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CHRONIC MUCOCUTANEOUS CANDIDOSIS: A REVIEW*

Iris K. ARONSON & Keyoumars SOLTANI

Section of Dermatology, Department of Medicine, The University of Chicago, and The Pritzker School of Medicine**

Clinical aspects

Chronic mucocutaneous candidosis (CMCC) is an uncommon from of candidal infection. It usually starts in early life as a limited or widespread chronic infection and involves mucous membranes, skin and nails (37).

The mucosal lesions of chronic mucocutaneous and acute candidosis are identical and consist of milk curd-like loosely adherent white patches on the oral and vaginal mucous membranes (47). The oral involvement may extend to the oropharynx and esophagus, but further visceral extension and sepsis are extremely rare.

The cutaneous lesions of CMCC are clinically distinctive and often diagnostic. Distal parts of the extremities, especially the hands, are the most common sites of skin involvement (37) and consist of asymptomatic patches which generally occur on the periorificial skin and the dorsa of the hands and feet. The lesions are characterized by their chronicity, slow peripheral expansion, brown-red color, sharp margins, loose hyperkeratosis and resistance to topical therapy (47). A clinical form called candidal granuloma features striking verrucous hyperkeratosis and cutaneous horn formation. In this form the scalp is also often affected with thick plaque-like hyperkeratotic scales (25).

Involvement of nails in CMCC is characterized by severe dystrophic nail changes with chronic swelling of the nail folds and marked thickening, distortion and fragmentation of the nail substance (37, 47). In contrast to acute candidiasis, onycholysis is not a feature of CMCC. CMCC also should not be confused with chronic candidal infections secondary to well-known factors such as diabetes mellitus, skin maceration from excessive exposure to moisture and ill-fitting dentures. Removal of such predisposing factors results in the clearing of the lesions.

There is no satisfactory classification for CMCC at the present time. In most patients CMCC is associated with one of the clearly defined genetically or congenitally determined immune deficiency syndromes. In others less well-defined immune deficiency states are strongly suspected (27, 29). Patients with CMCC who suffer from the classic severe immune deficiencies usually fail to thrive and nearly always die in early childhood (29, 37). The defective development of thymus in these cases leads to susceptibility to various infections including CMCC. In patients with Swiss type agammaglobulinemia which features defective function of both T and B cells, candidal infection may become very extensive and often is associated with oral ulcerations. Occasionally, systemic infection with renal, splenic and meningeal involvement may occur (27). Defective cell mediated immunity is believed to predispose these patients to CMCC. In B cell deficiency Bruton's type hypogammaglobulinemia which is characterized by recurrent bacterial infections without CMCC, T cell function is normal. In the Nezelof-Allibone syndrome, however, there is defective T cell function because of thymic dysplasia but no hypogammaglobulinemia and oropharyngeal candidosis does occur (27, 37). Superficial candidal infection may also occur in children with the DiGeorge syndrome. In this syndrome there is an absence of thymus and parathyroid glands because of embryonic developmental anomalies of the third and fourth branchial puches (29).

In patients with less severely disturbed immune mechanisms, CMCC which also generally begins in childhood is carried into adult life. In some cases the disorder appears to be inherited as an autosomal recessive trait. These patients all suffer from oral involvement which is not influenced by extrinsic factors or conventional anticandidal therapy (37, 75). The tongue is often enlarged and fissured.

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** Reprint requests to K. Soltani, M.D., 950 E. 59th Street, Box 409, Chicago, Illinois 60637, USA

Scraping the white coating from the mucosa leaves a shiny red eroded surface. Most patients also have bilateral angular stomatitis with significant discomfort (75). Over half of the patients have chronic paronychia and onychomycosis affecting one or more fingernails in a symmetrical distribution and without predilection for specific nails. Patients with more severely affected nails often give a history of chronic nail biting (75). Other sites of involvement include toenails, intertriginous areas, scalp, face, eyelids, pharynx and larynx. Some of these patients otherwise enjoy good general health and have no endocrine abnormalities (75). Multiple or widespread areas of cutaneous involvement occur in the more severely affected patients in whom persistent bacterial, viral and dermatophytic infections may also occur. The viral or bacterial infections may prove fatal. The severity of infections in such patients is indicative of more pronounced immunologic disturbance (75).

