[Frontiers in Bioscience 7, d1423-1438, June 1, 2002]

FUNGAL MYOCARDITIS

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TABLE OF CONTENTS

1. ABSTRACT

The incidence of invasive fungal disease has dramatically increased over the past few decades corresponding to the rising number of immunocompromised patients. The major risk factors for severe fungal disease include administration of broad-spectrum antibiotics, corticosteroids and cytotoxic agents, invasive medical procedures, and Human Immunodeficiency Virus (HIV) infection. Invasive fungal infections often affect multiple organs, and involvement of the myocardium frequently occurs in disseminated disease. Premortem diagnosis of fungal myocarditis is difficult since clinical findings of myocardial involvement are often absent or ambiguous and blood cultures are often negative. The major fungal pathogens responsible for myocardial infection and the clinical settings in which they occur are reviewed.

2. INTRODUCTION

Fungal myocarditis generally occurs in the setting of a disseminated fungal infection. For the purposes of this review, fungal myocarditis is defined as the presence of fungal organisms within the myocardium with or without inflammation. Disseminated fungal infections are often extremely difficult to diagnose. This difficulty is best demonstrated by data from studies on fungal endocarditis, an intravascular infection, where blood cultures are positive in only 53% of patients and delayed or incorrect diagnosis occurs in 82% of patients (1). Fungal myocarditis is frequently only detected at autopsy. No prospective investigations have been performed to determine the incidence of myocarditis during fungemia. The data has been derived from analyses of autopsy studies and case reports and the data indicates that fungal myocarditis is a common complication of disseminated fungal infection.

Severe fungal disease typically occurs in the setting of significant immune dysfunction. In the 1950s, physicians began to note an increase in the incidence of fungal diseases, particularly in patients with cancer (2-5). In 1953, Craig and Farber reported that fungal disease was not detected in autopsies of cancer patients at their institution prior to 1946 before the use of chemotherapy, whereas disseminated fungal disease was present in 13 (7.4%) of 175 children with leukemia who had received cytotoxic and hormonal therapies (2). In 1955,

Zimmerman recognized that candidiasis, aspergillosis, cryptococcosis, and mucormycosis, which rarely occurred in healthy individuals, were causing significant disease in patients with cancer and that these mycoses were significantly associated with the use of chemotherapy (3). In 1962, Baker specifically identified leukopenia as the primary predisposing factor for fatal outcomes in mycoses in patients with cancer (6).

Routine use of broad-spectrum antibiotics, corticosteroid administration, increased rates of abdominal and cardiac surgery, intravenous drug abuse, and frequent use of invasive catheters further increased the susceptibility of patients to fungal pathogens. In 1950, Zimmerman suggested that antibiotic use predisposed patients to disseminated fungal disease (7). This observation was confirmed by other clinicians (8-18). Corticosteroid therapy was also identified as a major predisposing factor for severe fungal disease (11, 14, 15, 18-22). Primary metabolic disorders, such as Cushing's syndrome and diabetes mellitus, were also determined to be important predisposing conditions (15, 23). Additionally, intravenous drug use (24-29), surgery (15, 28, 30, 31), and indwelling vascular catheters (15, 32) were identified as an important risk factors for severe fungal infections.

The epidemic from HIV has resulted in unprecedented numbers of immunocompromised individuals. Disseminated fungal infections occur relatively frequently in individuals with advanced HIV disease. For example, crytococcosis occurs in 6-8% of patients with HIV in the USA (33, 34) and up to 30% in these patients in underdeveloped countries (35, 36). Patients with advanced HIV disease are also at significant risk for severe infections due to *Candida*, *Aspergillus*, *Histoplasmosis*, *Coccidioides*, and *Blastomycosis* (37-41).

3. FUNGAL MYOCARDITIS

Prior to the 1950s, fungal myocarditis was rarely reported. In a 1942 literature review of myocarditis, Saphir identified only 20 cases due to fungi (42). In 1947, Gore and Saphir published an analysis of 1,402 autopsies with confirmed myocarditis and identified fungal myocardial infection in 14 (1%) patients (43). In a review of all autopsies performed at The Johns Hopkins Hospital from 1889 through 1977, Walsh et al identified 34 patients with fungal myocarditis, and all cases occurred after 1954 (44).

An association with fungal myocarditis and cancer, particularly hematological malignancies, was recognized by several investigators in the 1960s (5, 45). In an autopsy study of 420 hearts from patients with acute leukemia, Roberts et al found a 2.4% rate of fungal myocarditis which accounted for 32% of the total cardiac infections (45). Additional investigations of cancer patients identified antineoplastic drugs, antibiotics, corticosteroids, diabetes mellitus, indwelling catheters, and major surgery (particularly gastrointestinal surgery) as important risk factors for fungal myocardial disease (44, 46-48).

