Chronic Muco-cutaneous Candidiasis- A review

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Abstract :
Chronic Muco-cutaneous Candidiasis (CMCC) is a group of disorders characterized by chronic recurrent infections of skin, mucosae ,and nails due to candida albicans . The condition, though uncommon, is important because of the wide variations in clinical manifestations and the association with other diseases such as endocrinopathies , autoimmune diseases , infections, skin disorders and tumours. The condition presents an immunological puzzle as these patients have multiple, often highly variable defects in T cells, cytokines, polymorphonuclear cells, monocytes, complement, and immunoglobulins. The management remains a therapeutic challenge and involves the use of antifungals to reduce the fungal load and immunomodulatory therapy to correct the underlying immunological defect. The article reviews the current understanding of clinical, immunological and therapeutic aspects of this uncommon, but fascinating syndrome.

Introduction:

' Chronic mucocutaneous candidiasis (CMCC) ' denotes a group of disorders characterized by chronic, recurrent candidal infections of skin, mucosae ,and nails , caused by the inability of the immune system to mount defense mechanisms against candida . Patients with CMCC have highly variable clinical manifestations, immunological defects and are often associated with other manifestations such as endocrinopathies, thymomas and tumours [1]. There is no uniform acceptable classification of these disorders and they have been variously classified according to clinical manifestations, severity of disease, distribution of lesions, immunological defects, and genetic inheritance etc [1,2,3,4]. Table-1 shows the classification based on the clinical features, severity, and disease associations [1]

Clinical feature:

Most patients of CMCC have onset of symptoms in early childhood (except a subset of patients associated with thymoma and SLE, who have late onset disease) [1,2]. The initial lesions may initially present as oral lesions or as papular diaper dermatitis, followed later by skin lesions, paronychia , nail dystrophy, and vulvovaginitis . Skin lesions are wide spread over trunk, face, limbs and intertrigenous areas .The lesions may be hyperkeratotic, horn-like or may present as crusted granulomatous lesions on face, eye lids, lower lip, and anus. The author has reported a patient in whom the skin lesions resembled those of tinea versicolor [5]. The patients often have associated extensive dermatophytosis causing diagnostic confusion. In such patients, a 'trailing skin sign' has been described in the lesions of dermatophytosis, as a helpful diagnostic sign [6]. On the scalp, lesions may resemble favus and cause scarring alopecia. Nail dystrophy may resemble onychomycosis caused by dermatophytes. Rare proximal nail involvement with appearance of transverse leukonychia beneath the cuticle has been reported[7]. Oral lesions include thrush, which may often be hyperplastic. Patients with diffuse CMCC, particularly those with deficiency of IgG2 and IgG4, may have a severe disease with involvement of oesophagus [8], and bronchi [9] and meninges.[10]

Associated disorders:

A number of disorders have been reported to be associated with CMCC (table-1).

a) Infections:

20% of the patients have increased susceptibility to infections with other microorganisms such as staphylococcus, Klebsiella, Haemophilus influenza, varicella , herpes and human papilloma viruses, and dermatophytes [6,10,11]. Though the infections are usually mild, many patients have developed serious systemic infections such as disseminated tuberculosis[12], toxoplasmasis[12], pulmonary nocardiosis [13], cryptococcal meningitis[14] and histoplasmosis[15]

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b) Cutaneous diseases :
Many cutaneous diseases such as seborrheic dermatitis, aphthous ulcers, alopecia , vitiligo and icthyosis [16,17] may occur in-patients of CMCC. Ectodermal defects such as rough dry skin, brittle, coarse hair, lustreless , brittle nails[18] and enamel hypoplasia of teeth [19] have been described .

c) A number of haematological abnormalities including iron deficiency anemia[20], autoimmune hemolytic anemia[21], neutropenia, thrombocytopenia and asplenia[22] may occur. Myopathy and myasthenia gravis [23] are some of the other disorders reported in these patients.

