CASE REPORT

Arsenical keratosis coexists with chloracne

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ABSTRACT
Arsenical keratosis, a keratotic skin disorder caused by chronic arsenic exposure, generally presents as hyperkeratosis and hyperpigmentation. Here, we report a rare case of arsenical keratosis coexisted with chloracne in a 56-year-old man who presented with generalized multiple polymorphic eruptions: poikiloderma, punctate keratosis, keratosis plaques, verruca-like rashes and nail opacity. Chloracne were simultaneously observed. To our knowledge, this is the first case showed arsenical keratosis combined with chloracne. As skin eruptions induced by pesticide exposure might present variously and are related to several types of cutaneous malignancy, clarifying exposure history and toxicants detection are necessary to avoid misdiagnosis.

INTRODUCTION
Arsenical keratosis is a keratotic skin disorder caused by chronic arsenic exposure. Despite numerous efforts to decreased environmental contaminant in drinking water and occupational hazard, sporadic cases among farmers and prolonged arsenic medication ingestion still occur [1]. We here describe a rare case of arsenical keratosis presented with multiple polymorphic eruptions simultaneously combined with chloracne.

CASE
In February 2016, a 56-year-old man presented to us with an eight-month history of non-itchy skin eruption on face, trunk, extremities and palms. He was without any signs of acute toxicity or neuropathy. He has the exposure history of every month contact with pesticide containing dichlorodiphenyltrichloroethane, lead arsenate, calcium arsenate, sodium fluorosilicate, pyrethrum, rotenone tobacco carbaryl and carbofuran in his occupation as farmer for more than five years. Eight months ago, keratosis papules and plaques appeared on the dorsum of both hands and feet (Figure 1). Seven months ago, punctate keratosis on both palms, nails opacity and verruca-like keratoses on the upper lip were observed (Figure 2). Four months ago, he developed comedonal acne-like rashes on face which gradually involved the trunk and extremities combined with skin color anomaly (Figures 2 and 3).

Systemic examination was normal and lymphadenectasis not found. Urine arsenic test was 198 µg/L (reference value 2.6–22.7 µg/L). Laboratory blood tests were within normal range (Table 1). Fungal microscopic and culture examination were negative on both thumbs nails, palms and feet (KOH –). Multiple punch skin biopsy was done on the right-hand dorsum (keratosis popular), upper lip (verruca-like keratoses) and back (comedone-like lesion). Skin pathology of keratosis popular showed epidermis hyperplasia, lymphocytic infiltrating in superficial dermis and without vacuoles. Epidermal hyperplasia, mild papillary hyperplasia and pseudo-angle cyst were found in comedone-like lesions by histopathology (Figure 5). Cutaneous malignancy and skin virus infection were excluded.

The clinical and histopathological findings led to a diagnosis of arsenical keratosis combined with chloracne. The patient was given 10% sodium thiosulfate intravenous injection (0.64 g/day for 7 days) as antitoxic treatment. Verruca-like keratoses above the right upper lip was taken out by operation. Adapalene gel was topically used on both chloracne and arsenical keratosis lesions twice daily for 6 months. One month after treatment, the keratosis plaques and punctate keratosis on hands and foots became flattened and smaller, and the comedone-like lesions on trunk and face were decreased.

KEYWORDS
Arsenical keratosis; chloracne; arsenic trioxide; skin eruption
Figure 1. Arsenical keratosis lesions. Keratosis plaques, verruca-like keratoses and nails opacity on the dorsum of both hands and feet.

Figure 2. Chloracne lesions on face. Verruca-like keratoses above the right upper lip.
Urine arsenic re-test after 3 months treatment was within normal rage (19.1 μg/L, reference value 2.6–22.7 μg/L). This patient, on a regular follow-up monthly for 15 months until now, has not presented new eruptions.

**Discussion**

Dibenzofurans, dioxins and sodium 3,5,6-trichloropyridin-2-ol (STCP) are the main toxicants that cause chloracne in China. As early as 1993, Cheng et al. surveyed 109 Chinese workers and reported that the prevalence of chloracne was 73.4% (80/109) in total and 95.2% (20/21) in a trichlorobenzene (TCB) tank area where dioxin and dibenzofurans levels were in thousands of ppm [1]. Recently, Wu et al. and Niu et al. reported that the workers who worked in an STCP factory in China developed chloracne and peripheral nerve damage [2,3]. For pathogenesis investigation, Liu et al. found that the activation of mitogen-activated protein kinase pathway and upregulation of CK17 and TGK might play roles in the pathogenesis of chloracne related to dioxin exposures [4]. Tang et al. investigated the gene expression of Chinese chloracne patients and found that AhR, CYP1A1, GSTA1 and c-fos transactivations were significantly induced in chloracne lesions [5]. In this case, we report a Chinese chloracne patient, who exposed to pesticides which might contain a variety of toxic chemicals, simultaneously presented arsenical keratosis.

