Eyebrows have developed in patients with chronic mucocutaneous candidiasis

**Altered immune responses in patients with chronic mucocutaneous candidiasis**

**Altération des réponses immunitaires chez les patients atteints de candidose chronique cutanée-muqueuse**

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**KEYWORDS**

Chronic mucocutaneous candidiasis; Cellular immunity; Lymphocyte transformation; Cytokines

**Summary**

**Objective.** — The purpose of this study was to investigate the lymphocyte transformation responses and cytokine secretion of peripheral blood mononuclear cells (PBMC) from patients with chronic mucocutaneous candidiasis (CMC).

**Methods.** — Phytohaemagglutinin (PHA) mitogen and *Candida albicans* (*C. albicans*) antigen proliferation assays were performed by culturing PBMCs in RPMI 1640. The levels of interleukin (IL)-2, IL-10, IL-17 and interferon (IFN)-γ present in the supernatant of cultures were determined using enzyme-linked immunosorbent assay (ELISA).

**Results.** — The results showed that most patients (92.3%) had a low proliferative response to *C. albicans* antigens and PHA. PBMCs from CMC patients produced lower levels of T (h)-1 cytokines IL-2 (78.5 ± 59.8 pg/mL) and IFN-γ (115.1 ± 43.3 pg/mL) in response to *Candida* antigens when compared to controls (IL-2: 177 ± 103.6 pg/mL; IFN-γ: 330.3 ± 21.6 pg/mL) (P < 0.05). Conversely, we observed a partial enhancement of IL-10 in the patients (213.7 ± 86.1 pg/mL). Production of IL-17 indicated no significant differences between patients and controls when stimulated by *Candida* antigens (21.5 ± 8.6 pg/mL versus 32.4 ± 12.2 pg/mL) and PHA (27.7 ± 11.5 pg/mL versus 36.2 ± 9.1 pg/mL), respectively.

**Conclusion.** — These findings suggest that *Candida* antigens trigger a Th2 instead of Th1 cytokine response in patients with CMC. For better understanding, further studies require on a larger number of patients into the future.

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**MOTS CLÉS**
- Candidose chronique cutanéo-muqueuse ;
- L’immunitécellulaire lymphocyttaire ;
- Transformation ;
- Cytokines

Résumé

Objectifs. — Le but de cette étude était d’étudier la transformation lymphocytaire et la sécrétion cytokiniques des cellules mononucléées du sang périphérique (PBMC) chez des patients atteints de candidose chronique cutanéo-muqueuse (CMC).

Matériel et méthodes. — Les tests de prolifération avec la phytohémagglutinine (PHA) et avec les antigènes de Candida albicans (C. albicans) ont été effectués par la culture de PBMCs en RPMI 1640. Les niveaux de l’interleukine (IL) -2, IL-10, l’IL-17 et de l’interféron (IFN) -γ présents dans le surnageant des cultures ont été déterminés à l’aide test immuno-enzymatiques (Elsa).

Résultats. — Les résultats ont montré que la plupart des patients (92,3 %) avaient une faible réponse proliférative de C. albicans antigènes et à la PHA. Les PBMCs des patients atteints de CMC produisent des niveaux inférieurs de T (h)-1 cytokines IL-2 (78,5 ± 59,8 pg/mL) et L’IFN-γ (USD 115,1 millions ± 43,3 pg/ml) en réponse aux Candida antigènes de Candida comparés aux contrôles (IL-2 : 177 ± 103,6 pg/ml ; IFN-γ : 330,3 ± 21,6 pg/ml) (p < 0,05). Inversement, nous avons observé une amélioration partielle de l’IL-10 chez les patients (213,7 ± 86,1 pg/mL). La production de l’IL-17 ne montrait aucune différence significative entre les patients et les contrôles lorsque stimulé par les antigènes de Candida (21,5 ± 8,6 pg/mL versus 32,4 ± 12,2 pg/mL) et la PHA (27,7 ± 11,5 pg/mL versus 36,2 ± 9,1 pg/mL), respectivement.

Conclusion. — Ces résultats suggèrent que les antigènes de Candida déclenchent une production cytokinique Th2 au lieu de Th1 chez des patients avec CMC. Pour une meilleure compréhension, d’autres études ont besoin d’un plus grand nombre de patients dans l’avenir.

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References


Introduction

Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency disease presenting with debilitating, persistent and refractory infections of the skin, nails and mucosal tissues by Candida species; in particular Candida albicans in the majority of the cases [28]. Several clinical features of CMC have been described, some of which are associated with endocrinopathies or autoimmune diseases, such as hypothyroidism and hypoparathyroidism [4]. Patients with CMC rarely develop disseminated or invasive candidiasis, suggesting a defect in the host defense limited to superficial candidal infections [13, 17].

