Echocardiographically Silent Aspergillus Mural Endocarditis

DAVID M. LANG, MD
JAMES C. C. LEISEN, MD
JOSEPH P. ELLIOTT, MD
JOSEPH W. LEWIS, Jr, MD
Detroit

DAVID J. WENDT, MD
Iowa City

EDWARD L. QUINN, MD
Detroit

As predicted by Zimmerman1 in 1950, invasive mycotic infection has increased in frequency and importance. Aging of the population and burgeoning numbers of hosts compromised by severe underlying disease or immunosuppressive therapy are felt to account for this phenomenon.2,3 Aspergillosis has increased in incidence at a disquieting rate and has now become the third most common of the systemic mycoses.2

Embolization to peripheral vessels is a hallmark of Aspergillus endocarditis.4 Valvular vegetations are the usual source. We describe a case remarkable for a mural location of an echocardiographically silent Aspergillus vegetation and for the associated difficulty in establishing a diagnosis of endocarditis.

Report of a Case

The patient, a 42-year-old nurse with a 20-year history of systemic lupus erythematosus complicated by Raynaud’s phenomenon with recurrent ulcerations, was admitted to Henry Ford Hospital (Detroit) because of digital gangrene. Medications included prednisone, 20 mg per day, and azathioprine, 150 mg per day. On admission, fever and cough developed with new bilateral upper lobe nodular infiltrates.

A transbronchial biopsy specimen of a left upper lobe nodule showed nonspecific inflammatory findings, but no bacteria, mycobacteria, or fungi were cultured. The total serum hemolytic complement was diminished, and the erythrocyte sedimentation rate was elevated. The prednisone dose was increased to 60 mg per day, then tapered to 10 mg per day. The digital gangrene and pulmonary infiltrates, which were interpreted as manifestations of her systemic lupus erythematosus, resolved.

Six months later, she was readmitted with digital gangrene of the left hand. Her temperature was 37.6°C (99.7°F). The distal left upper extremity was tender, cold, and cyanotic. There were no splinter hemorrhages or funduscopic findings. On cardiac examination there were no murmurs, gallops, or rubs. Her chest was clear to auscultation; an x-ray film of the chest was normal. The leukocyte count was 6,400 per μl (95% polymorphonuclear leukocytes, 2%

Figure 1.—The photograph shows a surgically excised “thrombus” that extended into the left palmar arch.

Figure 2.—A histologic section of “thrombus” shows dichotomously branching, septate hyphae (Grocott-Gomori methenamine-silver stain, original magnification ×630).
bands, 1% lymphocytes, and 2% monocytes), and the hemoglobin was 10.3 grams per dl. Electrolyte levels, a urinalysis, prothrombin time, partial thromboplastin time, a platelet count, and assays for C3, C4, and CH50 were normal.

Aspirin, dipyridamole, intra-arterial reserpine, and topical nitroglycerin were given, and a stellate ganglion block was done without improvement. A "thrombus" that extended into the palmar arch was removed from the left ulnar artery (Figure 1). Dichotomously branching, septate hyphae were seen on microscopic examination (Figure 2), and Aspergillus fumigatus was cultured from the thrombus but not from four (venous and arterial) blood specimens. The prednisone dose was tapered, and antifungal therapy with amphotericin B, 0.6 mg per kg body weight per day, and rifampin, 600 mg per day, were added to her regimen. Three additional echocardiograms—M-mode and two-dimensional—were done serially on the 14th, 17th, and 21st hospital days and were unchanged. There were no echoes to suggest a valvular or a mural lesion. A digital subtraction angiogram of the aorta and pulmonary circuit, computed tomography of the head and sinuses, renal and liver-spleen scans, and serial electrocardiograms were done from the 14th to the 22nd hospital days and did not reveal a significant abnormality.