Autopsy series and reviews indicate that the prevalence of cardiac disease in patients with HIV ranges from 25-75%, with myocarditis identified in approximately half of these individuals (49-51). However, a specific etiology is determined in less than 20% of the cases of myocarditis. The incidence of myocarditis due to fungi ranges from 0 to approximately 20% (51-71). The patients identified with fungal myocardial infection all had advanced HIV disease.

3.1. *Candida*

Candida is the most prevalent cause of fungal myocarditis. Incidence rates for myocarditis in the setting of disseminated candidiasis range from approximately 10% (21, 72) to over 60% (30, 73-75). Prior to the routine use of cytotoxic and immunosuppressive medications, reports of myocardial involvement with candidiasis were uncommon (7, 10, 12, 24, 76-82). In a 1947 review of 1,402 pathologically confirmed cases of myocarditis, Gore and Safir found no cases of candidal involvement of the heart (43). In the 1950s, clinicians recognized the association of chemotherapeutically induced neutropenia with candidiasis (2, 3, 5, 6, 72). However, increased rates of *Candida* sepsis were first well documented in the 1960s (17, 83). The increased focus on mycotic infections in cancer patients led to careful autopsy studies that identified a significant incidence of cardiac candidiasis in these patients (5, 72). In an autopsy report of the hearts of 420 patients with acute leukemia in 1968, Roberts et al described 6 (1.4%) patients with *Candida* myocarditis (45). In a 1978 study of 85 cancer patients with disseminated candidal infections, Ihde et al identified 17 (20%) patients with *Candida* myocarditis (46). Eight patients had myocardial abscesses that were grossly visible. Additional metastatic foci of infection with *Candida* were detected in all patients, with abscesses occurring in the kidneys, gastrointestinal tract, lungs, liver and central nervous system in the majority of patients. Microscopically, *Candida* myocardial abscesses are characterized by the presence of numerous pseudohyphal and yeast forms involving tissue with central zones of necrotic myocytes and mononuclear infiltrates (5, 45, 46, 72, 75, 82). However, the extent of the inflammatory reaction varied according to the immune status of the patient, with the absence of neutrophils and dense fungal growth occurring in patients receiving high doses of cytotoxic or immunosuppressive agents compared to intense inflammatory reactions with few organisms in patients not receiving these medications (44, 75).

In 1972, Bernhardt et al reported that disseminated candidiasis in surgical patients resulted in myocardial infection in 13 of 14 patients who were autopsied during a 2 year period (30). Of the patients with myocarditis, all of the patients had central venous catheters, twelve of the patients underwent major surgical procedures, and all received multiple antibiotics. Five of the patients had positive premortem blood cultures. The myocardium was the most frequently involved organ, followed by the kidney and brain. The eye was involved in 5 cases. Notably, this paper was the first to identify ocular involvement as a manifestation of systemic

candidal disease and advocated fundiscopic examination in patients suspected of disseminated candidiasis (30).

In a review of autopsies from 1959 to 1974, Frankin et al identified 50 patients with systemic candidiasis and detected *Candida* myocarditis in 31 (62%) of the patients (75). Gross myocardial lesions were evident in 7 patients. Histological evaluations of the hearts revealed myocardial abscesses which varied in size and number and the inflammatory reactions ranged from complete lack of inflammation to acute suppuration with coagulative necrosis of myocytes. The distribution of the abscesses was random, which is consistent with seeding secondary to disseminated disease. All of the patients had significant medical illnesses including malignancy, autoimmune disorders, and bacterial infections. Half of the patients had undergone recent surgical procedures, 11 of which were major operations. Administration of antibacterial agents occurred in 27 of the 31 patients, antineoplastic drugs were given to 9, and 16 were receiving corticosteroids.

Walsh et al identified 34 patients with fungal myocarditis at autopsy and *Candida* accounted for 71% of the cases (44). Pathologic findings ranged from microabscesses to grossly visible lesions in necrotic myocardium. All of the patients with myocarditis had received prolonged antibiotic therapy. Prior gastrointestinal surgery or corticosteroid administration were also risk factors. In a separate analysis of the 14 children from their autopsy series with candidal cardiac infections, Walsh et al found 5 (36%) children with *Candida* myocarditis (84). The primary risk factor for myocarditis in each child was prior gastrointestinal surgery. Additional risk factors included prematurity, immune deficiency, antibiotic administration, and central venous catheter usage. Notably, the children had not received cytotoxic medications or steroids.

