J Microbiol Immunol Infect
2004;37:196-199

Chronic mucocutaneous candidiasis in a 6-year-old boy

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Received: May 5, 2003 Revised: September 2, 2003 Accepted: September 24, 2003

Chronic mucocutaneous candidiasis (CMC) is a complex disorder characterized by persistent or recurrent candidal infections of the skin, nails and/or mucous membranes. A familial occurrence has been reported in some instances, suggesting a genetic predisposition. CMC has also been suggested to be associated with a selective defect in T cell-mediated immunity to *Candida* antigens. Reports of cases in Asians are rare. We report a case of CMC in a 6-year-old boy with chronic candidal infection since 7 months of age. The patient presented with deficient cell-mediated immunity and decreased natural killer cells. This case highlights the need for detailed studies for evaluating the T-cell immunity in patients with chronic candial infection.

Key words: Case reports, cellular immunity, chronic mucocutaneous candidiasis, diagnosis

Chronic mucocutaneous candidiasis (CMC) is a primary T cell immunodeficiency characterized by persistent or recurrent candidal infections of the skin, nails and mucous membranes without *Candida* sepsis [1]. The initial presentation of CMC may be either chronic candidal infection or a variety of immunodeficiency disorders, such as human immunodeficiency virus (HIV) infection, severe combined immune deficiency disease, DiGeorge syndrome, and so on [2]. Although patients with CMC are classified as having primary immune deficiency, the nature of their immune defects remains unknown. Recent studies suggested that the impact of immunity defects could be the result of altering patterns of cytokine production, resulting in inadequate interleukin-2 and interferon-γ (INF-γ) production in response to *Candida* infections [3-5]. Children with CMC usually have the appearance of other disorders, including non-candidal infections (81%), idiopathic endocrinopathies (44%), and autoimmune diseases (32%) [6]. These findings suggest that patients with CMC have multiple or complex abnormalities in their immune systems.

Chronic candidal infection can be easily diagnosed by direct physical examination, potassium hydroxide (KOH) preparation and fungus culture [7]. However, chronic mucocutaneous candidiasis is considered an immune deficiency disorder and is usually accompanied by other diseases. There have been few reports concerning CMC in Asians [8-11], and only 1 report in Chinese children [11]. We report a case of CMC in a 6-year-old boy with chronic candidal infection since 7 months of age. The patient showed deficient T cell-mediated immunity to *Candida* antigens. This case highlights the need for detailed studies for evaluating the T cell immunity in patients with CMC, and for investigation and long-term follow-up for accompanying disorders.

Case Report

A 6-year-old boy was referred to our hospital because of persistent oral thrush and onychomycosis since 7 months of age. The boy had been born at term to healthy parents who had no history of immunologic or endocrine diseases. Intractable oral thrush first developed at 7 months of age. Mycosis involving the fingertips and perianal area developed at the age of 2 years, with poor response to cryotherapy and laser therapy. The oral thrush and onychomycosis were persistent in the following years, but he did not develop otitis media, sinusitis, pneumonia or other severe infections except for some episodes of upper respiratory infection. He was referred to our hospital at the age of 6 years for further work-up of candidal infection.

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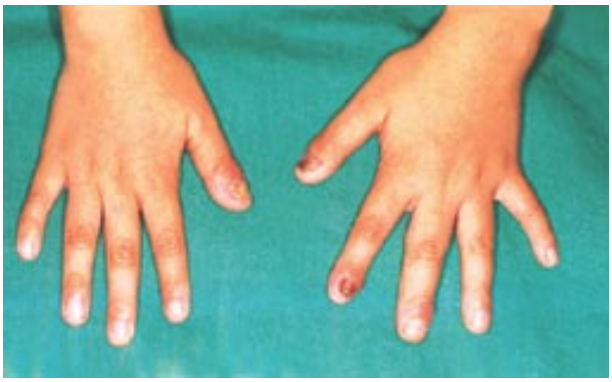

Fig. 1. Onychomycosis and *Candida* paronychia.