Common skin manifestations of arsenical keratosis are generally classified as hyperkeratosis and hyperpigmentation. Hyperkeratotic lesions include punctate keratoses, papule keratoses, corns-shaped keratosis mostly found predominantly on palms and soles [6]. There were other less common skin lesions reported, such as

![Figure 3. Chloracne lesions on trunk. Comedone-like lesions combined with skin color anomaly on trunk.](image-url)
verrucous hyperplasia, lichen planus-like keratosis, folliculitis-like lesion and capillaries expansion [7]. Changes of finger nails often present as Mees’ lines or koilonychia. High incidence of multiple carcinomas such as squamous-cell carcinoma and basal cell carcinoma are documented [8]. In this case, the patient presented with both typical and unusual lesions that included punctate keratoses, papule keratoses, keratosis plaques, poikiloderma and nail opacity.

Pathogenesis of arsenic-induced cutaneous changes includes disturbing epidermal keratinocyte differentiation and pigmented processes, vitiating nucleotide excision repairing mechanisms, regulating DNA methylation, interacting with unfolded protein response signaling and MAP kinase pathways. Recent research shows that oxidative stress, chromosomal abnormality and altered growth factors are also involved in arsenic-induced carcinogenesis [9]. Thompson et al. found that arsenic was a co-carcinogen with UV in skin carcinogenesis, likely by adversely influencing DNA repairing system and or ROS-mediated damages [10].

Antitoxic sodium thiosulfate which could delay toxicants-induced hemolysis and promote toxins excretion from kidney has been used in treating acute and chronic chemical poisoning conditions [11], including arsenic [12]. Rael et al. found that sodium thiosulfate could delay arsine-induced hemolysis in human erythrocytes in vitro.

| Blood test item        | Patient results | Reference normal values |
|------------------------|-----------------|-------------------------|
| White blood cell       | 5.69 × 10^9/L   | 3.5–9.5 × 10^9/L        |
| Red blood cell         | 4.48 × 10^12/L  | 4.3–5.8 × 10^12/L       |
| Platelet               | 184 × 10^9/L    | 100–350 × 10^9/L        |

| Biochemical indexes    |                 |                         |
|                       | Triglycerides   | 1.2 mmol/L              |
|                       | Blood glucose   | 5.07 mmol/L             |
|                       | Creatine kinase (Cr) | 80 IU/L              |
|                       | Myoglobin (Mb)  | 14 IU/L                 |
|                       | Troponin I (TnI)| 0.05 μg/L               |
|                       | Lactate dehydrogenase (LHD) | 32 IU/L           |

| Liver function         |                 |                         |
|                       | Aspartate aminotransferase (AST) | 25.0 U/L             |
|                       | Alanine aminotransferase (ALT) | 19 U/L                |
|                       | Bilirubin        | 12.1                    |

| Renal function         |                 |                         |
|                       | Creatinine      | 100.0 μmol/L            |
|                       | Urea nitrogen   | 374.0 μmol/L            |

| Autoimmune parameters  |                 |                         |
|                       | ANA             | Negative                |
|                       | ds-DNA          | Negative                |
|                       | Sm              | Negative                |
|                       | RNP             | Negative                |
|                       | SSA             | Negative                |
|                       | SSB             | Negative                |
|                       | Jo-1            | Negative                |
|                       | Scl-70          | Negative                |

Figure 4. Arsenical keratosis. Histopathology of keratosis plaques on acral limbs showed epidermis hyperplasia, diffuse lymphocyte infiltration and collagen fiber eosinophilic changes in the dermis.
Our case proposed that sodium thiosulfate could be used as one of the treatment options for arsenic associated with chlorine poisoning patients, but more clinical validation is needed and the pharmacological mechanisms are still unclear and need further investigation. Here we report a rare case of arsenical keratosis presented with multiple polymorphic eruptions combined with chloracne. As skin eruptions induced by pesticide exposure might present variously and are related to several types of cutaneous malignancy, clarifying exposure history and toxicants detection are necessary to avoid misdiagnosis.

Disclosure statement
The authors report no conflict of interest.

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