CASE REPORTS

Chronic Mucocutaneous Candidiasis; Report of Three Cases with Different Phenotypes

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ABSTRACT

Chronic Mucocutaneous Candidiasis (CMCC) refers to a group of immunodeficiencies, characterized by persistent or recurrent infections of the skin, nails, and mucus membranes caused by candida. A wide range of immunologic abnormality has been reported in CMCC. Defects in cellular limb of the immune system, mainly the specific response to antigens of candida species, are well documented in CMCC patients. A subgroup of patients is predisposed to development of autoimmune endocrinopathies. These patients need repeated monitoring of endocrine functions. Immunologic studies are needed to identify the extent of immunodeficiency and other abnormalities of immune functions. We report three cases of CMCC. These patients show different phenotypes and highlight the need for complete evaluation and long term follow-up for accompanying disorders.

Keywords: Candidia; Chronic Mucocutaneous Candidiasis; Immunologic Deficiency Syndromes

INTRODUCTION

Chronic Mucocutaneous Candidiasis (CMCC) refers to a group of immunodeficiencies, characterized by persistent or recurrent infections of the skin, nails, and mucus membranes caused by candida; in most cases, the infecting species is *Candida albicans*.[1] There is enough diversity of populations of patients with mucocutaneous candidiasis that several clinical syndromes have been identified. CMCC may be seen in patients with primary immunodeficiency conditions and the disorder is also associated with endocrinopathies and autoimmune disorders.[2]

Defects in the cellular limb of the immune system are well documented in CMCC patients, but non-specific immune defects, such as myeloperoxidase deficiency or phagocyte chemotaxis disorders, have also been described. Nonetheless, the underlying defect(s) remains poorly understood.[3] Some CMCC patients present serum factors that inhibit the proliferative responses of peripheral blood mononuclear cells (PBMC) from candida-sensitized normal subjects, and a wide spectrum of immune dysfunctions has been observed.[4] Most cases of CMCC are sporadic, but there are numerous reports of familial CMCC. Both autosomal dominant and recessive patterns of inheritance have been seen.[5]

We report three cases of chronic mucocutaneous candidiasis. These patients show different phenotypes and highlight the need for complete evaluation and long term follow-up for accompanying disorders which may lead to new perspectives on a poorly understood disease.

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Case 1

A 35-year-old man referred to our center due to persistent oral candidiasis and candida esophagaitis. He developed persistent oral thrush during infancy and onychomycosis at 36 months of age. The thrush was unresponsive to oral nystatin but was cleared with oral ketokonazole; however relapsed soon after

antifungal therapy was stopped. The oral thrush and onychomycosis were persistent in the following years but he did not developed pneumonia, sinusitis, otitis media and other serious infections. Furthermore he did not develop endocrinopathy and autoimmune disorders. Family history was negative for similar illness. Laboratory test showed normal skin test to tetanus and tuberculin but no response to candida antigens and decrease *in vitro* lymphocyte proliferation to candida antigens. Thyroid, parathyroid, and adrenal functions were normal (Table 1).

Case 2

A 14-year-old girl referred to our center with persistent oral candidiasis and perlesh from late childhood. She is the only affected family member and parents are not relatives. Delayed -type hypersensitivity skin test to candida was negative. At age 11 she developed progressive muscle weakness, petosis and with complete investigations diagnosise of myasthenia gravis was made. She was treated with plasmaphresis and now she is on low dose steroid on alternate days. Thymoma has been ruled out by mediastinal CT-Scan. At age 13, she developed macrocytic anemia due to B12 deficiency (pernicious anemia) and was treated successfully with B12 supplement. She has shown good response to conventional antifungal treatment; however, relapse has occurred after stopping the treatment (Figure 1).

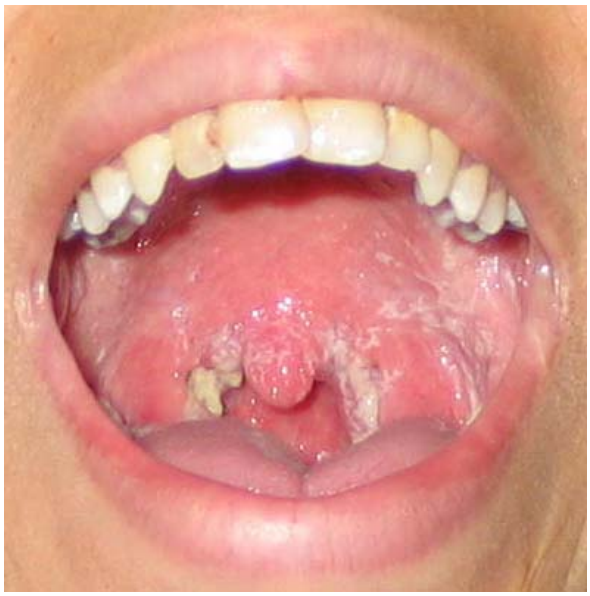
Case 3

A 27-year-old girl developed persistent oral candidiasis and onychomycosis during infancy. At ages 9 and 20 years she developed hypocalcemic seizure and severe weakness with skin hyper pigmentation and after complete evaluation revealed hypoparathyroidism and adrenal insufficiency, respectively. The oral thrush and onychomycosis were persistent in the following years. Laboratory tests showed normal skin test to tetanus antigen but negative response to candida antigen. In vitro lymphocyte proliferation to candida was subnormal (Table 1). She did not develop serious infections.

