

Treatment for Crusted Scabies: Limitations and Side Effects of Treatment with Ivermectin

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Abstract

Skin eruption with mild itching of the hands and feet developed in a man in his 90s 1 month after he was hospitalized following a traffic accident. Scabies was diagnosed in an attending nurse 3 months after the patient's hospitalization, and infection from the patient was suspected. Cornification of the patient's soles and marked hypertrophy of the nails of both feet were observed. After a large number of scabies mites were detected on microscopic examination, crusted scabies was diagnosed. The patient was given oral ivermectin, 6 mg, once per week for 3 weeks, and crotamiton topical ointment containing 30% benzyl benzoate was applied on the body from the neck down. However, because a large number of scabies mites were detected again on microscopic examination, the dose of ivermectin was increased to 12 mg and administered 3 times. One week after the sixth dose of ivermectin was administered, hemorrhagic scabs around the mouth and erosion of the tongue developed. Mucosal drug eruption was suspected, and eruptions around the mouth and on the tongue resolved within 1 week after ivermectin being discontinued. 1% gamma-benzene hexachloride ointment was applied topically on the body from the neck down once a week, crotamiton ointment containing benzyl benzoate was applied daily, and the hypertrophic parts of the nails were removed. The patient subsequently achieved a full recovery.

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Key words: crusted scabies, ivermectin, gamma-benzene hexachloride, drug eruption, pyrethroid

Introduction

Crusted scabies is a condition in which several million *Sarcoptes scabiei* var. *hominis* parasitize within the skin^{1,2}. When the patient scratches the scab and

causes it to become detached, the underlying scabies mites disseminate out into the patient's room, potentially triggering an outbreak. Ivermectin became covered by the Japanese health insurance system in 2006 and became the first-line drug for scabies treatment. However, in the elderly and

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Fig. 1 Clinical features on initial consultation

patients with crusted scabies, a single dose of ivermectin is not curative³. We treated a patient who had crusted scabies but did not recover despite 6 doses of ivermectin and was subsequently given a different treatment after side effects developed. We describe the limitations and side effects of ivermectin for the treatment of crusted scabies, as well as future treatment methods.

Case

A man in his 90s was admitted to our hospital after a traffic accident. He had a history of diabetes, and at the time of admission had a blood glucose level of 263 mg/dL, a hemoglobin A1c of 7.0%, and a urinary glucose of (3+).

On day 33 of admission, an attending nurse noticed skin eruptions between the toes and on the sole of the patient's feet, and the patient was referred to our department. Scales with mild itching were observed on the right leg and both hands. Xerotic skin was diagnosed, and dexamethasone propionate ointment was prescribed. On day 91 of admission, an attending nurse was found to have scabies at another hospital, and transmission from our patient was suspected. We observed cornification on the soles of both the patient's feet, and nail hypertrophy was observed on both feet

(**Fig. 1**). Microscopy showed a large number of scabies mites, and crusted scabies was diagnosed (**Fig. 2**). The attending physician estimated the patient's body weight to be around 30 kg and administered a single 6 mg dose of oral ivermectin (Stromectol[®], Merck & Co., Inc., Whitehouse Station, NJ, USA). In addition, crotamiton topical ointment containing 30% benzyl benzoate was applied twice a day. Furthermore, because 8 other patients in the same ward were strongly suspected to be infected, they were also treated with ivermectin.

The patient took oral ivermectin at both 1 and 2 weeks after the first dose, but a large number of scabies mites were still detected with microscopic examination after 3 weeks. Because the patient's body weight was measured as 60 kg, the dosage of ivermectin was increased to 12 mg. This dose was administered once a week for 3 weeks (**Fig. 3**). One week after the sixth dose of ivermectin, hemorrhagic scabs around the mouth and erosion of the tongue surface developed (**Fig. 4**). Mucosal drug eruption due to ivermectin was suspected, and ivermectin was discontinued. The differential diagnosis included herpes simplex, but the results of the Tzanck test was negative. The eruption around the mouth and on the tongue had resolved 1 week later. As an alternative to ivermectin, 1% gamma-benzene hexachloride (γ -BHC) ointment was applied topically once a week on the body from the neck down, and crotamiton ointment containing benzyl benzoate was applied topically every day. Later, because scabies mites were detected 3 times from the toenails, and the hypertrophic parts of the nails were also removed (**Fig. 5**). No new skin eruptions subsequently developed, microscopic examination yielded no scabies mites, and the patient was judged to have made a full recovery.

