Acquired chronic candidiasis treated with transfer factor

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SUMMARY
A patient with acquired chronic oral and vaginal candidiasis resistant to topical and parenteral therapy was found to have impaired cell mediated immunity to Candida antigen and loss of skin test response to tuberculin (Mantoux). Treatment with Candida-active transfer factor produced clinical remission lasting 1 year and restitution of in vitro and in vivo immune parameters. Relapse occurred while receiving a second lot of transfer factor from the same donor. Subsequent treatment with levamisole was associated with onset of agranulocytosis.

The subject of candidiasis and immunity has been extensively reviewed by Kirkpatrick (1971). Chronic mucocutaneous candidiasis is an uncommon syndrome with unremitting, superficial infections of skin, nail, and oral and vaginal mucous membranes. It is usually associated with defect(s) in cellular immune function. Subgroups include associations with superficial granulomatosis, lethal congenital immune deficiencies (DiGeorge, Nezeloff, Swiss-type, etc.), and polyendocrinopathies. This syndrome usually becomes manifest in infancy or childhood and the overall prognosis depends usually on the degree of endocrinopathy or the immune deficit. Treatment of the disfiguring and debilitating yeast infection has been discouraging until recent supplementation of chemotherapy with immune reconstitution. Parenteral amphotericin B or clotrimazole usually eradicates the Candida only transiently; treatment with repeated injections of candida positive transfer factor (TF), however, seems to provide long-lasting clinical remission in about one-half of treated patients (Kirkpatrick, 1975; Spitler, Levin & Fudenberg, 1975). It is impossible at present to predict which of these patients with their marked variability of immunological reactivity will respond to TF. Other immune reconstitutive measures have been tried and these include bone marrow stem cells, peripheral blood lymphocytes, thymus and/or fetal haematopoietic tissues (Kirkpatrick, 1971). Kirkpatrick (1976) has recently shown that where the risk of graft vs host reaction is low, a combination of fetal thymus (HL-A unmatched) and TF was successful in controlling this syndrome after TF alone had failed.

We wish to describe a patient with acquired chronic oral and vaginal candidiasis who did not have infected skin or nails. The finding of a mild immune deficit and her response to transfer factor treatments suggest that she may represent a variant within the syndrome of chronic mucocutaneous candidiasis.
MATERIALS AND METHODS

Intradermal skin testing was carried out using PPD 5 and 250 TU (Connaught), Candida albicans 100 PNU (Hollister-Stier), mumps (Eli Lilly), and streptokinase-streptodornase 40/10 U (SKSD, Lederle). Tests were read at 24 and 48 h and the diameter of induration recorded.

In vitro lymphocyte stimulation was performed using PHA, pokeweed, and Con A mitogens, and PPD, candida, mumps, and SKSD antigens. H²-thymidine incorporation was measured with a scintillation counter and values were recorded in disintegrations per minute (dpm). These techniques have been described in detail elsewhere (Thomas et al., 1976).

Transfer factor (TF) was prepared from lymphocytes of Candida skin test positive donors who were leukapheresed on an Aminco cell separator. The leukocytes were disrupted by freezing and thawing 10 times with addition of DNase, and the extract dialyzed, lyophilized, and reconstituted in sterile saline such that one unit was equivalent to 5 x 10⁸ lymphocytes. Injections of a single unit were given subcutaneously into the deltoid area. Activity of a given lot of TF was determined by its proven ability to either augment or transfer the Candida skin test response in other individuals. The primary donor for this TF (patient's brother) was leukapheresed on two occasions (11 months apart) resulting in two separate lots of TF. At the time of the second leukapheresis, he possessed an active BCG (Connaught) vaccination site and blood studies showed his lymphocyte response to Candida to be less than the control value. At this time his Candida skin test was still positive (> 15 mm).

