Chronic mucocutaneous candidiasis – an immunological mystery

Arthur R Rabson

Chronic mucocutaneous candidiasis (CMC) refers to a group of disorders which have in common recurrent and persistent infections of the skin, nails and mucous membranes by *Candida albicans* and occasionally other candida species. A proportion of these patients show an associated endocrinopathy as part of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome. Many cases, however, are not associated with endocrinopathy and demonstrate a variety of T-cell or antigen-presenting cell defects leading to abnormal cell-mediated responses to *C. albicans*.

Chronic mucocutaneous candidiasis (CMC) is a heterogeneous group of disorders characterised by a selective inability to clear candida organisms and occasionally dermatophytic fungi, especially *Trichophyton* and *Microsporum*. This results in debilitating, refractory and persistent mucocutaneous infections affecting the skin, mucous membranes and nails. The cutaneous lesions often present as thick crusts on the scalp and face and some patients may have cutaneous horn formation. On biopsy these skin lesions show infiltration by lymphocytes, plasma cells and giant cells and for this reason have been called candida granulomas (Fig. 1).[1] Patients rarely develop sepsis or life-threatening candida infection, suggesting that there is not a generalised immune deficiency but rather a defect in the specific anti-candida T-cell response. A variety of these defects have now been described, some of which are associated with endocrinopathies or autoimmune diseases such as hypothyroidism and hypoparathyroidism.

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)

This rare disease goes by a variety of other names including autoimmune polyglandular syndrome (APS), polyglandular autoimmune syndrome (PGA) and autoimmune polyendocrinopathy syndrome. Although APECED is generally rare, it is more frequent in certain populations: the Finnish,

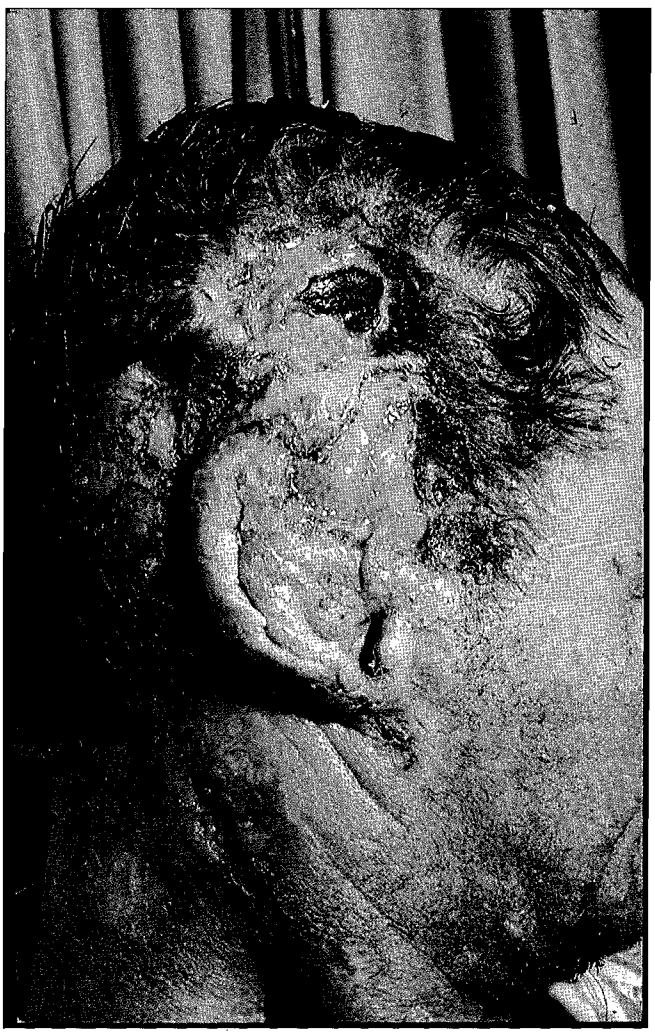

Fig. 1. A patient diagnosed by Professor Koornhof with a severe granulomatous form of chronic mucocutaneous candidiasis. The large lesion on the side of the face contained large numbers of Candida albicans *and a very marked granulomatous reaction.*

