Autoimmune Hemolytic Anemia in Chronic Mucocutaneous Candidiasis

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Chronic mucocutaneous candidiasis is an immunodeficiency disease characterized by T-cell dysregulation and chronic superficial candidal infections. We report on three patients with chronic mucocutaneous candidiasis who developed autoantibodies to erythrocytes. Our first patient, a 19-year-old female, developed autoimmune hemolytic anemia (AIHA) that required multiple courses of treatment, including corticosteroids, intravenous immunoglobulin, and danazol. During the last exacerbation of AIHA, intensive treatment with corticosteroids and intravenous immunoglobulin failed and yet the patient responded to plasmapheresis. Our second patient, a 21-year-old male, developed AIHA which responded to oral corticosteroid therapy. Our third patient, a 6-year-old female without evidence of hemolysis, was found to have erythrocyte autoantibodies on routine screening. These three patients had positive direct antiglobulin tests, and the first patient had both immunoglobulin G (IgG) and IgM erythrocyte autoantibodies, while the remaining two patients had only IgG autoantibody. This is the first report of the association of AIHA with chronic mucocutaneous candidiasis. We suggest that all patients with chronic mucocutaneous candidiasis be screened periodically for erythrocyte autoantibodies. Plasmapheresis, a safe ancillary procedure in the management of AIHA, may be life-saving in some cases. The occurrence of erythrocyte autoantibodies in mucocutaneous candidiasis may be related to immunoregulatory disorders in this disease.

Chronic mucocutaneous candidiasis (CMC) is a rare heterogeneous disorder characterized by chronic and recurrent infections of mucous membranes, nails, scalp, and skin with organisms of the genus Candida (3, 24). Although Candida albicans is the usual organism that causes these infections, the vulnerability of these patients to a variety of other noncandidal infections, some of which can be disseminated, has been observed (11, 15, 19, 22). Examples of such noncandidal infectious agents include Staphylococcus aureus, Pneumococcus spp., Haemophilus influenzae, Mycobacterium avium intracellulare, Histoplasma capsulatum, Cryptococcus neoformans, herpes simplex virus, and Giardia lamblia.

A wide variety of immunological abnormalities in patients with CMC have been reported. The primary immune defect is believed to be an impairment in the T-cell response to Candida organisms and is characterized by cutaneous anergy to Candida organisms as well as diminished or absent lymphocyte proliferative response to Candida antigen (11, 25). Durandy et al. (14) demonstrated mannan-specific and mannan-induced T-cell-suppressive activity in 18 patients with CMC. These workers speculated that defective presentation of mannan, a candidal antigen, by monocytes could result in the accumulation of mannan, leading to the activation of specific T suppressor cells and the consequent cellular immunodeficiency specific to C. albicans. Gupta (18) reported a deficiency of autologous mixed-lymphocyte reaction which was associated with increased suppressor T-cell activity or with functional deficiency of helper T cells in four of six patients with CMC. A deficiency of helper T cells (32) as well as excessive suppressor T-cell activity (36) have also been reported in association with CMC by others. In addition, mononuclear cells with deficient expression of CD8 but normal CD3 occur in CMC (30).

It has been speculated that the failure of Candida-stimulated T cells to produce lymphokines may be the significant defect in CMC (23). Consistent with that hypothesis, Sander et al. (33) recently reported a marked regression of mucocutaneous candidiasis in a patient with alopecia universalis, malignant thymoma, and mucocutaneous candidiasis who was treated with interleukin-2. Apart from the T-cell abnormalities, other immunologic defects in association with CMC include isolated immunoglobulin A (IgA) deficiency (4), deficient IgG response to diphtheria immunization (5), IgG2 subclass deficiency (17), chemotactic defects (38), defective monocyte-mediated antibody-dependent cellular cytotoxicity (31), the presence of plasma inhibitor to lymphocyte transformation (9), and decreased activity of total serum complement (13). Many of these abnormal findings frequently return to normal after treatment of the Candida infection, suggesting that some of these reported anomalies are epiphenomena and do not represent the basic immunologic defect (3). However, Mobacken et al. (28) studied eight patients with CMC and found that clinical improvement after treatment with ketoconazole for 6 months was not associated with reversal of either the cutaneous anergy or the in vitro lymphoproliferative response to candidal antigen. Together, all these studies suggest that the fundamental abnormality in CMC is a T-cell regulatory defect, but the molecular basis of the defect is unknown.

