

Candida endocarditis in a child with hyperimmunoglobulinemia E syndrome

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Hyperimmunoglobulin E syndrome (HIE) is a disorder characterized by extremely elevated serum levels of IgE and recurrent infections. Patients are particularly predisposed to have staphylococcal abscesses, usually involving skin, lungs, and joints; but they are also at risk for infections with other bacteria and fungi. We report the case of a 46-month-old boy with HIE who had *Candida* endocarditis and sepsis with a large fungal mass extending through the tricuspid valve and into the surrounding heart tissue, requiring surgical excision and replacement with a prosthetic valve. He had an indwelling central line for previous antibiotic therapy and had oral thrush for a month before presentation, which had been treated with oral nystatin. He was first seen with very dark urine, a new murmur, petechial rash, in shock, and disseminated intravascular coagulation. The white blood cell count was 38,700 with 70% segmented neutrophils, 9% banded neutrophils, 15% lymphocytes, 4% monocytes, and 2% eosinophils. Hemoglobin was 7.1, and platelet count was 14,000. Prothrombin time was 15.5, and partial thromboplastin time was 31; fibrinogen level was 110 mg/ml, and fibrin degradation products were greater than 40 mg/ml. Serum IgE was 38,664 and 44,510 on repeat measurement. He has had recurrent staphylococcal pneumonias with pneumatoceles, twice requiring segmental lung resection. Blood and tricuspid valve cultures grew *Candida albicans*. He was treated with amphotericin and flucytosine, and later switched to fluconazole, with good response to therapy. A literature search revealed no other reported case of *Candida* endocarditis in patients with HIE. Fungal endocarditis is a rare complication, which may occur in patients with HIE and indwelling central catheters. (J Allergy Clin Immunol 1997;99:770-2.)

Key words: Hyperimmunoglobulinemia E syndrome, *Candida* endocarditis, immunodeficiency

Hyperimmunoglobulinemia E syndrome (HIE) is a relatively rare type of primary immunodeficiency, first described by Buckley et al.¹ in 1972. It is first seen in infancy with recurrent, severe staphylococcal abscesses of the skin, lungs, bones, joints, and other sites. Affected individuals experience recurrent pneumonias and often persistent pneumatoceles, and many eventually require surgical resection of the involved lobe of the lung. Lung involvement may be much more extensive than indicated by radiographic evaluation. Patients with HIE often

Abbreviation used

HIE: Hyperimmunoglobulinemia E syndrome

have an atypical, pruritic dermatitis that differs from atopic dermatitis in both appearance and location. Many have coarse facial features. Septicemia and central nervous system infections are rare. Respiratory allergy symptoms are not usually found.²

Staphylococcus aureus accounts for 60% of all infections,³ but *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* are common bacterial pathogens. These patients are also at risk for fungal infections, including infection with *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans* and histoplasmosis. The syndrome features markedly elevated serum IgE levels and eosinophilia of the blood and sputum. Histologic sections of the walls of lung cysts often contain high numbers of eosinophils, as do other tissues such as those obtained from the spleen and abscess walls.²

Although detailed studies have identified several immunologic abnormalities associated with the disorder, the exact cause of the increased susceptibility to this spectrum of infections is not clearly defined. Quantitative immunoglobulin levels, other than IgE levels, are usually normal. However, antibody responses to recall antigen are usually impaired. Most patients with HIE also have deficient cell-mediated immunity with poor in vivo lymphocyte responses to antigens and poor responses in mixed leukocyte culture. Response to mitogens is usually normal. Studies of neutrophil and monocyte chemotaxis sometimes show abnormalities, but results are usually normal. Phagocytosis and complement are normal.²

Treatment of HIE involves long-term prophylaxis with an antistaphylococcal antibiotic and aggressive treatment of acute infections with appropriate antibiotic or antifungal agents. Surgical excision of pneumatoceles that persist for more than 6 months is recommended, because they tend not to resolve after that period and because they tend to become superinfected.^{2,4} Treatment with intravenous gamma globulin has been suggested for some patients who display antibody deficiency.^{4,5} We report a case of *Candida albicans* endocarditis in a patient with HIE. We found no previously reported cases of *Candida* endocarditis in patients with HIE.

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CASE REPORT

A 46-month-old boy with known HIE was first seen with bloody urine, emesis, lethargy, dehydration, a petechial rash, and new onset of systolic ejection murmur with gallop rhythm. He was treated for thrush with oral nystatin for 1 month before presentation. He had sepsis with disseminated intravascular coagulation and cardiogenic shock. A chest x-ray film revealed a small chronic pneumatocele in the left lung base but no acute infiltrate. A total white blood cell count was 37,900 with 57% neutrophils, 17% banded neutrophils, 15% lymphocytes, 7% monocytes, 3% eosinophils, and 1% metamyelocytes; platelet count was 24,000; and hemoglobin was 8.9. His prothrombin time was elevated at 14.8, but he had a normal partial thromboplastin time of 26. The fibrinogen level was low at 145 mg/dl, and fibrin degradation products were greater than 40 mg/ml. Urine was brown and cloudy, and urinalysis revealed 100 mg/dl protein, a large amount of blood, 21 white blood cells per high-power field, and 7 red blood cells per high-power field. His IgE level was 38,864 IU/ml. He was initially admitted to the pediatric intensive care unit and began receiving intravenous vancomycin and ceftriaxone with infusions of platelets, packed red blood cells, cryoprecipitate, and fresh-frozen plasma. He had an indwelling central venous catheter, which was obstructed. A urine culture grew *Xanthomonas maltophilia*, and the infection was treated with intravenous gentamicin and vancomycin for 8 days. Results of a blood culture were positive for budding yeast at 24 hours. An echocardiogram revealed a large fungal mass extending through the tricuspid valve, measuring 2 × 3 cm and obstructing the tricuspid inlet (Fig. 1). The right atrium and inferior vena cava were dilated as a result of the obstruction. Intravenous administration of amphotericin B was begun. At the time of surgery, the entire tricuspid valve was found to be destroyed, with extension of the fungi into the heart tissue; thus, it was resected, an artificial valve was placed, and the central venous line was removed. Cultures of both blood and the tricuspid valve grew *Candida albicans*. The patient was treated for 4 weeks with intravenous amphotericin B and 5-flucytosine, then was switched to oral fluconazole for 6 months with good recovery.