CMCC may also be associated with single or multiple endocrine deficiency syndromes involving parathyroids, adrenals, pancreatic islets, thyroid and ovaries. The endocrinopathy syndromes with associated CMCC can be inherited in autosomal recessive fashion (27, 28). These candidosis-endocrinopathy syndromes begin in childhood, although some components of endocrinopathy may be delayed until early adult life (27). Candidosis usually precedes the onset of endocrine disorders and starts between six months and 14 years of age (average four years). Although the interval between the appearance of candidosis and detection of endocrine disorder is usually less than a few years it has been reported to be as long as 13 years. Hypoparathyroidism precedes Addison's disease in most cases where both conditions develop (27).

Other disorders occasionally reported to be associated with CMCC-endocrinopathy syndromes include achlorhydria with or without pernicious anemia, gastrointestinal malabsorption, chronic keratoconjunctivitis, ulceration of the cornea, cataracts, dental dysplasia and cystic fibrosis (27, 37, 38). Preceding viral infections such as measles, encephalomyelitis and viral hepatitis also have been noted (27). Autopsy findings in 11 cases with both hypoparathyroidism and Addison's disease revealed absence of parathyroid glands in nine, fatty replacement in one and atrophy in another. In some cases an atrophic adrenal cortex with lymphocytic infiltration was present. In addition some lymphocytic infiltration was also occasionally found in thyroid and pancreatic tissues, in hepatic periportal areas and in the renal interstitium (27). This lymphocytic infiltration suggests a possible immunological pathogenesis.

It is clear that the associated endocrine abnormalities are not directly caused by candidal infection. Candida has never been recovered from the adrenal or parathyroid glands and systemic candidiasis has never been found in the postmortem studies of such cases. In addition endocrine disorders may occur in relatives of the patients in the absence of CMCC (27). It is noteworthy that CMCC does not develop in adults with primary and postoperative hypoparathyroidism or Addison's disease.

Circulating auto-antibodies to parathyroid, adrenal cortical, thyroid and gastric parietal cell antigens have been detected in patients with CMCC (27, 37, 78). Wuepper & Fudenberg (78) studied a patient with CMCC, keratitis, steatorrhea, Addison's disease and hypoparathyroidism. The patient was found to have circulating antibodies to adrenal cortical, thyroglobulin, thyroid cytoplasm and colon antigens as well as rheumatoid factor. Of the 28 members of this patient's family studied, eight had antibodies to colon, four to thyroglobulin or thyroid cytoplasm, four to liver, and nine had rheumatoid factor.

The detection of these auto-antibodies, although suggestive, does not prove that such endocrinopathies are immunologically mediated and there is no clear evidence that these antibodies are directly pathogenic. They may only be markers indicative of a genetic predisposition to immunological disorders or represent responses to tissue antigenic modification by viruses in patients with such genetic predisposition (78).

In other groups of patients CMCC can have a late onset. In such cases it may develop after age 35 but generally after age 50 years (75). Manifestations are usually confined to chronic oral candidosis which does not respond to conventional therapy. Patients in this late onset group belong to a heterogeneous population without traceable genetic anomalies but may be classified into the following clinical forms:

1) *Idiopathic form:* the clinical picture in this type is similar to other varieties of chronic oral candidosis except in that it is usually less severe. Patients are resistant to conventional topical therapy. The general health is good. Some may have deficiencies of iron, folates, pyridoxine or vitamin A and may improve when such deficiencies are corrected (30).

2) *Association with malignancy:* CMCC of long duration has also been reported in association with underlying neoplasms, often of an unusual type such as pancreatic islet cell carcinoma or carinomas of the oral cavity (29, 60). The skin is often involved in the syndrome of thymoma, myopathy (myasthenia gravis) and CMCC (42, 51, 61). Some patients also have a Coombs positive hemolytic anemia and thrombocytopenic purpura which suggests the likelihood of

an immunological disorder probably secondary to the thymic tumor (30).