Discussion

Scabies is caused by *S. scabiei*, a mite that parasitizes the stratum corneum in human skin. It is transmitted by direct contact with infected persons. Epidemic scabies in nursing hospitals and nursing homes has recently become a problem^{1,2,4}. Nurses and caregivers frequently hold the patient to provide

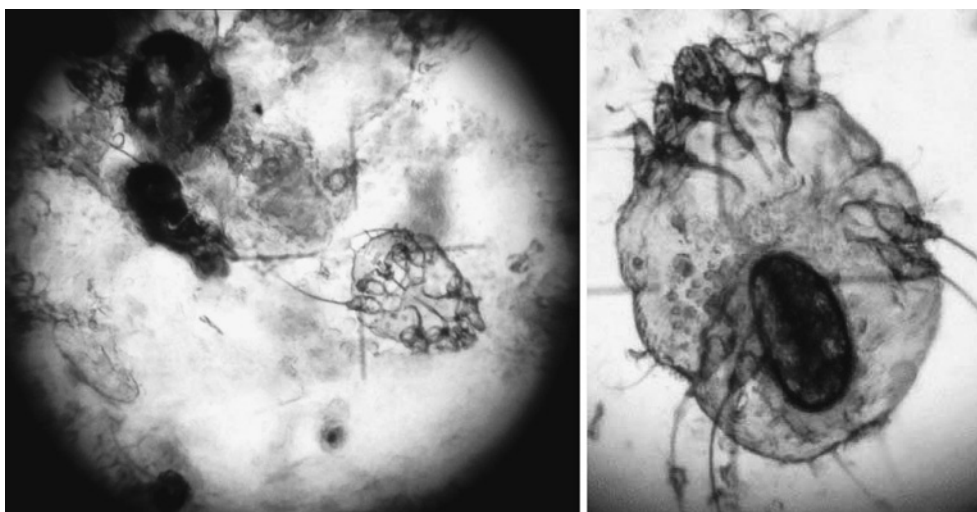


Fig. 2 Microscopic view of *Sarcoptes scabiei* var. *hominis*.

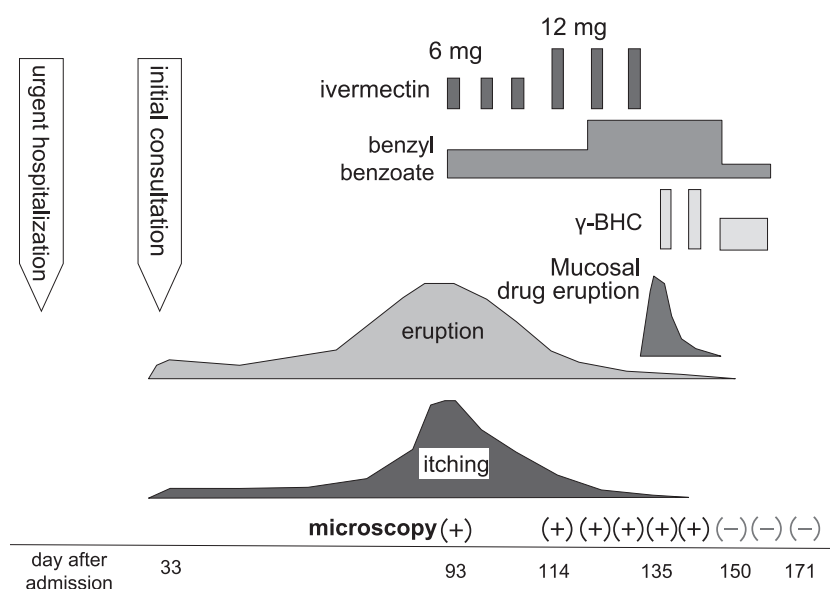


Fig. 3 Clinical course of the patient

care or hold the patient's hands. Healthcare workers who are become infected by patients with scabies often become vehicles for spreading scabies mites to other patients.