Several reports have shown that the defects are almost exclusively in the cellular branch of the immune system, mainly the specific responses to antigens of Candida species [26]. The balance between T helper (Th)1 and Th2 cytokines is important in the initiation of the type of immune response. A Th1 cytokine response is associated with resistance to candidiasis, whereas a Th2 response results in susceptibility to infection [24]. Some CMC patients present serum factors that inhibit the proliferative responses of peripheral blood mononuclear cells (PBMC) from Candida-sensitized normal subjects [3]. Durandy et al. [10] demonstrated that infection with C. albicans leads to an accumulation of mannan (a Candida polysaccharide antigen). This causes activation of suppressor T-cells capable of inhibiting both the proliferation and the activation of T-helper cells.

It is generally accepted that defense mechanisms encompass macrophages, cytotoxic lymphocytes and natural killer (NK) cells. For activation of these cells, pro-inflammatory cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α are major mediators, whereas anti-inflammatory cytokines, such as interleukin (IL)-4 and IL-10, antagonize the cellular anti-candidal defense [23]. Moreover, other recent studies demonstrated deficient production and secretion of IL-2 by PBMC in response to Candida antigen [21]. It has also been revealed that other cytokines can influence the balance of cytokines produced, as is the case with IFNγ, which stimulate Th1 responses. Specifically, the pro-inflammatory IL-17—producing Th17 subset is implicated in protection against Candida at epithelial surfaces [7].

Due to the several controversial aspects of CMC, we assessed the pro- and anti-inflammatory cytokine responses in a whole-blood culture model after stimulation with C. albicans antigens and phytohaemagglutinin (PHA) mitogen in patients with CMC.

Patients and methods

Patients and sample collection

The CMC patient group consisted of 13 cases (5 male and 8 female) between 6 and 17 years of age, representing clinical criteria for persistent and refractory candidiasis of skin, nails and mucosal tissues. Thirteen patients presented oral thrush, 5 had nail lesions, 13 trunk skin involvement, 3 scalp skin involvement, 4 oesophageal lesions and 1 conjunctivitis. During the study, the CMC patients did not suffer from other concurrent disorders or acute infections. In all patients, endocrinopathy was excluded as judged by absence of clinical manifestations and laboratory evidence of autoimmune endocrinopathy. The control group consisted of 13 age- and sex-matched healthy individuals. Ethical approval was granted by Ethical Committee of Imam Khomeini Hospital, Tehran, Iran. After obtaining informed consent, blood samples were obtained from both patients and controls at the same time, using 2 ml glass tubes containing lithium heparin (Becton Dickinson, Franklin Lakes, NJ).

Cell separation and cell cultures

Peripheral blood mononuclear cells (PBMCs) were obtained by centrifugation on Ficoll-Hypaque. The cells were washed twice with RPMI 1640 (Gibco, Grand Island, N.Y.), the number of viable lymphocytes was determined by trypan blue...
staining, and the cells were counted on a hemocytometer. The cells were resuspended in RPMI 1640 with 20% fetal calf serum (FCS) at a concentration of $10^5$ cells per mL.

Mitogen proliferation assay was performed by incubating $10^5$ PBMCs in RPMI 1640 supplemented with penicillin (100 U/mL), streptomycin (100 μg/mL), L-glutamine, and 20% FCS. The cells were cultured in triplicate for 72 h with PHA (1 mg/mL; Sigma, St. Louis, Mo.) at 37 °C in 5% CO2. After 72 h, they received a 6-h pulse with 0.5 μCi of [3H]thymidine (Sigma) and were then harvested and washed on glass filters. [3H]thymidine incorporation was measured in a liquid scintillation counter (Beckman). Antigen proliferation assay was also performed in triplicate with $2 \times 10^5$ PBMCs per microwell cultured with C. albicans antigens (Hollister-Stier, Spokane, Wash.) which had been dialyzed against RPMI 1640, filter sterilized, and tiritated against control PBMCs. An optimal dilution of 1:4 was used in all subsequent studies. Cells were cultured for 5 to 7 days at 37 °C in 5% CO2. At the end of the incubation, the cells received a 6-h pulse of [3H]thymidine and were then harvested and counted as described above. The results were presented as stimulation index (SI).

