

BRIEF COMMUNICATION

Toxic epidermal necrolysis after extensive dermal use of realgar-containing (arsenic sulfide) herbal ointment

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Background. Realgar (arsenic sulfide) is thought to be safe with few reports on toxicities or adverse effects and has been used in Traditional Chinese Medicine for many centuries. Serious realgar poisoning is rare, and we report a fatal case resulted from short-term use of realgar-containing herbal medicine through dermal route. **Case details.** A 24-year-old man with atopic dermatitis had received 18 days of oral herbal medicine and realgar-containing herbal ointments over whole body from a Traditional Chinese Medicine (TCM) practitioner. Seven days after the herbal use, he had diminished appetite, dizziness, abdomen discomfort, itching rash, and skin scaling. He later developed generalized edema, nausea, vomiting, decreased urine amount, diarrhea, vesico-edematous exanthems, malodorous perspiration, fever, and shortness of breath. He was taken to the hospital on Day 19 when the dyspnea became worse. Toxic epidermal necrolysis complicated with soft tissue infection and sepsis was noted, and he later died of septic shock and multiple organ failure. The post-mortem blood arsenic level was 1225 µg/L. Herbal analysis yielded a very high concentration of arsenic in three unlabeled realgar-containing ointments (45427, 5512, and 4229 ppm). **Conclusion.** Realgar-containing herbal remedy may cause severe cutaneous adverse reactions. The arsenic in realgar can be absorbed systemically from repeated application to non-intact skin and thus should not be extensively used on compromised skin.

Keywords: Arsenic poisoning; Dermal; Realgar (arsenic sulfide); Toxic epidermal necrolysis; Traditional Chinese medicine

Realgar, with an active ingredient of arsenic sulfide compound (As_4S_4), has been used in the practice of TCM for many centuries. It is used externally for the treatment for various skin problems; and internally for treatment of fever, inflammation, infection, convulsion, and allergy in TCM.^{1,2} Lately, realgar is also used for hematological malignancies. Serious realgar poisoning is rare, and we herein report a fatal case resulted from short-term use of realgar-containing herbal medicine through dermal route.

Case report

A 24-year-old man presented to the emergency department (ED) with a history of progressively worsening of skin condition, gastrointestinal upset for 10 days and fever, generalized edema and shortness of breath for 3 days. His history included beta-thalassemia trait, allergic rhinitis, and atopic dermatitis. At age 18, his hematological and biochemical tests were normal except microcytosis (mean corpuscular volume 62.2 fl, normal 80–100 fl). At age 22, a generalized

atopic dermatitis developed, which involved about 40% of total body surface area. Hematological tests were unremarkable except for a microcytic anemia (hemoglobin 12.8 g/dL and mean corpuscular volume 62 fl), eosinophilia (7.6%) and an elevated immunoglobulin E concentration (6,620 IU/mL, normal <100 IU/mL). Eighteen days prior to this ED visit, he was prescribed oral herbal medications (Table 1) and topical herbal ointments for his skin disease by a licensed TCM practitioner. The ointments included (1) anti-psoriasis revitalizing herbal ointment and (2) analgesic and anti-inflammatory herbal ointment, which were prepared by the TCM practitioner himself. The actual compositions were not known; however, the major ingredients were realgar and da huang (*Radix et Rhizoma Rhei*). The anti-psoriasis revitalizing herbal ointments were applied to whole body several times per day.

The patient developed diminished appetite, dizziness, abdomen discomfort, itching rash, and scaling of his skin 7 days after starting TCM treatment. However, the topical use of herbs was recommended to be continued. The patient developed generalized edema, nausea, vomiting, decreased urine amount, diarrhea, vesico-edematous exanthems, and malodorous perspiration on Day 12 of herbal use. On Day 15, the oral TCM prescription was changed to treat his edema (Table 1). On Days 16 and 17, the patient developed fever, shortness of breath, and 2–3 episodes of near syncope.

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Table 1. Oral herbal prescriptions used by a 24-year-old man who had extensive dermal use of realgar-containing herbal ointment and presented with toxic epidermal necrolysis.