Candidal granuloma is a rare disease entity. It begins in infancy or early childhood often as a simple oral thrush and ultimately involves three sites: the oral mucosa, the fingernails and paronychial tissues and the skin of the face and scalp. Rarely the skin of the trunk and lower extremities can also be involved. The cutaneous lesions of candidal granuloma are distinct from those in other forms of candidosis including CMCC. The lesions are highly vascular erythematous papules and plaques covered with thick yellow-brown adherent scaly crusts and are surrounded by bizarre hornlike structures which are hard, dark brown, columnar, either homogenous or lamellated, and may exceed 2 cm in length. Histologically the epidermis shows hyperkeratosis, acanthosis, papillomatosis and pseudoepitheliomatous hyperplasia. The dermis contains a dense inflammatory granulomatous infiltrate consisting of lymphocytes, plasma cells, polymorphonuclear leukocytes, histiocytes and foreign body giant cells. The inflammatory infiltrate surrounds adnexal structures and can extend to the subcutaneous tissues. The organisms are restricted to the keratotic horns and do not invade living tissue. There is a very heavy filamentous proliferation of the organism in the infected sites as contrasted with the common types of cutaneous and mucocutaneous candidosis. Predominance. of yeasts in the more mycelial elements are not readily observed in direct potassium hydroxide preparations from patients with these later forms of disease. The overwhelming number of filaments seen in preparations from candida granuloma is so unusual for a yeast infection that even experienced mycologists may doubt their candidal nature. Especially confusing is the great elongation of the filaments which resemble in appearance the 'dissociation forms' described in fungi which have grown on Sabouraud's medium for several years. If the organism is transferred to a normal person, the types of infections which can be initiated are the ordinary superficial types of candidosis which clear readily with treatment. Thus the organism in candidal granuloma is the ordinary *Candida albicans* and not some particularly virulent strain (27).

Immunologic abnormalities

Studies in patients with CMCC have revealed a spectrum of immunologic disorders. There is often no clear-cut correlation between the clinical forms of CMCC and the patterns of immunologic disturbance, and also there is apparently no single immunological denominator for this disease (72). Comprehensive investigations of host defense mechanisms including the complement system, phagocytosis, humoral and cellular immunity have been of interest and are useful parameters in defining patients with CMCC. With a few exceptions the levels of complement components are within the normal range (19, 38) and in most patients the serum levels of immunoglobulins including IgA and titers of candida agglutinins and precipitins are either normal or increased (37). The other parameters however are often marked by changes.

Chilgren et al. (12) reported two patients who demonstrated both anergy and a deficiency of parotid fluid IgA specific for *Candida albicans* while possessing normal levels of total parotid fluid IgA as well as a normal serum immunoglobulin pattern. This finding may be of importance in light of the present concept that IgA, being the predominant immunoglobulin in secretory fluids, provides the local immunological protection for mucous membranes (70).

Of eight patients with widespread candidosis studied by Lehner et al. (42), seven showed deficient salivary candida specific IgA antibodies. However, in four patients with chronic candidosis limited to the oral mucosa such specific IgA levels were increased. In Lehner's report deficient salivary candida specific IgA appeared to be more closely related to deficient cell mediated immune responses than to serum anticandidal immunoglobulin levels which were present in significant titers in patients with defective cell mediated immunity. IgA abnormalities have been linked to other conditions such as ataxia telangiectasia in which CMI is compromised (20).

Buckley et al. (6) postulated that salivary candida specific IgA deficiency may be caused by impaired transport of IgA through the gland. However, total salivary IgA levels have been found to be normal in many of these patients (14, 36). Strober et al. (68) studied a patient with chronic intestinal candidosis who had normal serum IgA levels yet lacked IgA in his secretions. Despite evidence for normal IgA synthetic capacity, the patient had greatly diminished levels of IgA in the saliva and jejunal fluid and, as estimated by ^{14}C-L-leucine incorporation, could not synthesize IgA locally at intestinal-mucosal sites. Finally, the patient had no detectable free secretory component in contrast to normal persons and to patients with IgA deficiency. These authors suggested that the basis of this disorder is probably a defect in the homing of IgA precursor cells to secretory sites or in the selective proliferation and/or differentiation of IgA producing cells at such sites.