In a review of 8,975 autopsies, Parker identified 18 cases of *Candida* myocarditis (85). The primary risk factor for candidiasis was antibiotic therapy for suspected or documented Gram negative sepsis. The patients also had candidal involvement of at least one other organ, most commonly the kidney or brain. Five of the patients had concomitant endocarditis and an additional 2 patients had *Candida* endocarditis without myocarditis. From an analysis of 3,601 autopsies, Atkinson et al described 15 cases of *Candida* myocarditis (48). The infections occurred in patients with malignancy, renal disease, or intercurrent infection. In a second study evaluating the hearts of 60 patients with cardiac fungal infections, Atkinson et al identified *Candida* myocarditis in 23 patients (47). Blood cultures were positive for *Candida* prior to death in 14 (61%) patients. The patients had all received antibiotic, antineoplastic, or steroid therapy. Four patients had undergone cardiac surgery. Three of the 4 patients had concomitant endocardial candidal infection.

Since the 1960s, fungal endocarditis has been a well recognized complication of cardiac surgery, intravenous drug use, and immmunosuppression, with *Candida* being the most frequently identified pathogen (1, 28, 31, 44, 84, 86-90). Infection of the myocardium in the setting of *Candida* endocarditis was first reported by Polayes in 1940 (76) and additional case reports followed (77-79, 81, 91-96). Myocarditis occurs in 16 to 71% of cases of *Candida* endocarditis (28, 44, 47, 85, 86). The pathogenesis of myocarditis in *Candida* endocarditis was not due to direct extension of valvular candidal vegetations into the myocardium, rather there were discrete myocardial abscesses, which corresponds to hematogenous seeding. However, myocardial abscesses can extend to involve the endocardium or pericardium (47, 48, 97). Mural endocardial candidal infections due to extension of myocardial abscesses have also been described by Buchbinder et at in 4 patients with leukemia (98) and Ihde et al in 5 of 17 patients with *Candida* myocarditis (46).

Disseminated candidiasis is a well recognized complication in patients with advanced HIV disease (37-39, 41). However, few cases of *Candida* myocarditis have been reported in these patients (54, 56, 62, 64, 66, 99, 100). In two reports by Hoffman and colleagues (66, 100), intravenous drug use was an important risk factor for myocardial infection with *Candida*, which is consistent with prior reports of *Candida* myocarditis in non-HIV infected intravenous drug users (24-26, 28, 76, 101).

C. albicans was the species isolated from the vast majority of myocarditis cases reported. *C. albicans* continues to be the most prevalent species of *Candida* causing disseminated disease (102). However, the first report of *Candida* myocarditis was due to *C. parapsilosis* (103). Many of the cases of *C. parapsilosis* myocarditis (24, 28, 31, 77, 78, 104) have been associated with endocarditis, particularly in intravenous drug users. C. *tropicalis*, which is currently the third most commonly isolated species of *Candida* in blood cultures (105), has been associated with *Candida* myocarditis in patients with leukemia or lymphoma (28, 45, 81, 98, 106-109). Myocardial infections with *C. kruzei* (28, 79, 85), *C. stellatoidea* (28, 85, 87), and *C. guilliermondi* (31) have also been reported.

Candida myocarditis is frequently clinically asymptomatic. Although nonspecific, electrocardiographic (ECG) abnormalities frequently occur (46, 75, 85). The frequency at which ECG changes occur is not significantly different from that in other critically ill patients with or without myocarditis, or even from patients with disseminated candidiasis without cardiac infection (46, 75, 110). In the 31 patients with myocarditis described by Franklin et al, ECG evidence of conduction disturbances was seen in 10 patients, supraventricular arrhythmias in 5, QRS abnormalities consistent with myocardial infarction in 3, and significant T wave abnormalities in 13 (75). Van Kirk et al describe a case of complete atrioventricular block in a patient with acute myelomonocytic leukemia were *C. albicans* microabscesses where found in the His bundle (111). Pseudohyphal invasion of the conduction system can also occur (75). Additionally, *Candida* invasion of blood vessels resulting in infarction of myocardium has been described (75).

3.2. *Aspergillus*

Invasive aspergillosis usually occurs in immunocompromised patients and is associated with a high mortality rate (112). In a recent review of invasive

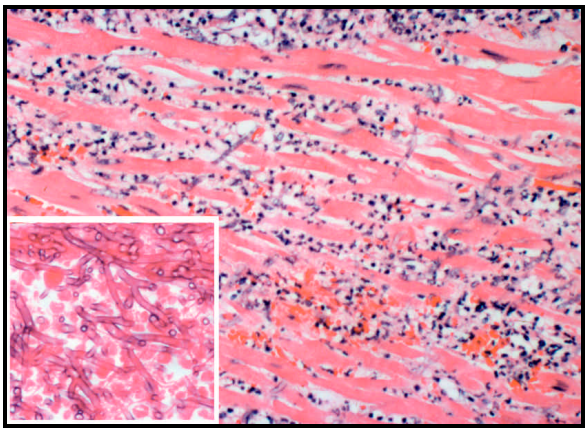

Figure 1. *Aspergillus* myocarditis characterized by a dense neutrophilic inflammatory response with myocyte necrosis and diffuse septated hyphae. Haemotoxylin and eosin stain, original magnification X25, inset X250. Courtesy of Dr. Bella Sablay.

