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Fungal Infections Occurring under Bandages in Leg Ulcer Patients

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In 49 consecutive leg ulcer patients fungal cultures were taken from 4 different locations: the ulcer; the ulcer edge; 10 cm below the knee; and the toe-web. The patients had been treated with ACO Medicated Stockings in half of the cases, and the others were treated with several different bandages. Sera were analysed for antibodies against *Candida albicans* with the indirect immunofluorescence technique (IIF). The mean antibody titer was 434 in the patients with *C. albicans* in their ulcers, 123 in control patients with negative cultures in their ulcers and 258 in control patients with basalioma or actinic keratoses. Seven patients were culture positive for *C. albicans*, two patients had *C. parapsilosis* and one had growth of *Trichophyton rubrum* in their ulcers. Nine out of 10 patients with positive cultures had been treated with ACO Medicated Stockings ($p<0.05$). Covering a large area of the leg with an ointment impregnated stocking without preservatives seems to increase the risk for fungal infections. *Key words: Candidiasis; Wound infection; Bandages; Varicose ulcer; Serum antibodies.* (Received December 22, 1986.)

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The importance of fungi in leg ulcers has been investigated in a few studies only (1, 2, 3, 4).

We have earlier reported *Candida albicans* infections in patients with leg ulcers treated with double elastic bandages (5). Cultures were only made from patients where a candida infection was suspected on the basis of the clinical picture.

In the present study cultures were made from 25 consecutive patients using ACO Medicated Stockings compared to a similar number of patients using other bandages, in order to further investigate the role of fungi in leg ulcers and the predisposing effects of various bandages. Cultures for fungi were taken from various locations, circulating antibodies against *C. albicans* studied and the antimycotic activity of various substances tested.

MATERIAL AND METHODS

Patients referred to the outpatient dermatology department have mostly longterm bandages. It was decided to include approximately 25 consecutive patients with ACO Medicated Stockings and 25 patients with other bandages in the study. The referring doctors recommend the treatments.

Characteristics of patients

Forty-nine leg ulcer patients were investigated, 10 men and 39 women with a mean age of 74 years (age range 29–93). Twenty-five patients (7 men, 18 women, mean age 69) had been treated with the ACO Medicated Stocking as an inner protective layer. It consists of a knitted tube impregnated with an ointment, which contains 20% zinc oxide, soft and liquid paraffin, but no preservatives. The outer adhesive layer gives the compressive effect and is called Coban Self-Adherent Wrap (Medical Products Division/ 3M). Four patients were treated with Zincaband N (Seton Products), which consists of gauze impregnated with 15% zinc oxide, 2% acid. boric., amyl. hydrolys., glycerol. propyl. parahydroxybenz. and ricini oleum. Zincaband N was used as an inner protective layer with the Coban Wrap outside. The double-elastic bandages were changed once or twice a week. Thirteen patients were treated with Unitulle (Roussel Laboratories Ltd) soft paraffin impregnated gauze, changed each other day. Four pa-

tients were treated with Duoderm (ConvaTec, Squibb) non-permeable hydrocolloid occlusive dressing made of polyisobutylene 40%, gelatin 20%, pectin 20%, carboxymethylcellulose sodium 20%. It was changed once or twice a week. One patient was treated with Sorbsan (Steriseal, N.I. Medical) surgical dressing which consists of alginate fibers, it was changed daily. One patient was treated with Release non-adherent dry absorbent dressing (Johnson & Johnson). This was changed daily. One patient was treated with chloramine 0.25% wet dressings, which were changed twice daily. The 24 patients (3 men, 21 women) with other treatments than the ACO Medicated Stocking had a mean age of 79 years.

The clinical status of the ulcer, the skin of the same leg and foot including the toe webs was noted in each case at the time of culture. All ulcers were cleaned with tepid tap water. The ulcers in the four patients treated with Duoderm were cleaned with 3% hydrogen peroxide during 1 min. The patients without double elastic bandages all had elastic compression bandages on at daytime, but not at night except for one patient who changed Unitulle and elastic bandages three times weekly at our department.

Anti fungal treatments

Patients with positive cultures in their ulcers were treated with clotrimazole cream Canesten® (Bayer) in the ulcer, on the skin of the same leg and foot from the knee to the toe webs.

Cultures

Cultures were taken on Sabourauds agar and Dermatophyte Test Medium (DTM) from four places in each patient. I) On the front of the leg 10 cm beneath the knee; II) at the edge of the leg ulcer; III) in the ulcer, and IV) in toe web number 4–5. If the patient had several ulcers on both legs the clinically most infected ulcer and leg was selected. The cultures were taken with sterile cotton swabs on to the media. The cultures were incubated at 25°C and read at weekly intervals for 3 weeks.

