Therapeutic Trial of Ointment Base Including Urea and Antifungal Agent as the Treatment of Onychomycosis

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A nonsurgical and atraumatic method for treating onychomycosis is described. Eight patients with onychomycosis were sucessfully treated with a paste formulation of clotrimazole and 20% urea. Scanning electron microscopic (SEM) findings showed that morphologic changes in the structures of fungi were gradually destructed as the frequency of the application was increased. This method should be considered for partially affected onychomycosis.
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Key Words: Onychomycosis, SEM, Topical treatment

Onychomycosis, a fungal infection of the nail unit, includes infection with yeast and non-dermatophyte molds as well as dermatophyte fungi.

Most reviews indicate the difficulty in the treatment of onychomycosis[1]. The use of an oral antifungal agent such as griseofulvin or ketoconazole often limited by drug side effects or the emergence of a resistant strain of the fungi. Consequently oral antifungal therapy with surgical removal of the affected nail is not always possible. Attention has been directed to the affected nail is recommended. Still, surgical removal of the affected nail is not always possible. Attention had been directed to the development of an effective topical therapy for onychomycoses[2-6]. Recently there have been published studies on topical treatment of onychomycosis using urea plaster[2], urea ointment[3, 4], urea with antifungal agent[5] or salicylic acid[6]. In this study, we treated onychomycosis with 20% urea ointment containing clotrimazole under an occlusive dressing and during the course of treatment serially examined fungal morphology by means of electron microscopy.

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MATERIALS AND METHODS

The study group was composed of a total sixteen patients, nine males and seven females. The sites of lesions were eight fingernails and eight toenails. The ointment used in this study was a paste formulation named Onychomal Plus® (Hermal-Chemie, Hamburg, Germany) composed of clotrimazole and 20% urea etc.

For each treatment, a pre-treatment biopsy of the affected nail was taken. At the start of treatment, 3% zinc oxide was used to protect the normal skin surrounding the affected nail. Onychomal Plus® was applied to the affected nail in a layer approximately 2mm thick and covered with transparent cellophane wrap, followed by adhesive plaster (Fig. 1). The patients were instructed to keep the area completely dry. The patients returned to our clinic after an average of five days. At that time, the adhesive plaster was taken off and the softened nail plate curetted. In those cases in which the affected nail was not yet softened, the same procedure was repeated for three to six times (mean 3.4 times) every three

microscopy according to the method described by Lee et al[7]. After air drying, the removed nails were uniformly coated with about 400 angstrom of gold in a vacuum evaporator to ensure good electrical conductivity and were then observed under a field emission scanning electron microscope (Hitachi S-450, Japan). The electron voltage was 15 kV.

RESULTS

Sixteen patients were treated with the clotrim-

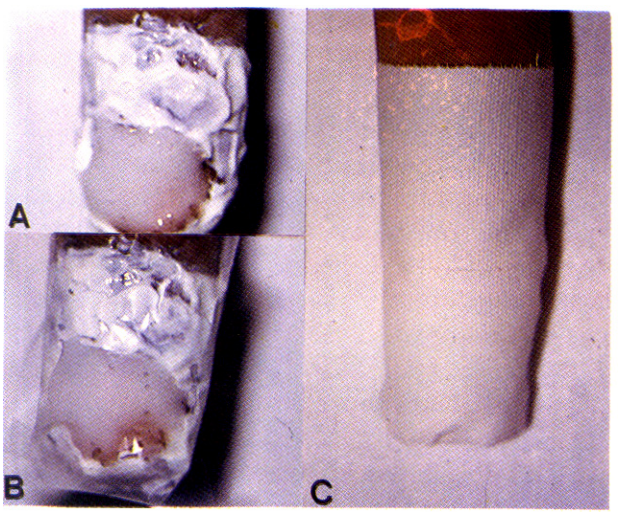

Fig. 1. The procedures of the clotrimazole/urea paste application.
A. 3% zinc oxide is used to cover the normal skin, and the clotrimazole/urea paste is applied directly to the affected nail.
B. The nail is covered with plastic wrap.
C. The entire digit is covered with cloth adhesive plaster.