aspergillosis, Patterson et al reported that 19% of patients developed disseminated disease and 84% of these individuals died (113). Prior to the 1950s, aspergillosis was exceedingly uncommon. *Aspergillus sp.* were considered "plebeians among fungi [that] attained chief notoriety as vexatious laboratory contaminants" (114). There were no cases of *Aspergillus* myocarditis in either a 1942 review of the medical literature (42) or in a 1947 autopsy study of 1,402 cases of myocarditis (43). Since then, there have been numerous case descriptions of *Aspergillus* myocarditis (1, 5, 7, 19, 21, 22, 44, 45, 47, 48, 64, 66, 68, 72, 97, 98, 100, 107, 114-164). In a manner similar to the rise in rates of candidiasis, the increased incidence of invasive aspergillosis corresponds to the more frequent use of chemotherapeutics, immunomodulators, broad-spectrum antibiotics, and invasive procedures (3, 5, 21, 45, 72, 107, 113, 136). In 1962, Baker recognized that leukopenia was the primary predisposing factor for fatal aspergillosis (6). As cancer therapy became more intensive, prolonged granulocytopenia was identified as the major risk factor for invasive aspergillosis (21, 165). By the early 1980s, concern for the increased incidence of severe fungal disease, particularly aspergillosis, in cancer patients resulted in the advocation of empiric antifungal therapy in persistently febrile neutropenics (166).

In 1970, Young et al described the spectrum of aspergillosis in 98 patients with significant underlying illnesses, primarily leukemia, and identified 5 (5%) patients with myocardial infection (107). Although two patients had a few, small (1 to 3 mm) abscesses that the authors deemed clinically insignificant, three patients had severe disease characterized by both small and large abscesses with extensive invasion of adjacent myocardium by *Aspergillus.* The typical histologic appearance of *Aspergillus* myocardial infection is abscesses containing septated hyphae associated with necrosis and infarction (Figure 1) (44, 120, 126, 167). The abscesses may be either focal or diffuse. Mycotic thrombosis of cardiac vessels is common, which is consistent with the predilection of the fungus for vascular structures. A neutrophilic inflammatory response is commonly seen, however this may be absent in the setting of severe neutropenia (44). Hyphae often extend though the thrombosed vessels into the necrotic myocardium (107, 147, 167).

In 1974, Willliams described 2 patients with *Aspergillus* myocarditis and reviewed 37 cases reported in the literature (167). Risk factors identified included debilitating diseases, cytotoxic drugs, immunosuppressive drugs, steroids, radiation, leucopenia, and antibiotics. Blood cultures for *Aspergillus* were positive in one of the 39 patients. An additional patient had a positive urine culture for *Aspergillus* and another had a positive sputum culture. Aspergillosis was the suspected cause of death in the majority of patients, but the extent to which myocarditis contributed to death was unclear, since extensive necrotizing pneumonia and cerebral abscesses were common.

Aspergillus is the second most common cause of fungal endocarditis (1) and the second most common fungal etiology of postoperative endocarditis (28, 47, 89). In 1950, Zimmerman reported the first cases of *Aspergillus* endocarditis, which occurred in a trauma patient who received intensive antibiotic therapy. In 1964, Newman and Cordell reported the first case of *Aspergillus* endocarditis after open-heart surgery (168). In a 1975 autopsy study, Rubinstein et al reported 5 patients with prior valve replacements who developed *Aspergillus* endocarditis with myocardial abscesses (28). Premortem blood cultures were negative. Since these studies, cardiac surgery, particularly valve replacement procedures, has been associated with *Aspergillus* endocarditis and concomitant myocarditis often occurs. In contrast to *Candida,* intravenous drug use is infrequently associated *Aspergillus* endocarditis (55, 107, 169).

In a review of 3,801 autopsies, Atkinson et al identified 8 patients with *Aspergillus* myocarditis (48). In a subsequent analysis of cardiac fungal infections in 60 patients, Atkinson et al described an additional 8 cases of *Aspergillus* myocarditis (47). Risk factors for aspergillosis included chemotherapy, broad-spectrum antibiotics, corticosteroids, cardiac surgery, and renal disease. Three patients had positive premortem blood cultures for *Aspergillus.* Of the 16 patients with *Aspergillus* myocarditis, the myocardium was solely involved in 10 cases, the myocardium and endocardium in 5, the myocardium and pericardium in 2, and pancarditis in 1. There were two additional cases of cardiac aspergillosis, 1 involving only the pericardium and 1 the endocardium.