Iranian Jews, and Sardinians. It appears early in life, typically in infants presenting with persistent candidal infection (Fig. 2). This form of candidiasis is associated with a variety of autoimmune disorders including hypoparathyroidism, alopecia areata, vitiligo, adrenal insufficiency and pernicious anaemia. Autoimmune disorders may continue to appear throughout the life of these patients and type 1 diabetes will appear in about 18% of them.[2] Typically, the patients display a variety of autoantibodies against intracellular key enzymes present in the affected organs.[3] The disease, which is a rare autosomal recessive disorder, is caused by mutations in the

Professor of Pathology, Tufts-New England Medical Center, Boston, USA
Arthur R Rabson, MB BCh, FRCPath

Corresponding author: *A Rabson (Arabson@tufts-nemc.org)*

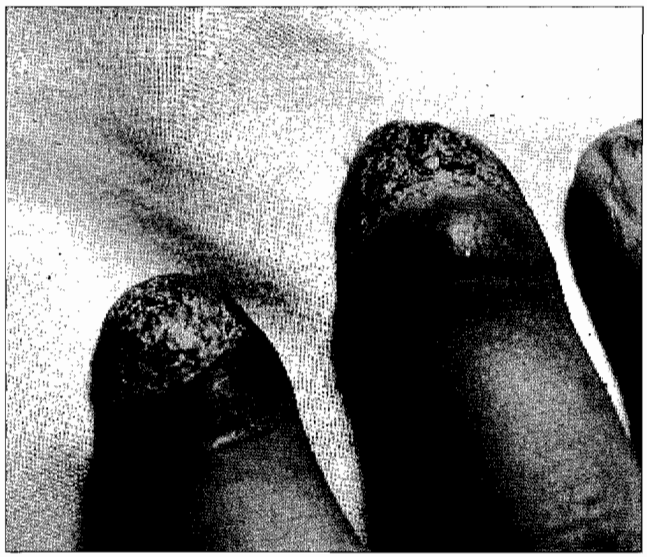

Fig. 2. Candida infection of the nails in a child with the APECED syndrome.

autoimmune regulator gene (AIRE) that has been mapped to chromosome region 21q22.3. The gene encodes a protein with the characteristics of a transcription factor and is expressed in various tissues, including the thymus and the lymph nodes.

AIRE normally plays a role in the thymus in regulating expression of a subset of autoantigens derived from peripheral tissues. Normally, potentially autoaggressive T-cells that recognise these antigens are deleted, but they are presumed to escape to the periphery in patients with AIRE mutations leading to autoimmune attack on selected organs. AIRE is also expressed in peripheral dendritic cells and is thought to be involved in the maintenance of peripheral immunological tolerance.[4] Recently,[5] it has been shown that AIRE-deficient patients show reduced regulatory T-cell (TREG) activity. The CD4+CD25+ cells show decreased function in these patients and this could account for their lack of self-tolerance and the development of autoimmune disease. How mutations of this gene lead to susceptibility to candida organisms is unclear, but the infection is difficult to treat and has resulted in oral or oesophageal squamous carcinoma in 10% of patients.[6] Of particular interest is the observation that most of these patients have high-titre IgG auto-antibodies against interferon-alpha and especially against its subtype interferon-omega.[7] Many of the patients also have antibodies to interferon-beta. These antibodies are neutralising in nature and may offer some clues to the susceptibility to candida and other fungal organisms.[7]

Chronic mucocutaneous candidiasis is associated with various immunological defects

Protection against systemic disseminated candida infection relies on antibodies interacting with neutrophils, hence the observation that invasion is usually seen in patients on immunosuppressive or cytotoxic therapy. Protection against mucocutaneous candidiasis, however, depends on cell-mediated immunity, hence its occurrence in patients with AIDS or severe combined immunodeficiency. It is not surprising therefore that numerous reports have documented abnormal T-lymphocyte function in patients with CMC and a variety of defects have been described mainly related to deficient cytokine production. In a detailed study of 24 CMC patients Lilic *et al.*[8] showed that some CMC patients have abnormal cytokine production specifically against candida antigen, whereas others fail to produce certain cytokines when their lymphocytes are activated even by non-candida antigens. Most of the patients have impaired cytokine production by the TH1 cell population and this includes IL-12, IL-2 and IFNγ. This impairment was more general in nature although it was most pronounced in response to candida antigens. In a study of 7 CMC patients, Van der Graaf *et al.*[9] demonstrated decreased IFNγ production when whole blood was stimulated with *C. albicans* antigens. This was associated with an increase in the IL-10 production.

