Transfer factor in chronic mucocutaneous candidiasis

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Abstract

Fifteen patients suffering from chronic mucocutaneous candidiasis were treated with an in vitro produced TF specific for Candida albicans antigens and/or with TF extracted from pooled buffy coats of blood donors. CMI of the patients was assessed using the LMT and the LST in presence of candidine. The aim of the study was the clinical evaluation of TF treatment and the incidence of positive tests before, during, and after therapy. Immunological data were matched using the Chi square test. 87 LMT were performed for each antigen dose and at the dilution of 1/50, 58.9% (33/56) tests were positive during non-treatment or non-specific TF treatment. On the contrary 83.9% (26/31) were positive during specific TF treatment (P<0.05). In the LST, a significant decrease of thymidine uptake in the control cultures in presence of autologous or AB serum was observed when patients were matched according to non-treatment, and both non specific (P<0.05) and specific TF treatment (P<0.01). Only during specific TF treatment was a significant increase of reactivity against the Candida antigen at the highest concentration noticed, when compared with the period of non specific treatment (P<0.01). Clinical observations were encouraging: all but one patient experienced significant improvement during treatment with specific TF. These data confirm that orally administered specific TF, extracted from induced lymphoblastoid cell-lines, increases the incidence of reactivity against Candida antigens in the LMT. LST reactivity appeared not significantly increased with respect to the periods of non treatment, but was significantly increased when it was compared to the non-specific TF treatment periods. At the same time, a clinical improvement was noticed.

Abbreviations: CMI: cell-mediated immunity; CMCC: chronic mucocutaneous candidiasis; LMT: leucocyte migration inhibition test; LST: lymphocyte stimulation test; PBL: Peripheral blood lymphocytes; TF: transfer factor.

Introduction

Chronic mucocutaneous candidiasis (CMCC) is a primary immunodeficiency characterized by chronic or chronically relapsing Candida albicans infections. Generally, skin, mucosa and hairs, as well as finger and toe nails, are involved [1,2]. The disease is characterized by a broad spectrum of clinical manifestations regarding localisation and/or severity, and evolution. The immune response against Candida antigens is often impaired although the type and degree of impairment may vary in different patients. For these reasons, CMCC is now recognised as a syndrome, rather than as a single disease.

As regards clinical manifestations, three different entities have been described according to age and appearance of the syndrome: 1) an early onset in children, usually very severe; 2) a late onset, less severe, and, 3) one associated with juvenile familiar polyendocrinopathy. The early onset severe form is characterized by oral candidiasis, frequently extended to larynx and oesophagus, nails and skin, with hyperchertotic areas progressing towards granulomas. Endocrine abnormalities have been described in about half of the cases. The late onset form is clinically less severe than
the previous one; generally, candidiasis is limited to the mouth and/or to the finger and toe nails.

In the variety associated with polyendocrinopathy, the multiple autoimmune endocrine dysfunctions provide the major features of the clinical pattern, in association with ectodermal dystrophy and candidiasis. This form, also defined by the acronym “APECED” (Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy), is characterised by a severe derangement of many endocrine parameters. Endocrinological symptoms may have an early onset or begin many years after candidiasis; alopecia and chronic active hepatitis are less frequent. Generally, autoantibodies against parathyroid, adrenal glands, gonads, endocrine (B cells) pancreas, gastric wall and thyroid are present; circulating autoantibodies in chronic candidiasis strongly suggest an autoimmune pathogenesis for endocrine disease.

In analogy with the clinical heterogeneity, an equally marked immunologic heterogeneity is described. Usually, an in vivo selective cell mediated anergy towards Candida albicans antigens is found; intradermal response to candidine is, therefore, frequently negative in most of the patients. In vitro lymphocyte proliferative response to Candida albicans antigens, like to other antigens [1,2], is frequently depressed, although PBL number and percentage are normal. High antibody response to Candida albicans antigens is often noticed, with immunoglobulin serum levels within the normal range. T and B lymphocyte subsets are normal (both as percentage or as absolute number), as is the T4/T8 ratio. It is unclear whether the immunologic deficiency is primitive or secondary. Some authors think that Candida albicans infection becomes chronic for unknown non-immunologic reasons and immunodeficiency is secondary to the release of inhibitory factors by Candida: mannan is frequently elevated in the blood of these subjects. A mannan deficiency has been also observed in the monocytes of some of these patients. Conventional treatment of CMCC is unsuccessful. Chemotherapy improves the symptomatology, although relapses are frequently observed, but often candidiasis is resistant to treatment. Encouraging immunologic [3] and clinical results [4–5] have been reported using TF obtained from immunised individuals. Since the source of anticandida-specific-TF is limited and the batches are frequently exhausted, and it has been showed that TF can be replicated in vitro using lymphoblastoid cell-lines, thus providing in unlimited amounts of specific material, and has been utilised with success for treating viral diseases [6–14], we attempted to produce large batches of anticandida-specific-TF and to evaluate its clinical and immunological potency in CMCC.

Material and methods

Patients

Fifteen subjects (3 males and 12 females; age 7–62) entered the study; 6 were affected by oral and 9 by vaginal candidiasis. All patients could be ascribed to the late onset variety of CMCC; none of the patients were affected by associated polyendocrinopathy. In most cases candidiasis has been present for several years. In some patients antifungal treatment administered for several months failed to eradicate the infection.

Transfer factor

For specific TF (TF-S), highly reactive healthy partners of infected patients, showing a strong CMI against candidine as assessed both by the LMT and the LST, were selected as TF donors. The TF thus obtained was replicated in vitro as described elsewhere [13–14]. “Unspecific” TF (-U), i.e. whose specificities were unknown, was prepared from pooled lymphocytes obtained from blood donors' buffy coats using standard techniques. Both TF-S and TF-U were encapsulated and orally administered at an average dose of 4x10⁸ cell equivalent (c.equ.) per week in the first 2 weeks of treatment (induction phase) and then at 10⁸ c.equ. per week for the following 6–12 months. Antimycotic treatment was continued during TF treatment, but was gradually discontinued. TF-S treatment was carried out for approximately 12 months (6–30 months). Patients were also periodically treated with TF-U because of temporary unavailability of TF-S.

Immunological studies

LMT was carried out as described by Centifanto et al [15] and by Söberg et al [16]. Briefly, 20 ml of blood were taken in a heparinized (1500 IU) syringe and gently mixed with an equal volume of plasmagel (Bieffe, Modena). The blood was allowed to settle 45–90 min, and the cells recovered from the enriched leucocyte fraction after 3 washings in RPMI-1640 medium. They were subsequently suspended at 6x10⁷ cell/ml. The leucocytes suspension was carefully placed in capillary tubes (Clay Adams, 75 mm long, 1.1 mm internal diameter) whose one extremity was sealed with