Patients with AIDS are at significantly increased risk for invasive aspergillosis (37, 38, 40, 113). However, there are relatively few reports of *Aspergillus* myocarditis in patients with AIDS (64, 66, 68, 100, 143, 153, 154, 156, 170). In a 1992 review of invasive aspergillosis in patients with AIDS, Minamoto et al identified myocardial infection in 5 (14%) of 37 cases (170).

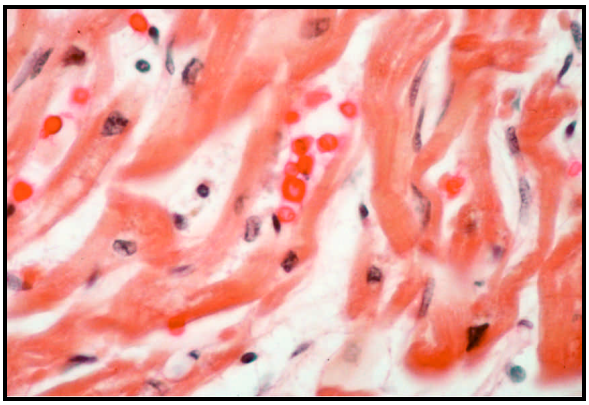

Figure 2. Cryptococcal myocarditis characterized by numerous yeast cells (red) and the absence of inflammation. Mucicarmine stain, original magnification X250. Courtesy of Dr. Maria Abadi.

Infection of the myocardium by *Aspergillus* typically occurs by direct extension, usually from the lung. *Aspergillus* invades the pulmonary vessels, ascends to infect the endocardium and subsequently involves the myocardium (97, 98, 107, 116). As described in Zimmerman's report of the first identified case of *Aspegillus* endocarditis (7), infected cardiac valves are also a common point of origin for subsequent myocardial invasion. Myocarditis also occurs following seeding during fungemia (107). As in the case of *Candida* myocarditis, *Aspergillus* mural endocardial or pericardial infection can occur secondary to hyphal invasion from or rupture of myocardial abscesses established by hematogenous seeding (44, 97, 98, 114, 141, 164).

Despite the extensive necrosis and infarction that frequently accompany cardiac aspergillosis, ECG findings are often absent or nonspecific (107, 167). In Williams' review, 6 (15%) of 39 patients had electrocardiographic changes consistent with ischemia or infarction (167). *Aspergillus* myocarditis has been identified in patients who died due to complications of arrhythmias and congestive heart failure (129). Lethal infarctions secondary to direct extension of myocardial abscesses into major cardiac vessels or by embolic seeding of the coronary vessels with subsequent thrombosis and invasion of myocardial tissue have been documented (144, 151). Cases where *Aspergillus* myocarditis involved the conduction system resulting in heart block and death have also been described (151, 171).

In the majority of cases of *Aspergillus* myocarditis, the species was not identified. However when speciation was performed, *A. fumigatus* was most commonly identified (Gerkin, 1950 #168)(1, 28, 66, 121, 122, 131, 138, 147, 148, 154, 156, 157, 161, 164, 167). Although a rare cause of disease, *A. terres* has been the etiologic agent of myocarditis in 7 patients reported in the literature (127, 137, 140, 146, 149, 152). Multi-organ involvement occurred in all patients with *A. terres* myocarditis, and concomitant endocarditis is typical. All cases of *A. terres* myocarditis occurred after cardiac valve surgery or in immunosuppressed patients. Additionally, several cases of myocardial infection with *A. flavus* have been reported (117, 125, 142, 147, 167, 171).

3.3. *Cryptococcus neoformans*

Prior to 1981, cryptococcal infections were uncommon, with less than 1,000 cases reported in the United States (172). In the 1950s, *C. neoformans* became identified as an opportunistic pathogen, particularly causing disease in the setting of steroid use (11, 173, 174) or in patients with lymphoproliferative disorders (175, 176). With the onset of the AIDS epidemic, *C. neoformans* became the most common cause of culture-positive meningitis in adults in New York City (33, 177). In the United States, 5-10% of patients with AIDS develop cryptococcosis (33, 34). In immunocompromised individuals, *C. neoformans* primarily causes a life-threatening menigo-encephalitis, and dissemination is common.

In 1956, Littman and Zimmerman first documented *C. neoformans* myocarditis in a patient with sarcoma and cryptococcosis (178). In 1962, Hutter and Collins identified 2 cancer patients with cryptococcal cardiac involvement (5). In 1965, Jones et al described a patient with *C. neoformans* myocarditis who developed a cardiomyopathy that resulted in congestive heart failure, heart block, and death (179). The patient had no clinical evidence of CNS involvement. Bergman et al described *C. neoformans* myocarditis in a patient with endstage cirrhosis on steroids (180). Although no specific clinical histories were provided, Walsh et al reported 3 patients with *C. neoformans* myocarditis (44) and Atkinson et al identified 1 additional patient (47).