On the 23rd hospital day, an exploratory cardiotomy was...
done. Inspecting the surface of the heart revealed no abnormality. Exploring the proximal pulmonary veins by Fogarty catheter also showed no abnormalities. The findings of a visual inspection of the aortic and mitral valve leaflets were unremarkable. A 5-mm cylindrical excrescence was found on the anteromedial papillary muscle and its adjacent chordae tendineae. Microscopic examination of periodic acid-Schiff-stained endocardial and myocardial tissue showed necrotizing inflammation (Figure 3) containing dichotomously branching, sepsate hyphae (Figure 4). The mitral valve and papillary muscle were excised and replaced with a porcine xenograft. Cultures of specimens of mural endocardium, clear pericardial fluid, and mitral valve yielded *A. fumigatus*.

The postoperative course was complicated by a fluid overload and pneumonia (*Enterobacter cloacae*) with ensuing respiratory failure. On the fifth day following the cardiomyotomy, refractory hypotension developed, and death ensued. An autopsy was not permitted.

**Discussion**

This report suggests that in an immunocompromised host presenting with peripheral mycotic embolization, a diagnosis of mural endocarditis should be suspected even when vegetations are absent on serial echocardiograms. Cardiomyotomy may be required to confirm the diagnosis. The optimal management of mural endocarditis has not been established; we would recommend, however, surgically excising the vegetation and circumjacent involved endocardium and myocardium to remove a possible source for further embolization and giving combination antifungal chemotherapy.

Emboli to major vessels was first heralded by Andriole and co-workers as characteristic of fungal valvular endocarditis.5 This phenomenon has been confirmed particularly in *Aspergillus* species endocarditis.4-8 In the first two reported cases of *Aspergillus* valvular endocarditis1 and in 9 of 40 cases in a more recent review,9 peripheral embolization was described. This latter review included six cases with mural involvement alone.9-14 Of the remaining 34 patients in this series with valvular endocarditis, an antemortem diagnosis was achieved in 9 (26%). In eight of these cases, the diagnosis was established by a histologic examination and culture of specimens of excised emboli. *Aspergillus* emboli alone are not pathognomonic of valvular endocarditis, since a mycotic aneurysm of the thoracic aorta may present with embolization.15 We would note from this and two other recent reports16,17 that *Aspergillus* mural endocarditis may also have this presentation.

Infection of the endocardium may involve either its valvular or its mural components. The pathogenesis of valvular endocarditis relates to blood flow turbulence and resultant platelet or fibrin thrombi that become colonized with circulating microorganisms.18 Mural endocarditis has been described in association with congenital defects,19,20 prior infarction,21 and damage from a transvenous cardiac pacemaker,22 but may develop without a previous endocardial injury. Mural endocarditis may arise from a subendocardial focus or from the spread of adjacent infection.19,23 Nonvegetative endocardial plaques may result from the extension of myocardiab abscesses.3,24 Left atrial mural endocarditis may also be acquired from the extension of a pulmonary abscess through a pulmonary vein.25 In rare cases, vegetative

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mural endocarditis may occur that mimics valvular endocarditis, as illustrated in this report.

Aspergillus species mural endocarditis was first reported by Cawley in 1947. A literature search for subsequent cases is complicated by reports containing imprecise descriptions of mural lesions. Cases are included in this analysis if valvular vegetations were absent and dichotomously branching septate hyphae were seen microscopically or Aspergillus species were cultured from mural endocardial lesions.

On this basis, 15 cases of Aspergillus mural (nonvalvular) endocarditis have been previously reported. The clinical and pathologic features of these cases and the case reported here are given in Table 1. All patients had had fever and prior antibiotic therapy. Myocardial abscesses were found in all cases (14/14) in which an autopsy was done, including one case in which “focal acute myocarditis” was described. Prior corticosteroid administration and concomitant cytotoxic therapy were predisposing factors in 80% (12/15) and 31% (5/16) of cases, respectively. Preclinical murmurs were noted in only 36% (4/11) of cases. A blood culture was positive in only one case (8%), in which it was reported as showing “no growth, with mold contamination” ten days before death.