Cytokine assay

Quantification of cytokines in the supernatant was obtained by stimulation of $5 \times 10^5$ cells/mL in RPMI/10% AB serum in 24-well plates with PHA 1 mg/mL and C. albicans antigens 1 μg/mL. The supernatant samples were harvested 24 h after PHA stimulation and 72 h after Candida stimulation, according to preliminary experiments in which harvesting time was determined (data not shown). The supernatants were stored in aliquots at −70 °C until quantification of cytokines. The amounts of IL-2, IL-10, IL-17 and IFN-γ present in the supernatant of cultures were determined using human enzyme-linked immunosorbent assay (ELISA) kits (BioSource International, Camarillo, Calif.). Briefly, 100 μL of supernatant or human cytokine standard was added in duplicate to each well of a plate precoated with anti-human cytokine monoclonal antibody, and the plate was incubated for 1 h at 24 °C. The plate was then washed once with a buffered detergent wash solution, 100 μL of a rabbit polyclonal anti-human cytokine antibody was added to each well, and the plate was incubated for 1 h at 24 °C. The plate was washed, 100 μL of an anti-rabbit antibody conjugated to horseradish peroxidase (HRP) was added to each well, and the plate was incubated for 1 h. After washing four times, an HRP substrate solution was added for 1 h. The reaction was stopped by adding 5% sulfuric acid to each well, and the plate was read at 490 nm. The values were calculated by comparison with the standard curve.

Statistics

One-way analysis of variance (ANOVA) test was used for multiple group comparisons followed by Tukey post-hoc for group-wise comparisons. $P$ value < 0.05 was considered statistically significant.

Results and discussion

The controversial reports of cellular immune response of CMC patients reflect the clinical and immunological variability of these patients [28]. Due to the dominant role of the cellular compartment of the immune system in the defense against fungi, several parameters of the cell-mediated immunity such as T lymphocyte proliferation and cytokine secretion in patients with CMC were investigated.

The lymphocyte transformation responses were evaluated after stimulation with PHA and C. albicans antigens. In this study, most patients (12/13; 92.3%) revealed a low proliferative response to Candida antigens (Fig. 1). The proliferative response to PHA was also below the lower normal limit in 12 of 13 patients tested (Fig. 2). These proportions were different in relation to the control group: as 9 and 8 of them showed low stimulation indices (SIs) against Candida antigens and PHA, respectively (Table 1). Despite the depressed proliferative response from PBMC to Candida antigens, most patients presented the same specific immune response, failing to recognize PHA, as observed previously [15,18]. It should be noted that serum from the patients suppressed both mitogen- and antigen-induced lymphocyte proliferation. De Moraes-Vasconcelos et al. [9] studied eight CMC patients without endocrinopathies, who showed low normal proliferative response to PHA and impaired response to Candida antigens. Durandy et al. [10] demonstrated that infection with C. albicans leads to an accumulation of mannann (a Candida polysaccharide antigen). This causes activation of suppressor T cells capable of inhibiting both the proliferation and the activation of T-helper cells.

The analysis of mean IL-10 production by PBMC of the patients showed lower levels than those found for the control group; i.e. 157.9 ± 103.1 pg/mL in the patients and 173.2 ± 94.1 pg/mL in the controls, when stimulated by PHA (Table 1). In addition, production of IL-10 was not significantly altered in the patients (213 ± 74 pg/mL) when compared to the controls (205.05 ± 123.16 pg/mL) upon Candida antigens stimulus. The secretion of IL-2 (Figs. 3 and 4) and IFN-γ (Figs. 5 and 6) revealed significantly lower levels than those found for the control group; i.e. 78.5 ± 59.8 pg/mL in the patients and 177 ± 103.6 pg/mL

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in the controls for IL-2, and 115.1 ± 43.3 pg/mL in the patients and 330.3 ± 121.6 pg/mL in the controls for IFN-γ, when stimulated by Candida antigens (P < 0.05). The mean levels of production of IL-2 and IFN-γ after stimulation with PHA were not different between patient (172 ± 106.5 and 315.8 ± 116.9 pg/mL) and control groups (219.4 ± 127.8 and 379 ± 141.3 pg/mL), respectively (Table 1).

Our results demonstrated significant alterations in the patterns of cytokine production seen in patients with CMC; specifically in response to C. albicans antigens, representing a significant decrease in the production of Th1 cytokines including IL-2 and IFN-γ. In contrast, the production of the anti-inflammatory cytokine IL-10 tended to be higher in CMC patients. A similar lack of responses was also noted in proliferation assay. Our data are in accordance with those of Gravenor et al. [14] demonstrating higher IL-10 levels and deficient IL-2 production in CMC patients after C. albicans stimulation. In a comprehensive study conducted by Lilic and

Table 1  The levels of cytokines production of peripheral blood mononuclear cells from patients with mucocutaneous candidiasis and controls stimulated with Candida albicans antigens and phytophaemagglutinin mitogen (pg/mL).

