her extremities and could not keep herself on a bed or chair. On examination, livedo reticular is noted, and her extremities were cold. Arterial blood gas analysis demonstrated a pH of 6.917, a lactate level of 169 mg/dL, and a glucose level of 13 mg/dL. Computed tomography of the abdomen without contrast medium showed fat stranding around the bilateral kidneys and adrenal glands. The patient's hemodynamics gradually deteriorated, and she died four hours after presentation, despite the administration of aggressive hydration, noradrenaline, and broad-spectrum antibiotics. Her family declined an autopsy. It was later confirmed that cultures of her blood and urine demonstrated *E. coli*. Our case highlights the importance of clinicians being aware of WFS in order to facilitate its early diagnosis.

Keywords

Adrenal Glands; *Escherichia coli*; Hypoglycemia; Waterhouse-Friderichsen syndrome.

Introduction

Waterhouse-Friderichsen syndrome (WFS) is characterized by adrenal insufficiency due to acute hemorrhagic necrosis with various etiologies, such as bacterial and viral infections [1]. WFS is rare, but physicians need to be aware of its existence because of its rapidly progressive features and high mortality rate [1]. We report a case of probable WFS due to *Escherichia coli*.

Case Report

A 70-year-old woman was brought to the emergency room of our hospital due to general fatigue and breathing difficulties. The patient had been in her usual state of health until four days earlier, when she had developed general fatigue. She had also noticed a reduction in her blood pressure, e.g., a systolic pressure of around 90 mmHg, during daily measurements. Her condition had gradually deteriorated, and she had difficulty breathing, even at rest, leading her to call an ambulance. On arrival, she reported severe pain in her extremities and could not keep herself on a bed or chair. She stated that she had not experienced any antecedent trauma, been exposed to chemicals or animals, been in contact with sick people, consumed fresh food, or recently engaged in travel or outdoor activities. Her medical history included surgery for a right femoral neck fracture 13 years earlier; alcoholic cirrhosis; osteoporosis; hypertension; and diabetes mellitus, which had been controlled well without insulin. Her medications included irbesartan, amlodipine, rosuvastatin, metformin, alendronic acid, alfacalcidol, limaprost alfadex, magnesium oxide, and loxoprofen. She had stopped drinking alcohol six years earlier, quit smoking after a 22 pack-year history, did not use illicit drugs, and had no known allergies.

On examination, she was lethargic. Her blood pressure was 123/67 mmHg, her pulse rate was 101 beats per minute, her body temperature was 35.4°C, her respiratory rate was 26 breaths per minute, and her oxygen saturation level was 98% while she was breathing ambient air. Livedo reticular is noted on her trunk, her extremities were cold, and a petechial rash was present on her torso. Her neck was supple, both lungs were clear on auscultation, and a cardiac examination produced normal findings. There was no edema in her legs, and the remainder of the examination was normal.

Electrocardiography showed atrial fibrillation, ST-segment depressions in all leads except for aV_R, and premature ventricular contractions. A chest radiograph exhibited normal findings. Arterial blood gas analysis demonstrated a pH of 6.917, a partial carbon dioxide pressure of 22.3 mmHg, a bicarbonate level of 4.3 mmol/L, a lactate level of 169 mg/dL, and a glucose level of 13 mg/dL. The patient's levels of creatinine and urea nitrogen were 5.94 mg/dL and 57 mg/dL, respectively, both of which had been normal six months earlier. Her other laboratory data were consistent with disseminated intravascular coagulation, such as a low platelet count, a high fibrin degradation product level, and a prolonged partial thromboplastin time (Table 1). Her blood sugar level was restored by administering 40 ml of a 40% glucose infusion, and hydration was started with the initiation of meropenem under a presumptive diagnosis of sepsis.

Table 1: Laboratory Data.