Table 1. Laboratory data of 3 cases with chronic mucocutaneous candidiasis.

Test		Case 1	Case 2	Case 3
CBC (cell//mm³)	White Blood Cell	10600	7400	7800
	Absolute Neutrophil Count	7000	4500	4000
	Absolute Lymphocyte Count	2800	2500	2950
Flowcytometry	CD3	70	57	85
(%)	CD4	47	35	40
	CD8	29	23	18
	CD19	12	8	10
	CD16	13	14	10
Immunoglobulins	IgG	1448	1360	3000
(mg/dl)	IgG1	705	800	1400
	IgG2	210	250	490
	IgG3	95	100	180
	IgG4	52	40	65
	IgM	81	210	350
	IgA	300	60	150
	IgE (IU/ml)	16	195	100
Chemotaxis		Normal	Normal	Subnormal
Calcium (mg/dl)		8.8	8.7	6
Phosphorus (mg/dl)		3.5	4.6	7
Alkaline Phosphatase		400	374	700
Parathyroid hormone		-	-	low
Thyroid functions test		Normal	Normal	Normal
Autoimmune Markers (ANA, Anti dsDNA)		Negative	Negative	Negative
Delayed-typed hypersensitivity test (Candida)		Negative	Negative	Negative
Lymphocyte Transformation Test (Candida)		Subnormal	Not determined	Subnormal
Lymphocyte Transformation Test (Mitogen)		Normal	Not determined	Normal

Figure 1. Oral candidiasis in a patient with CMCC.



DISCUSSION

CMCC is a rare condition with a frequency of less than 3% in Iran.[6,7] Recent reports from Iranian Primary Immunodeficiency Registry demonstrated that only 13 cases with CMCC have been referred to this national database till now.[6] CMCC does not represent a specific disease but rather a phenotypic presentation of a spectrum of immunologic, endocrinologic, and autoimmune disorders. There is enough diversity of populations of patients with mucocutaneous candidiasis that several clinical syndromes within the category of CMCC have been described based by the extent and location of the candida infections and associated disorders. They differ in their clinical manifestations, immunologic findings and genetic features.[5,8] These include: 1) chronic oral candidiasis; 2) familial CMCC; 3) autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy or autoimmune polyendocrinopathy syndrome (APECED or APS); 4) chronic localized candidisis; 5) CMCC with thymoma; 6) candidiasis with chronic keratitis; and 7) candidiasis with the hyper- IgE syndrome.[1]

A wide range of immunologic abnormalities have been reported in CMCC.[4] Defects in cellular limb of the immune system, mainly the specific response to antigens of candida species, are well documented in CMCC patients. Their T cells do not secrete some cytokines such as macrophage inhibitory factor (MIF), when they are stimulated by candida antigens.[4,9] Other specific immune defects, such as phagocyte chemotaxis disorders, impairment of natural killer cell activity and B-cell defects have also been described.[3]

Our patients have less marked immunologic defects. They have normal number of lymphocytes, circulatory T- cells, natural killer cell (NK), and normal distribution of T cell subsets. Their T cells have normal proliferation to mitogens but don't have response to candida antigens.

Most patients with CMCC have normal concentration of serum immunoglobulins and high titers of antibodies against *Candida albicans* and normal response to vaccines. Although many patients have only persistent and recurrent candidiasis, some patients have additional infections with other fungi, viruses and bacteria.[2] It has been suggested that most of these patients have an antibody deficiency.[3] In our patients, we have not found any antibody deficiency and so they did not develop pneumonia, sinusitis, otitis media and other serious infections; however, humoral deficiency such as IgA deficiency, decrease or absent subclasses of IgG2 and/or IgG4 have been identified in several CMCC patients with recurrent pyogenic infections.[3,10] Other immunologic defects such as neutrophil chemotaxis defect or abnormal serum complement function may predispose to bacterial infections. Neutrophil chemotaxis of case 3 was subnormal but she had not developed serious infections.

Our patients presented with typical features of CMCC at an early age and then developed endocrinopathy (Addison disease and hypopara-thyroidism) in case 3 and autoimmunity (myasthenia gravis and pernicious anemia) in case 2.