Intradermal skin testing with candidal antigens in 10 out of 12 patients with CMCC reported by Kirkpatrick et al. (36) caused large wheal and flare reactions thus pointing to at least a partially intact humoral immunity. The presence or absence of circulating antibodies to candidal antigens appears to bear no significance in either clinical or experimental disease (58).

Defective cell mediated immunity (CMI) is the most frequently found immunological abnormality in patients with CMCC (72). The CMI abnormalities which have been described so far include deficiency in antigenic recognition and processing, defective production of lymphokines and defects in the effector cells. Lymphokines, which are mediators produced by antigen stimulated lymphocytes, have various functions which include chemotaxis, cytotoxicity, inhibition of macrophage migration and recruitment of cells into DNA synthesis (17). It is believed that the cells which divide and those which synthesize the mediators belong to two different pools of small lymphocytes (17).

From studies of cellular immunity *in vivo,* Kirkpatrick et al. have separated patients with CMCC into three categories: patients with generally defective CMI, patients in whom CMI defects are limited to responses elicited by candidal antigens, and patients in whom no cellular immune abnormalities are recognized (36, 37, 38, 39, 40).

Often lymphocytes from patients of the first category do not respond to stimulation with antigens especially candidal antigens (36, 37, 72). Occasionally there may be inability to demonstrate both antigen-induced thymidine uptake and MIF production (40, 58, 72). In other patients a dissociation of these two responses may be observed with a defect in either thymidine uptake or in the production of lymphokines such as MIF (24, 42, 70, 71). Such dissociation appears to be an important pathophysiological abnormality common to many patients with CMCC (65).

Goldberg et al. (24) and Valdimarsson et al. (71) have independently described patients with granulomatous CMCC with cutaneous anergy in whom normal MIF production was demonstrated whose lymphocytes could not incorporate thymidine upon stimulation with candidal antigens. A patient with granulomatous CMCC reported by Valdimarsson et al. (71) was unable to express delayed hypersensitivity to candidal antigen *in vivo* despite the fact that he had a normal capacity for MIF production and accumulation of macrophages at sites where either antigen or MIF were applied. They postulated that this patient had a functional defect in his monocyte-macrophage cells.

Valdimarsson et al. have also studied lymphocytes *in vitro* from patients with granulomatous CMCC. These lymphocytes transformed normally with phytohemagglutinin, a response which does not require the presence of macrophages. Such lymphocytes, however, were unable to transform in response to soluble antigens (which is probably a macrophage dependent reaction). These cells, nevertheless, could be normally activated to blastoid transformation in a mixted lymphocyte culture system in which competent macrophages were provided in the form of Mitomycin treated foreign mononuclear cells. CMCC patients studied by Valdimarsson et al. (71, 72) who were MIF deficient had macular and scaly dermatitis without skin granulomas. If MIF acts *in vivo* as a macrophage immobilizer it might explain why patients who are able to produce MIF but whose infiltrating macrophages are unable to eliminate the antigenic substances from the tissues respond by forming granulomas. For the same reason MIF deficient patients are not expected to respond to their candida infection by such excessive accumulation of macrophages around the foreign material. There is circumstantial evidence for the existence of a mutually stimulating interaction between macrophages and lymphocytes *in vivo* and thus a defect in one would result in dysfunction of the other (72).

Investigators have recently described patients with CMCC with defective chemotaxis of polymorphonuclear and mononuclear leukocytes (15, 65, 73). These patients with CMCC had in addition to CMI defects limited to candidal antigens, eczema, recurrent bacterial infections, increased levels of serum IgE and an intrinsic cellular defect in neutrophil chemotaxis.