Previous immunologic evaluation of this child (from 5 to 7 months of age) revealed an IgE level of 6202 IU/ml. Other quantitative immunoglobulins were normal for age with an IgG of 714 mg/dl, IgA of 48 mg/dl, and IgM of 119 mg/dl. Results of delayed hypersensitivity skin testing with *Candida* species were positive (2 × 2.5 cm induration). Lymphocyte subset analysis showed a low CD₈ of 13% but normal CD₂ of 80%, CD₃ of 77%, and CD₄ of 59%. The CD₅₆ was low at 1%, and CD₁₉ was elevated at 16% with an absolute lymphocyte count of 7440/mm³. Mitogen stimulation studies were low with phytohemagglutinin 25% of normal, concanavalin A 11% of normal, pokeweed mitogen 38% of normal, and *Staphylococcus* protein A 30% of normal. Results of HIV ELISA were negative, and nitroblue tetrazolium reduction test was normal at 91% (stimulated). Initially, specific antibody titers to diphtheria and tetanus were low (0.008 U/ml and 0.05 IU/ml, respectively) but improved with age and subsequent immunizations (diphtheria, 0.029 U/ml, and tetanus, 0.19 IU/ml at age 4½ years). Specific antibody titers to *Pneumococcus* species were 3420 ng AbN/ml to type 3, 840 ng AbN/ml to type 7F, and 620 ng AbN/ml to type 9N, but only 90 ng AbN/ml to type 14, at age 4½ years. His most recent IgE levels ranged from 38,864 to 44,520 IU/ml.

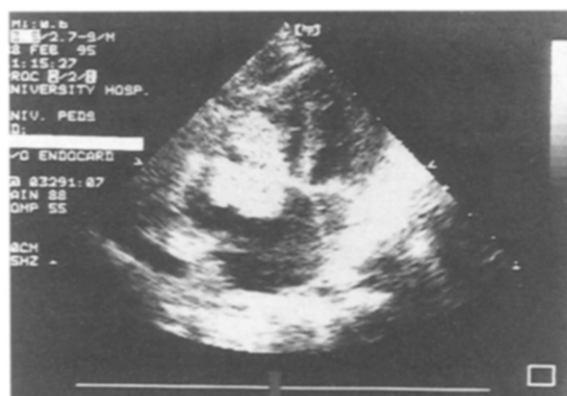


FIG. 1. Echocardiogram showing large fungal mass extending through the tricuspid valve, measuring 2 × 3 cm and obstructing the tricuspid inlet.

DISCUSSION

Extensive review of the literature revealed no other reported cases of fungal endocarditis in patients with HIE. A review of 62 cases of endocarditis in children by Saiman et al.,⁶ from January 1977 to February 1992, showed that the majority of patients with endocarditis (70%) had an underlying structural heart defect (either congenital or acquired). Of the 19 children with normal cardiac anatomy, 32% (6 patients) had community-acquired endocarditis, and 68% (13 patients) had nosocomially acquired disease. Eighty-five percent of the children with nosocomially acquired disease had a central venous catheter. Fungal endocarditis was only found in 10% of the patients, with a mortality rate of 67%. Overall mortality rate for children with endocarditis in their series was 21%. Eleven percent were diagnosed only by post mortem examination.⁶

Dato and Dajani⁷ reported a retrospective analysis of 31 cases of candidemia in children with central venous catheters. The annual rate for candidemia in patients with central venous catheters was 3% to 4%. Fifty-two percent were infants, and 87% were under 5 years of age. To determine the risk of candidemia in various age groups, Dato and Dajani⁷ reviewed the records of all children in whom catheters were inserted at their institution. The highest infection rate overall (bacteria and fungi) was found in 1- to 2-year-olds. Toddlers aged 1 to 5 years had a significantly higher rate of *Candida* infection (8.4% vs 2.2% overall). *Candida* endocarditis developed in two of 31 patients (6%) in this series.⁷

The recommendation for treatment of candidemia varies, but most advise removal of the central venous catheter and use of intravenous amphotericin B.⁷ There have been a few reports of successful treatment of catheter-related *Candida* sepsis in which amphotericin B was used and the central line was retained, but this carries greater risk for developing complications such as endocarditis, renal abscess, meningitis, arthritis, and osteomyelitis, as well as greater risk for death. Surgical resection of the involved valve is indicated for extensive fungal valve involvement.^{8,9}

Interestingly, in the previously reported cases of *Candida* endocarditis, none of the patients had an underlying immunodeficiency. Factors that we suspect placed our patient at increased risk for fungal endocarditis included: (1) an indwelling central venous catheter, (2) oral candidiasis, (3) immunodeficiency disease, and (4) young age. With the increased use of central venous lines in children with immunodeficiency syndromes, we conclude that fungal endocarditis should be considered in immunodeficient children who have an indwelling central venous catheter. Also, chronic mucocutaneous candidiasis in children with HIE may require aggressive treatment with oral ketoconazole or fluconazole to prevent more severe, disseminated disease.

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