Case Reports

Chronic mucocutaneous candidiasis treated with transfer factor

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SUMMARY

A patient with chronic mucocutaneous candidiasis resistant to all topical therapy has had extensive tests of immunological function carried out before and after administration of transfer factor. Immunological testing has been both specific, directed at responses to candida antigen, and non-specific, directed at general assessment of the patient's immune status. Transfer factor has been administered on three occasions in the past year. After each treatment temporary clinical improvement accompanied by changes in both specific and non-specific immunological responses have been observed. The possible mode of action of transfer factor in this case is discussed.

The clinical value of dialysable leukocyte extract or transfer factor (TF) in patients with defective cellular immune responses was first recorded by Lawrence over 20 years ago and since this time reports of its value in the management of viral and fungal diseases, immunodeficiency states, and malignancies have accumulated steadily (Lawrence, 1974a,b). Despite this therapeutic record the precise structure of TF and its point or points of action in the immune system have not yet been defined.

The value of TF in chronic mucocutaneous candidiasis is well recorded (Schulkind et al., 1972; Kirkpatrick, Rich & Bennett, 1971; Valdimarsson et al., 1972) and for this reason a patient presenting with chronic mucocutaneous candidiasis has undergone intensive immunological assessment before and after TF administration.

MATERIALS AND METHODS

The responsiveness of the patient's peripheral blood lymphocytes was assessed by incorporation of $^{14}$C thymidine at 3 days in culture after stimulation with phytohaemagglutinin (PHA) at a concentration of 1/10, and pokeweed mitogen, (PWM) (Baker & Farnes) at a concentration of 1/100. The specific lymphocyte response to candida antigen was measured by the method of Valdimarsson et al. (1972).
Antibody to candida antigen was estimated by the radiolabelled antiglobulin technique of Nielsen, Parratt & White (1973). Leukocyte migration inhibition to candida antigen was carried out according to the method of MacKie et al. (1972). Intradermal skin tests were carried out to Mantoux 1/1000, Candida antigen, T. rubrum (Bencard), mumps (Eli Lilly) and varidase (Lederle). All tests were read at 20 min and 48 h.

Dialysable TF preparation. 400 ml blood were obtained from donors who gave positive 48 h skin tests to PPD, candida and varidase. Leukocytes were isolated, washed and disrupted by freezing and thawing 9 times, followed by sonication. The extract was then filtered, lyophilized, reconstituted with sterile water and checked for sterility. It was administered by subcutaneous injection into all four limbs.

Case history
A 25-year-old Caucasian female presented with a 20-year history of oral candidiasis, a 13-year history of candidal paronychia and vaginitis, and a 3-year history of keratitis considered to be candidal in origin. There was no family history of candidiasis or immunodeficiency, but the patient had had recurrent respiratory infections throughout childhood, some of which necessitated hospital admission. In infancy she had chickenpox, measles, mumps, scarlet fever and whooping cough, all of which ran a normal course; at the age of 12 years, she had bilateral herpes zoster. One pregnancy and 3 years’ oral contraceptive therapy had not affected her condition and continuous therapy with topical anti-candida agents had had no beneficial effect on her lesions.

On examination the patient had extensive oral candidiasis, paronychia involving both thumbs and the right index finger, vaginitis, and keratoconjunctivitis involving the right eye with possible early involvement of the left eye.

General examination revealed an otherwise healthy patient with no endocrinological abnormalities. Candida albicans was isolated on several occasions from oral, vaginal, and paronychial swabs. Serum iron was at the lower limit of normal on one occasion but on four other occasions was within normal limits. Other tests carried out with normal or negative results included full blood count, serum urea, electrolytes and calcium, liver function tests, chest X-ray and total serum iron binding capacity.