Variable	Reference range	Six months earlier	At presentation	One hour after presentation	2.5 hours after presentation
White blood cell count (/μL)	4,000-9,000	5,700	25,200		
Neutrophils (%)	40-70		86.5		
Lymphocytes (%)	15-60		8		
Hemoglobin (g/dL)	11.5-16.5		10.7		
Mean corpuscular volume (μm^3)	80-100		107.1		
Platelet count (/μL)	150,000-	157,000	89,000		
	420,000				

Fibrinogen (mg/dL)	150-450		531		
Fibrin degradation products (μg/mL)	≤5		61.2		
D-Dimer (μg/mL)	≤1.0		42.5		
Partial thromboplastin time (s)	11-14		25.3		
International normalized ratio			2.19		
Activated partial thromboplastin time (s)					
Total bilirubin (mg/dL)	≤1.2	0.5	1.3		
Aspartate aminotransferase (U/L)	≤30	43	106		
Alanine aminotransferase (U/L)	≤30	32	76		
Lactate dehydrogenase (U/L)	110-120	138	224	265	
Alkaline phosphatase (U/L)	38-113	175	392		
Total protein (g/dL)	6.7-8.8	8.4	6.7		
Albumin (g/dL)	≥4.0	3.9	2.7		
Sodium (mEq/L)	135-147	139	133		
Potassium (mEq/L)	3.6-5.0	4.9	5.7		
Urea nitrogen (mg/dL)	8-20	17	57		
Creatinine (mg/dL)	0.45-0.81	1.03	5.94		
Creatine kinase (U/L)	≤175	35	28		
C-reactive protein (mg/dL)	≤0.25	0.08	23.65		
Blood sugar (mg/dL)	70-108	195	17		
eGFR (mL/min/1.73 m^2)	≥60	41.2	6		
Brain natriuretic peptide (pg/mL)	≤18.4		455.1		
Troponin T (ng/mL)	≤0.014		0.036		
Blood gases					
Sources			Venous	Arterial	Arterial
pH	7.35-7.45		6.917	6.84	6.676
Partial pressure of carbon dioxide (mmHg)	32-48 (arterial)		22.3	19.8	27.5
Partial pressure of oxygen (mmHg)	83-108 (arterial)		115	122	123
Bicarbonate (mmol/L)	22-31 (arterial)		4.3	3.2	3
Base excess (mmol/L)			-27.3	-29.4	-31.1
Lactic acid (mg/dL)	4.5-14.4		169	183	185

eGFR = estimated glomerular filtration rate.

Computed tomography of the abdomen without contrast medium revealed fat stranding around the bilateral kidneys and adrenal glands (Figure 1). Soon after, the patient was admitted to the intensive care unit, when her consciousness level decreased (i.e., Glasgow coma scale: E3, V3, M5). Her blood pressure was 135/95 mmHg, her pulse rate was 100 beats per minute, her respiratory rate was 30 breaths per minute, and her oxygen saturation level was 92% under the inhalation of oxygen via a mask at a rate of three liters per minute. The patient's blood pressure gradually fell despite rapid fluid resuscitation and the continuous infusion of noradrenaline. Four hours after presentation, the patient died. No autopsy was performed. Cultures of the patient's blood and urine subsequently revealed *E. coli*.