CASE HISTORY

A 36-year-old Caucasian female first presented in 1974 with a 5-year history of persistent vaginal candidiasis and recurrent throat infections due to C. albicans, proven by culture. As a public health nurse she had extensive prior exposure to tuberculosis and a markedly positive tuberculin skin test documented in the past. Her family history was unremarkable, and her prior medical history was negative up to 1969 when she underwent a hysterectomy for cancer of the cervix, complicated by surgical infection and a subsequent prolonged course of multiple antibiotics. (Repeated follow-up evaluations have yielded no evidence of recurrent malignancy). She reports that her first symptoms of vaginal and oral candidiasis occurred immediately following this hospitalization. Both vaginitis and pharyngitis were controlled transiently, but soon she was requiring topical antifungals and vaginal pessaries almost continuously. By January 1974 her condition was virtually resistant to this therapy and she was hospitalized and received a full course of parenteral amphotericin B. Resolution of the infection in March lasted only a month; she was then referred for immunological evaluation and therapy with the diagnosis of suspected chronic mucocutaneous candidiasis. She has never had skin or nail involvement with yeasts nor any evidence of allergies or endocrinopathy.

Evaluation in August 1974 showed her to have an otherwise normal physical examination with evidence of vaginitis and no pharyngitis; a vaginal swab grew Candida and a throat swab was negative. Complete blood count, renal and liver function tests, serum iron, immunoglobulins and protein electrophoresis were all normal. Candida precipitins were positive in a titre > 1:16. Neutrophil chemotaxis was not assessed. Studies of her cell mediated immunity showed specific in vivo and in vitro anergy to Candida antigen and a negative skin test to tuberculin (250TU), despite a strongly positive PPD lymphocyte response in vitro (Table 1). Her serum did not contain any specific blocking activity against Candida stimulated lymphocytes, and her own lymphocytes could not be activated by Candida positive homologous plasma, multiple washings, or neuraminidase pretreatment. Lymphocyte response to mitogens, PHA, pokeweed and Con A were normal and remained so throughout the study interval.
**Table 1. Skin test and lymphocyte response with treatment**

<table>
<thead>
<tr>
<th>Treatment course</th>
<th>Initial evaluation 0 units TF</th>
<th>Remission 2 units TF</th>
<th>Remission 3 units TF</th>
<th>Remission 5 units TF</th>
<th>Relapse, 1 year 8 units TF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin*</td>
<td>0/0</td>
<td>20/0</td>
<td>15/0</td>
<td>20/0</td>
<td>10/10</td>
</tr>
<tr>
<td><strong>LSI†</strong></td>
<td>&gt; 10 0</td>
<td>7.7</td>
<td>&gt; 10 0</td>
<td>&gt; 10 0</td>
<td>&gt; 10 0</td>
</tr>
<tr>
<td><strong>Candida</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>0/0</td>
<td>30/0</td>
<td>30/30</td>
<td>30/25</td>
<td>20/25</td>
</tr>
<tr>
<td><strong>LSI</strong></td>
<td>&lt; 1 0</td>
<td>&lt; 1 0</td>
<td>1.5</td>
<td>3.2</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Mumps</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>30/30</td>
<td>30/30</td>
<td>30/30</td>
<td>—</td>
<td>15/15</td>
</tr>
<tr>
<td><strong>LSI</strong></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&gt; 10 0</td>
</tr>
<tr>
<td><strong>SKSD</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>30/30</td>
<td>30/30</td>
<td>30/30</td>
<td>—</td>
<td>30/30</td>
</tr>
<tr>
<td><strong>LSI</strong></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&gt; 10 0</td>
</tr>
<tr>
<td><strong>Other therapy</strong></td>
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<td></td>
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<tr>
<td>Prior amphotericin B.</td>
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<td></td>
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<tr>
<td>Continuous topical</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>None</td>
<td>Topical</td>
</tr>
</tbody>
</table>

* Skin test response, mm induration at 24 h/48 h. † Lymphocyte stimulation index, dpm antigen-stimulated/dpm control.

Following this evaluation she was given 3 units of *inactive* TF over a 2 month period with no change in symptoms, culture growth, skin tests or lymphocyte response. Off all other medication, she was then started on monthly treatments with *active* TF prepared from her brother, whose initial skin tests and lymphocyte response were markedly positive. Within 2 months her symptoms cleared, vaginal and throat cultures were normal, and skin tests were showing transient positivity at 24 h (Table 1).

