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Clinical Manifestations, Treatment, and Prevention of Acute Irritant Contact Dermatitis Caused by 2,4-Dichloro-5-Methylpyrimidine

Wenge Fan, MD,* Qingsong Zhang, MD,† Jing Zhang, MD,‡ and Ling Wang, MD‡

Background: **There are no reported cases of 2,4-dichloro-5-methylpyrimidine (DCP)–induced irritant contact dermatitis (ICD).**

Objective: **The aim of the study was to summarize the clinical features, treatment, and protective measures for DCP-induced ICD.**

Methods: **We retrospectively reviewed the clinical data from 64 patients with DCP-induced ICD and the protective measures in a DCP manufacturing factory.**

Results: **Disease onset occurred 1 to 10 minutes after DCP single exposure in all 64 patients. The contact site developed edematous erythematous skin lesions with clear boundaries. Other symptoms included a burning sensation (n = 48), pruritus (n = 16), headache (n = 4), nausea/vomiting (n = 3), and syncope (n = 1). Ten patients developed pruritic rash over the whole body 1 to 4 days after contacting DCP. Histopathologic examination of the lesions was performed in 8 patients; all 8 showed manifestations of ICD. A patch test with 1% DCP ethanol solution was performed in 7 patients. One patient withdrew because of pruritus and massive erythema over the whole body. Four patients had a strong reaction, and 2 patients had a very strong reaction. All patients were cured. Positive-pressure inflatable protective clothing protected workers from the outside environment to prevent DCP-induced ICD.**

Conclusions: **2,4-Dichloro-5-methylpyrimidine exposure induces acute ICD and a delayed allergic reaction in some patients (15.6%). Positive-pressure inflatable protective clothing prevents DCP-induced ICD.**

2,4-Dichloro-5-methylpyrimidine (DCP) is a white crystal with a chemical structure of  , a molecular formula of $C_5H_4C_{l2}N_2$, and a molecular weight of 163.00 g/mol. 2,4-Dichloro-5-methylpyrimidine is an intermediate product of 2-amino-5,8-dimethoxy-[1,2,4]triazolo[1,5-c]pyrimidine, which is an important intermediate of the herbicide penoxsulam.[1] 2,4-Dichloro-5-methylpyrimidine is toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment.[2] Skin exposure to DCP can cause chemical burns.[2] 2,4-Dichloro-5-methylpyrimidine can also cause systemic damage after entering the blood system via skin wounds.[2] Inhalation or ingestion of DCP can cause chemical burns of the respiratory and gastrointestinal tracts,[2] leading to coughing, chest tightness, shortness of breath, mouth ulcers, and esophageal inflammation.

Because there are only a small number of DCP manufacturers worldwide, no cases of DCP-induced irritant contact dermatitis (ICD) have been reported in the literature. Between 1998 and 2014, 64 workers in a chemical plant in Changshu City, Jiangsu Province, China, developed ICD after exposure to DCP. All patients were treated in our department, and we participated in the improvement of protective measures used by the workers in the chemical plant. The present study aimed to summarize the clinical features, treatment methods, and protective measures for DCP-induced ICD.

METHODS

The present study was approved by the ethics committee of the First People's Hospital of Changshu City, Soochow University, Jiangsu Province, China. All participants gave informed consent for study participation.

*From the *Department of Dermatology, First People's Hospital of Changshu City, Changshu Hospital Affiliated to Soochow University; †Department of Dermatology, Traditional Chinese Medical Hospital of Changshu City; and ‡Department of Dermatology, First People's Hospital of Changshu City, Changshu Hospital Affiliated to Soochow University, Jiangsu Province, People's Republic of China.*

Address reprint requests to Wenge Fan, MD, Department of Dermatology, First People's Hospital of Changshu City, Changshu Hospital Affiliated to Soochow University, 1 Shuyuan St, Changshu 215500, Jiangsu Province, People's Republic of China. E-mail: csyyfwg@163.com.

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We retrospectively reviewed the clinical data from 64 patients with DCP-induced ICD and reviewed the protection measures for workers in a DCP manufacturing facility. The clinical data included demographic data, clinical manifestations, laboratory tests results, histopathologic examination findings, treatment methods and outcomes, patch test results, and follow-up findings.

Patch Testing

Patch testing is essential in distinguishing allergic contact dermatitis (ACD) from ICD.[3] A positive result indicates ACD, whereas a resultant bulla or necrosis suggests ICD.[4] Because there is no standard concentration for DCP patch testing reported in the literature, we performed a DCP patch test with 1% DCP ethanol solution; ethanol is a relatively stable polar organic solvent that is widely used in the pharmaceutical industry, and the molecular structures of ethanol and DCP suggest that the 2 substances will not react with each other at room temperature. A DCP patch test with serial dilutions was not performed because of ethical principles, as DCP causes chemical skin injury.