d) Candida Endocrinopathy Syndrome (CES):
A specific subgroup of patients(table-1) have endocrinopathies such as hypothyroidism, hypoparathyroidism, hypocorticism, ovarian failure, impotence,diabetes mellitus and polyendocrinopathies. Thus CMCC may be part of candida endocrinopathy syndrome, also referred to as autoimmune polyglandular endocrine syndrome (APES , APECS) [19,22,23,24] . Two subsets of CES - an autosomal recessive variant with candidiasis , hypoparathyroidism, hypoadrenalism and the other autosomal dominant variant with candidiasis and hypoparathyroidism have been recognised [24]. Since the onset of endocrinal manifestations may occur at a much later age than candida infection, it has been suggested that all children diagnosed as having CMCC should undergo periodic investigations to rule out associated hypothyroidism and hypoparathyroidism[24]s

e) Association with neoplasms:
In another subgroup of CMCC, neoplasms such as thymomas have been reported to be common[1,25]. More recently, other neoplasms, such as squamous cell carcinoma of oral cavity have been described [26,27]. Whether these patients are at increased risk for malignancy remains to be established[1]

Immunological abnormalities :

Recognition of the underlying immunological defects in these patients has lead to the understanding of the pathogenesis of these disorders. However, there has been a surfeit of publications on the subject, with a wide variety of abnormalities being described (table-2). The defects described are variable, and in many patients, reversible after therapy. While in most patients the immunological defect is specific against candida, many patients, particularly those with early onset disease, have extensive global defects, as demonstrated by anergy to different antigens1. It is also important, while investigating any patient of CMCC, to rule out a global immunological defect such as severe combined immunodeficiency .

The central immunological defect in patients of CMCC is the inability of the cell mediated immune system to mount defence against Candida Albicans , as demonstrated by cutaneous anergy to candida antigen, poor blast transformation in response to Candida antigen, altered cytokine secretion by lymphocytes, altered T helper and T-suppressor cell functions [1,12,28,29,30,31,32]. Defective phagocytosis and killing, both in the monocytes, and polymorphonuclear cells have been described [28,30,33]. Other reported abnormalities include altered IgG subclasses[8,34], circulating antibodies and immune complexes[35], and abnormalities of complement36 . As mentioned earlier, IgG2 and IgG4 deficiency have been associated with serious systemic disease [8].Serum of patients with CMCC has been shown to be cytotoxic, thus contributing to the immune deficiency[37,38]. Various autoantibodies against nuclear antigens, smooth muscle, mitochondria, gastric parietal cell, RBCs have been described[21,23,24]. Many patients have subnormal immune response after immunization and hence all patients with CMCC should undergo B cell function studies.

Genetic transmission has been proposed for these disorders, particularly for those associated with endocrinopathy[24]. Both autosomal recessive and dominant forms of inheritance have been described. Familial clustering of cases with interstitial keratitis has been reported.[39] While there has been no specific linkage to HLA markers [40], a recent report claims significant linkage to chromosome 22.[41]

Investigation of a patient with CMCC [1,2,4] :
All patients with CMCC should have their diagnosis confirmed by simple investigations such as KOH smears and cultures for candida from different affected sites. It is particularly important to rule out associated dermatophyte infection by appropriate culture. Once the diagnosis has been confirmed, the search for underlying cause should be undertaken. Baseline investigations such as X-ray chest, periph-

eral blood smear(to rule out anemia of different types), serum iron, transferrin and ferritin to rule out iron deficiency, liver function tests for monitoring antifungal therapy are essential. Investigations to detect any associated endocrine disorder include blood sugar, calcium, phosphorus, thyroid function tests and serum cortisol levels. Various autoantibodies as mentioned above will rule out associated autoimmune diseases. Investigations for detection of underlying immunological defects have been mentioned already (table-2).