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Si: stimulation index; CA: Candida albicans antigens; PHA: phytohaemagglutinin.

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Gravenor [22] on a larger number of patients with CMC, it was
demonstrated increased IL-10 production in response to
Candida antigens in all patients. This was paralleled by
decreased values of IL-2 and IFN-γ. As IL-10 is a potent
anti-inflammatory cytokine which counteracts the actions of
IFN-γ, the IFN-γ/IL-10 ratio is considered to be important
in defense against C. albicans [27]. Therefore, the greater
release of IL-10 in CMC patients further contributes to a
reduced IFN-γ/IL-10 ratio and is likely to also be involved in
the defective activation of anti-candidal mechanisms.

Low IL-2 and IFN-γ production in response to C. albicans
antigens could largely explain impaired cell-mediated immu-
nity previously reported in these patients [9,18]. It is likely
that low IL-2 and IFN-γ levels are the results of decreased Th1
cell numbers. Differences in some studies may in part depend
on the type of C. albicans antigens used to stimulated
responses [16]. It is important to mention that the sera of
the patients clearly modulated immune reactivity, suppres-
sing the production of Th1-type but not Th2-type cytokines.
The fact that little patients secreted adequate concentrations
of the Th1 cytokines can be a consequence of the heterogeneity of the disease or, on the other hand, of the
clinical status at the time of evaluation. Considering that
these defects are not consistently found in CMC patients,
they are unlikely to be the only or the main underlying cause
of susceptibility to persistent Candida infections.

The defective IFN-γ release appeared to be rather specific
for candidal stimulation. Microbial components stimulate
IFN-γ production through intermediary release of monocyte
products such as IL-12 and IL-18, while PHA directly stimu-
lates T lymphocytes [2]. Thus, the difference between
Candida and PHA stimulation suggests that the defect in CMC
patients may be localized at the level of monocytes.

Th17 cells that produce IL-17 are crucial in protection
against oral or mucocutaneous candidiasis [7,8]. Indeed,
the natural Th17 memory repertoire includes many
C. albicans — specific Th17 cells, which trigger the production
of neutrophil-recruiting and -activating cytokines and chemokines,
pro-inflammatory cytokines, and anti-microbial peptides
in many cell types [1,12,20]. As illustrated in Table 1,
production of IL-17 showed no significant differences between
patients and controls when stimulated by Candida antigens
(21.5 ± 8.6 pg/mL versus 32.4 ± 12.2 pg/mL) and PHA
(27.7 ± 11.5 versus 36.2 ± 9.1 pg/mL), respectively. Little
is known about the defects underlying susceptibility to Can-
dida in patients with autosomal dominant CMC (related to
Th17). In a previous study, investigators found defective Th17
responses in patients with this disorder [5]. The exact role
of these cells in anti-Candida immunity is not fully understood,
with evidence to suggest both a positive [6] and negative [29]
role, although it is becoming clear that cytokines secreted by
these cells, most notably IL-17, play a significant role in anti-
fungal immunity. IL-17 acts on epithelial cells and neutrophils,
functioning as a bridge between the adaptive and innate immune responses. Its effects on epithelial cells include
induction of anti-microbial peptides, matrix metalloproteases
and other inflammatory mediators. The importance of the

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Th17 response in mucosal immunity to Candida infections is underlined by several recent studies linking defects in the Th17 response and production of IL-17 to cases of CMC [11,25]. This link is further supported by the finding that in cases of autoimmunity with neutralizing antibodies to Th17 cytokines (IL-17A, IL-17F, and IL-22), there is an increased incidence of CMC [19]. Despite this, the report that IL-17 may play a deleterious role in anti-Candida immunity suggests that the situation may be far more complex in vivo [11].

In conclusion, our data suggest that altered cytokine production may be an important mechanism underlying increased susceptibility to Candida infections seen in patients with CMC. Our findings of an impaired ability to produce IL-2, IL-17, and IFN-γ and a mild production of IL-10 suggest that in patients with CMC, Candida antigens seem unable to trigger adequate production of Th1 cytokines, but instead trigger increased production of Th2 cytokines. However, even though our findings support this scenario, further studies addressing production of other cytokines characteristic of a Th1 or Th2 type response are needed to confirm this bias.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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