One gram of DCP was dissolved in 100 mL of 75% ethanol to prepare a 1% DCP ethanol solution, whereas 2% sodium lauryl sulfate (SLS) was used as a positive control, and 75% ethanol solution was used as a negative control. All test substances were contained in individual Finn Chambers applied to the upper back. After 24 hours, the chambers were removed to observe the skin changes; observations were repeated after 48 hours. The patch test results were interpreted in accordance with the European Society of Contact Dermatitis guidelines for clinical scoring of acute SLS irritant reactions.[5] The reactions were defined as negative (no visible reaction), weak (very weak erythema or minute scaling), moderate (moderate degree of erythema, edema, scaling and/or roughness, or minor degree of erosions, vesicles, crusting, and/or fissuring), strong (marked degree of erythema, edema, scaling, roughness, erosions, vesicles, bullae, crusting, and/or fissuring), and very strong (all symptoms as for the "strong reaction" plus necrotic and caustic lesions).

RESULTS

Clinical Data

The mean age of the 64 patients with DCP-induced ICD (63 men and 1 woman) was 28.5 years (range = 20–48 years). Thirty-eight patients were married, whereas 26 patients were unmarried. All 64 patients worked in the DCP production and packaging workshops. The average time between the onset of symptoms and the initiation of treatment was 15.6 hours (range = 3 hours to 4 days). All patients were physically healthy and had no history of drug or food allergy before the onset of DCP-induced ICD.

In the total cohort, the mean time from single exposure to DCP at work to the onset of ICD was 7 minutes (1–12 minutes). The lesions were limited to the DCP contact site in 48 cases and had spread to surrounding areas as a result of sweat streaming in 16 cases. The 64 patients had lesions on the upper limbs (n = 37), chest (n = 21), neck (n = 18), abdomen (n = 16), lower limbs (n = 15), back (n = 14), waist (n = 11), face (n = 8), and external genitalia (n = 3). The typical skin lesion was an edematous erythematous lesion with clear boundaries. Erythema with papules or papulovesicles occurred in 15 cases, whereas erythema with vesicles occurred in 10 cases. The lesion area ranged from 58 to 5600 cm^2 (approximately 0.4%–33% of the body surface area).

The symptoms comprised a burning sensation in 48 patients and pruritus in 16. Four patients experienced headaches, 3 developed nausea and vomiting, and 1 had syncope. Ten patients developed delayed diffuse erythema on the whole body and severe pruritus despite avoiding contact with DCP for 1 to 4 days; 1 of these 10 patients had a fever of 39°C for 3 days. None of the 64 patients developed respiratory symptoms, such as coughing, chest tightness, or shortness of breath.

Forty-eight patients underwent routine blood/urine tests and liver function. The abnormal findings included the following: white blood cell counts ranging from 10.2×10^9 to 20.2×10^9/L (reference value = 4.0×10^9–10.0×10^9/L) in 7 cases; neutrophil counts ranging from 7.9×10^9 to 18.2×10^9/L (reference value = 2.2–7.0×10^9/L) in 9 cases; eosinophil counts ranging from 0.75×10^9 to 1.0×10^9/L (reference value = 0.02–0.50×10^9/L) in 4 cases; C-reactive protein levels ranging from 11 to 68 mg/L (reference value = 0–8 mg/L) in 6 cases; alanine aminotransferase levels ranging from 46 to 96 U/L (reference value = 5–40 U/L) in 3 cases; and aspartate aminotransferase levels ranging from 42 to 75 U/L (reference value = 10–40 U/L) in 3 cases. Testing to assess renal function, electrolytes, blood glucose, and myocardial enzymes was performed in 39 patients, and all results were within reference ranges. Electrocardiogram, radiography, and abdominal ultrasound were performed in 31 patients, with normal results in all 31 cases. Histopathologic examination of the lesions in 8 patients showed intracellular and intercellular edema and spongiosis in the epidermis in all 8 patients, intraepidermal blisters in 5 patients, and dermal papillary edema with inflammatory cell infiltration in 7 patients.

The clothing of all patients was removed promptly and placed in a special garment decontamination container, and all patients were washed with clean water for 15 to 30 minutes after hospital admission. Calamine lotion was applied twice daily to the affected areas. For patients with skin breakage, zinc oxide oil was applied to the affected areas twice daily. The 10 patients with delayed allergic reactions were administered 10 mg of intravenous dexamethasone daily for 4 to 7 days and 10 mg of oral loratadine daily for 9 to 14 days. The 7 patients with secondary infections were administered 3 g of intravenous cefuroxime sodium twice daily. The rash showed improvement 3 to 6 days (mean = 4.8 days) after treatment initiation and completely resolved by 9 to 14 days (mean = 12.3 days) after treatment initiation.