No.	Prescriptions	Contents of the prescription used
1.	Days 1–6: dong quai yin zi (compound) ren shen yeang rong tang (compound) di fu zi (Fructus Kochiae) pu gong ying (Herba Taraxaci)	bai ji li (Fructus Tribuli), bai shao (Radix Paeoniae alba), bai zhu (Rhizoma Atractylodis macrocephalae), chen pi (Pericarpium Citri reticulatae), chuan xiong (Rhizoma Ligusticum wallichii), da zao (Fructus jujubae), di fu zi (Fructus Kochiae), di huang (Radix Rehmanniae), dong quai (Radix Angelicae sinensis), fang feng (Radix Saposhnikoviae), fu ling (Poria cocos), gan cao (Radix glycyrrhizae), he shau wu (Radix Polygoni multiflori), huang qi (Radix Astragali), jing jie (Herba Schizonepetae), pu gong ying (Herba Taraxaci), ren shen (Panax ginseng), rou gui (Cortex cinnamomi), sheng jiang (Rhizoma Gingeris), wu wei zi (Fructus Schisandrae chinensis), yuan zhi (Radix Polygalae)
2.	Days 7–12: dong quai yin zi (compound) wen jing tang(compound) di fu zi (Fructus Kochiae) pu gong ying (Herba Taraxaci)	bai ji li (Fructus Tribuli), bai shao (Radix Paeoniae alba), ban xia (Rhizoma Pinelliae), chuan xiong (Rhizoma Ligusticum wallichii), di fu zi (Fructus Kochiae), di huang (Radix Rehmanniae), dong quai (Radix Angelicae sinensis), e jiao (Donkey-hide gelatin), fang feng (Radix Saposhnikoviae), gan cao (Radix glycyrrhizae), gui zhi (Cinnamomum cassia bark), he shau wu (Radix Polygoni multiflori), huang qi (Astragali Radix), jing jie (Herba Schizonepetae), mai dong (Radix Ophiopogonis), mu dan pi (Cortex Moutan Radicis), pu gong ying (Herba Taraxaci), ren shen (Panax ginseng), shaoyao (Chinese peony, Paeonia lactiflora), sheng jiang (Rhizoma Gingeris), wúzhūyú (Fructus Evodiae)
3.	Days 15–18: gui zhi tang (compound) yue bi jia shu tang (compound) wuling san (compound) huang qi (Radix Astragali)	bai shao (Radix Paeoniae alba), bai zhu (Rhizoma Atractylodis macrocephalae), da zao (Fructus jujubae), fu ling (Poria cocos), gan cao (Radix glycyrrhizae), gui zhi (Cinnamomum cassia bark), huang qi (Radix Astragali), ma huang (Herba Ephedrae), sheng jiang (Rhizoma Gingeris), shigao (Gypsum fibrosum), ze xie (Rhizoma Alismatis), zhu ling (Polyporus umbellatus)

He presented to the TCM clinic for help on Day 18, and received acupuncture and bloodletting therapy. The patient was taken to the ED at midnight when his shortness of breath became worse.

The patient's presenting vital signs were blood pressure 106/39 mmHg, pulse 142/min, respiration 36/min, and temperature 38.8°C. Physical examination revealed an ill-appearing man in moderate respiratory distress. There were generalized erythematous macules with vesicles, scaling, and residual orange ointment over face, trunk, and extremities. The skin lesions involved about 70% of body surface area. Sheet-like loss of epidermis was noted over chest, back, and both thighs. Patient was noted to have rice water-like diarrhea. Hematological tests showed a hemoglobin of 9.9 g/dL, mean corpuscular volume 55 fl, white blood cell count 11,264/cumm with 7% banded neutrophils, 73% segmented neutrophils, and 12% lymphocytes. The prothrombin time was 1.72 INR, and activated partial thromboplastin time was 58.1 s (control 27.5 s). Biochemical tests were remarkable with alanine transaminase 83 U/L (normal < 40 U/L), aspartate transaminase 115 U/L (normal 5–45 U/L), blood urea nitrogen 35 mg/dL (normal 7–20 mg/dL), creatinine of 1.6 mg/dL (normal 0.7–1.5 mg/dL), sodium 122 mmol/L (normal 135–147 mmol/L), and C-reactive protein 15.4 mg/dL (normal < 0.5 mg/dL). His urinalysis revealed ketonuria (2+) and proteinuria (1+). Arterial blood gas while on 3 L of oxygen showed pH of 7.396, PCO₂ of 22.5 mmHg, PO₂ of 144.9 mmHg, and HCO₃ of 13.5 mmol/L. His chest X-ray showed no active lung lesions. An electrocardiogram showed sinus tachycardia with a rate of 150 per min, T waves flattening and poor R wave progression; normal QRS 80 ms and QTC 380 ms. The patient was admitted to intensive care unit with a presumptive diagnosis of toxic epidermal necrolysis (TEN), complicated with soft-tissue infection and sepsis. At 8.5 h after arrival of ED, the patient developed profound

shock and severe metabolic acidosis. Bradycardia and asystole were noted at 34 h, which was followed by pulseless electric activity, and he died at 35.5 h. The direct cause of death was *Pseudomonas aeruginosa* bacteremia with septic shock and multiple organ failure.

The herbal prescriptions which he had used were brought in for toxic screening. The mineral contents were determined by Inductively Coupled Plasma Mass Spectrometry, which yielded a very high concentration of arsenic in three unlabeled realgar-containing ointments of left-over (45427, 5512, and 4229 ppm). The post-mortem blood arsenic level was 1225 µg/L (reference for antemortem blood: 18 µg/L).