His growth and development history indicated a healthy and well developed boy. Physical examination revealed onychomycosis (Fig. 1), extensive oral thrush, 2 pustules over the perioral area, and a few old scars resulting from laser therapy in the perineal area. Breathing sound was clear, and heartbeat was regular without murmur. Abdominal examination was normal without any organ enlargement.

The results of tests, including a complete blood count, liver function tests, serum calcium, C-reactive protein, plasma cortisol, thyroxin, thyroid-stimulating hormone, and immunoglobulin G (IgG), IgM, IgA, and IgE were all normal or negative. The phenotypes of lymphocytes showed an increased proportion of B lymphocytes (CD19) and a decreased proportion of T lymphocytes (CD3) and natural killer cells (CD16/CD56) [Table 1].

The subsets of T lymphocytes showed a mildly decreased proportion of CD4 cells. Peripheral blood lymphocyte proliferation test showed a normal response to phytohemoagglutinin (PHA) and *Staphylococcus aureas* Cowan I (SAC) but negative response to *Candida* antigens. Delayed-type hypersensitivity skin test to candida, tetanus, tuberculin, and trichophyton were also negative. Nitroblue tetrazolium test demonstrated normal reduction ability. KOH preparation of the skin, mucosa, and nail scrapings revealed fungus pseudohyphae, and the culture results all showed *Candida albicans* growth.

Table 1. Patient's cell-mediated immunologic data

Test	Value	Reference range
WBC (10^9/L)	12.3	5.0-14.5
Lymphocytes (10^9/L)	8.85	1.5-7.0
CD3 (%)	48.7	62-80
CD4 (%)	24.1	35-51
CD8 (%)	27.7	22-38
CD4/CD8 ratio	0.87	0.84-3.05
CD16/CD56 (%)	2.8	4-20
CD19 (%)	36.4	14-23
Th1 (%)	3.89	4-12
Th2 (%)	1.47	0.44-0.67
Th1/Th2 ratio	2.65	1.16-12

Abbreviations: WBC = white blood cells; Th1 = T-helper 1 cells; Th2 = T-helper 2 cells

On the basis of clinical manifestations and laboratory investigations during hospitalization, the diagnosis of CMC was made, and ketoconazole at a dosage of 3.3 mg/kg/day was prescribed for 6 months to control the candidal infection. Oral thrush resolved 4 weeks later but relapsed soon after, while onychomycosis persisted.

Discussion

Mucocutaneous candidiasis can be diagnosed based on the findings of physical examination, KOH preparation, and fungus culture. Multiple intrinsic and extrinsic factors contribute to the development of clinical infections [7]. These conditions should be differentiated from a persistent inability to clear C*andida*, as is seen in our patient with the primary T cell immunodeficiency. After failure of clinical treatment for the infection, CMC should be considered. Further evaluation of immune status and accompanying disorders is also important.

Immunologic studies of this patient showed a mildly increased lymphocyte count. The lymphocyte phenotypes showed an increased proportion of B cells (CD19) and a decreased proportion of T cells (CD3). The subsets of T lymphocyte showed a mildly decreased proportion of CD4 cells. Peripheral blood lymphocytes responded normally to PHA and SAC, but there was no response to *Candida* antigens, although he had recurrent candidal infections since the age of 7 months. Delayed-type hypersensitivity skin test to *Candida*, tetanus, tuberculin, and trichophyton were negative. These data suggested the patient had a selective defect in T cell-mediated immunity to *Candida* antigens. These findings are similar to the immunologic features of patients with CMC in previous studies [12,13].

Protection from mucocutaneous candidiasis has been shown to depend on cellular immunity [1]. Although the nature of these defects remains elusive, studies on animal models have highlighted the essential role of type 1 cytokines in the protection against candidal infection [14]. Further evaluation of the T-helper 1 (Th1) and Th2 cells in this patient showed a mildly decreased proportion of Th1 cells, an increased proportion of Th2

cells and a normal Th1/Th2 ratio. However, recent data in patients with CMC have documented altered patterns of cytokine production in response to *Candida* antigens with decreased production of some but not all type 1 cytokines and increased levels of IL-10 [3-5]. The underlying defects responsible for altered patterns of cytokine production remain unknown, but recent studies have addressed the putative role of dendritic cells and pattern recognition receptors in directing cytokine responses [15].