The 10 patients with delayed allergic reaction were not suitable for patch testing. Forty-seven patients refused to undergo patch testing because they were afraid that the DCP would cause a rash again. Thus, patch testing was performed on 7 patients 1 month after the resolution of symptoms. Informed consent was obtained from these

7 patients before testing commenced. Seven hours into the patch test, 1 patient withdrew because of pruritus and massive erythema over the whole body. At the DCP contact site, 4 patients demonstrated a strong reaction after 24 hours, and 2 demonstrated a very strong reaction (skin lesions did not subside after 72 hours). At the SLS contact site, 6 patients showed a strong reaction after 24 hours, but the skin lesions had somewhat subsided after 72 hours. No rash occurred in the negative control group after 24 and 72 hours.

The 64 workers with DCP-induced ICD were transferred from their original positions at the factory. Among them, 17 workers left the factory and were lost to follow-up. The remaining 47 people were still working in the factory, and their annual health checkups showed no abnormalities.

Continued Improvements in Protective Measures

The chemical plant began to manufacture DCP in 1998 with limited knowledge about the potential risks of the compound, and thus, no protective measures were taken. A total of 15 workers were exposed to DCP in 1998, and all of them developed ICD, giving an incidence of 100%. From 1999 to 2007, the factory protected the workers with plastic bags, raincoats, and chemical protective clothing. Despite these measures, all 43 workers who were exposed to DCP developed ICD, again giving an incidence of 100%. In 2008, our department recommended that the factory used the Honeywell Mururoa V4F1 protective suit against radioactive contamination, which is a positive-pressure inflatable protective suit. From 2008 to 2014, a total of 25 workers wore the protective suit in the DCP production and packaging workshops (Fig. 1); none of these 25 workers developed ICD, giving an incidence of 0%. From 2008 to 2014, 6 workers experienced ICD because of indirect contact with public items contaminated with DCP, such as door handles, chalk, and paper.

Determination of the pH of DCP

We commissioned the Changshu Municipal Product Quality Supervision and Inspection Institute to determine the pH of DCP in accordance with the Chinese national standard GB\T1601-1993 "Determination Method of Pesticide pH Value." The pH of DCP was found to be 6.2.

DISCUSSION

The patients in our current series had the following features: (*a*) definite history of DCP exposure; (*b*) a shared workshop; (*c*) rapid onset of ICD after single DCP exposure; (*d*) clinical manifestations including edematous erythema and vesicles on exposed skin, along with a burning sensation and pruritus; and (*e*) histopathologic manifestations of ICD.[6] Therefore, our series met the diagnostic criteria of DCP-induced acute ICD,[7] which is cutaneous inflammation without the production of specific antibodies. We think that the DCP caused the skin irritation via a mechanism unrelated to its pH of 6.2.

There have been a few reports in the literature of primary ICD caused by industrial chemicals. One study reported that 182 male workers experienced ICD after exposure to carbon disulfide, emphasizing the importance of skin protection,[8] whereas another study reported that ICD developed in 70% people who contacted diallylglycol carbonate monomer, and experiments on animals confirmed the irritant nature of the product.[9] Contact dermatitis is usually classified into ICD and ACD in accordance with the pathogenesis.[3] Irritant contact dermatitis is generally considered to be a nonimmune inflammatory response, but a variety of cytokines (eg, tumor necrosis factors α and r) also play important roles in the pathogenesis of ICD.[10] Furthermore, ICD can trigger or promote the development of ACD. In our study, in addition to the primary irritant response, delayed allergic reaction also occurred after DCP exposure in 10 patients (15.6%). These patients required glucocorticoid therapy.