Scabies symptoms often appear first on the hand or forearm, and skin eruptions can spread to the axillae, shoulders, lower abdomen, vulva, and buttocks. Severe itching is a characteristic symptom of scabies. Itching increases during sleep and can often lead to insomnia. However, owing to the long incubation time, patients often remain asymptomatic for 2 to 4 weeks after scabies infection⁴.

Crusted scabies is caused by normal *S. scabiei* but

involves several million scabies mites⁵. This condition often develops in the elderly or persons with decreased cellular immunity. Patients have large numbers of scratches and scabs on the skin of the whole body. In particular, scabs that overlap, are thickened like oyster shells, and are easily peeled off are observed on the palms and soles. Scabs that fall off after scratching are spread throughout the patient's room, and because extremely large numbers of scabies mites live on the scabs, outbreaks can readily result. However, patients whose general condition is extremely poor may not complain of itching.



Fig. 4 Mucosal drug eruption 135 days after admission



Fig. 5 Clinical features 150 days after admission

Because scabies mites parasitize only the skin, topical medications with a scabidicidal effect have traditionally been used for treatment⁴. Current topical treatments include γ -BHC, benzyl benzoate, pyrethroid insecticides (phenothrin and permethrin), crotamiton, and sulfa drugs. Except for crotamiton and sulfa drugs, all are special formulations prescribed by a physician.

As an organochlorine insecticide with potent neurotoxic effects and strong permeability, γ -BHC is effective against adult mites and eggs just before hatching⁶⁻⁸. This agent is used once a week, 2 to 3 times in total, topically from the neck down. The efficacy rate of γ -BHC is nearly 100%, but the agent has no antipruritic effects.

Benzyl benzoate paralyzes the respiratory muscles of insects and mites but does not have any effect on the eggs of scabies mites⁹. Because it has little effect on the respiratory muscles of mammals, benzyl benzoate has no serious side effects. This agent is used every day for 2 to 4 weeks, 1 or 2 times daily, topically from the neck down. Benzyl

benzoate has an efficacy rate greater than 90% and also has antipruritic effects. Because this drug is safe and inexpensive, benzyl benzoate is the first-line topical medication in our department⁴.

Pyrethroid insecticides, such as permethrin and phenothrin, have immediate effects and do not accumulate to create toxicity in human patients⁴. These drugs paralyze the motor nerves of insects and mites, but are extremely safe in mammals. However, they have no effects on the eggs of scabies mites. Topical application is performed as with benzyl benzoate, and the efficacy rate is greater than 90%. In Western countries, 5% permethrin creams are available without a prescription⁶. In Japan, these creams can be obtained through the Internet.

Crotamiton has no serious side effects and has excellent antipruritic effects¹⁰. However, the scabidicidal effects are weak. In Japan, sulfur springs have been used for scabies treatment. Sulfa drugs are covered by health insurance but have only weak scabidicidal effects⁴.

Western reports since the 1990s have described ivermectin as also being effective against *S. scabiei*¹¹. In Japan, ivermectin has been covered by health insurance since 2006. Ivermectin is semisynthesized from avermectin, a substance isolated from the actinomycete *Streptomyces avermitilis*¹². Ivermectin has superior ability to travel to the skin, where it reaches a maximum concentration 8 hours after oral administration¹³.