Treatment ;

Treatment strategy aims at reducing the fungal load by administration of systemic antifungals, and correcting the underlying immunodeficiency by immunomodulatory therapy (Table-3). Supportive therapy such as correction of anemia is essential. Often intravenous iron administration brings about rapid improvement [20]. Local antifungal treatments are rarely adequate. Various systemic antifungal drugs such as ketoconazole , itraconazole, fluconazole , amphotercin B , 5 flucytosine [42,43,44,45,46] have been used , both intermittently or continuously . However, this approach has serious limitations as the underlying immunological defects are not corrected and the condition usually recurs on stopping the drug. Long-term administration is associated with risk of hepatotoxicity, thus limiting the usefulness of these drugs [5]. Emergence of drug resistance with continued administration of the drugs is another important problem. Despite these limitations, these drugs, particularly the newer drugs such as fluconazole and itraconazole are extremely useful in inducing clinical remissions, while planning for immunomodulatory therapy.

Several approaches have been tried for immunomodulation (table -3). These include administration of cimetidine with zinc sulphate[47], blood or lymphocytes transfusion 48, cytokines such as transfer factor[49,50], Interleukine-2 51, transplants of thymus[52], and bone marrow [53,54] The choice of the treatment would depend on the severity of clinical manifestations and the type of underlying immunological defect. Most of the reported treatments are in isolated case reports and hence each case has to be assessed on an individual basis. Many of the drugs, such as cytokines are expensive . Others such as bone marrow transplant are justified only in patients with severe disease. A simple and inexpensive treatment, consisting of daily oral administration of a combination of cimetidine 400 mg three times and zinc sulphate 200 mg over a period of sixteen months has been reported [47]. In contrast to previous reports of the efficacy of transfer factor[49,50], it was found to be ineffective in a case-report by the author [5]. More recently, Gm-CSF, a cytokine with several immunomodulatory effects on moncytes, polymorphs and T cells has been found to be useful[5,55].

TABLE-1 ; Different syndromes of chronic mucocutaneous candidiasis

Syndrome	Inheritance	Age at onset	Lesions	Associated findings	Remarks
chronic oral candidiasis	Sporadic	Any	Oral mucosa, lips,perleche skin/nails not involved	Oesophagitis	Associated with denture stomatitis,inhaled steroids, HIV associated candidiasis
CMCC with polyendocrinopathy	AR/AD	Childhood Endocrinopathy May be delayed	Mucosae, skin,nails	Type-1(AR) hypocorticism, hypoparathyroidism Type-2(AD) hypoparathyroidim	Associated with vitiligo, alopecia, gonadal failure, hepatitis, thyroiditis, pernicious anemia diabetes mellites, malabsorption
CMCC without endocrinpathy	AR/AD	Childhood	Mucosae, skin,nails	Oesophagitis Viral infections Dermatophytosis	
Chronic localized mucocutaneous candidiasis	Sporadic	Childhood	Mucosae, skin,nails	Oesophagitis, pulmonary infections	Hyperkeratotic crusted lesions-candida granuloma
Chronic diffuse mucocutaneous candidiasis	AR	Childhood or adolescence	mucosae, skin,nails Widespread	serpigenous	Erythematous lesions
CMCC with thymoma	Sporadic	Adult	Mucosae, skin,nails	Thymoma, myasthenia gravis, aplastic anemia, neutropenia	CMCC may preceed thymoma

AR= autosomal recessive AD=autosomal dominant

Table 2 Immunological abnormalities in CMCC

Cellular immunity	Humoral immunity
a) decreased skin reactivity to candida antigen	a) Defective phagocytosis and killing in polymorphonuclear cells
b) cutaneous anergy to other antigens	b) Altered IgG subclasses-deficiency of IgG2 and IgG4
c) poor blast transformation in response to candida antigen	c) Increased IgE levels
d) altered cytokine secretion by lymphocytes	d) Circulating antibodies and immune complexes against candida antigen
e) Defective T suppressor cell function	e) Cytotoxic effect of serum to lymphocyte transformation by candida
f) Impaired generation of T helper cells.	f) Serum inhibitor of PMN chemotaxis
g) Defective phagocytosis and killing in monocytes,	g) Abnormal complement levels
	h) Autoantibodies against several tissue antigens

Table-3 Therapeutic alternatives in CMCC

1.systemic antifungals

a) Imidazole derivatives- ketoconazole, itraconazole, fluconazole
b) amphotercin B ,
c) 5 flucytosine

2.immunomodulation.

a) cimetidine with zinc sulphate
b) blood transfusion, transfusion with lymphocytes,
c) cytokines ; transfer factor, Interleukine-2,Gamma interferon,GmCSF
d) vaccination with candida vaccine
e) thymic factors
f) transplants of thymus and bone marrow

Reference:

1. Kirkpatrick C.H. : Chronic mucocutaneous candidiasis. Journal of the American Academy of Dermatology 1994;Vol.31, No.3, Part 2.S14-17.