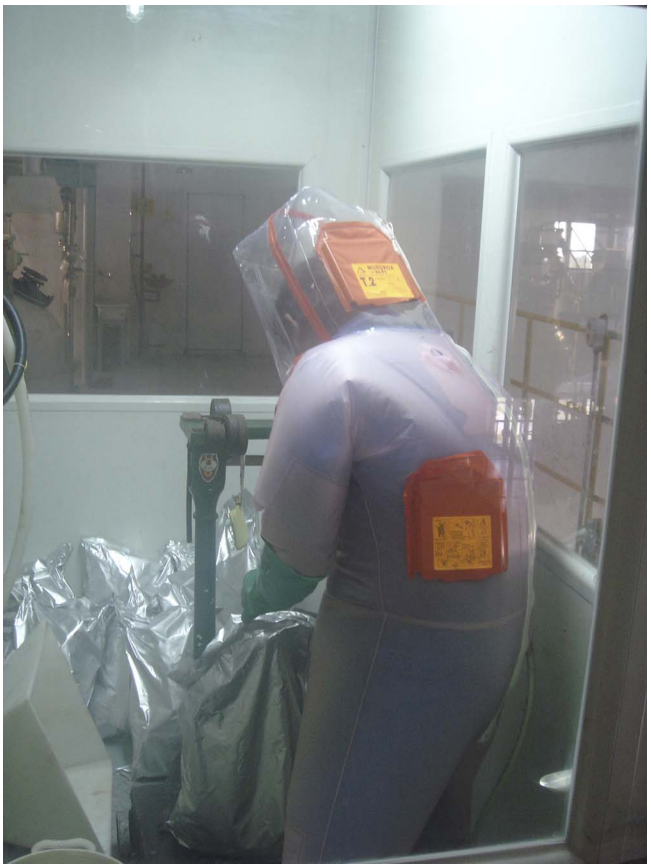

Figure 1. Photograph showing the positive-pressure inflatable protective clothing being used by a worker.

Irritant reactions may lead to false-positive patch test results, particularly when a new compound is tested.[3] Because there is no standard concentration for the DCP patch test in the literature, we performed a DCP patch test using a 1% DCP ethanol solution in 7 patients. One patient who withdrew from the patch test could be diagnosed with a DCP allergy. Two patients with a very strong reaction could be diagnosed with a DCP irritant reaction, whereas 4 patients with a strong reaction may have developed false-positive patch test results because of an irritant reaction to DCP.

Our study also showed that DCP-induced ICD was more likely to occur on the upper limbs, probably because the hands were most frequently in contact with DCP. As the chest of the workers was used to support the barrels containing DCP during transport, the chest was the second most frequently affected site. 2,4-Dichloro-5-methylpyrimidine–induced ICD can occur on any part of the body surface, as DCP penetrates clothing and is vaporized at high temperatures.[2] The degree of injury may be closely related to the dose, concentration, physical state (solid, liquid, or gas), exposure time, and contact area of DCP. One study found that the degree of skin irritation caused by SLS increased significantly with increasing concentration and duration of contact, suggesting that prolonged exposure to high SLS concentration results in enhanced skin penetration and therefore more intense skin irritation.[11] In addition, studies have found no obvious ethnic differences in the skin response to chemical stimuli.[12,13]

Previous studies have shown that dysfunction of the skin's moisture barrier is one of the earliest changes after injury and inflammatory reactions caused by chemical irritants. This skin barrier dysfunction occurs much earlier than the appearance of clinical erythema.[14] In our current series, we did not observe the dysfunction of the skin's moisture barrier because of the acute and severe disease conditions.

Although DCP enters the blood through skin wounds and causes systemic damage[2]; no systemic damage was observed in our series. This may be explained by the lack of skin wounds in the present patients; however, the role of DCP in causing system damage should not be ignored. The factory should prohibit workers with skin wounds from entering the DCP production and packaging workshops. Once DCP-induced ICD develops, the affected workers should leave the workplace immediately, their clothing should be removed promptly and placed in a special container for decontamination, and the skin surface at the DCP contact site should be continuously washed with water for 15 minutes. Patients with severe DCP-induced ICD need to be hospitalized immediately and undergo systematic examinations.

Continuous water irrigation remains the preferred method of decontamination in acute chemical burn management.[15] The mechanisms of water skin decontamination include the following[16]: rinsing off the chemical substance (main effect), dilution of the chemical agent, decreasing the rate of the chemical reaction, decreasing the hygroscopic effects of the chemical(s) responsible for its production, restoration of the skin pH to normal in cases of acidic or alkaline injuries, and decreasing tissue metabolism and minimizing the inflammatory reaction. Although water decontamination can decrease the severity of chemical skin burns,[16] this traditional method may not be completely effective, and contaminants left on the skin after traditional washing procedures can have toxic consequences.[17] However, water decontamination is still considered the primary intervention in dermal chemical exposure.[17] The ideal replacement decontamination solution would be sterile, nontoxic, chelating, polyvalent, amphoteric, and slightly hypertonic to retard skin or corneal penetration of the chemical.[16] Diphoterine seems to be safe and is probably superior to other rinsing solutions.[18,19]

2,4-Dichloro-5-methylpyrimidine is volatile and can exist in the air.[2] Raincoats and chemical protective clothing were ineffective in preventing DCP-induced ICD. After the confirmation of cases of DCP-induced ICD, the positive-pressure inflatable protective suit was introduced in the factory. These suits completely isolated the workers from the outside environment to prevent DCP-induced ICD. However, ICD still occurred because of indirect exposure to public items contaminated with DCP. Therefore, increased worker awareness about safety protection is urgently needed.[20] We believe that the most essential preventive measures against DCP-induced ICD are hermetization and channelization of production equipment, as well as the mechanization, automation, and continuity of operation processes.

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