Ivermectin binds to the glutamate-gated chloride channel of muscle cells and neurons of mites and other parasites, paralyzing them by suppressing peripheral motor nerve signaling¹⁴⁻²². In addition, ivermectin is presumed to act on γ -aminobutyric acid-activated chloride channels^{23,24}. Consequently, ivermectin has no effect on mite eggs. Ivermectin is extremely effective, and a dose of 0.2 mg/kg body weight once before a meal causes scabies mites to become undetectable in most patients and leads to clinical recovery. In addition, the blood concentration becomes 2.6-times greater if the medication is taken immediately after a meal rather than during fasting^{16,25}. Therefore, even if only half of the normal dose is taken after a meal, neither the treatment effect nor safety is affected. On the other hand, higher-than-recommended doses should not be used even for refractory or severe cases. Because ivermectin is ineffective against eggs, administration of 2 or more doses is necessary for a 100% cure rate²⁶. There are no regulations on dosing interval when multiple doses are administered, and a 2-week interval has been recommended²⁵. However, the life cycle of scabies mites is 10 to 14 days². If ivermectin is administered with a 2-week interval, the eggs can survive. Therefore, in our department, if a single dose of ivermectin does not have sufficient effect, the same dose is generally given again 1 week later³. In particular, because penetration to the stratum corneum is reduced in the elderly, a sufficient effect is often not achieved with a single dose of ivermectin. Also, if the ivermectin tablet is pulverized and administered with a gastric tube or nasogastric tube in patients who cannot orally receive medications, the effect of 2 doses is inadequate. For these patients, concomitant use of topical treatments, such as benzyl benzoate and γ -

BHC, is preferable to the use of ivermectin alone. In addition, ivermectin has difficulty passing through the thickened stratum corneum. Therefore, in patients with crusted scabies, 2 doses might not be curative, and additional doses may be necessary. In particular, because ivermectin does not travel to the inside of the nail, concomitant usage of topical treatments, such as benzyl benzoate lotion may be necessary^{3,27}.

As a side effect of ivermectin, itching may become more intense during early administration¹¹. However, because itching is often prolonged, the symptom may be mistaken as resistance to ivermectin. Resistance of *S. scabiei* to ivermectin is rarely reported in humans, but to prevent resistance from developing, predetermined dosages and methods should be followed, and long-term continuous use should be avoided²⁸.

Serious side effects of ivermectin have been reported where acute toxicities, such as convulsions, were induced in an overdose study in animals²⁹. In addition, when ivermectin is used in humans with filariasis, deaths have also been reported. When used for scabies, severe drug eruption (toxic epidermal necrosis), nausea, and vomiting have been reported overseas, and Stevens-Johnson syndrome has been reported domestically³⁰. In the present patient, erosion developed on the lips, oral mucosa, and tongue after 6 doses of ivermectin had been administered. The frequency and mechanisms of mucosal symptoms have not been clarified. For abnormal laboratory test values, liver function abnormalities, such as elevated aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels, and hematological abnormalities, such as decreased platelets have been reported^{31,32}. Our department has also treated patients presenting with liver function abnormalities after ivermectin administration, and we, therefore, perform blood tests at the time of initial prescription of the drug and at the second consultation.

How the present patient became infected with scabies is unknown; however, because skin eruptions developed 1 month after the patient was hospitalized following a traffic accident and because no other patients with scabies were identified within the

hospital at the same time, we assumed that he was already infected before hospitalization. In addition, the patient complained very little of itching at the initial consultation, and scabies was not suspected, leading to a delay in diagnosis. However, the attending nurse earlier suspected scabies.

The present case involved a man in his 90s who had untreated diabetes, and consequently we postulated that he had decreased immunity. As a result, he did not become aware of the itching for quite some time after onset and continued to be treated with topical steroids, which may have led to the proliferation of scabies mites and progression to crusted scabies.

Because the patient's body weight was not measured on admission, the first 3 doses of ivermectin were exceedingly low. When treating scabies with ivermectin, it is important to always weigh the patient and administer the specified dose. In addition, as described in the drug information, ivermectin is ineffective against nail scabies. In the present case, once the hypertrophic parts of the nails were scraped off with a nail file, scabies mites were no longer detected from the toenails.

Ivermectin is currently the first-line drug for the treatment of scabies in Japan. However, countries that use ivermectin as the first-line drug are a minority in the world, and in a majority of countries the primary treatment is topical 5% permethrin, which is reportedly more effective than ivermectin³³. The "Stockholm Convention on Persistent Organic Pollutants" in 2009 recommended that the use of γ -BHC be prohibited. Consequently, obtaining the drug has become difficult. In Japan, 5% lotion of phenothrin, a pyrethroid insecticide similar to permethrin, is now under clinical trial. Concomitant use of oral ivermectin and topical phenothrin is anticipated to offer a safe and effective treatment method in the near future.

Conflict of Interest: None.

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