The clinical manifestations of CMC are also variable, and at least six different clinical variants have been described (24). A wide variety of autoimmune diseases have also been reported in association with CMC. These include hypoparathyroidism,
hypothyroidism, Addison's disease, diabetes mellitus, hypogonadism, chronic active hepatitis, alopecia totalis, pernicious anemia, aplastic anemia, and immune thrombocytopenia (7, 12, 19, 39). Although a recent clinical review of cases throughout the United States (19) mentioned the occurrence of erythrocyte autoantibodies in CMC, clinical evidence of hemolysis was not cited. We report on three patients with CMC who developed erythrocyte autoantibodies. Two of these patients developed exacerbations of acute hemolytic anemia that required therapy. We also reviewed the records of our six patients with CMC to determine whether there were distinctive clinical or laboratory findings that could distinguish those who developed autoimmune hemolytic anemia (AIHA).

### CASE REPORTS

**Case 1.** This patient is a 19-year-old caucasian female who weighed 5 lb (ca. 2 kg) at birth after a full-term gestation. At age 6 months, this patient developed generalized candidal skin infections that responded poorly to local therapy (Table 1). She also demonstrated cutaneous anergy to candidant antigen at this time. A skin biopsy sample revealed *C. albicans*, and she was admitted to the hospital and treated with intravenous amphotericin B. Transfer factor therapy was also initiated during this admission, using transfer factor that was prepared from her father, who had a positive delayed-type hypersensitivity (DTH) skin test to candidal antigen.

When the patient was 4 years old and receiving transfer factor, her DTH skin test to candidal antigen converted from negative to positive. Clinically, she had minimal candidal skin involvement, although she was also receiving oral ketoconazole therapy. In the same year, the patient developed hypothyroidism and was started on levothyroxine therapy. At age 6 years, she developed a persistent malar rash which was diagnosed as acne rosacea. Serological tests for antinuclear and anti-DNA antibodies were negative at ages 6, 8, and 11 years. At age 10 years, transfer factor therapy was stopped. She continued to have recurrent episodes of oral thrush which responded to oral ketoconazole treatment. At age 12 years, she developed herpes/zoster in the T3 dermatome, which resolved without complications.

At age 15 years, she had her first episode of Coombs’ test-positive hemolytic anemia and was admitted to the hospital with a hemoglobin level of 2.9 g/dl, an elevated reticulocyte count, elevated indirect bilirubin, elevated lactic dehydrogenase, and a reduced serum haptoglobin level (Table 2). This episode of hemolytic anemia was preceded by a few days of viral upper respiratory tract infection. She was treated with intravenous gammaglobulin (1 g/kg/day) and intravenous methylprednisolone (1 mg/kg every 12 h). She was also cautiously transfused with packed erythrocytes (3 ml/kg for four doses) between days 2 and 4 of admission. She improved slowly, and by day 8 after admission, her hemoglobin level had reached 12.2 g/dl. She was discharged on an oral prednisone regimen (1 mg/kg/day), which was tapered off slowly over the next 4 weeks. Serological tests for cytomegalovirus, Epstein-Barr virus, cryoglobulins, and cold agglutinins were negative. Determination of antinuclear antibodies during this admission demonstrated a titer of 1:80 (homogeneous). Other positive autoantibodies included antimitochondrial, anti-smooth muscle, antipariaetal, and antithyroglobulin antibodies. Rheumatoid factor and antinuclear pattern antibodies tests were negative (Table 3).

