A rare case of severe systemic life-threatening botulism caused by a local botulinum toxin-A injection

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INTRODUCTION

Botulinum toxin (BTX) is produced by a gram-positive anaerobic bacterium called *Clostridium botulinum*. BTX is among the deadliest natural substances known to humans with an estimated lethal dose of 1 ng/kg.[1,2] There are 7 types of this neurotoxin- BTX-A, -B, -C1, -C2, -D, -E and -F. Human botulism is caused mainly by types A, B, E, and rarely F.[3] BTX can cleave the presynaptic protein snap-25, inhibit acetylcholine release, and block the neuromuscular junction.[4,5] BTX was first used in humans to treat strabismus in 1973, and later its applications were extended to many other conditions such as neurogenic detrusor overactivity, chronic migraine, muscle spasticity, axillary hyperhidrosis, and blepharospasm.[6] Furthermore, BTX has been approved in more than 50 countries and has become the first-choice nonsurgical procedure for facial rejuvenation since 2000.[7] However, many adverse events have been described such as dry mouth, pain at injection site, fatigue, headache, neck pain, weakness, and eye problems including double vision, blurred vision, decreased eye sight, eyelid ptosis, eyelid swelling, brow ptosis, and dry eyes. More serious adverse events such as asthenia, excessive weakness, dysphagia, dysphonia, dysarthria, urinary incontinence, and aspiration pneumonia have been documented.[8-10] Here, we report a rare case of a patient who had systemic life-threatening complications after self-administration of an overdose of BTX-A which was obtained from an underground market.

Abbreviations used:

BTX:	botulinum toxin
CMAP:	compound muscle action potentials
EMG:	electromyogram
Ref:	reference
SXCDC:	Shaanxi Provincial Center for Disease Control and Prevention

CASE REPORT

A 25-year-old woman who just graduated from a nursing school was admitted into our emergency care unit on April 11, 2019. She presented with sudden dizziness, severe headache, fainting, and blurred vision for 7 days and a recent development of dysphagia for 1 day. She described that she purchased 1 bottle labeled as "Thigh Slimming Injection" from a local cosmetic spa store and administered it into her left lower extremity at multiple sites in a single session 11 days prior. There was no essential product information on the label of the bottle, including brand name, ingredients, expiration date, or manufacturer. Her symptoms immediately after injection included edema and muscle tenderness in her left lower extremity, but the patient disregarded these initial symptoms. Then, 5 days after injection, she reported

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feeling fatigue, general weakness, shortness of breath, dizziness, diplopia, and visual disturbance. She went to the first local hospital for regular checks on days 5 and 7 but was told that she was normal on examinations. At a second hospital, she was given a Chinese traditional cupping therapy on days 9 and 10. She had no improvement of her signs or symptoms. Subsequently, she became very weak, was unable to walk, and had dysphagia and a choking sensation to water. At our hospital, she was admitted to the emergency department on day 11 after the injection.

The patient had an unremarkable medical history and was in overall good health prior to this incident. Upon admission, a series of laboratory examinations were performed (Table I). The abnormal laboratory tests were as follows. (1) The complete blood count showed higher levels of white blood cells (11.3; reference [ref], 3.2-9.7 $\times 10^9$/L) and monocytes (0.71; ref, 0-0.45 $\times$ 10^9/L), and mean corpuscular hemoglobin (34.4; ref, 26.9-33 pg). (2) Coagulation assays showed elevated prothrombin time (13.2; ref, 9.8-12.1 seconds) and decreased percentage of plasma thromboplastin antecedent (69.5; ref, 80%-120%). (3) Metabolic profiles showed increased levels of total protein (91.0; ref, 63-82 g/L), albumin (52.5; ref, 35-50 g/L), globulins (38.5; ref, 20-32 g/L), total bilirubin (58.76; ref, 3-22 μmol/L), conjugated bilirubin (6.91; ref, 0-5.0 μmol/L), and unconjugated bilirubin (51.85; ref, 0-19, μmol/L). Other laboratory findings appeared to be normal (Table I). The results from electrocardiography and head, neck, and chest computed tomography scans were normal.

