Occasional Survey

CANDIDA AND AIDS: EVIDENCE FOR PROTECTIVE ANTIBODY

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Summary Clinical observation and animal models of candidosis suggest that, although T lymphocytes are important in preventing superficial candidosis, defence against systemic candidosis depends upon humoral immunity. An antibody response to the immunodominant 47 kD antigen of *Candida albicans* is invariably associated with recovery. The presence of this antibody in patients with chronic mucocutaneous candidosis and the acquired immunodeficiency syndrome (AIDS) could account for the rarity of disseminated candidal infection in these conditions. Polyclonal B cell activation may be responsible for the frequency with which this antibody is produced in AIDS. Antibody to the 47 kD antigen could be useful in the treatment and prevention of systemic candidosis, though not in the superficial candidosis of AIDS.

INTRODUCTION

ORAL and oesophageal candidosis are common in patients with the acquired immunodeficiency syndrome (AIDS), but disseminated infection is rare despite the presence of a severe, progressive immunodeficiency.[1,2] In contrast, systemic candidosis is an increasingly common cause of death amongst non-AIDS immunocompromised and debilitated patients, with a mortality of over 70%.[3] We argue here that AIDS patients are protected by antibody and that antibody to a 47 kD component of *Candida albicans* is particularly important.

CLINICAL OBSERVATIONS

Chronic Mucocutaneous Candidosis

This heterogeneous group of patients have protracted candidal infections of the mouth, nails, skin, and vagina. Investigation into their immunological status led to the belief that T lymphocytes are important in defence against candida since most of them have subtle, non-lethal defects in T lymphocytes and macrophages.[4] Some have selective antibody deficiencies, particularly in secretory IgA, but serum antibodies to candida are usually high.[5] These patients are no more susceptible to life-threatening systemic candidosis than immunocompetent individuals.

Primary Immunodeficiency States

Oral thrush is a common complication of severe primary immunodeficiency syndromes affecting T lymphocytes, such as Di George syndrome[6] and Glanzmann-Riniker syndrome.[7] In contrast, both oral and systemic candidosis occur in Swiss type agammaglobulinaemia, a variant of hereditary thymic dysplasia with defects in both immunoglobulin production and cell-mediated immunity.[8]

Systemic Candidosis

Systemic candidosis occurs in two different high-risk groups.[9,10] The first consists of patients rendered neutropenic by cytotoxic chemotherapy or their underlying disease. In vitro, neutrophils ingest and kill yeasts and small hyphae or use an extracellular killing mechanism against hyphae too large for phagocytosis.[11] In the second group, systemic candidosis follows one or more of a variety of predisposing factors including major bowel surgery, broad spectrum antibiotics, and urinary or vascular catheterisation. These patients are not neutropenic so that a deficiency in a different part of the host's immune system must be responsible for the development of systemic candidosis. Moreover, mortality from candidosis is similar in the two groups. Mortality correlates with the ability to produce antibody against *C albicans*, being lowest (47%) in patients producing both IgG and IgM and highest (100%) in those with no antibody response.[10] Before the advent of amphotericin B, Hiatt and Martin[12] reported the recovery of a patient with pulmonary candidosis after treatment with hyperimmune rabbit antiserum to *C albicans*.

AIDS

Oral thrush is often the initial manifestation of the syndrome[13] and oesophageal candidosis is a diagnostic criterion of "full-blown" AIDS.[14] Candidal enteritis has been described[15] but dissemination beyond the gastrointestinal tract is unusual. There have been occasional reports of pulmonary candidosis and brain abscesses,[16,17] but widespread visceral candidosis is much less frequent than in immunosuppressed non-AIDS patients.[1]

The above clinical observations suggest that in AIDS patients cell-mediated immunodeficiency is responsible for superficial candidosis whilst the host's humoral immunity protects against systemic invasion.

SEROLOGICAL STUDIES

Chronic Mucocutaneous Candidosis

When the immunoblot technique was applied to sera from three patients with chronic mucocutaneous candidosis a major IgM or IgA antibody response to the 47 kD component of *C albicans* was observed.[18]

Systemic Candidosis

When antibody responses were examined serially in patients with systemic candidosis, all survivors produced a major response to the 47 kD component of *C albicans* whereas in fatal cases there was little response, no response, or a fading response.[9] The 47 kD antigen was immunodominant, 74% of patients having antibody to this antigen compared with 32% having antibody to the second most commonly recognised antigen, of 60 kD. Neutropenic patients as a group differed from other patients with systemic candidosis in that they produced, in 45% of cases, a mainly IgM response. Those who showed this pattern did not have a lower survival rate than patients producing mainly IgG.[10]