At age 17 years, the patient had another exacerbation of Coombs’ test-positive hemolytic anemia during a viral syndrome. She was admitted with a hemoglobin level of 4.6 g/dl, an elevated reticulocyte count, elevated indirect bilirubin, elevated lactic dehydrogenase, and a reduced serum haptoglobin level (Table 2). The patient demonstrated both IgG and IgM erythrocyte antibodies. An erythrocyte eluate was tested against a panel of erythrocyte antigens, and it reacted with all of the antigens (broad specificity). Treatment with intravenous gammaglobulin (1 g/kg/day) and intravenous methylprednisolone (1 mg/kg every 12 h) was started. On the third day after admission, intravenous gammaglobulin treatment was discontinued because of worsening of her anemia, with a hemoglobin level of 4.3 g/dl, and plasmapheresis was started daily for 5 days. A total of 360 ml of plasma per kg of body

### TABLE 1. Clinical characteristics of six patients with CMC

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Age at diagnosis (mo)</th>
<th>Mode of presentation</th>
<th>Family history of CMC</th>
<th>Clinical complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>6</td>
<td>Chronic oral, vaginal, and skin candidiasis</td>
<td>Negative</td>
<td>Autoimmune hemolytic anemia, hypothyroidism</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>14</td>
<td>Chronic <em>Candida</em> infection of scalp and nails</td>
<td>Negative</td>
<td>Autoimmune hemolytic anemia, bronchiectasis, hypothyroidism, chronic sinusitis; died of respiratory failure secondary to disseminated aspergillosis</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>F</td>
<td>11</td>
<td>Chronic oral and skin candidiasis</td>
<td>Negative</td>
<td>Bronchiectasis, failure to thrive; died of measles pneumonia at age 6 yr</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>F</td>
<td>13</td>
<td>Chronic oral candidiasis</td>
<td>Negative</td>
<td>Hypoparathyroidism, alopecia totalis, rheumatic fever, reactive airways disease</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>F</td>
<td>8</td>
<td>Chronic oral, perineal, and scalp candidiasis</td>
<td>Negative</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>M</td>
<td>8</td>
<td>Chronic oral and perineal candidiasis</td>
<td>Negative</td>
<td>Meatal stenosis, delayed puberty, iron deficiency anemia, penicillin allergy, bilateral inguinal hernia, atypical mycobacterial infection of cervical and mesenteric nodes; died of disseminated <em>Mycobacterium avium</em>-M. <em>intracellulare</em> infection</td>
</tr>
</tbody>
</table>

### TABLE 2. Hematologic data at time of active AIHA

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Hemoglobin (g/dl)</th>
<th>Reticulocyte count (%)</th>
<th>Indirect bilirubin (mg/dl)</th>
<th>Haptoglobin (mg/dl)</th>
<th>Lactate dehydrogenase (U/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.9</td>
<td>31.7</td>
<td>1.8</td>
<td>&lt;8</td>
<td>1,191</td>
</tr>
<tr>
<td>2</td>
<td>4.3</td>
<td>53.1</td>
<td>4.1</td>
<td>&lt;7</td>
<td>5,148</td>
</tr>
<tr>
<td>3</td>
<td>6.2</td>
<td>50.6</td>
<td>3.1</td>
<td>&lt;8</td>
<td>910</td>
</tr>
</tbody>
</table>

* ND, not done.
weight was exchanged over 5 days, with 5% human serum albumin and physiologic saline as the replacement solution. For the last plasma exchange, 2 units of fresh frozen plasma were infused to treat oozing from the catheter site due to depletion of clotting factors. Intravenous methylprednisolone (1 mg/kg every 12 h) treatment was continued throughout the period of admission. She improved very slowly, and by day 10 after admission, her hemoglobin level had reached 8 g/dl (Fig. 1). She was discharged on a regimen of oral prednisone (1 mg/kg/day), and by day 41 of therapy, her hemoglobin level had reached 12.2 g/dl. Alternate-day prednisone therapy was then started. This patient continued to have evidence of chronic but compensated hemolysis for several months after discharge from the hospital. A trial of danazol for several weeks was unsuccessful in controlling her hemolysis. Splenectomy was suggested as a therapeutic option, but the patient refused. She is currently off prednisone therapy, and her hemoglobin level on 4 April 1993 was 11.2 g/dl, with a reticulocyte count of 2.5%.