Discussion

TEN is an uncommon, but potential life-threatening adverse event, most commonly associated with xenobiotic use (e.g., antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs, and allopurinol).³ Herbs are another common cause of TEN in herbal-using community. An epidemiological study carried out in China revealed that TCM was the third most common offending xenobiotics causing severe cutaneous adverse drug reactions (SCADRs), after antibiotics and anticonvulsants.⁴ In that study, SCADRs induced by TCM monotherapy were found in seven patients. TCM monotherapy accounted for 50% (3/6) of TEN, 13% (2/16) of exfoliative dermatitis, 9% (2/23) of Steven-Johnsons syndrome, and 10% (1/10) of DRESS (drug reaction with eosinophilia and systemic symptoms) cases.⁴ Most TCM are unlabeled compound formulas, so the ingredients in TCM were not identified. Four of the seven patients had known TCM formula, Paishi Chongji and Shilintong Pian for renal lithiasis, Fenghanganmao Chongji for common cold, Danshentong for acne vulgaris, and Yinxiedi for psoriasis vulgaris.⁴ Our patient developed TEN after extensive use of realgar-

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containing herbal ointment and several TCM compound formulas. In oral medicine, ginseng and ephedrine had been rarely reported to be responsible of toxic dermatitis.^{5–7} Allergy to pseudoephedrine may cause urticaria, fixed non-pigmenting erythema, pseudoscarlatina, erythema multiforme, and TEN. Ginseng can induce skin eruption and Stevens–Johnson syndrome in sensitive individuals. Though the pathogenesis of TCM-related severe skin reaction remains to be determined, specific diagnostic test is not available. In our case, TEN may be related to realgar, other ingredients in TCM, or their combinations.

Realgar is widely used in combination with traditional medicines for both external and internal uses. It is believed that the practice of TCM is much more emphasized and relied on so-called “experienced practice”, instead of “the way of evidence based” practiced in modern medicine. Both the TCM doctor and the patient had amazing faith to the traditional medicine. They believed that the adverse reaction is a phenomenon of Herxheimer reaction (It is also referred to as a healing crisis, a detox reaction, or die-off syndrome). In TCM, they advise the patient to continue with the therapy and they can be cured eventually. This is sometimes a misconception; however, it is not an uncommon practice observed in TCM.

Though arsenic can be highly toxic and carcinogenic, realgar has poor bioavailability and is thought to be safe with few reports on their toxicities or adverse effects in TCM.^{1,2} However, inorganic arsenic is a well-known poison. Common clinical features following acute inorganic arsenic poisoning include nausea, vomiting, abdominal pain, diarrhea, and skin rash. Patients with more severe poisoning may present with cardiovascular signs and symptoms (e.g., QTc prolongation, ventricular dysrhythmia, hypotension, and shock), acute renal failure, liver injury, and acute encephalopathy. Delayed symptoms include leucopenia, anemia, thrombocytopenia, hair loss, skin lesion, and peripheral neuropathy.^{8–11} Dermatological features may include a maculopapular eruption, vesico-edematous erythroderma, and generalized desquamation.^{8,9}

In fatal cases of arsenic poisoning, the blood arsenic concentration has been reported in the 160–41,000 µg/L range, in patients who have survived poisoning have had blood arsenic concentration of 100–500 µg/L.^{10,11} In our case, the antemortem arsenic concentration was not available, however the post-mortem arsenic concentration (1225 µg/L) was considered to be fatal based on literature.

Our case presented with gastrointestinal disturbance 1 week after TCM use, aggravation of skin lesion, and decreased urine amount at about 2 weeks of TCM use. TEN, acute renal failure, liver injury, anemia, and bacteremia were documented 18 days following TCM therapy. The observed clinical signs and symptoms and the post-mortem blood arsenic concentration were consistent with arsenic poisoning.

In literatures, fatal arsenic poisoning usually occurred after ingestion, and the cause of death is generally caused by circulatory collapse. Our patient had realgar exposure through dermal route, and the realgar was associated with TEN and increased systemic arsenic absorption. The

gastrointestinal and dermatological symptomatology was related to arsenic toxicity. The patient subsequently developed bacterial sepsis and died. The cause of death was multifactorial and might predominately come from TEN-related sepsis and multiple organ failure.

In the practice of TCM, realgar-containing compound has been used in the treatment of skin illness since ancient time. It was deemed to be less toxic due to its low solubility and bioavailability. Dermal use of realgar was said to be safe in the practice of TCM among Chinese communities. Our case demonstrated that extensive dermal use can cause significant systemic absorption and severe cutaneous adverse drug event, which might result in irreversible toxicity. Though realgar has a long and remarkable history of pharmacological utility in TCM communities, it should not be extensively used on compromised skin. In the practice of TCM, differential diagnosis between adverse drug reaction and so called “detox reaction” is important.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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