The first report of cryptococcal myocarditis in a patient with AIDS was in 1983 (181). In 1985, Lewis and colleagues subsequently reported several cases of *C. neoformans* myocarditis in patients with AIDS (58, 182). Since then, myocardial infection with *C. neoformans* has been observed in numerous autopsy studies on patients with AIDS (61, 62, 64, 66, 67, 69-71, 99, 100, 183, 184). Cryptococcal infection of the myocardium is characterized by the presence of yeast cells diffusely infiltrating the myocardium with minimal acute or chronic inflammation (Figure 2). Foci of myocardial cell necrosis may be present. Although overt cardiac manifestations were infrequently seen in AIDS patients with myocarditis (66, 99), ECG abnormalities and congestive heart failure associated with a fatal outcome has been described (185).

3.4. *Coccidioides immitis*

Symptomatic disseminated disease occurs in 0.5% of people infected with *C. immitis*, which is an endemic dimorphic fungus found in the lower Sonoran life zone of the Americas, which in the US corresponds to the southwestern states (186). Although severe coccidioidomycosis is more common in patients with immunodeficiencies, dissemination can occur in immunocompetent hosts (186). Autopsy studies indicate that 9 to 28% of patients with disseminated coccidioidomycosis have myocarditis (43, 187, 188). There are numerous cases reported of disseminated

infection with spherules identified in the myocardium (43, 104, 187-195). Myocardial abscesses are characterized by central zones of necrosis containing spherules both inside and outside of multinucleated giant cells accompanied by a diffuse interstitial mononuclear cell infiltrate (104, 188). Of note, organisms are not always found in the inflammatory lesions (188, 190). Patients with AIDS are at high risk for hematogenous disseminated infection from *C. immitis* (37, 38, 196) and spherules have been identified in the myocardium of patients with AIDS (197). *C. immitis* is an uncommon cause of fungal endocarditis which may involve the mural endocardium and the underlying myocardium (188, 191). Also in endocarditis, myocardial infection can occur due to hematogenous seeding of the organism (191). Dyspnea and non-specific ECG abnormalities have been reported in myocarditis (188), but these findings are also common in patients with primary pulmonary coccidioidomycosis (187, 198). Symptomatic concomitant pericarditis can occur due to rupture of myocardial abscesses into the pericardial space (187, 188, 194).

3.5. *Histoplasma capsulatum*

The dimorphic fungus *Histoplasma capsulatum* var. *capsulatum* is the most prevalent cause of fungal respiratory infections, infecting approximately 500,000 individuals in the USA each year (199, 200). Severe histoplasmosis is more common in the setting of immunodeficiency, particularly in patients with malignancy (3) or AIDS (37, 38, 201). Prior to the 1980s, infection of the myocardium by *H. capsulatum* was reported infrequently and usually occurred in patients with cancer (21, 202-205). Since then, there have been several cases of *H. capsulatum* myocarditis identified during autopsy studies of patients with AIDS (60, 61, 70, 99, 206). After *Candida* and *Aspergillus*, *H. capsulatum* is the most common cause of fungal endocarditis (1) and myocarditis can occur by hematogenous dissemination (191, 207, 208). Histoplasma granulomas typically contain numerous macrophages filled with yeast cells and have substantial destruction of adjacent myocytes (207). However, in the setting of AIDS, histocytes with intracellular yeast cells may be present between myocardial fibers with minimal inflammation and without granuloma formation (60, 70). Clinically, *H. capsulatum* myocarditis is usually silent; however nonspecific ECG changes and cardiomegaly can occur (209)

3.6. *Blastomyces dermatitidis*

Blastomyces dermatitidis is an endemic dimorphic fungus most prevalent in the midwest and southcentral US. In 1904, Cleary reported a case of disseminated *Blastomyces dermatitidis* where fungal cells were identified in the patient's myocardium (210). Since then many cases of myocardial infection due to hematogenous seeding have been reported (42, 43, 211-217). *B. dermatitidis* endocarditis secondary to direct extension from a pulmonary or mediastinal blastomycotic lesion have been described with associated myocardial abscesses (211, 214, 216). Advanced HIV infection may predispose to severe blastomycosis (218) and cases of disseminated disease with myocardial infection have been reported (65, 218). Myocardial abscesses are characterized by granulomas with central caseation surrounded by giant cells containing *B. dermatitidis* yeast cells (212-214, 219). Myocardial infection with *B. immitis* is usually clinically asymptomatic, but impaired cardiac function has been described (214).