Indirect immunofluorescence (IIF) technique on sera

In all 49 patients blood was drawn. Sera were analysed in patients where *C. albicans* was found in the ulcer. Patients with leg ulcers but without positive *C. albicans* culture and patients with basalioma or actinic keratoses without any history of fungal infection were used as controls. Antibodies against *C. albicans* were estimated as earlier described (6) using fluorescein isothiocyanate (FITC)-labelled anti-human IgG from DAKO (Copenhagen, Denmark, Lot 034, F 202).

In vitro activity of various materials used in the treatment of leg ulcers against C. albicans

The antimycotic activity of chloramine 0.25% in water, potassium permanganate 0.015% in water, hydrogen peroxide 3% in water, ACO Medicated Stocking, Zincaband N, Release, Sorbsan, Duoderm, Iodosorb powder, Coban Wrap and Unitulle compress against *C. albicans* was tested. DST-agar (Diagnostic Sensitivity Test medium, Oxoid, England) was inoculated with 0.3 ml of a suspension of 10^5 *C. albicans* cells ml^{-1}. Chloramine, potassium permanganate, hydrogen peroxide and Iodosorb Powder were poured into 6 mm basins and the other materials were applied as 6 mm disks on the medium and the plates were incubated at 37°C and read after one and 2 days.

Statistics

Patients with positive fungal cultures treated with ACO Medicated Stockings were compared to patients with positive fungal cultures and other treatments using the chi-square method with Yates' correction. The Wilcoxon rank sum test was used to compare the groups of sera.

RESULTS

Results of cultures are seen in Table I. In patients treated with ACO Medicated Stockings *C. albicans* was cultured from the ulcer in 6 patients and in one patient treated with chloramine 0.25% solution.

No other pathogenic fungi were found in the ulcers of patients treated with other types of bandages than ACO Medicated Stocking. In patients treated with ACO Medicated Stockings *C. parapsilosis* was cultured in 2 patients and *Trichophyton rubrum* in one patient. The age and sex of the patients with positive and negative cultures are seen in Table II.

Of the 10 patients with positive fungal cultures one patient had an insuline treated diabetes mellitus and one patient was a chronic alcoholic. No other treatments like glucocorticosteroids or other predisposing factors were known among the 10 patients.

Patients treated with ACO Medicated Stockings had a significantly higher number of posi-

Table I. *Type and distribution of fungal species in patients with positive cultures in leg ulcers*

Organism	No. of patients	Type of bandage	Location of fungi[a]			
			I	II	III	IV
Candida albicans	6	ACO Medicated Stocking	4	5	6	3
C. albicans	1	Choramine 0.25% solution	1	1	1	1
C. parapsilosis	2	ACO Medicated Stocking	0	0	2	1
Trichophyton rubrum	1	ACO Medicated Stocking	1	1	1	1

[a] I: Below the knee. II: Ulcer edge. III: Leg ulcer. IV: toe web.

tive fungal cultures ($p<0.05$). The 10 patients with positive cultures in their ulcers were all treated with 1% clotrimazole cream. The 9 patients treated with ACO Medicated Stockings continued this treatment in addition to clotrimazole cream under the bandage twice weekly for 3–12 weeks (mean 4.4 weeks). The 7 patients with positive *C. albicans* cultures in their ulcers, all had clinical signs compatible with candidiasis. Treatment with clotrimazole cream had a positive effect especially on the skin lesions around the ulcers. One patient however did not completely heal from the eruptions until the ACO Medicated Stocking treatment was stopped and she got daily clotrimazole cream only. The lesions then healed in a week. She had no remaining ulcer at this time. The other patients all had persisting leg ulcers. The red scaly skin changes in the patient with *T. rubrum* on both legs and feet disappeared after treatment with clotrimazole cream for 4 weeks. The 2 patients with *C. parapsilosis* in their ulcers had less pronounced skin changes with slight redness around their ulcers, pain and draining ulcers. They were treated with clotrimazole cream and ACO Medicated Stocking twice weekly. Treatment was stopped after 3 weeks; in one patient because of a burning sensation in the ulcer and in the other because only a slight effect on the skin lesions around the ulcers was seen.

The patient treated with chloramine wet dressings twice daily had insisted on its longterm use (more than 6 months). He had a clinical picture consistent with candida infection. Treatment twice daily with clotrimazole cream had an excellent effect on the skin lesions, but was stopped after 2 weeks because of a burning, uncomfortable sensation in the ulcer. The *C. albicans* infection reappeared with positive cultures after another few weeks of chloramine wet dressing. The superficial erosions made the ulcer larger. Treatment with Iodosorb powder in the ulcer and miconazole cream on the superficial erosions was then started. This treatment has been well accepted by the patient and the ulcer is shrinking gradually.