Case 2. The patient was a 21-year-old caucasian male, who weighed 9 lb 6 oz (ca. 4 kg) at birth after a full-term uncomplicated pregnancy. At 14 months of age, he developed candidal infections of his scalp and nails which persisted despite appropriate medical therapy. He was hospitalized for pneumonia at ages 3.5, 11, and 15 years. At age 15 years, his chest x-ray revealed chronic bronchiectasis. In the same year, he underwent a Caldwell-Luc surgical procedure for chronic sinusitis. Evaluation of his thyroid status at age 15 demonstrated hypothyroidism, for which levothyroxine therapy was begun. At ages 16.5, 18, and 21 years, he had exacerbations of Coombs’ test-positive hemolytic anemia, with dramatic decreases in hemoglobin level. During the first episode, which was diagnosed on a routine follow-up visit, his hemoglobin level had decreased from 13 g/dl 6 months prior to that visit to 6.2 g/dl. His reticulocyte count was 50.6%; the indirect bilirubin level was 3.1 mg/dl, the haptoglobin level was <8 mg/dl, and the serum lactate dehydrogenase level was 910 U/liter (Table 2). This patient developed warm erythrocyte antibody (IgG) (Table 4). An erythrocyte eluate was tested against a panel of erythrocyte antigens, and it exhibited broad specificity.

He responded well to oral prednisone given initially at a dose of 2 mg/kg/day for the first 2 to 3 days, with a gradual dose reduction over the next 4 to 6 weeks. The second exacerbation of hemolysis, which was diagnosed by his private physician, also responded well to oral prednisone therapy. His hemoglobin level during the clinic visit on 6 February 1992 was 13 g/dl, with a reticulocyte count of 1.2%, while on a maintenance dose of prednisone (10 mg/day). The last exacerbation of hemolysis occurred during the course of a lower respiratory tract infection. His hemoglobin level on 14 June 1993 was 10.3 g/dl, with a reticulocyte count of 11.2%. His oral prednisone dose was increased to 50 mg/day, and by the fourth day of therapy, his hemoglobin level had increased to 11 g/dl, with a reticulocyte count of 6.8%. In July 1993, the patient died of respiratory failure secondary to disseminated aspergillosis.

Case 3. A 6-year-old caucasian female at age 11 months had a history of chronic oral and skin infections with Candida organisms which responded poorly to local therapy (Table 1). By age 24 months, she had started failing to thrive. In addition, she developed chronic sinopulmonary infection and candidal esophagitis. At age 5 years, the patient was admitted for pneumonia and required a left lower lobectomy because of isolated bronchiectasis. A bronchoscopic culture at this time revealed Pseudomonas aeruginosa. Prior to this time, cystic fibrosis had been ruled out by a normal sweat chloride test. The patient did well postlobectomy and was discharged.

At age 6 years, she was readmitted for pneumonia which was preceded by a viral upper respiratory tract infection. A sputum culture revealed Pseudomonas aeruginosa, and appropriate antibiotic therapy was begun. While in the hospital, the patient had a complete immunologic reevaluation, including an antoantibody screen. A positive Coombs’ test was discovered, but there was no clinical or laboratory evidence of hemolysis. The patient improved initially but ultimately died from meases pneumonitis despite intensive therapy with intravenous gamma globulin, nebulized and intravenous ribavirin, and mechanical ventilatory support.

Autopsy revealed chronic bronchiectasis, giant cell pneumonia, chronic esophagitis, absent Hassall’s corpuscles in the thymus, and absent follicles in lymph nodes and appendix.

Clinical and immunological characteristics of CMC patients. As illustrated in Table 1, all the patients were diagnosed within the first 2 years of life, and as expected, they all presented with chronic superficial candidal infections. In addition, autoantibodies to various autoantigens were detected in all the patients (Table 3), but only two of the six patients (33%) developed AIHA.