IL-12 is a key cytokine in the activation of TH1 cells and the subsequent production of IFNγ, an important activator of macrophages and dendritic cells. The IL-12 and IFNγ signalling pathways are therefore crucial for the intracellular microbicidal function of cell-mediated immunity. In a mouse candida model IFNγ was shown to be important for development of IL-12-dependent protective TH1 responses to candida.[10] In those studies mice deficient in IFNγ receptors failed to mount protective TH1-mediated immunity to candida. A group of patients with inborn deficiencies of the receptors for IFNγ and IL-12 have been shown to be susceptible to infection with atypical mycobacteria but some also had persistent candidiasis.[10] Most patients with CMC, however, show normal cytokine receptor expression for both IFNγ and IL-12 receptors.[11] This eliminates the possibility that the defect in CMC might be due to impaired binding of cytokine.

Concomitant with the decreased production of TH1-type cytokines, Lilic and Gravenor[12] have demonstrated increased production of inflammatory cytokines including tumour necrosis factor (TNFα) and IL-6 as well as significant increases in IL-10. They suggest that these high IL-10 levels could lead to down-regulation of the TH1 cells which would explain the low levels of IL-12 and IFNγ in these patients.

It is unclear whether the defect in CMC is at the level of the T-cell or the antigen-presenting cell. It is unlikely that the TH1 defect is due to increased production of TH2 cytokines as it has been shown that there is no overproduction of IL-4 and IL-10 in CMC.[13] T-cells in these patients usually respond to nonspecific mitogens and other non-candida antigens suggesting that the defect probably involves the accessory cells. It is possible therefore that macrophages or dendritic cells may have defective candida antigen-presenting ability

or may have defective cytokine production. Romani *et al.*[14] have shown that dendritic cells using mannose receptors to phagocytose candida, activate type-1 cytokine responses from T-cells. However, if the organisms gained entrance through the dendritic cell's Fcγ receptor this led to the onset of type-2 responses with associated pathology in experimental animals. It is possible therefore that the organism and the dendritic cell share the responsibility for pathogenicity of *C. albicans*.

Familial chronic nail candidiasis associated with ICAM-1 deficiency

Zuccarello *et al.*[15] described a rare and unique Sicilian family with candidiasis affecting only the nails of the hands and the feet. This family included 11 affected subjects in five generations, all of whom had low serum levels of intercellular adhesion molecule-1 (ICAM-1). This is a glycoprotein adhesion molecule which plays a central role in cell-to-cell interactions especially in T-cell activation and in leucocyte recruitment. Of particular interest in this family was the restriction of the disease to nails only, and the neonatal onset of the disorder.

Chronic mucocutaneous candidiasis and thyroid disease

Patients with CMC have a high incidence of endocrinopathies usually associated with APECED (see above). Such patients typically develop hypoparathyroidism and adrenal failure and thyroid disease is not a major feature. Atkinson *et al.*[16] have described a large family with an autosomal dominant form of CMC associated with hypothyroidism and with a gene defect localised to chromosome 2p. Interestingly in this family the most consistent immunological feature was a depressed serum IgM concentration, although there were also significant aberrant T-cell responses.

Chronic mucocutaneous candidiasis with selective antibody deficiency

Most patients with CMC have a selective defect of cell-mediated immunity. Kalfa *et al.*,[17] however, have identified 9 CMC patients with selective antibody deficiencies and bacterial infections. IgG2 deficiency was present in all these patients and was associated with IgG4 and IgA deficiency in a number of them.