3.7. *Zygomycetes*

Fungi of the Order *Zygomycetes* are uncommon causes of invasive, life-threatening mycoses that characteristically occur in severely immunocompromised individuals or in patients with diabetic ketoacidosis (220). Myocardial infections most often occur in patients undergoing treatment for cancer, particularly leukemia and lymphoma (3, 11, 21, 45, 221-223). Myocardial zygomycosis has also been described in patients with extensive burns (224, 225) and following abdominal surgery (18). Disseminated disease frequently involves multiple organs (223). The pathogenesis of myocardial zygomycosis is by direct extension from adjacent foci of infection (98) or via hematogenous seeding (223). The myocardium is often diffusely infected (223). In only one case was the *Zygomycetes* responsible for myocardial infection speciated, *Cunninghamella bertholletiae* (226). *Zygomycetes* have a propensity to invade blood vessels (225). Cardiac infection has been associated with thrombosis of coronary arteries and subsequent hyphal invasion through the walls of vessels resulting in myocardial infarction (3, 11, 104, 223, 225, 226).

3.8. *Phaeohyphomycoses*

Disseminated phaeohyphomycoses are uncommon infections due to dematiaceous or pigmented (melanized) filamentous fungi. In a recent literature review of disseminated phaeohyphomycosis, Revankar et al reported that cardiac infection occurred in 25 of 72 patients, with myocardial involvement in 14 (19%) cases (227). Malignancy (47, 228-233) and organ transplantation (227, 234, 235) were common risk factors for invasive disease. Myocardial phaeohyphomycosis has occurred in a patient with AIDS (230), following cardiac surgery (236), and in a premature infant (237). Although no specific clinical information was provided, Atkinson et al identified 7 patients with cardiac phaeohyphomycosis (47). Six patients had myocardial involvement, with the myocardium solely involved in 3 patients, myocardium and endocardium in 1, and pericardium and myocardium in 2. Myocardial involvement was characterized by the presence of numberous dark hyphae with chlamydoconidia with extensive necrosis and vascular invasion (234). Species identified in cases of myocardial infection included *Scedosporium prolificans* (229-233, 235), *Myceliophthora thermophilia* (228), *Exophiala jeanselmei* (236), *Bipolaris specifera* (227, 234), and *Bipolaris* species (237).

3.9. *Fusarium*

Fusarium species rarely cause systemic disease, and are only pathogenic in the setting of severe immune dysfunction (238). Myocardial infection has been reported in patients with severe burns (239), during treatment for lymphoma (240), and following bone marrow transplantation (241, 242). All cases of myocardial

infection have occurred in patients with multi-organ infection. Numerous myocardial microabcesses are commonly identified with prominent fungal angioinvasion (241, 242). *Fusarium* species identified in these patients include *F. moniliforme* (240, 241) and *F. oxysporum* (242).

3.10. *Trichosporon beigelli (cutaneum)*

Trichosporon beigelli (cutaneum) is a frequent cause of superficial mycotic infection and also associated with invasive disease in significantly immunosuppressed hosts (243-245). Disseminated multiorgan infection (82%) is the most common form of invasive disease, which includes frequent infection of the heart (244). Disseminated disease with myocardial abscesses most often occurs in patients with acute leukemia (245-252). Myocardial infection has also been reported during immunosuppressive therapy (253). Myocardial abscesses consist of necrotic tissue with dense masses of hyphae and yeast cells and varying amounts of inflammatory cells in surrounding tissue (248(Walsh, 1986 #349))(251).

3.11. *Blastoschizomyces capitatus*

Blastoschizomyces capitatus is a member of the Phyllum Ascomycota that until recently was considered to be in the Phyllum Basidiomycota and was formerly identified as *T. captitatum. B. capitatus* is an emerging opportunistic fungus in immunosuppressed patients (254). Myocardial infection during disseminated disease has been demonstrated in patients undergoing bone marrow transplantation (255, 256) or chemotherapy for leukemia (257, 258). Myocardial abscesses are characterized by the presence of pleomorphic yeast-like cells and septate hyphae with myocardial necrosis. Hyphae may also have affinity for vessel walls (258).