Transfer factor (16 ml) was administered subcutaneously in December 1973. Within 1 week of therapy the vaginal discharge had decreased, and within 1 month the paronychia and keratoconjunctivitis had become much less troublesome. Four months after the first dose of transfer factor her condition was static, and in view of this, and of the accompanying changes in immunological function tests, a second dose was given in May 1974. Forty-eight hours after this, she experienced a

<table>
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<td>Migration inhibition factor production to candida</td>
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+, positive; —, negative.
Candidiasis treated with transfer factor

brief exacerbation of her oral and vaginal lesions, followed by complete clearing of lesions at three sites for 4 months. The candida paronychia also became quiescent for this period.

Because of clinical and immunological deterioration, further treatment with TF was carried out in November 1974. Once again clinical benefit was observed within the week of therapy. This improvement was maintained for 4 months when mild deterioration in oral and vaginal lesions were noted. It is anticipated that the patient will continue to require TF therapy at regular intervals to maintain her clinical improvement. Throughout TF therapy vigorous topical treatment with nystatin has been maintained in an effort to reduce the antigen load.

![Figure 1. Specific anti-candida IgG, A and M levels before and after TF therapy. Normal levels are 100 units for each immunoglobulin class. Arrows indicate treatment with TF.](image)

**Immunological observations**

The candida-specific tests carried out and their results are outlined in Table 1. Prior to TF therapy there was no lymphocyte transformation on exposure to candida antigen, no migration inhibition factor (MIF) was observed on exposure of the patient’s leukocytes to candida, and 48 h skin tests to candida were negative. Specific anti-candida antibodies were abnormal, with a high level of IgG, low IgM and absent IgA. In view of the history of repeated bacterial infections, tests of neutrophil function including the NBT tests were performed, and were within normal limits.
After TF therapy, candida mediated lymphocyte transformation remained negative, but candida induced MIF production and candida skin tests became positive; this positivity was maintained for 8–10 weeks. Reversion of these two tests on all three occasions preceded clinical deterioration. After TF administration on the first occasion the specific anti-candida IgG level rose rapidly to a very high level, and thereafter rapidly fell to below pretreatment values. Anti-candida IgM also rose temporarily, and anticandida IgA was observed for the first time. Sequential antibody changes are illustrated in Fig. 1. Total antibody levels of these three subclasses were normal before therapy, and remained unchanged during treatment.

The most significant finding in the non-specific tests of immune function prior to therapy was the low lymphocyte response to PHA and high response to pokeweed mitogen. This ‘reversed ratio’, suggesting an imbalance between the T and B lymphocyte systems, was corrected after the first dose of TF and has remained normal since then. The patient had a negative Mantoux test at 1/1000 despite a history of BCG vaccination 10 years previously. After the first dose of TF from a Mantoux positive donor, this reaction became positive and has remained so.

An interesting observation was the activation of the sites of skin tests within 4 h of TF administration. Seventy-two hours prior to TF administration the patient had received intradermal skin tests to Mantoux 1/1000, mumps, T. rubrum, candida and varidase. At 48 h, only varidase was positive, but after TF from a donor, who was skin test positive to Mantoux and candida, both those sites became markedly inflamed and indurated.

**DISCUSSION**

The classification of chronic mucocutaneous candidiasis is at present complex; the patient here discussed does not suffer from any of the clearly defined immunodeficiency syndromes, from familial candidiasis or from the candida-endocrinopathy syndrome. She therefore falls into the group of diffuse chronic nongranulomatous mucocutaneous candidiasis who are found to have a variety of defects of cell mediated immunity in the absence of iron deficiency. It would appear to be the first case recorded in which specific anticandida antibodies have been measured.

In this case it would appear that the patient has a basic imbalance in humoral and cell mediated responses to candida leading to overproduction of anti-candida IgG, and complete failure of cell mediated immune response to candida. TF partially restores cellular immune function as indicated by temporary MIF production and positive skin tests. The persistent lack of transformation of the patient’s lymphocytes on exposure to candida shows, however, that this is not a complete correction. A possible explanation of this sequence of events is that there is in this patient a lack of a sub-population of T cells which control antibody synthesis and that TF has acted on this sub-population in stimulating cell mediated responses, and secondarily controlling humoral responses.

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**REFERENCES**

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