HIV Infected Patients

Immunoblotting was used to examine the candidal serology of 75 HIV infected patients, 38 having AIDS, 26

PERCENTAGE OF HIV INFECTED PATIENTS WITH ANTIBODY TO THE 47 KD ANTIGEN

Clinical status (No of patients)	IgM	IgA	IgG
AIDS			
Oesophageal candidosis (12)	100%	92%	84%
Oral thrush (22)	100%	100%	59%
No candida clinically (4)	100%	100%	50%
ARC			
Oral thrush (20)	95%	90%	50%
No candida clinically (6)	67%	67%	33%
HIV+			
Lymphadenopathy (6)	50%	50%	33%
No lymphadenopathy (5)	40%	60%	20%

having the AIDS-related complex (ARC), and 11 being free of clinical signs apart from lymphadenopathy (6 patients). The diagnostic criteria for AIDS were those recommended by the Centers for Disease Control—namely, the occurrence of Kaposi's sarcoma or a severe opportunistic infection indicative of an unexplained deficiency in cell-mediated immunity.[14,19] A distinction was made between symptomless HIV antibody positive individuals, with or without lymphadenopathy, and patients with clinical features indicative of ARC, including unexplained fever, fatigue, weight loss, night sweats, oral thrush, and diarrhoea.[19] We also examined sera from one patient with AIDS who died of pulmonary candidosis. *C albicans* was cultured from a lung abscess biopsy specimen just before death from respiratory failure. There was no evidence of other respiratory opportunistic infections; permission for necropsy was declined.

The AIDS patient who died from pulmonary candidosis had no antibody to the 47 kD antigen except for some low titre IgA. All the other AIDS patients had IgM to the 47 kD antigen and all but one had IgA to the 47 kD antigen (see table). These antibodies occurred independently of whether they had oesophageal or oral candidosis or no clinical evidence of candida, although titres tended to be higher in patients with symptoms. AIDS patients with oesophageal candidosis were more likely to have IgG to the 47 kD antigen. The second most commonly produced antibody was IgM to a 50 kD band (45%) and less than a third had other candidal antibodies.

20 of 26 patients with ARC had oral candidosis and 19 of these had IgM to the 47 kD antigen, 18 had IgA, and 10 had IgG. The prevalence of these antibodies in ARC patients with no clinical history of candidosis was lower but IgM and IgA were still present in the majority (67%). Of the 11 well patients with HIV antibody, about half had IgM and IgA to the 47 kD antigen and under a third had IgG. The second most commonly produced antibody in ARC patients (56%) and symptomless HIV antibody positive patients (36%) was to the 60 kD antigen.

Prevalence of antibodies to the 47 kD antigen is much less in non-AIDS patients with superficial candidosis. The antibody is present in 30% of neutropenic patients with severe oral or oesophageal candidosis and 38% of superficially infected surgical patients.[10] The antibody occurs in less than 5% of hospital inpatients with no clinical or laboratory evidence of candidosis.

DNA FINGERPRINTING OF CANDIDA

We investigated the possibility that the rarity of systemic candidosis in AIDS patients was due to cross-infection with strains of *C albicans* that were less invasive than the strains causing systemic candidosis. We applied DNA fingerprinting[20] and immunoblot fingerprinting[21] to 51 isolates of *C albicans* cultured from the throats of patients with AIDS or ARC. 61% of isolates, including two strains kindly supplied by Dr Lowell Young from San Francisco, typed the same as the strain responsible for outbreaks of systemic candidosis in two London teaching hospitals.[22] There was therefore no evidence that the strains of *C albicans* responsible for oral and oesophageal candidosis in AIDS and ARC patients were incapable of systemic invasion.

ANIMAL EXPERIMENTS

Evidence from animal models of systemic candidosis suggests that humoral immunity is more important than cell-mediated immunity in protection against disseminated infections. Congenitally athymic (nude) mice were more resistant to intravenous *C albicans* than their phenotypically normal littermates[23,24] and their susceptibility increased when they were reconstituted with a syngeneic thymus graft. This may be due to reconstitution of T lymphocyte suppressor activity. Similarly, thymectomised, irradiated, and bone-marrow-reconstituted mice were no more susceptible than normal (euthymic) mice to disseminated candidosis.[25] The injection of non-immune mice with serum from hyperimmune vaccinated mice conferred resistance to candida,[26,27] whereas transfer of immune lymphocytes conferred cutaneous delayed hypersensitivity to candida but no protection.[27] Resistance was greater in mice passively immunised with immune serum than mice injected with normal serum. Serum from a baboon that died from candidosis conferred passive immunity to other baboons such that they became resistant to intravenous challenge with a lethal dose of *C albicans*.[28]