4. CONCLUSIONS

Invasive fungal disease became increasingly common in the second half of the 20th century. In particular, the incidence of serious candidal infections has risen dramatically (259) and *Candida sp.* are currently responsible for nearly 8% of nosocomial bloodstream infections (260). *Candida sp.* are a major cause of morbiditity and mortality, particularly in premature infants, patients infected with HIV and neutropenic patients (39, 261-265). Mortality rates of 39% in neonates (266) and 38% in patients with AIDS (39) have recently been reported. The use of intensive cytotoxic and immunosuppressive therapies for malignancies and organ transplants has substantially increased and the incidence of fungal disease has similarly risen (267-270). Prior to the modern use of chemotherapy, less than 5% of patients with hematological malignancies died of fungal infection compared to more recent reports of death rates of 40% or higher (271). Severe fungal infections now occur in up to 50% of bone marrow transplant patients and 10% of solid organ transplant recipients (272). In neutropenic patients, as many as 40% of fungal infections are disseminated and more than 70% of these mycoses are fatal (262). At present, antimicrobial use continues to have tremendous impact on the epidemiology of nosocomial infections, including fungal disease (273). Catheters, particularly central venous catheters, continue to be a major source of entry for fungal pathogens, particularly *Candida* (264, 266, 273, 274), and recent data suggest that the use of heparin to maintain patency of catheters may significantly enhance the pathogenicity of *Candida* (275).

The reviewed data indicate that a significant number of individuals with disseminated fungal disease will develop myocardial infection. However, invasive fungal diseases are frequently difficult to diagnose. Routine microbiological testing often fails to identify fungal pathogens. For some pathogens, such as *H. capsulatum*, serological testing may facilitate proper diagnosis (276, 277). Although not routinely available, molecular methods such as PCR for detecting DNA from clinical specimens are being developed (278-290). Myocardial involvement is often clinically silent. Clinical symptoms of dyspnea usually are attributable to concomitant pulmonary infection. In general, ECG findings are not helpful in determining whether there is myocardial infection (110). Similarly, endomyocardial biopsy is insensitive (291, 292). Nevertheless, if a patient mounts an inflammatory response in the cardiac tissues, analysis of the infiltrating cell type in the myocardium may be helpful. In most cases of infectious myocarditis, T-lymphocytes and macrophages predominate, whereas neutrophils and macrophages are more common in fungal myocarditis (292). Echocardiography, particularly, transesophageal echocardiography, has had some success in diagnosing fungal myocarditis when endocardial abnormalities were present (143, 158, 162, 293). Magnetic resonance(MR) imaging, particularly using spin echo, cine MR angiography and contrast enhanced spin echo imaging, has been used to identify the presence of myocarditis (294-297). MR imaging may be helpful in diagnosing myocarditis in the setting of disseminated fungal disease with signs or symptoms of disturbed cardiac function.

In order to better define the current incidence of myocardial infection by fungi, prospective investigations examining rates of dissemination, clinical findings, and outcomes are necessary. Although new methods for diagnosing fungal infections by microbiological and radiographic methods are being investigated, diagnosis of fungal disease remains problematic. Unsuspected fungal infections are often detected during autopsy (160). This is in agreement with publications noting that clinical and autopsy diagnoses can differ by over 44% (298, 299). However, autopsy rates have significantly declined (300) to rates of around 9% for most hospitals, and many hospitals have autopsy rates at 0% (301). Autopsy studies can assist in defining the pathogenesis of fungal infection (ie. hematogenous or contiguous spread) and continue to play an important role in identifying fungal disease.

Given the increased risk of fungal infection, standard clinical practice empirically employs antifungal therapy in febrile immunocompromised individuals unresponsive to antibacterial drugs (302-306). Current clinical practice dictates that all candidemias should be treated since this pathogen frequently causes metastatic disease (261). Additionally, primary prophylaxis is

standard in the management of immunosuppressed oncology patients (304). Prophylactic antifungal therapy directed against *Candida* also decreases the incidence of serious candidiasis in premature infants (307) and in patients with AIDS (303, 308-311). Although costly, the introduction of liposomal amphotericin, with its reduced nephrotoxicity and infusion-related reactions, has improved our ability to treat certain patients with invasive fungal disease (312). The first available pneumocandin, Caspofungin, which inhibits the synthesis of the 1,3-beta-D-glucan component of the cell wall in diverse pathogenic fungi, may increase our ability to treat fungal infections (313, 314). Voriconizole, a second-generation triazole, is currently in phase III clinical trials and has recently been shown to be comparable with amphotericin B preparations for the empirical treatment of febrile neutropenics (315) and effective in the primary treatment of invasive pulmonary aspergillosis (316). Better treatment regimens and more rapid institution of antifungal therapy may reduce the incidence and improve the outcome of disseminated fungal disease.

5. ACKNOWLEDGEMENTS

This work was supported by NIH grant AI-01489. The author sincerely thanks Drs. P. Murphy and J.S. Nosanchuk for their critical reading of the manuscript.

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Key words: Fungus, Blastoschizomycoses, Candidiasis, Myocarditis, Aspergillosis,Cryptococcosis, Histoplasmosis, Phaeohyphomycosis, Trichosporosis, Fusarium, Zygomycosis, Review

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