Electromyogram (EMG) recordings on various motor and sensory nerves were carried out. Amplitudes of compound muscle action potentials (CMAP) for motor branches of musculocutaneous (biceps brachii-Erb point) and axillary (deltoid-Erb point) nerves were below the normal ranges (Table II). The amplitudes of CMAP for bilateral ulnar motor nerves (wrist-below elbow) were at the low threshold levels of the normal ranges (Table II). The tests on other muscles and nerves appeared to be normal (Table II).

In addition, a serum sample was sent to Shaanxi Provincial Center for Disease Control and Prevention (SXCDC) for a toxin detection. It was found to be positive for BTX-A and negative for BTX-B using a colloidal gold-based immunochromatographic assay. Severe botulism caused by an overdose of BTX-A was the diagnosis. The incident was reported to SXCDC.

The patient was treated by intramuscular injection of 10,000 U of a botulinum antitoxin (HBAT) into the ventrogluteal muscle of the hip daily for 17 days. The patient felt an immediate alleviation of dysphagia

Table I. Patient's laboratory values on admission

Testing category	Results	Reference	Unit
Complete blood count			
White blood cells	11.3↑	3.2-9.7	$\times 10^9$/L
Lymphocytes	3.50	0.64-3.88	$\times 10^9$/L
Monocytes	0.71↑	0 -0.45	$\times 10^9$/L
Neutrophils	7.03	1.6-7.3	$\times 10^9$/L
Eosinophils	0.05	0-0.45	$\times 10^9$/L
Basophils	0.02	0-0.2	$\times 10^9$/L
Platelets	256	100-300	$\times 10^9$/L
Platelet distribution width	12.3	15.5-18.1	%
Red blood cells	4.54	3.5-5	$\times 10^9$/L
Mean corpuscular hemoglobin	34.4↑	26.9-33	pg
Coagulation tests			
Prothrombin time	13.2↑	9.8-12.1	s
Plasma thromboplastin antecedent	69.5↓	80-120	%
Activated partial thrombo-plastin time	27.2	21.1-36.5	s
Fibrinogen	2.69	1.8-3.5	g/L
Thrombin time	17.4	14-21	s
Fibrinogen degradation products	2.20	0-5	μg/mL
D-dimer	0.64	0-1	μg/mL
Blood gas analysis			
PH	7.390	7.35-7.45	
PaCO2	30.8	38-42	mmHg
PaO2	84.7	80-100	mmHg
Cerebrospinal fluid analysis			
Chloride	124.3	120-132	mmol/L
Glucose	2.56	2.2-3.9	mmol/L
Protein	447.64	120-600	mg/L
Metabolic markers			
Creatine kinase myocardial band	0.63	0-2.37	ng/mL
Troponin I (cTnI)	<0.012	0-0.04	ng/mL
Myoglobin	58.33	0-61.5	ng/mL
Total protein	91.0↑	63-82	g/L
Albumin	52.5↑	35-50	g/L
Globulins	38.5↑	20-32	g/L
ALB/GLO	1.4↓	1.5-2.5	
Total bilirubin	58.76↑	3-22	μmol/L
Conjugated bilirubin	6.91↑	0.0-5.0	μmol/L
Unconjugated bilirubin	51.85↑	0-19	μmol/L
Alanine aminotransferase	28	15-46	U/L
Alanine transaminase	28	11-66	U/L
Gamma-glutamyl transferase	24	12-43	U/L
Alkaline phosphatase	85	38-126	U/L
Glucose	6.02	4.1-5.9	mmol/L
Blood urea nitrogen	6.36	3.2-7.1	mmol/L
Creatinine	72.2	28-110	μmol/L
Uric acid	391.8	208-506	μmol/L
Procalcitonin	<0.20	<0.5	ng/mL
Chloride	104.9	98-107	mmol/L
Calcium	2.47	2.1-2.55	mmol/L
Potassium	3.63	3.5-5.1	mmol/L
Sodium	143.7	137-145	mmol/L

ALB/GLO, Albumin to globulin ratio.