We found that in mice passively immunised with a single injection of rabbit hyperimmune serum to *C albicans* candidal peritonitis was less severe than in mice immunised with control antibodies (unpublished observations). Immunoblotting showed that all the mice produced antibody to the 47 kD component of *C albicans* as they recovered. The rabbit serum, which could be distinguished from the murine antibody response by probing with a species-specific labelled second antibody, was a potent source of antibody to the 47 kD antigen.

THE 47 kD ANTIGEN

We have isolated the 47 kD antigen from the sera of patients with systemic candidosis[10] and have developed a serodiagnostic test based on detection of this antigen.[29] Immunodominant antigens with similar molecular weights have been described by Strockbine et al[30] (44–52 kD), Greenfield and Jones[31] (48·9–59·7), and Au-Young and coworkers[32] (45), and circulating immune complexes containing the 47 kD antigen have been isolated by Neale et al.[33] The 47 kD antigen is present in both the yeast and the mycelial phases of *C albicans* and is conserved between different strains; it is not detectable in other yeast species.[34]

INTERPRETATION

The evidence from animal models that humoral immunity rather than cellular immunity protects against disseminated candidosis supports the clinical observation that T lymphocyte abnormalities do not predispose to systemic candidosis. In systemic *C albicans* infections, only those patients maintaining a good antibody response to the

immunodominant 47 kD antigen survive. Neutropenic patients recover even when they produce only an IgM response to the 47 kD antigen, the failure to switch to IgG presumably being due to the lack of T cell help.[35] We conclude that both IgG and IgM to the 47 kD antigen can be protective.

The universal presence of IgM to the 47 kD antigen in AIDS patients, with the notable exception of the patient who died from pulmonary candidosis, suggests this antibody is responsible for the rarity of dissemination beyond the gastrointestinal tract in these patients. The much lower prevalence of this antibody in non-AIDS immunocompromised patients would account for their susceptibility to disseminated infections.

MODEL FOR CANDIDOSIS IN AIDS

In AIDS, a deficiency of T4 "helper" lymphocytes results from the presence of the C4 antigen, which acts as the cellular receptor for HIV.[36,37] In the early stages of HIV infection, the depression in T4 lymphocytes is due exclusively to a reduction in the Leu 8 + subset, which is not primarily involved in helper function for B cells.[38] The numerically small Leu 8 − subset provides most of the help for immunoglobulin production. Therefore humoral immunity remains functional early on in the course of HIV infections. Hypergammaglobulinaemia is a feature at this stage, and is probably due to polyclonal B cell activation by HIV, or by Epstein-Barr Virus (EBV), or to chronic antigen-stimulation; the effect in healthy homosexuals[39] is a raised IgM, and in ARC patients a raised IgG and IgA.[2] Immunoglobulin levels generally fall with the development of full-blown AIDS, IgA being the exception. Could the polyclonal B cell activation in HIV infection, exemplified by raised antiviral antibody titres, hypergammaglobulinaemia, and follicular B cell hyperplasia, account for the occurrence of candidal antibodies in AIDS patients?

Colonisation with *C albicans*, present in most people, does not cause detectable antibody to the 47 kD antigen. Even in patients with symptomatic superficial candidal infections this antibody occurs in only a minority of cases. It is therefore uncertain whether or not memory B cells to the 47 kD antigen commonly exist. The high incidence of IgM to the 47 kD antigen in ARC patients with oral thrush (95%) and even in ARC patients with no clinical history of candidosis (67%) indicates exposure to the 47 kD antigen. Perhaps the explanation is these patients' deficiency of cell-mediated immunity, which would normally inhibit superficial candidal infections and so prevent activation of B lymphocytes by the 47 kD antigen. Humoral immunity being largely intact (although lack of T cell help may prevent seroconversion to IgG), this would lead to the development of memory B cells to the 47 kD antigen. The serological responses in ARC and well HIV infected patients are similar to those of patients with systemic candidosis, in that the second most commonly produced antibody is to the 60 kD antigen. Their antibody response to *C albicans* may therefore be near normal. By contrast, in patients with full-blown AIDS humoral immunity is abnormal and the ability to mount an antibody response to new antigens is decreased.[40] These patients now have memory B lymphocytes capable of producing antibody to the 47 kD antigen, and activation of these cells, by HIV or EBV or by chronic candidal stimulation, would result in generation of IgM to the 47 kD antigen and protect them against systemic infection. Some AIDS patients can produce IgG; others cannot do so owing to lack of T cell help. Despite the frequent occurrence of serum IgA the patient is unable to eradicate oral or oesophageal candida. Apart from the cell-mediated immunodeficiency, lack of secretory IgA may be a contributory cause since IgA plasma cells are reduced in the intestinal mucous membrane in AIDS.[41] As a result, the AIDS patient's immune system becomes chronically overstimulated by a high antigenic load and this may contribute to the host's inability to eliminate other infectious agents.[40] Both mannan[42] and a cell wall glycoprotein of *C albicans*[43] can suppress the cellular immune response, so candidosis may itself aggravate a pre-existing T lymphocyte deficiency. It is possible that candida may act as a cofactor in the development of overt AIDS in HIV infected individuals. Klein et al[13] found that AIDS developed significantly more often in high-risk patients with unexplained oral thrush (13 of 22 patients) than in ARC patients without candidosis (0 of 20).