The patients also exhibited variable immunologic characteristics (Tables 4, 5, and 6). An observation made for all the
patients was cutaneous anergy to *Candida* antigens and other antigens as well as defective lymphoproliferative response to *Candida* antigen. Lymphoproliferative responses to mitogens were also impaired to a variable degree. There is no evident immunological predictor of AIHA.

### RESULTS AND DISCUSSION

A wide range of autoimmune disorders have been reported in association with CMC (7, 12, 19). This is the first report of the occurrence of clinically significant autoimmune hemolytic anemia in association with CMC. Two of six patients (33%) with CMC who were included in this study developed AIHA that required therapy. Case 3 developed erythrocyte autoantibodies without clinical or laboratory evidence of hemolysis.

AIHA is a clinical disorder characterized by the development of erythrocyte autoantibodies, which result in decreased erythrocyte survival, ultimately leading to anemia (20). The autoantibodies in AIHA may be warm-reacting IgG or cold-reacting IgM (16, 20). One of the patients developed both IgG and IgM erythrocyte autoantibodies, whereas the remaining two patients had only IgG autoantibody. Eluates prepared from the patients' erythrocytes confirmed the presence of IgG autoantibody which reacted with all the erythrocyte antigens tested.

A review of clinical as well as immunologic markers in the six patients with CMC did not yield any marker that distinguishes between the patients who developed AIHA and those who did not. The occurrence of autoantibodies to various autoantigens in all six patients with CMC, including those who did not have erythrocyte autoantibodies, is consistent with previous reports that patients with CMC are very likely to develop autoimmunity (7, 12, 19). Indeed, an attractive unifying hypothesis to explain the heterogeneous features of CMC suggested an autoimmune disorder directed at the lymphoid apparatus, causing a cell-mediated defect which in turn results in chronic candidiasis and progressive endocrinopathy (3).

Evidence from a number of animal model systems of autoimmunity has suggested that loss of effective suppressor T-cell function can lead to autoimmune disease (26). Extensive studies carried out in the New Zealand Black mice model of autoimmunity and with hybrids produced by crossing New Zealand Black and New Zealand White mice have shed some light on the pathogenesis of AIHA. New Zealand Black mice spontaneously develop anterythrocyte antibodies by 3 months of age; the direct antiglobulin test is positive by 9 months of age, and then typical signs of AIHA appear (37). The anti-erythrocyte autoantibodies are both IgG and IgM. Autoantibodies also develop in the hybrid mice. The pathogenesis of autoantibody formation in these animals has been suggested to be the result of loss of suppressor cell activity as they age, which allows the development of forbidden clones of lymphocytes with self-antigen specificity (26). Consistent with reports by other investigators (4, 25), our patients with CMC have some defects in T-cell immunity. The idea that the development of erythrocyte autoantibodies in these patients is related to some T-cell regulatory defects is therefore very attractive.

Therapeutic intervention in AIHA depends largely on the extent of symptoms, which correlate with the level and rate of destruction of erythrocytes. Overall, the goals of therapy include immediate restoration of adequate oxygen transport by increasing circulatory erythrocyte mass; decreased destruction of opsonized erythrocytes; control of the population of B-cells that secrete the pathogenic autoantibody; and treatment of any associated underlying disease in secondary forms of AIHA (20). Corticosteroids constitute the cornerstone of treatment for both the primary and secondary forms of AIHA (20). Corticosteroids downregulate Fe receptor expression and thus decrease the splenic clearance of erythrocytes that are opsonized with IgG or C3b (5, 35). The second patient had insidious onset of hemolytic anemia which responded well to treatment with oral prednisone on three occasions. On the other hand, the first patient had a much more rapid onset of symptoms and more severe hemolytic anemia that required multiple therapeutic modalities, including intravenous steroids, intravenous gammaglobulin, packed erythrocyte transfusion, and plasmapheresis. During the two admissions, intravenous gammaglobulin and intravenous steroids were started at almost the same time. It is therefore impossible to comment on the relative efficacy of these two forms of therapy for this patient. Intravenous gammaglobulin has been used successfully in the treatment of other autoimmune cytopenias, especially immune thrombocytopenia (20). The proposed mechanisms for its action include Fe receptor blockage, heightened T-suppressor function, anti-idiotypic counterregulation, and interference with the cytokine cascade (27). However, intravenous gammaglobulin has occasional but limited efficacy in AIHA (6). The observation that the first patient required packed erythrocyte transfusion during the first admission and plasmapheresis during the second admission despite treatment with high-dose intravenous gammaglobulin tends to support the limited efficacy of this form of treatment in AIHA.