Table II. EMG recordings to show the amplitude of CMAP of targeted nerves

Nerves	Amplitude (mV)	Reference (mV)
Ulnar, left		
Wrist-below elbow	4.7*	≥ 5
Wrist-above elbow	6.4	≥ 5
Ulnar, right		
Wrist-below elbow	5.0	≥ 5
Wrist-above elbow	6.7	≥ 5
Median, wrist-elbow		
Left	6.6	≥ 5
Right	6.6	≥ 5
Radial, above elbow-spiral groove		
Left	4.4	≥ 3
Right	4.5	≥ 3
Musculocutaneous, biceps brachii-Erb point		
Left	3.9*	≥ 5
Right	3.9*	≥ 5
Peroneal, fibula-popliteal fossa		
Left	10.5	≥ 3
Right	11.5	≥ 3
Axillary, deltoid-Erb point		
Left	3.2*	≥ 5
Right	3.0*	≥ 5

*These are the abnormally low values, which caused concern for systemic botulism.

3 hours after the first injection, and showed a progressive and full recovery from dysphagia 2 days later. However, the symptoms such as weakness, dizziness, diplopia, and blurred vision remained. After 3 days of treatment, the patient could walk and had a clear vision within 1 meter. On day 10, the patient felt no dizziness but still had weakness, diplopia, and blurred vision at farther distances. On day 14, the patient's diplopia improved, and her vision was clear to 3 meters. On day 17, the patient had full resolution of the diplopia and blurred vision, but she still felt weak. The patient was discharged the next day. The patient was fully recovered at her 1-week follow-up. The patient did not show any long-term adverse events at her evaluation 6 months after hospitalization.

DISCUSSION

In the past decades, BTX has emerged as the most popular minimally invasive procedure for facial rejuvenation. The safety profile for BTX applications has always been a major concern in cosmetic clinics, although the adverse events caused by BTX are generally considered reversible, short term, localized, and not life threatening. In 2009, the US Food and Drug Administration issued a safety warning that said the toxin "may spread from the area of injection to produce symptoms of botulism." Adverse effects such as muscle weakness, dizziness, and difficulty breathing can occur hours or weeks after an injection, depending on the volume and dosage (the number of units) of injected of BTX. Recent evidence shows that BTX can spread to distant sites either via the neuroaxonal or hematogenous transport,[11] which may account for the systemic complications observed in our patient. Affected individuals may feel fatigue, headache, and dizziness at early stage but generally have normal basic laboratory examinations and imaging scans, which makes early diagnosis difficult. Our patient's botulism was misdiagnosed twice at a local hospital; therefore, the early diagnosis window was missed to prevent the development of systemic complications. Based on the history of patient's administration of unknown substances, we performed neurophysiologic tests and blood tests. A typical CMAP amplitude decrease was found in EMG recordings in some types of motor nerves from the patient such as musculocutaneous, axillary, and ulnar branches. Furthermore, the SXCDC confirmed the presence of BTX-A in the patient's serum. Therefore, the combination of these tests confirmed the diagnosis of systemic botulism.

A few good lessons came from this case. First, both practitioners and patients should have full knowledge of and be aware of the dangerous side effects of using BTX, including the possible systemic complications, although rare. Educating patients is of particular importance. The injection of BTX should be performed by well-trained practitioners using a standard protocol. The volume and dosage must be very tightly controlled to avoid any severe adverse outcomes. Second, the cosmetic industry is largely unregulated in China, including both the black-market products and the places in which cosmeticians practice. For example, many practitioners employed by cosmetic private clinics, spas, or salons have not received standard medical training nor have they been certified. Regardless, they have been regularly performing injectable procedures such as BTX and dermal fillers since release of these substances to the market in China. Our patient bought a bottle labeled as Thigh Slimming Injection from a local cosmetic spa store without any prescription. This cosmetic store was not authorized to provide that patient with BTX. Thigh Slimming Injection is not a Chinese Food and Drug Administration—approved

product and was sold in the underground market. The policymakers need to close these loopholes and implement appropriate measures to regulate both the injectors and the sales of illegal products with the entire industry both nationally and locally.

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