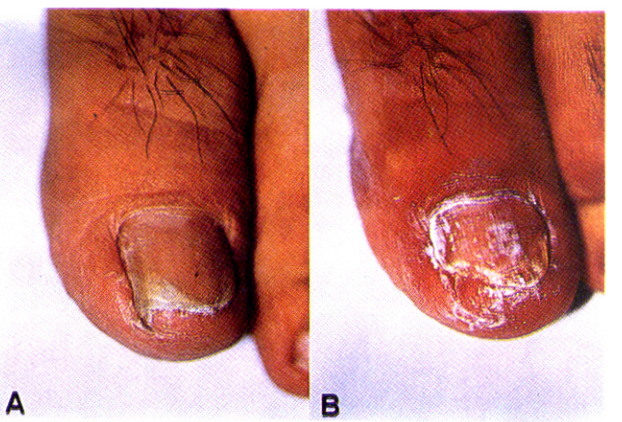

Fig. 2. Distal subungual onychomycosis.
A. Before treatment. **B.** After treatment.

Table 1. The response to treatment with the clotrimazole/urea paste

Case	Sex	No. of application	Efficacy
1	M	6	good
2	F	5	poor
3	M	6	NF
4	M	5	NF
5	M	3	NF
6	F	3+2	P-E
7	M	3	good
8	M	3	good
9	F	3	good
10	M	3	NF
11	F	5	NF
12	M	4	excellent
13	F	3	NF
14	F	2	good
15	F	2	NF
16	M	3	good

NF: cannot follow-up.
P-E: second therapeutic trial was excellent.

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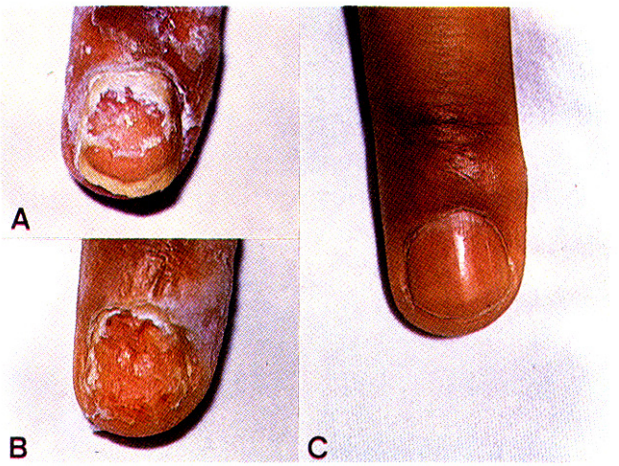

Fig. 3. Proximal subungual onychomycosis.
A. Before treatment
B. Immediately after nail removal
C. After treatment

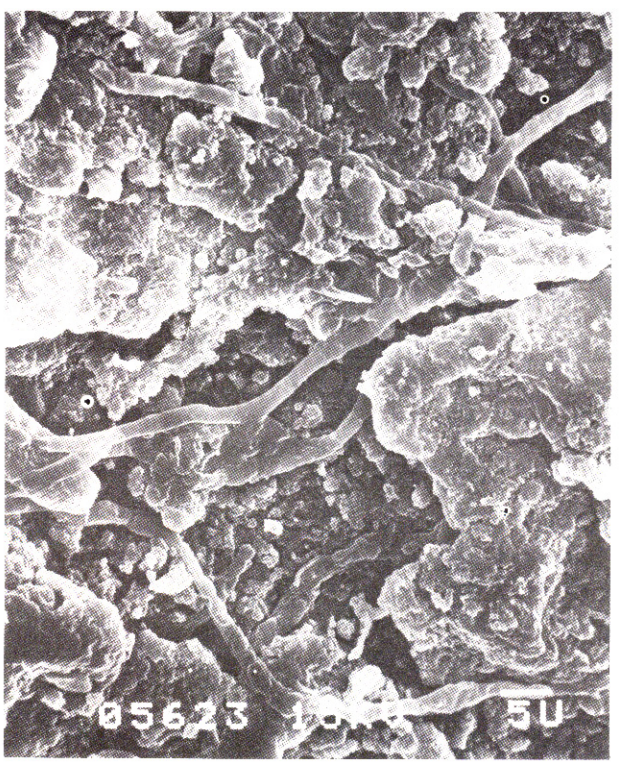

Fig. 4. Scanning electron microscopic finding before treatment shows distinct hyphae invading nail plate.

azole/urea paste. There was no follow-up on seven patients (Table 1). Among nine patients whom we could follow-up, complete cure was achieved in 2 out of 16 patients and a good therapeutic response without complete cure was achieved in 6 out of 16 patients (Fig. 2, 3). One patient showed no clinical improvement. Before treatment, the scanning electron microscopic findings showed intact hyphae and spores. Following treatment with Onychomal Plus® and occlusive dressing, fragmentation of fungal spores and hyphae was observed (Fig. 4, 5, 6).