2. Hay RJ, Roberts SOB , Mackenzie DWR. Chronic mucocutaneous candidiasis; In Rook/ Wilkinson / Ebling Textbook of dermatology; Eds Champion RH, Burton JL, Ebling FJG.1992; vol 2; chapter27; 1191-93.

3. Lehner T. Classification and clinicopathological features of candida infections of mouth;in symposium on candida infections.Eds; Winner HI, Hurly R.Baltimore . William and Wilkins/1966;119

4. Well RS,Higgs JM, McDonald A, et al: Familial Chronic mucocutaneous candidiasis.J Med Gent. 1972;302;9

5. Venkataram M, Suwaid AR, RaoKD: Efficacy of GM-CSF in Chronic mucocutaneous candidiasis; J dermatol treat;1999;10;289-292.

6. Rosen RM. Chronic mucocutaneous candidiasis with wide spread dermatophytosis the trailing skin sign. Cutis . 1996;7(2); 82-4.

7. Baran-R ;Proximal subungual Candida onychomycosis. Anunusual manifestation of chronic mucocutaneous candidosis.

Br-J-Dermatol. 1997 Aug; 137(2): 286-8

8. Bragger-C; Seger-RA; Aeppli-R; Halle-F; Hitzig-WH .IgG2/IgG4 subclass deficiency in a patient with chronic mucocutaneous candidiasis and bronchiectasis. Eur-J-Pediatr. 1989 Dec; 149(3): 168-9

9. Sakano-T; Hamasaki-T; Mori-M; Takahashi-H ;Haemophilus influenzae type D infection and IgG2 deficiency in a patient with chronic mucocutaneous candidiasis. Acta-Paediatr-Jpn. 1994 ; 36(2):220-2

10. Germain-M; Gourdeau-M; Hebert-J ;Case report: familial chronic mucocutaneous candidiasis complicated by deep candida infection. Am-J-Med-Sci.

1994 Apr; 307(4): 282-3

11. 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;116:377-82.

12. Noh-LM; Hussein-SH; Sukumaran-KD; Rose-I; Abdullah-N . Chronic mucocutaneous candidiasis with deficient CD2 (E receptor) but normal CD3 mononuclear cells.J-Clin-Lab-Immunol.1991; 35(2): 89-93

13. Seggev-JS ;Fatal pulmonary nocardiosis in a patient with chronic mucocutaneous candidiasis. J-Allergy-Clin-Immunol.1994 Aug; 94(2Pt1):259-62

14. Kauffman-CA; Shea-MJ; Frame-PT Invasive fungal infections in patients with chronic mucocutaneous candidiasis. Arch-Intern-Med. 1981 Jul; 141(8): 1076-9

15. Miller-CR; Grossmann-H ; Disseminated histoplasmosis in chronic mucocutaneous candidiasis. Pediatr-Radiol. 1993; 23(2): 104-5

16. Kirkpatrick-CH. Chronic mucocutaneous candidiasis.Eur-J-Clin-Microbiol Infect-Dis.1989; 8(5):449-56.

17. Harms M, Giardi S, Levy PM,Saurat JH. KID syndrome(keratitis, icthyosis, deafness) and chronic mucocutaneous candidiasis; a case report and review of literature. Peadiatr dermatol ;1984;2;1