In the case of these patients, *in vitro* studies revealed defective response of granulocytes to chemotactic stimuli. The patients' sera, however, demonstrated normal chemotactic activity and absence of inhibitors of cell migration. The relation betweem the elevated serum IgE levels and the defective granulocyte migration response to specific chemotactic factor, if any, is as yet unclear (50, 56). It has been suggested that histamine might be responsible for the deficient polymorphonuclear leukocyte chemotaxis (32). Snyderman et al. (65) described a patient with CMCC and cutaneous anergy whose monocytes migrated poorly in response to either C5a or leukocyte-derived chemotactic factor. Serum inhibitory factors were not detected in this patient. The patient's lymphocytes furthermore were unable unable to generate leukocyte-derived chemotactic factors when cultured with *Candida albicans* extracts although the same leukocytes could produce normal amounts of such when cultured with either PHA or streptolysin O.

In contrast to earlier reports, recent studies have

demonstrated that in some cases of CMCC phagocytic killing of ingested *Candida albicans* by polymorphonuclear leukocytes is decreased (5). The occurrence of candidal infections in chronic granulomatous disease of childhood is felt to be more related to the use of broad spectrum antibiotics and generalized debility than to defective killing of candidal organisms by polymorphonuclear cells (30).

In some patients whose lymphocytes demonstrate a selective lack of response to candidal antigens, a serum factor has been found which specifically depresses the reaction of normal lymphocytes to the candidal antigen (72). Such sera may also inhibit the reaction of normal lymphocytes to other antigenic stimulation (8, 55). There is no correlation between this inhibitory activity and the serum levels of agglutinins or precipitins. When non-reactive lymphocytes from such patients were thoroughly washed and subsequently cultured with homologous serum their responsiveness to candidal antigen could be partially restored (72).

Specific inhibitory effects of serum in CMI have been described in histoplasmosis, tuberculosis and chronic dermatophytic infections (26, 53, 74). Nonspecific serum inhibitory factors of CMI have been found in secondary syphilis, ataxia telangiectasia, multiple sclerosis, sarcoidosis, carcinomas, leprosy, hepatitis, and pregnancy (4, 23, 32, 41, 44, 49, 54, 63, 76). Such serum inhibitory factors have been reported to appear and disappear in some patients with time and the clinical status of the individuals. The significance of such variations is difficult to interpret (22, 55, 72). Lymphocyte transformation was reported to be most depressed by serum inhibitory factor in some patients with recurrent carcinoma of the breast, while such transformation was normal in patients who remained free from recurrence of tumors after treatment. This may suggest that the phenomenon is of secondary rather than of primary importance (72, 76).

The nature of serum inhibitory factor varies in different cases. It has been reported to be antigen-antibody complex, circulating antigen, circulating antibody, peptides and other small molecules. Serum inhibitory factor may function by inhibiting the reactivity of lymphocytes or by stimulating suppressor cells (2, 3, 16, 23, 67). It is yet to be determined whether such serum inhibitory effects are primary or secondary to CMCC. Other circulating factors such as transferrin and clumping factor have also exhibited *in vito* anticandidal activity (12, 19).

Zinc deficiency

Acrodermatitis enteropathica, probably an autosomal recessive disease, occurs in infants and young children and may extend into adulthood. It is characterized by a triad of dermatitis, diarrhea and alopecia which classically appear at weaning. The initial skin lesions are small vesiculobullae which become pustular, crusted, and coalesce to form plaques surrounded by an erythematous skin. These lesions are symmetrically distributed about the mouth, nose, eyes, scalp, elbows, knees and on the hands and feet, especially the paronychial areas. This pattern of distribution of lesions around body orifices and distal parts of the extremities is characteristic of acrodermatitis enteropathica. Most lesions are superinfected with *Candida albicans* (31). Recently, acrodermatitis enteropathica has been found to be a zinc deficiency disorder (52). Serum zinc levels have been found to be low in relatives of patients with acrodermatitis enteropathica. Similar syndromes found in animal models, namely cows, have the characteristic skin lesions and also hypoplasia of the thymus, lymph nodes, Peyer's patches and spleen. When these cows are given oral zinc the condition disappears with restoration of normal immunological responses (1). Candidosis in acrodermatitis enteropathica might be speculated to be secondary to metabolic impairment of the epidermis which might allow easier colonization of the skin by candida species (33). Zinc deficiency has not yet been studied in CMCC, but because of increasing evidence that CMCC in many patients may be secondary to nutritionally related abnormalities of CMI it may be an important avenue to investigate.