Free of infection for 4 months, she missed the next 2 months of therapy and returned with a mild bout of vaginitis which quickly responded to a short course of topical therapy. She resumed monthly TF treatment and remained symptom-free and off other medication for another 6 months. Twelve months after initiating TF therapy she developed a severe attack of both vaginal and oral candidiasis, which remained refractory to antifungals, and another four units of TF were given over the next 4 weeks. The onset of this attack occurred about 6 weeks after starting injections from the second lot of TF prepared from her brother.

Because of a lack of more Candida active TF at this time, and with her previous clinical and laboratory remission suggesting that further immunotherapy might be helpful, the patient was started on levamisole (McNeil Ltd., Canada) 50 mg three times daily for 2 days every week. Three weeks later she developed fever, sore throat, arthralgia, rash and peripheral oedema. She was hospitalized and found to have agranulocytosis, with oral and vaginal candidiasis and a positive Paul–Bunnell test.

* This particular preparation was given and presumed to be active based on donor's skin test response. It was prepared not by dialysis and lyophilization but rather as an ultrafiltrate through an Aminco PM-10 Diaflo membrane, and later tests found that it lacked both PPD and Candida blastogenic and skin test activity.
Four weeks after hospitalization she was fully recovered with the exception of her persistent oral and vaginal yeast infection. In the ensuing 4 months she received 4 units of TF prepared from an unrelated, skin test positive donor; this was without clinical benefit. She has recently been started on a combination of TF and BCG in an effort to regain long-lasting control over her chronic infection.

DISCUSSION

The existence of many diffuse subgroups within the syndrome of chronic mucocutaneous candidiasis has been suggested by several investigators (Kirkpatrick, 1971; DeSousa et al., 1976) but continues to defy clinical or laboratory elucidation (Kirkpatrick, 1971). Late onset of chronicity, partial responses to local or systemic therapy, involvement of mucous membranes alone, and mild but demonstrable forms of immune impairment, all may characterize a hitherto unrecognized subgroup of chronic mucocutaneous candidiasis. Our case report describes such an individual. Following some apparent insult (possibly antibiotics, surgery) to a genetically predisposed immune system, a mild and relatively specific form of immunodeficiency may have developed in our patient. Her loss of PPD skin sensitivity and anergy to Candida antigen seem to have correlated with clinical disease. Reconstitution at monthly intervals with active and specific TF produced a clinical remission lasting approximately 1 year (Table 1) while antifungal agents and another inactive preparation of TF were of no significant benefit.

The explanation of our patient’s relapse while on treatment must be purely conjecture. From in vitro studies it appears that some TF preparations contain both blastogenic (non-specific) and MIF (specific) mediator activity, whereas many preparations cannot be shown to have multiple activities (Burger, 1975; Ascher, 1975; Dabrowska, 1975). Lawton et al. (1976) have also demonstrated that TF injections can restore impaired neutrophil chemotaxis and produce clinical improvement in chronic mucocutaneous candidiasis. As yet, no analysis of our TF preparation has been done checking for soluble mediator activity. It is likely that the lots of TF prepared from our patient’s brother were not identical in their activity. The initial lot may have corrected more than one deficit since both the patient’s skin test and lymphocyte response to Candida antigen were regained during her remission period. At the time of her relapse she was still able to produce a positive Candida skin test, but her in vitro lymphocyte response was slipping back to pre-treatment levels. This change in her immune status, occurring with clinical relapse, corresponded to the same change in her brother’s immune response which distinguished the first lot of TF from the second.

We believe that TF as well as other forms of immunotherapy should be used in conjunction with antifungal agents to treat patients with chronic candidiasis and demonstrable immune deficiencies only after the risks of treatment are carefully weighed against symptom severity and chronicity of infection.

ACKNOWLEDGMENTS

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REFERENCES


Chronic candidiasis and transfer factor


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