18. Kalb-RE; Grossman-ME ; Ectodermal defects and chronic mucocutaneous candidiasis in idiopathic hypoparathyroidism.

J-Am-Acad-Dermatol. 1986 Aug; 15(2 Pt 2): 353-6

19. Porter-SR; Eveson-JW; Scully-C ; Enamel hypoplasia secondary to candidiasis endocrinopathy syndrome: case report. Pediatr-Dent. 1995 May-Jun; 17(3): 216-9

20. Higgs JM, Wels RS. chronic mucocutaneous candidiasis associated with abnormalities of iron metabolism.Br J Dermatol; 1972;86(suppl8)88-102

21. Oyefara-BI; Kim-HC; Danziger-RN; Carroll-M; Greene-JM; Douglas-SD

Autoimmune hemolytic anemia in chronic mucocutaneous candidiasis.

Clin-Diagn-Lab-Immunol. 1994 Jan; 1(1): 38-43

22. Parker-RI; O'Shea-P; Forman-EN Acquired splenic atrophy in a sibling with the autoimmune

polyendocrinopathy-candidiasis syndrome.

23. Evans-RA; Carter-JN; Tension-B; Smith-A; Hills-E; Walls-R; Corbett-A Candidiasis-endocrinopathy syndrome with progressive myopathy.Q-

J-Med. 1989 Feb; 70(262): 139-44

24.Coleman-R; Hay-RJ ; Chronic mucocutaneous candidosis associated with hypothyroidism: a distinct syndrome? Br-J-Dermatol. 1997 Jan; 136(1): 24-9 .

25. Kirckpatrick CH, Thomas PM, Windhorst DB. Mucocutaneous candidiasis and thymoma. Am J Med. 1979; 66;939-45.

26. Firth-NA; O'Grady-JF; Reade-PC; Oral squamous cell carcinoma in ayoung person with candidosis endocrinopathy syndrome: a case report.

Int-J-Oral-Maxillofac-Surg.1997 Feb; 26(1): 42-4

27. McGurk-M; Holmes-M Chronic muco-cutaneous candidiasis and oral neoplasia. J-Laryngol-Otol. 1988 Jul; 102(7): 643-5

28. Chilgren RA, Quie PG, Muwissen HJ, et al. Chronic mucocutaneous candidiasis, deficiency of delayed hypersensitivity, and selective local antibody defect. Lancet 1967; ii: 688-93.

29. Kirkpatrick CH, Chandler JW, Schimke RN. Chronic moniliasis with impaired delayed hypersensitivity. Clin Exp Immunol 1970;6:375-85.

30. Valdimarsson H, Higs JM, Wells RS, et al. Immune abnormalities associated with chronic mucocutaneous candidiasis.

Cell Immunol 1973;6:348-61.

31. Lehner T, Wilton JMA, Ivanyi L. Immunodeficiencies in chronic mucocutaneous candidiasis. Immunology 1972:22:775-87.

32. Arulanantham K, Dwyer JM, Genel M Evidence for defective immunoregulation in the syndrome of familial candidiasis endocrinopathy; N Engl J Med 1979 Jan 25;300(4):164-8

33.Van Scoy RE,Hill HR, Ritts RE, Quie PG. Familial neutrophil chemotaxis defect, recurrent bacterial infections, mucocutaneous candidiasis, and hyperimmunoglobulinemia E.Ann Intern Med. 1975 Jun;82(6):766-71.

34.Valdimarson H, Higgs JM, Wells RS, et al. Immune abnormalities associated with chronic mucocutaneous candidiasis.

Cell Immunol 1973;6:348-61.

35. Drew JH; Chronic mucocutaneous candidiasis with complement abnormal function of serum complement. Med J Aust. 1973;164;300

36.Lebedeva-TN;Mirzabalaeva-AK; Chernopiatova-RM et al. Specific circulating immune complexes and antibody titers in candidiasis.

Zh-Mikrobiol-Epidemiol-Immunobiol. 1992(11-12):41-2.

37.Fischer A. Ballet J-J, Griscelli C. Specific inhibition of in vitro Candida induced lymphocyte proliferation by polysaccharide antigens present in the serum of patients with chronic mucocutaneous candidiasis. J Clin Invest 1978;62:1005-13.