Natural killer (NK) cells are able to kill tumor cells and virally infected cells [16]. The relationship between NK cell function and candidal infections remains unclear. There have been few reports of NK cell deficiency in CMC patients. Recently, Manz et al [17] and Palma-Carlos and Palma-Carlos [18] reported that patients with CMC have a decreased number and killing function of NK cells. Our patient also had significantly decreased proportion (2.8%) of NK cells (CD16/CD56). These data suggest that the count and function of NK cells should be evaluated in CMC patients. NK cell deficiency has been documented in Chediak-Higashi syndrome, X-linked lymphoproliferative syndrome, and leukocyte adhesion defect. NK cell deficiency has also been detected in severe combined immunodeficiency disease. The association between NK cell deficiency and CMC remains to be determined.

Most patients with CMC have normal concentrations of serum immunoglobulins, high titers of antibodies against *C. albicans* and normal response to vaccines [6,19]. This boy had normal B cell counts. His IgG, IgM, IgA, and IgE levels were also normal. However, B cell defects have been reported in several CMC patients, especially subclasses of IgG2 and IgG4 deficiency [6,20-22]. Most of these patients had repeated bacterial infections and pneumonia, but our patient did not have a history of any other significant infection. Although humoral deficiencies are uncommon in CMC patients, humoral immunity should be checked once CMC patients develop bacterial infections.

Chronic mucocutaneous candidiasis is a heterogeneous clinical syndrome which results in numerous descriptive classifications depending mostly on the time of onset, accompanying clinical features, and mode of inheritance [1]. Our patient had only oral mucosa, nail, and skin infection with *C. albicans* without any other accompanying endocrinopathy, such as hypoparathyroidism, hypoadrenalism, or other autoimmune diseases. Long-term follow-up is needed due to the possibility of the development of accompanying disorders, because patients with CMC usually have or develop other disorders, including other infectious diseases, enamel dysplasia, alopecia, vitiligo, malabsoption, hemolytic anemia and autoimmune polyendocrinopathy [6]. These disorders are especially common in patients with candidiasis that begins in early childhood and in patients with the polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [23,24]. CMC was the initial manifestation of APECED in 93% of cases [23]. Hypoparathyroidism and adrenal failure usually occurred after CMC in these patients, with mean age of onset of 9.2 years and 13.6 years, respectively. There is some evidence favoring autosomal recessive inheritance for this form of candidiasis. In 1997, two groups simultaneously reported mapping of the gene for APECED to chromosome 21 (21q22.3) [25,26].

Topical therapies are not usually effective in patients with CMC. Oral involvement in CMC can be aided by clotrimazole troches or oral nystatin solution. Orally administered systemic antifungal drugs are effective and can improve quality of life [27]. However, most patients have a relapse within a few weeks or months after the antifungal treatment is stopped, and the underlying immunologic defect often cannot be corrected. Our patient received therapy with ketoconazole at the dosage of 3.3 mg/kg/day for 6 months. During this period, oral thrush resolved but relapsed soon after discontinuation of treatment. Onycomycosis did not resolve during treatment. Prolonged treatment (at least 6 to 9 months) may be required for the onychomycosis to clear [28, 29]. Jorizzo et al [30] and Polizzi et al [31] reported successful treatment with cimetidine and zinc sulphate in patients with CMC who failed in long-term antifungal therapy. This may be an alternative treatment for CMC.

In summary, it is difficult to make a timely diagnosis of CMC in patients with multiple attempts to eradicate the infection using standard cutaneous treatment with candicidal drugs. Once the diagnosis is made, detailed immunologic studies should be performed and the possibility of accompanying disorders, such as endocrinopathy, thymoma, or autoimmune diseases should be investigated. Long-term follow-up is needed because of the high likelihood that many accompanying disorders may occur in the years after CMC is diagnosed.

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