### TABLE 4. Immunohematologic data

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Direct antiglobulin</th>
<th>Indirect antiglobulin</th>
<th>Erythrocyte eluate anti- IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poly-specific Ig</td>
<td>Anti-IgG</td>
<td>Anti-C3b</td>
</tr>
<tr>
<td>1 First episode</td>
<td>+ + +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Second episode</td>
<td>+ + + +</td>
<td>+ +</td>
<td>+</td>
</tr>
</tbody>
</table>

^a—, no agglutination; + to +++, increasing degree of agglutination.

^b NA, not available.

^c IgG and IgM.

### TABLE 5. Humoral immune data

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Quantitative Ig titer</th>
<th>Functional antibodies</th>
<th>Isohemagglutinins (titer)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgA</td>
<td>IgM</td>
</tr>
<tr>
<td>1</td>
<td>1,820</td>
<td>324</td>
<td>607</td>
</tr>
<tr>
<td>2</td>
<td>1,170</td>
<td>116</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>1,040</td>
<td>99</td>
<td>130</td>
</tr>
</tbody>
</table>

^a—, not protective; +, protective; ND, not determined.

^b Blood group AB.
During the second admission, the first patient required daily plasmapheresis for 5 days. Plasmapheresis acts by removing autoantibodies from the circulation, thereby slowing down hemolysis before the effects of corticosteroid or other immunosuppressive drugs are established (20). However, plasmapheresis is more effective in AIHA caused by IgM autoantibodies, since, at any given time, most of the IgG autoantibodies are bound to erythrocytes. Of note, the first patient had both IgM and IgG autoantibodies. In addition, high-dose methylprednisolone was continued throughout the period of plasmapheresis. It is therefore possible that plasmapheresis only slowed down hemolysis before the full effects of the steroid became established.

The synthetic androgen danazol has been reported to be effective in some patients with immune thrombocytopenia (34) and AIHA (2, 10). The proposed mechanisms for its action include downregulation of Fc receptors in monocytes (34), immune modulation by normalization of CD4/CD8 lymphocyte ratios (29), and increased resistance of erythrocyte membranes to osmotic lysis (2). However, an outpatient trial of danazol for our second patient was unsuccessful and had to be discontinued because of the development of significant side effects, especially hirsutism.

In general, splenectomy is an alternative therapeutic option for patients with AIHA who require high maintenance prednisone doses (10 to 20 mg/day) or who have multiple and frequent relapses or serious side effects from steroid therapy (20). Splenectomy removes a major portion of both the phago-cytic reticuloendothelial system and the autoantibody-producing B cells (20). At least 50% of patients with AIHA have a good initial response to splenectomy, but there is no clinical or laboratory measurement that can predict who will benefit from splenectomy (20, 21). Our first patient refused splenectomy.

In conclusion, these case reports indicate that clinically significant AIHA occurs in patients with CMC. We therefore suggest that all patients with CMC be screened periodically for erythrocyte autoantibodies. When frank hemolysis occurs or patients become refractory to corticosteroids and/or intravenous gammaglobulin, plasmapheresis should be considered as a therapeutic option before the addition of potent immunosuppressive therapy, which could be detrimental for patients who are already immunosuppressed. Further studies are needed to elucidate the precise immunoregulatory defect that is responsible for the development of erythrocyte autoantibodies in patients with CMC.

REFERENCES
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