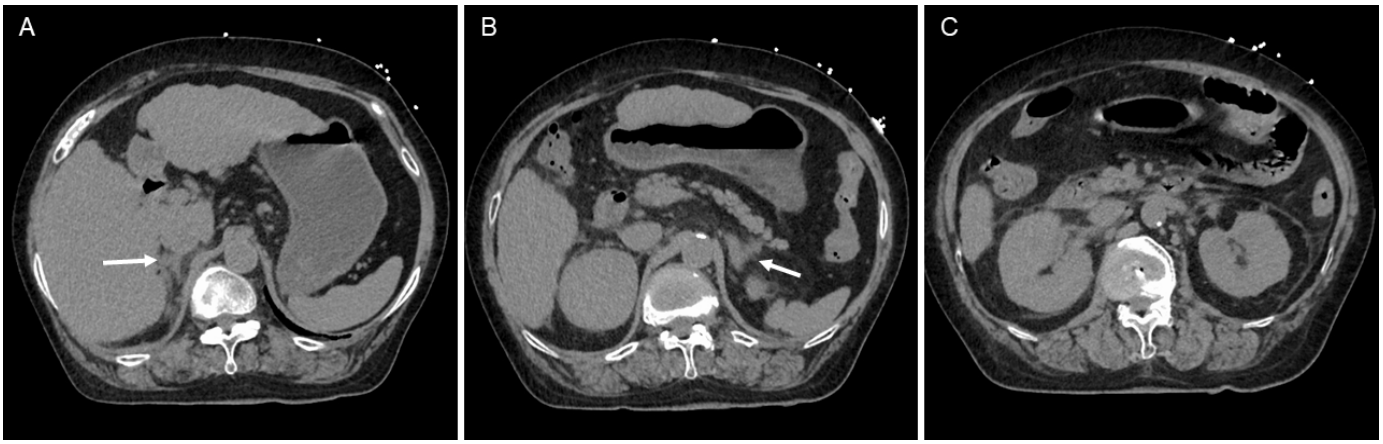

Figure 1: Computed tomography of the abdomen: A non-contrast-enhanced image shows fat stranding around the right adrenal gland (A, arrow), left adrenal gland (B, arrow), and bilateral kidneys (C).

Discussion

Our patient's clinical course was characterized by non-specific initial symptoms, rapid progression with severe pain in the extremities, and a poor outcome. A diagnosis of urosepsis due to *E. coli* was initially suspected, but acute adrenal insufficiency should be considered as a possible underlying condition since our patient showed hypoglycemia and hyponatremia. Given the concomitant conditions of livedo reticularis and severe pain in the extremities, we may safely assume that the patient had WFS [2], although no autopsy was performed to confirm the occurrence of adrenal hemorrhaging The presence of disseminated intravascular coagulation was also consistent with this rare, fatal syndrome.

WFS was first reported by Waterhouse in 1911 [3], followed by Friderichsen in 1918 [4], and it was defined by Newcomb in 1946 [5]. Adrenal hemorrhaging is the most important finding in patients with WFS, but its clinical identification is difficult in most cases [5], which makes it challenging to make an ante mortem diagnosis of WFS. In our patient, no adrenal hemorrhaging was noted on computed tomographic images, although fat stranding was seen around the adrenal glands. The exact incidence of WFS remains unclear, but it may be more common than is realized, given the fact that most physicians are unfamiliar with the condition. It was reported that in 800 consecutive autopsies, non-traumatic adrenal hemorrhaging was observed in five otherwise healthy individuals who died suddenly as a result of a bacterial infection [6]. WFS is likely to be confused with septic shock unless WFS is highly suspected [1]. It is worth noting that in our medium-sized hospital, we experience the case of WFS secondary to a *Streptococcus pneumonia* infection a few years earlier [7].

The mechanism underlying WFS remains unclear, but it is reported that the adrenal glands are vulnerable to hemorrhaging when the adrenal venous pressure increases [8]. Potential causes of adrenal hemorrhaging include bacterial sepsis, trauma, a bleeding tendency (i.e., due to disseminated intravascular coagulation or anticoagulant treatment), and antiphospholipid syndrome [1,8,9]. One of the most common bacterial infections that leads to WFS is *meningococcal* sepsis, but other Gram-negative organisms, such as *S. pneumoniae*, *Klebsiella*, and *Haemophilus influenza*, can also provoke this fatal condition [8]. In a study including 51 children with septicemic adrenal hemorrhaging, *Pseudomonas aeruginosa* was reported to be

the most commonly identified pathogen [10]. The pathogen identified in our patient was *E. coli*, which has only been reported in a few cases of WFS [11,12].

Asplenia, hyposplenia, splenectomy, and splenic atrophy can be risk factors for WFS [13], but there was no evidence of hyposplenism in imaging studies in the current case. Cirrhosis, which was observed in our case, may be associated with the development of WFS [14], although the relationship between the two conditions has not been fully investigated. Other risk factors include anticoagulants, thrombocytopenia, hypercoagulable states, antiphospholipid syndrome, trauma to the adrenals, and a postoperative state [1], none of which applied to our patient. In addition to supportive therapy for sepsis, including volume resuscitation, broad-spectrum antibiotics, and vasopressors, treatment for adrenal failure with mineralocorticoids and glucocorticoids may be effective in some cases, although the response to such treatment is unpredictable, and the mortality rate of patients treated in this manner is still high [1]. No steroid treatment was initiated during our patient's clinical course.

In conclusion, our case highlights the importance of clinicians being aware of WFS in order to facilitate its early diagnosis and prompt treatment.

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Conflicts of interest: No potential conflicts of interest exist.

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