Table II. *Age and sex distribution of the leg ulcer patients*

Ulcer cultures	No. of men	No. of women	Mean age in years
ACO Medicated Stocking			
Positive cultures	2	7	70
Negative cultures	5	11	69
The other treatments			
Positive cultures	1	0	76
Negative cultures	2	21	80

IIF

The highest mean antibody titer against *C. albicans* (434±448; mean ± SD) was seen in 7 leg ulcer patients where *C. albicans* was cultured from the leg ulcers. This titer was significantly higher than in the 12 control leg ulcer patients with negative *C. albicans* cultures from the leg ulcers (123±182; mean ± SD) ($p<0.05$). No statistically significant difference was seen between the mean antibody titer from patients with positive *C. albicans* cultures in their leg ulcers and the 12 basalioma or actinic keratoses control patients (258±250; mean ± SD) ($p>0.05$).

In the culture positive leg ulcer patients the mean antibody titer was statistically significantly higher ($p<0.05$) than in the culture negative leg ulcer patients. There was no statistically significant difference in antibody titers against *C. albicans* between sera from patients with *C. albicans* in ulcers and the basalioma and actinic keratoses controls.

In vitro activity of various materials used in the treatment of leg ulcers against C. albicans

Only hydrogen peroxide, Zincaband N and Iodosorb had antimycotic activities. The inhibition zone was 60 mm for hydrogen peroxide 3%, 25 mm for Zincaband N, and for Iodosorb powder no growth on the plate was seen. Potassium permanganate oxidates easily and this interferes with in vitro testing.

DISCUSSION

In an earlier study of 6 elderly women with leg ulcers were found to have candidiasis on their legs (5). They had all been treated with ACO Medicated Stockings.

In the present study 25 patients treated with ACO Medicated Stockings were compared to 24 patients treated with other bandages. There was a statistically significant higher number of positive fungal cultures in patients treated with ACO Medicated Stockings. Seven patients with *C. albicans* and one patient with *T. rubrum* had clinical signs of infection, and all benefitted from the treatment with imidazole cream. In 2 patients with *C. parapsilosis* a clinical suspicion of fungal infection was found but the result of treatment was more dubious.

C. parapsilosis was in 6 patients cultured from the toe web as only location. *C. albicans* was often present in the same patient on other locations than in the ulcers. In 6 of 7 patients it was cultured from the edge of the ulcer and in 4 of 7 patients it was found in the toe web of the same leg.

A few patients complained of a burning sensation when treated with clotrimazole cream in the ulcer. Probably this is not the treatment of choice, and it is preferable to change the treatment.

Circulating antibodies against *C. albicans* were found in the highest titer in patients with positive cultures for *C. albicans*. The mean titer was significantly ($p<0.05$) higher than in controls with leg ulcers but with negative *C. albicans* cultures. No statistically significant difference was seen when the mean titer of the group with positive cultures was compared with patients with basalioma or actinic keratoses without a history of candida infection. According to other studies antibodies are often found in patients without candida infection (7). The patient with the highest titer of 1280 had a deep large ulcer covering most of the leg and a history of an earlier candida infection in the ulcer. The IIF-technique for testing circulating antibodies against *C. albicans* was used because we thought that patients with *C. albicans* in their leg ulcers might have a higher antibody titer against *C. albicans* than patients with negative *C. albicans* cultures and healthy controls.

Antibody titers against *C. albicans* are often found even in healthy individuals (7). We thought that the presence of *C. albicans* in the leg ulcers might stimulate the immune system better, but obviously antibody titers (IgG) cannot be used for diagnostic purposes.

The ACO Medicated Stocking is put on from the foot and drawn up on the leg and a fungal transport from the foot is possible. Covering a large area of the leg including the ulcer with an ointment impregnated stocking for several days seems to increase the risk for fungal infections. Other paraffin impregnated dressings cover only the ulcer area.

The in vitro tests for 0.25% chloramine shows that it had no inhibitory activity against *C. albicans*. The ACO Medicated Stocking had no inhibitory activity either, but Zincaband N used for longtime treatment with double bandages shows an inhibitory zone of 25 mm. The 4 patients treated with Zincaband N had no growth of any pathogenic fungi. In the 13 patients treated with Unitulle which had no inhibitory activity against *C. albicans*, no positive fungal cultures were found.

Clinical signs of *C. albicans* infection in leg ulcer patients are lesions situated around the ulcers with red, glistening and scaly skin, pustules and skin erosions (1). Ulcers do not in themselves have any typical appearance but can be irritated, oozing and painful. In patients with clinical signs of fungal infection both positive and negative cultures were obtained. Therefore, fungal culture is necessary for obtaining the correct diagnosis. In patients treated with ACO Medicated Stockings fungal infections occur more often than with other treatments.

The patients included in this study were patients admitted to the outpatient dermatology department. The type of treatment was chosen by the doctor who referred the patients before they came to the department. No suspicion of fungal infections was present when treatment was started. Therefore, predisposing properties in the ACO Medicated Stockings are presumed to be responsible for the high number of fungal infections seen in leg ulcer patients treated with this bandage. One predisposing property can be the lack of preservatives.

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