A high degree of suspicion is an important prerequisite to diagnosing Aspergillus mural endocarditis, and suspicion is warranted when an underlying disease is present or immunosuppressive therapy has been given (Table 1). The specific diagnosis of mural endocarditis may be important to establish in that it suggests the presence of myocardial abscesses. Factors that may predispose to Aspergillus infection have been enumerated. In a series of 98 cases of aspergillosis, Young and associates reported that 97% had an underlying predisposing condition, 85% had received chemotherapy, 70% had granulocytopenia, 87% had had corticosteroid therapy, and 97% had received antibiotics.

An antemortem diagnosis of Aspergillus endocarditis is rarely made. Negative blood cultures and serologic studies, both encountered in the present case, are well described in this setting. The 8% blood culture yield reported herein is consistent with previous yields of 8% and 11% in two large series of Aspergillus endocarditis. In the 98 cases of aspergillosis described by Young and colleagues, none showed a positive blood culture. This low frequency has been attributed to fungemia that is intermittent and circulating hyphae too large to traverse systemic capillaries. Serology has also been of dubious diagnostic value, although serocconversion, if documented, has been associated with increased survival in disseminated aspergillosis.

M-mode and two-dimensional echocardiography has been of diagnostic and prognostic value in bacterial and fungal endocarditis. Due to the larger size of vegetations seen in cases of fungal endocarditis, greater sensitivity with echocardiography would be expected. Although Dillon and co-workers reported being able to visualize masses of 2 mm or greater, the 5-mm mural vegetation in our patient was not seen. Peterson and colleagues have reported echocardiographic nonvisualization of four-chamber Aspergillus endocarditis and myocarditis, with a postmortem examination revealing mural vegetations as large as 1 cm in diameter. Factors other than size that may explain nonvisualization include location, configuration, and acoustic properties. More recently, Mullen and associates have reported serial echocardiographic visualization of an Aspergillus mural endocardial mass measuring 4 by 2 cm. The identification of this mass led to an appropriate surgical excision with continued antifungal chemotherapy; death ensued in this case, however, despite the antemortem diagnosis.

Aspergillus infection limited to mural endocardium has been less commonly reported than Aspergillus valvular endocarditis, for which more extensive experience indicates aggressive therapy is desirable. Following echocardiographic confirmation of the diagnosis, the optimal management entails early valve replacement and prolonged antifungal chemotherapy. Cures have been reported with this combined approach and with surgical treatment alone. Survival without valve replacement has not been described.

Aspergillus mural endocarditis has been uniformly fatal. Despite achieving an antemortem diagnosis in this case at cardiology, and in a recent report by serial echocardiography, cure did not result. Earlier recognition of this process permitting an earlier initiation of aggressive therapy may be required for a successful outcome.

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Alopecia Universalis as a Feature of Polyglandular Autoimmunity Type I

KHALED IMAM, MD
Allen Park, Michigan
MOHAMMED ABDULLAH, MD
New Orleans
JAMES V. FELICETTA, MD
Phoenix

The occurrence of two or more endocrine diseases in the same patient has been noted since the 19th century. Numerous workers have described an association of multiple autoimmune diseases of the endocrine organs, including the adrenal glands, endocrine pancreas, thyroid, parathyroid, and ovaries. These endocrine disorders are frequently associated with other disorders of tissue-specific autoimmunity, such as pernicious anemia, vitiligo, and alopecia.

These polyglandular autoimmunity (PGA) syndromes have been classified into two major types, based on familial clustering. Type I manifests at least two features from the triad of Addison’s disease, hypoparathyroidism, and chronic mucocutaneous candidiasis. Type II is present in patients who have Addison’s disease with autoimmune thyroid disease or insulin-dependent diabetes mellitus, or both, who do not have hypoparathyroidism or candidiasis. Associated immune disorders other than hypoparathyroidism and candidiasis may also be present with either type.