Iron deficiency

The role of iron deficieny, if any, in the pathogenesis of CMCC has yet to be clarified. Some iron deficient patients with negative skin tests to candidal antigen develop a positive delayed hypersensitivity reaction to this antigen following iron therapy (28). In some patients with candidosis who do not respond to nystatin alone, the addition of oral iron preparations may prove helpful (28). A two year course of iron and folic acid in a patient with late onset of CMCC who had iron and folate deficiency resulted in complete clearing of lesions. Six weeks after discontinuing her iron therapy CMCC with angular cheilitis recurred. A second course of iron therapy resulted in the complete clearing of oral lesions, although the serum iron levels remained low in the presence of normal hemoglobin levels and normal iron uptake (28, 29).

Of the 31 patients with CMCC studied by Higgs & Wells, 23 showed evidence of overt or latent iron deficiency. Of the 11 patients who were treated with oral or parenteral iron preparations, nine showed significant improvement of oral and skin lesions, and swab preparations stopped yielding heavy candida growth.

The importance of iron for maintaining tissue integrity has been appreciated for some time. A low plasma and cellular iron concentration might impair synthesis of iron-containing enzymes and this may slow cell proliferation. Wear and tear, which is heavy in epithelial tissues, might then cause epithelial impairment (59). There may be underlying predisposing structural and biochemical abnormalities in the epithelium of patients who develop candidosis secondary to iron deficiency, because there are many iron deficient patients who do not develop CMCC (28).

In vitro studies of lymphocyte response to soluble antigens (candida, PPD) and to the mitogen (PHA) as well as the phagocytosis and killing by polymorphonuclear leukocytes have been reported to be impaired in iron deficient patients according to some investigators (10, 34, 35, 45). It should be mentioned, however, that some recent reports have challenged the former views and have indicated that the resistance to infections may be higher in iron deficient anemic patients than in the comparably anemic patients (48). It has even been demonstrated that unsaturated iron binding protein (transferrin) has a candidacidal effect. The administration of iron could possibly diminish this activity (9, 19). Long standing candidosis associated with iron deficiency may be an early sign of underlying malignancy, often of unusual type such as pancreatic islet cell carcinoma (28).

Treatment

Lesions of CMCC are generally resistant to conventional anticandidal therapeutic modalities. Identification of the specific immunological disturbance in each patient can be important for devising appropriate therapy in CMCC (38). Several approaches have been explored for correcting some of the underlying immunological defects. A few attempts have been made with modest success to achieve immunological reconstitution by administrating HL-A compatible marrow cells (6) or by fetal thymus grafts. Graft versus host (GVH) reaction can be a serious risk with these modalities. Transfusion of normal lymphocytes also has been attempted by several groups with variable results. While some investigators have observed some success (37, 38), others have experienced partial or complete failure with such infusions (14). GVH reaction might also be a hazard in patients for whom HL-A matched leukocytes from healthy siblings are not available. Transfer factor has, therefore, been preferred in attempts at immunological reconstitution. Sixty percent of patients with CMCC treated with transfer factor have shown some clinical improvement and also normalization of laboratory parameters of CMI (46). Such improvements have been of relatively short duration and have been followed by relapses (66). The rate of success seems to be increased when transfer factor is used in combination with anticandidal chemotherapeutic agents such as amphotericin-B, 5-fluocytosine and clotrimazole (43, 39, 62). Reduction of a possibly tolerogenic load of antigen by systemic chemotherapy may permit the immune system to express an adequate CMI response (40). As a supplementary measure to chemotherapy and immunotherapy some have tried to remove reservoirs of organisms by avulsing affected nails and by the use of topical anticandidal preparations. General supportive therapy and the correction of nutritional deficiencies should be included in the treatment planning of the patients.

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