DISCUSSION

Long-term oral antifungal therapy is used in the routine treatment of onychomycosis today[1]. However, the use of these drugs is limited because of possible side effects such as nausea, headache, alcohol intolerance and the risk, however rare, of hepatotoxicity. Although the surgical excision of the diseased nail shortens the course of oral antifungal therapy, it has disadvantages inherent in any surgical procedure. Furthermore, many patients because of underlying disease are poor surgical candidates. Therefore, there has been repeated efforts to develop an effetive topical therapy without surgical removal for onychomycosis[2-6].

In recent years, increased attention has been paid to topical urea as a keratolytic agent. Urea reportedly has antibacterial[8], antifungal[9], antipruritic[10], keratolytic[11], hydrating[12], wound healing, and even antineoplastic properties[13]. Urea is neither toxic nor allergenic[8]. Urea has been used in the Soviet Union for many years to avulse mycotic nails[2]. Since Farber and South discussed the use of urea in the avulsion of nail dystrophies[2], there have been numerous reports on the effect of urea with or without antimycotic agents in the treatment of onychomycosis[3-5, 13-18].

In this study, eight of the nine patients we could follow had an excellent or good response to the clotrimazole/urea paste treatment. In most cases, we could confirm by scanning electron microscopy destruction of hyphal forms, but intact fungi were found in some cases. Therefore, we thought that the reformulation of antimycotic agent included in the ointment base will be necessary. To maximize the cure rate, the patients should receive the repeated treatment, if the recurrence looked suspicious in the fungus study during the follow-