Major components of autoimmune polyendocrine syndrome (APS) include CMCC, hypoparathyroidism and Addison disease. Other associated diseases with APS include primary hypothyroidism, vitiligo, pernicious anemia, diabetes and myasthenia gravis (APS-2). The onset of disease is usually in infancy. CMCC is often the first disease detected, followed by the later development of adrenal insufficiency. The etiology and pathogenesis of many of these candida-associated disorders are unknown; but this syndrome is inherited as an autosomal recessive manner linked to mutation of the AIRE gene (AIRE: autoimmune regulator gene) on chromosome 21.[11-13]

Other complications described are hematologic, myopathic, and vasculitis, as well as stroke and a higher incidence of cancer, basically of the oral cavity, and thymoma.[14-16] Also, thymoma-associated disorders such as aplastic anemia, myasthenia gravis or hypogammaglobulinemia may be developed. In

case 2 who had CMCC with myasthenia gravis, thymoma was ruled out by chest computed tomographic scan.

The management of CMCC has been revolutionized by the use of the azole drugs Ketokonazole and Itraconazol have been successfully used in the treatment of patients, but long term treatment may be used. CMCC associated disorders need special treatment.[1]

Chronic mucocutaneous candidiasis is a group of disorders. A subgroup of patients is predisposed to development of autoimmune endocrinopathies; these patients need repeated monitoring of endocrine functions. Immunogic studies are needed to identify the extent of immunodeficiency and other abnormaities of immune functions.

REFERENCES

1. Kirkpatrick CH. Chronic mucocutaneous candidiasis In: Stiehm ER. Immunologic disorders in infants and children. Philadelphia: Saunders, 2003: 530-538.
2. Kirkpatrick CH. Chronic mucocutaneous candidiasis. Pediatr Infect Dis J 2001; 20(2):197-206.
3. Kalfa VC, Robert RL, Stiehm ER. The syndrome of chronic mucocutaneous candidiasis with selective antibody deficiency. Ann Allergy Asthma Immunol 2003; 90(2):259-64.
4. de Moraes-Vasconcelos D, Orii NM, Romano CC, Iqueoka RY, Duarte AJ. Characterization of the cellular immune function of patients with chronic mucocutaneous candidiasis. Clin Exp Immunol 2001; 123(2):247-53.
5. Myhre AG, Stray-Pedersen A, Spangen S, Eide E, Veimo D, Knappskog PM, et al. Chronic mucocutaneous candidiasis and primary hypohyroidism in two families. Eur J Pediatr 2004; 163(10):604-11
6. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunoeficiency in Iran: first report of the national registry of PID in children and adults. Clin Immunol 2002; 22(6):375-80.
7. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Movahedi M, et al. Neutropenia in Iranian patients with primary immunodeficiency disorders. Haematologica 2005; 90(4):554-6.
8. Dixon TC, Steinbach WJ, Benjamin DK Jr, Williams LW, Myers LA. Disseminated candida tropicalis in a patient with chronic mucocutaneous candidiasis. South Med J 2004; 97(8):788-90.
9. Herrod HG. Chronic mucocutaneous candidiasis in childhood and complications of non-Candida infection: a report of the Pediatric Immunodeficiency Collaborative Study Group. J Pediatr 1990; 116(3):377-82.
10. Bentur L, Nisbet-Brown E, Levison H, Roifman CM. Lung disease associated with IgG subclass deficiency in chronic mucocutaneous candidiasis. J Pediatr 1991; 118(1):82-6.
11. Eisenbarth GS, Gottlieb PA. Autoimmune polyndocrine syndromes. N Engl J Med 2004; 13,350(20):2068-79.
12. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy candidiasis ectodermaldystrophy (APECED) in a series of 68 patients. N Engl J Med 1990; 28,322(26):1829-36.
13. Perniola R, Falorni A, Clemente MG, Forini F, Accogli E, Lobreglio G. Organ-specific and non-organspecific autoantibodies in children and young adults with autoimmune polyendocrinopathy-candidiasis-ectodermal Dystrophy (APECED). Eur J Endocrinol 2000; 143(4):497-503.
14. Garcia YH, Diez SG, Aizpun LT, Oliva NP. Antigliadin antibodies associated with chronic mucocutaneous candidiasis. Pediatric Dermatol 2002; 19(5):415-8.
15. Groubi M, Dalal I, Nisbet-Brown E, Roifman M. Cerebral vasculitis associated with chronic mucocutaneous candidiasis. J Pediatr 1998; 133(4):571-4.
16. Firth NA, O'Grady JF, Reade PC. Oral squamous cell carcinoma in a young person with candidosis endocrinopathy syndrome: a case report. Int J Oral Maxillofac Surg 1997; 26(1):42-4.