Conclusions

A significant subgroup of CMC patients will develop a variety of autoimmune endocrinopathies as part of APECED due to a mutation of the AIRE gene. The reason for the chronic candidiasis and its relationship to the endocrinopathies in these patients is unclear.

Most CMC patients show abnormal T-cell function, especially deficient production of TH1-type cytokines including IFNγ, which is an important macrophage and dendritic cell-activating factor. It is unclear if the defect is primarily a T-cell aberration or if it is due to an antigen-presenting cell abnormality. It is becoming clear that innate immune mechanisms play a significant role in protection against candidiasis and there appears to be an essential requirement for the IL-1R-dependent pathway.[18] It is possible that abnormal innate immune reactions to a candida infection might result in aberrant activation of T-regulatory cells negatively affecting TH1 cell function. These areas of cell-mediated immunity need to be explored in patients with CMC before significant therapeutic progress will be made in this disease.

References

1. Kirkpatrick C, Hill H. Chronic mucocutaneous candidiasis: Immunology for the pediatrician. *Pediatr Infect Dis J* 2001; 20: 197-206.
2. Eisenbarth GS, Gottlieb, PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004; 350: 2068-2079.
3. Wolff AS, Erichsen MM, Meager A, *et al.* Autoimmune polyendocrine syndrome type 1 in Norway: phenotypic variation, autoantibodies, and novel mutations in the autoimmune regulator gene. *J Clin Endocrinol Metab* 2007; 92: 595-603.
4. Anderson MS, Venanzi ES, Klein L, *et al.* Projection of an immunological self shadow within the thymus by the Aire protein. *Science* 2002; 298: 1395-1401.
5. Kekalainen E, Tuovinen H, Joensuu J, *et al.* A defect of regulatory T cells in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Immunol* 2007; 178: 1208-1215.
6. Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006; 91: 2843-2850.
7. Meager A, Visvalingam K, Peterson P, *et al.* Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med* 2006; 3: e289.
8. Lilic D, Gravenor I, Robson N, *et al.* Deregulated production of protective cytokines in response to *Candida albicans* infection in patients with chronic mucocutaneous candidiasis. *Infect Immun* 2003; 71: 5690-5699.
9. Van der Graaf CAA, Netea MG, Drenth JPH, *et al.* Candida-specific interferon-γ deficiency and Toll-like receptor polymorphisms in patients with chronic mucocutaneous candidiasis. *Neth J Med* 2003; 61: 365-369.
10. Cenci E, Mencacci A, Del Sero G, *et al.* IFN- γ is required for IL-12 responsiveness in mice with *Candida albicans* infection. *J Immunol* 1998; 161: 3543-3550.
11. Ottenhoff HM, Kumararatne D, Casanova JL. Novel human immunodeficiencies reveal the essential role of type-1 cytokines in immunity to intracellular bacteria. *Immunology Today* 1998; 19: 491-494.
12. Lilic D, Gravenor I. Immunology of chronic mucocutaneous candidiasis. *J Clin Pathol* 2001; 54: 81-83.
13. De Moraes-Vasconcelos D, Orii NM, Romano CC, *et al.* Characterization of the cellular immune function of patients with chronic mucocutaneous candidiasis. *Clin Exp Immunol* 2001; 123: 247-253.
14. Romani L, Montagnoli C, Bozza S, *et al.* The exploitation of distinct recognition receptors in dendritic cells determines the full range of host immune relationships with *Candida albicans*. *International Immunology* 2004; 16: 149-161.
15. Zuccarello D, Salpietro DC, Gangemi S, *et al.* Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis. *J Med Genet* 2002; 39: 671-675.
16. Atkinson TP, Schaffer AA, Grimbacher B, *et al.* An immune defect causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. *Am J Hum Genet* 2001; 69: 791-803.
17. Kalfa VC, Roberts RL, Stiehm ER. The syndrome of chronic mucocutaneous candidiasis with selective antibody deficiency. *Ann Allergy Asthma Immunol* 2003; 90: 259-264.
18. Romani L. Immunity to fungal infections. *Nat Rev Immunol* 2004; 4: 11-24.