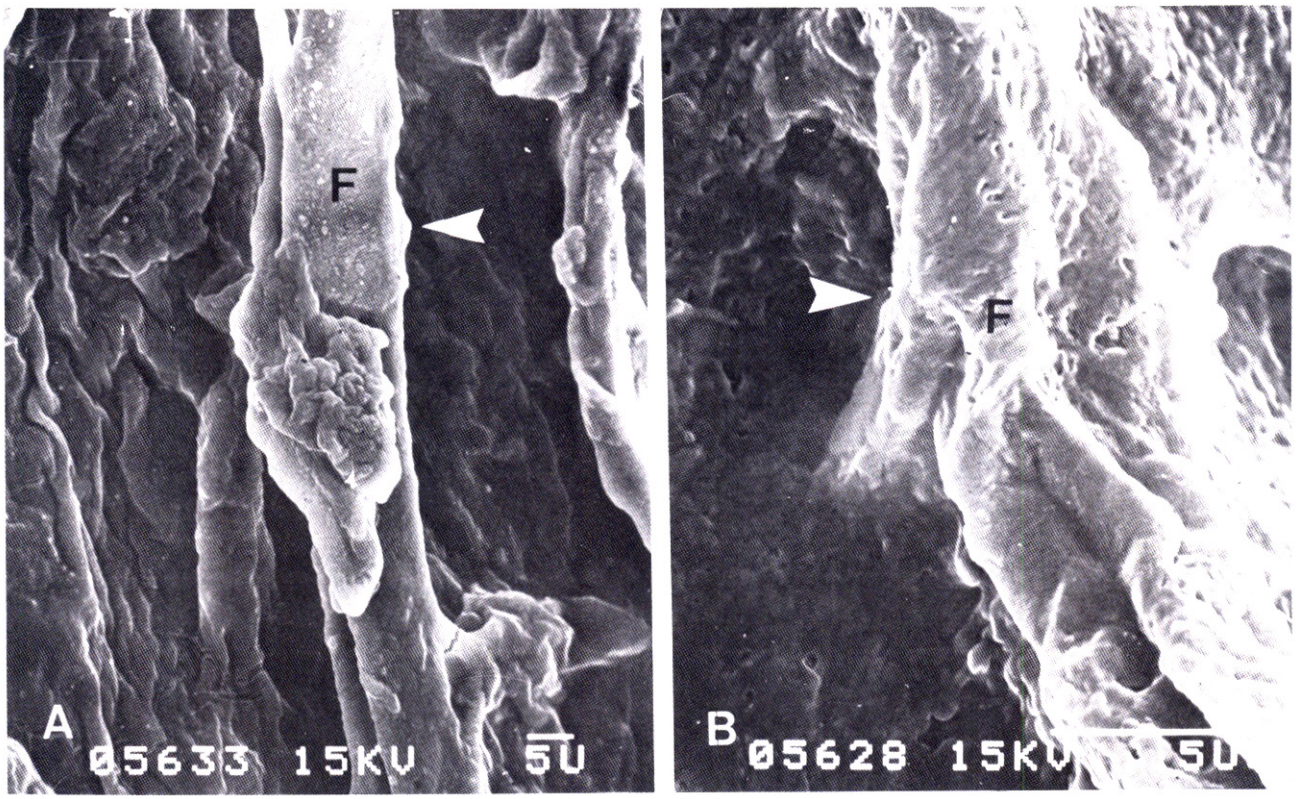

Fig. 5. A. After the first treatment, the fungi are beginning to destruct (SEM). **B.** The findings after the second treatment (SEM). F; fungus (indicated by arrowhead)

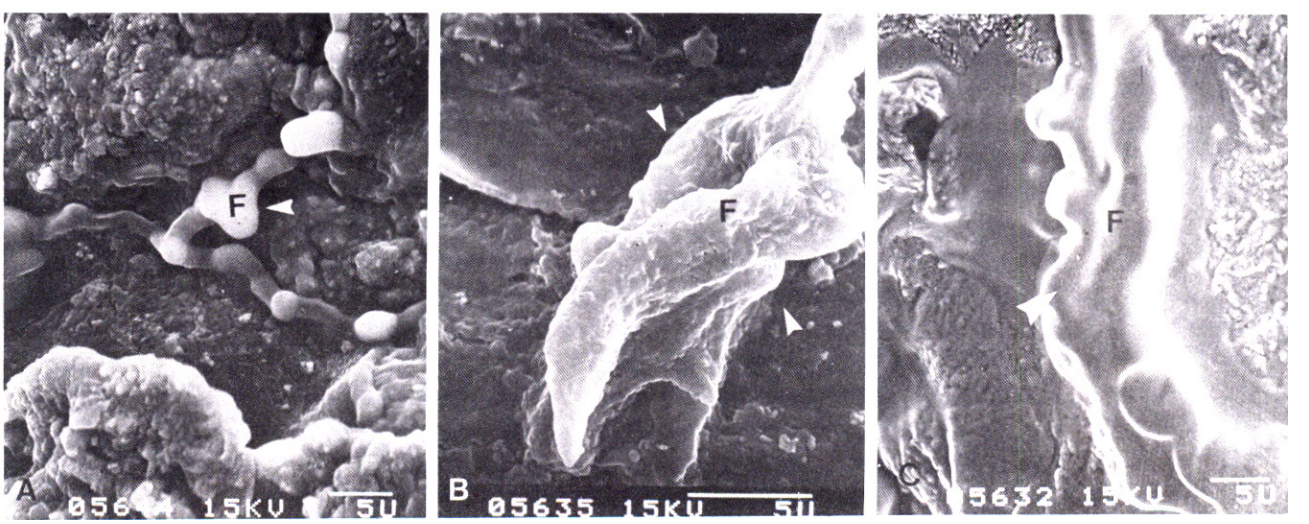

Fig. 6. The findings after the third treatment showing variable features (A, B, C) of destruction of hyphae (SEM). F; fungus (indicated by arrowhead)

Table 2. Comparison between surgical nail extraction and this method

	Surgical nail extraction	This method
Duration of treatment (wk)	1–2	2–3
Hemorrhage	+	–
Pain	+	–
Possibility of infection	+	–
Use of the systemic anti-fungal agent	+	–
Operation time per one nail (min.)	20–30	10–15
Local anesthesia	+	–
Emotional stress	++	–

up period. The procedure described here has several advantages summarized in Table 2. It is a nonsurgical method, and therefore, inexpensive and not painful or emotionally stressful for the patients. There are no risks of hemorrhage or infection and no need for anesthesia. These reasons making it ideal for treating patients with pregnancy or diabetes and others with vascular insufficiency and neuropthy of the digits.

In conclsion, if the recomposition of antimycotic agent is possible, the procedure described here is an especially convenient and available method for treating partially affected onychmycosis.

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