CLINICAL IMPLICATIONS

These arguments lead us to the view that antibody to the 47 kD antigen has therapeutic potential in the treatment and prevention of systemic candidosis. It prevents dissemination of candidal infections in AIDS but does not eradicate mucosal candidosis, which is controlled by cell-mediated immunity. Although the risk of dissemination is low, chronic superficial candidosis is likely to aggravate the underlying T lymphocyte deficiency via the immunosuppressive effects of *C albicans* itself. If the infection is a cofactor in the development of overt AIDS, antifungal therapy might be of particular benefit to ARC patients with mucosal candidosis.

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Public Health

TRENDS IN DENTAL HEALTH OF TEN-YEAR-OLD SCHOOLCHILDREN IN SOUTH-WEST SCOTLAND AFTER CESSATION OF WATER FLUORIDATION

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Summary The prevalence of dental caries in 10-year-old children in Stranraer has increased since the withdrawal of water fluoridation, with a 115% increase in the mean cost of restorative dental work due to caries and a 21% increase in the mean cost of all dental treatment. In Annan, a similar town which has never had fluoride added to the water supply, caries prevalence fell significantly, with little change in the cost of dental treatment. The findings suggest an association between cessation of water fluoridation and the increased prevalence of caries in Stranraer children.

INTRODUCTION

IN 1980, a comparison was made between the dental health of 10-year-old schoolchildren in Stranraer, 10 years after the introduction of water fluoridation, and those in Annan, which had a negligible concentration of fluoride in the public water supply.[1] The study showed striking differences in the dental health of the children, with a 50% greater prevalence of caries in the non-fluoridated town, and a similar percentage difference in overall treatment costs calculated from the standard National Health Service fee scale.[2] However, fluoridation of Stranraer's water supply—to a level that would benefit dental health—was stopped in 1983, after a court judgment which held that Scottish law was not clear about the compulsory fluoridation of public water supplies.[3]

This study was undertaken to assess the effects of the withdrawal of fluoridation on the dental health of 10-year-old children in Stranraer, by comparison with changes in a control town (Annan) where the water supply had never been fluoridated. Stranraer and Annan are similar small towns in the south-west of Scotland, with approximately equal dentist/population ratios and clinical care provided by general and community dental services.

METHODS

All 10-year-old children (primary class 6) in non-denominational primary schools were examined, but only life-time residents were included in the analysis. Dental inspections were undertaken by one of the 1980 examiners, who used diagnostic criteria described elsewhere.[4] The equipment and methods duplicated those used in 1980.

The projected cost of dental care provision for the children in each town was calculated in terms of the resource related index (RRI).[5] This uses the scale of fees on which the payment of general dental practitioners contracted to the National Health Service is based. Treatment cost data for 1980 and 1986 were both calculated from a standard NHS dental fee scale (that of 1984). Data were compared by Student's *t*-test.

RESULTS

Table I shows that the mean decayed, missing, and filled scores (DMFT) for the permanent dentition amongst the Annan subjects was 3·35 in 1980 and 2·81 in 1986, a reduction of 16%. If the decayed component (DT) of the index is examined separately, the DT score was 1·34 in 1980 compared with 0·90 in 1986, a reduction of 33%. The mean cost of restorative care per patient rose by 9%, but the cost of all dental treatment fell slightly by 4%. A 52% reduction in the mean cost of extractions was found: this difference was

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