38.Lee WM, Holley HP, Stewart J, et al. Refractory esophageal candidiasis associated with a low molecular weight plasma inhibitor of T-lymphocyte function. Am J Med Sci 1986;292:47-52.

39. Okamoto GA, Hall JG, Ochs H et al; New syndrome of chronic mucocutaneous candidiasis. Birth defects Orig Art Ser. 1977; 13; 117-25.

40. Ahonen P, Koskimies S, Lokk ML, et al. The expression of autoimmune polyglandular disease type I appears associated with several HLA-A antigens, but not HLA-DR. J Clin Endocrinol Metab 1988;66:1152-7.

41. Aaltonen J, Komulainen J, Vikman A et al. Autoimmune polyglandular disease type-1;exclusion map using amplifiable multiallelic markers in a microtitre well format; Eur J Human Genet; 1993; 1; 164-71.

42. Corbeel-L; Ceuppens-JL; Van-den-Berghe-G et al. Immunological observations before and after successful treatment of chronic mucocutaneous candidiasis with ketoconazole and transfer factor.

Eur-J-Pediatr. 1984 Nov; 143(1):45-8.

43.Drew RH; Perfect-JR; Gallis-HA. Clin-Pharm. 1988 Aug; 7(8):622-3. Use of fluconazole in a patient with documented malabsorption of ketoconazole.

44. Burke-WA. Use of itraconazole in a patient with chronic mucocutaneous candidiasis., J. Am.Acad-Dermatol. 1989 Dec; 21(6): 1309-10.

45. Waweru-HW; Owili-DM. Chronic mucocutaneous candidiasis treated with amphotercin B. Case report. East-Afr-Med-J. 1983 Aug; 60(8):588-91

46. Lin-CY. Treatment of chronic mucocutaneous candidiasis with 5-fluorocytosine. Ann-Allergy. 1982 Nov; 49(5): 298-300.

47. Ploizzi B, Origgi L, Zuccaro G, Mati P , Scoria K. Casereport ; successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis . Am J med sci.1996; 311(4) ;189-90

48. Kirkpatrick CH, Rich RR, Graw RG, et al. Treatment of chronic mucocutaneous moniliasis by immunologic reconstitution.

Clin Exp Immunol 1971;9:733-48.

49. Miksiewicz-Wasilewska-H; Grubek-Jaworska-A et al. Transfer factor (TFd). Part IV. Transfer factor in mucocutaneous candidiasis treatment.

Mater-Med-Pol. 1981. Apr-Jun; 13(2): 108-12.

50. Kirkpatrick CH, Greenberg LE. Treatment of chronic mucocutaneous candidiasis with transfer factor. In: Kahn A, Kirkpatrick CH, Hill NO, eds. Immune regulators in transfer factor. New York: Academic Press,1979:547-62Æ

51. Sander-E; Prolla-G; Marques-AR et al. Reversal by interleukin-2 of alopecia universalis, mucocutaneous candidiasis, and sexual impotence in a patient with malignant thymoma (letter).

J-Natl-Cancer-Inst. 1993 Apr 21; 85(8):673.

52. Trevisan-G; Kokelj-F; Chronic candidiasis: treatment with bovine thymic extract. Case report. Perticarari-S et al..

G-Ital-Dermatol-Venereol. 1982 May-Jun; 117 (3): 161-4.

53.Hoh-MC; Lin-HP; Chan-LL; Lam-SK ; Successful allogeneic bone marrow transplantation in severe chronic mucocutaneous candidiasis syndrome.Bone-Marrow-Transplant. 1996 Oct; 18(4): 797-800

54. Deeg-HJ; Lum-LG; Sanders-J; Levy-GJ; Sullivan-KM; Beatty-P et al: Severe aplastic anemia associated with chronic mucocutaneous candidiasis. Immunologic and hematologic reconstitution after allogeneic bone marrow transplantation. Transplantation. 1986 May; 41(5): 583-6

54. Shahar E., Kriboy N,. Pollack S. White cell enhancement in the treatment of severe candidosis. Lancet. 1995. 346 ;23