We report here the case of a patient who had the added feature of alopecia universalis as a manifestation of her type I polyglandular autoimmunity syndrome. Although alopecia areata is frequent in patients with the type I form, alopecia universalis is rare. Alopecia universalis was one of the most striking features in our patient, contributing greatly to her morbidity by exacerbating her emotional instability.

Report of a Case

The patient initially presented to Detroit Children’s Hospital in 1962 at age 3 with a history of generalized seizures for one month and a chronic fungal infection of the nails. Laboratory studies at that time showed a serum calcium level of 4.4 mg per dl and a phosphorus of 13.5 mg per dl. A diagnosis of primary hypoparathyroidism was made on the basis of a pronounced phosphaturic response to the intravenous administration of parathyroid hormone and a return to normal of calcium and phosphorus levels after giving the hormone. An adrenocorticotropic hormone (ACTH) stimulation test (cosyntropin test) reportedly showed an appropriate rise in the urinary cortisol level. Therapy was initiated with elemental calcium and vitamin D.

She did well initially except for the progressive development of alopecia areata beginning at age 5. This had progressed to alopecia universalis by age 8, and she always wore a wig after that time. According to her parents, emotional instability of increasing severity first became manifest at the time she began wearing the hairpiece. The diagnosis of hypoparathyroidism was confirmed at Grace Hospital in Detroit in 1979 when she was 20. At that time a C-terminal parathyroid hormone (PTH) level was less than 150 pg per dl (normal 197 to 315), with a simultaneous serum calcium level of 6.4 mg per dl (normal 8.8 to 10.0) and an ionized calcium of 2.56 mg per dl (normal 3.7 to 4.5). An 8 AM plasma cortisol level was 10 μg per dl, a 4 PM cortisol level 8.7 μg per dl, thyroxine 9.8 mg per dl, triiodothyronine resin uptake 40%, follicle-stimulating hormone (FSH) 12 mIU per ml, and lutetizing hormone (LH) 66 mIU per ml. Calcium supplementation and vitamin D therapy were continued.

At age 23, she presented to a North Carolina hospital with nausea, vomiting, weakness, dizziness, salt craving, increasing skin pigmentation, and an 18-kg (40-lb) weight loss over three months. Her blood pressure was 80/40 mm of mercury. Her serum calcium level was 6.5 mg per dl; an 8 AM cortisol level was undetectable. An intravenous ACTH stimulation test elicited values of less than 1 μg per dl at baseline, 30 minutes, and 60 minutes. Her baseline ACTH level was more than 250 pg per ml (normal 20 to 100). A computed tomographic scan of the head revealed bilateral basal ganglia calcification, consistent with hypoparathyroidism. A regimen of calcium carbonate; calcitriol, 0.5 μg daily; and cortisone acetate, 37.5 mg daily in divided doses, was started.

She was first admitted to Wayne County General Hospital in Detroit in December 1981 because of profound somnolence and weakness. According to her boyfriend, she had been extremely sporadic in taking her medications. She had also been experiencing considerable emotional stress related to her alopecia universalis and had noted intermittent amenorrhea and irregular menstrual cycles for more than two

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
FSH = follicle-stimulating hormone
HLA = human leukocyte antigen
LH = lutetizing hormone
PGA = polyglandular autoimmunity
PTH = parathyroid hormone


From the Division of Endocrinology and Hypertension, Department of Medicine, Wayne State University School of Medicine, Detroit, and the Veterans Administration Medical Center, Allen Park, Michigan (Dr Imam); the Division of Endocrinology, Tulane University School of Medicine, New Orleans (Dr Abdullah); and the Medical Services, Veterans Administration Medical Center, Phoenix (Dr Felicetta).

Reprint requests to James V. Felicetta, MD, Chief, Medical Services, Veterans Administration Medical Center, 7th St and Indian School Rd, Phoenix, AZ 85012.

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