

# *Aspergillus Pericarditis:*

## *Clinical and Pathologic Features in the Immunocompromised Patient*

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There has been a proliferation of infectious complications due to Aspergillus in patients receiving chemotherapy for cancer and transplantation; however, aspergillus pericarditis has been rarely described. Reported here are the clinical and pathologic findings of Aspergillus pericarditis in six immunocompromised patients who came to autopsy in the past 11 years. Five had leukemia, one had received a renal transplant. All had pulmonary aspergillosis. Two had clinically overt pericarditis leading to cardiac tamponade and death. Pulmonary aspergillosis preceded development of pericardial signs. Chest radiographs, serial electrocardiograms, and echocardiograms showed abnormality but were nonspecific. Pericardiocentesis was performed in one patient but proved nondiagnostic and yielded only transient hemodynamic improvement; postmortem Gram stain of the spun sediment of that pericardial fluid revealed branched hyphae. Although five patients received Amphotericin B, whether it entered the pericardial space is uncertain. Postmortem examination revealed extensive pericardial involvement by Aspergillus associated with effusions as large as 1000 ml. Aspergillus penetrated the pericardium by rupture of myocardial abscesses and invasion from contiguous pulmonary foci into the pericardial space. A clinical diagnosis of Aspergillus pericarditis was never established, and at least two died of their pericardial disease. Aspergillus pericarditis is a lethal cardiac infection, which is likely to increase in frequency, and should be considered in the hemodynamically unstable immunocompromised patient, especially when signs of pericarditis or pulmonary aspergillosis are present.

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THE SPECTRUM OF INFECTIVE pericarditis has changed over the past four decades; opportunistic fungi now constitute an infrequent but important group of agents causing pericarditis.<sup>1-3</sup> Invasive aspergillosis has become an increasingly prevalent disease in immunocompromised patients.<sup>4,5</sup> A recent study has described a substantial increase in the incidence of systemic aspergillosis in hospitalized patients between 1970 and 1976.<sup>6</sup> Aspergillus pericarditis has been described as a fatal complication of invasive aspergillosis in only two reported cases<sup>7,8</sup>; it has been mentioned as one of many conditions produced by this organism in patients with systemic Aspergillus infections.<sup>4,5</sup> Aspergillosis is difficult to diagnose clinically and, as a cause of pericarditis, often eludes recognition until postmortem examination. To determine the clinical features and

underlying pathology that may facilitate earlier clinical recognition of Aspergillus pericarditis in the immunocompromised patient, we studied the six such patients coming to autopsy.

### Materials and Methods

The medical records from the past 20 years and the autopsy files since 1889 of the Johns Hopkins Hospital were reviewed for a diagnosis of Aspergillus pericarditis or Aspergillus infection of the heart. The hearts of all autopsied patients with aspergillosis were examined for evidence of infection of the heart. Patients were included in this study if Aspergillus organisms histologically involved the pericardial space and the parietal or visceral pericardium. All available medical records, electrocardiograms, radiologic studies, autopsy records, and postmortem material were analyzed. A seventh patient with adenocarcinoma of the colon also had Aspergillus pericarditis, but since evidence for his immuno-suppressed state was insufficient, he was not included in this study. During their hospital courses, all patients had multiple cultures of blood, urine and sputum. Cerebrospinal fluid (CSF), stool, and nasopharyngeal cultures were available from the leukemia patients. Only one pericardiocentesis was performed.

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TABLE I. Pertinent Clinical Findings in *Aspergillus* Pericarditis

	Age	Sex	Primary disease	Fever	Physical signs	Multiple or prolonged antibiotics	Cortico-steroids	Chemo-therapy	Amphotericin
Patient 1	29	F	Renal transplantation	+	Hypotension	+	+	+	-
Patient 2	16	F	Myelomonocytic leukemia	+	Rales, jugular venous distention, hypotension	+	+	+	+(&)
Patient 3	61	F	Chronic lymphocytic leukemia	+	Pericardial friction rub, hypotension, pulsus paradoxus	+	+	+	+
Patient 4	16	F	Acute myelogenous leukemia	+	Rales, hypotension, pleural effusion	+	-	+	+
Patient 5	27	F	Chronic myelogenous leukemia	+	Pleural effusion, pericardial friction rub, hypotension, pulsus paradoxus, jugular venous distention, Kussmaul's sign	+	+	+	+(&)
Patient 6	29	F	Acute myelogenous leukemia*	+	Rales, decreased breath sounds in LLL	+	+	+	+

\* Bone marrow transplantation and amphotericin with 5-fluorocytosine.

### Patients Studied

For the six patients identified at autopsy with *Aspergillus* pericarditis, 4 to 11 blocks of heart and pericardium were studied. Sections suspected of having fungi were stained with Gomori's methenamine silver stain and periodic acid Schiff stain. A diagnosis of *Aspergillus* was based upon fungi in tissue histologically consistent with *Aspergillus*. Postmortem cultures were obtained of lung in five cases and from pericardium in one case. Four cases had positive cultures for *Aspergillus*. Microscopically, *Aspergillus* was characterized by dichotomously angular branching septate hyphae with branching at approximately 45°. The uniform hyphal diameter ranged from 4 to 6 µm, and focal cystic hyphal dilatation was occasionally present. Lesions typically had parallel arrangement of hyphae and in one culture-proven case also had radial arrangement of hyphae. *Aspergillus* pericarditis was defined by histologic evidence of hyphae penetration into the pericardial space in all six patients postmortem. Disseminated aspergillosis confirmed postmortem over an 11-year period occurred in 74 patients, of whom 21 had *Aspergillus* infections of the heart. Four with *Aspergillus* pericarditis died within the last three years.

### Results

#### Clinical Findings (Tables 1 and 2)

All six patients were women. Ages ranged from 16 to 61 years with a mean age of 30; two patients were 16 years old. Mean duration of hospitalization was 47

days. All patients received cytotoxic agents. Corticosteroids were administered to four leukemics and the renal transplant recipient. The five treated leukemic patients had leukopenia with leukocyte counts ranging from less than 100 to 1000/mm.<sup>3</sup> All patients were febrile despite broad spectrum antibiotic therapy. Five patients had sepsis due to another organism. Three of these had at least one documented episode of gram-negative sepsis, and a fourth had *Candida* sepsis and meningitis. Two patients had overt clinical features of pericarditis, pericardial effusion, and pericardial tamponade, including jugular venous distention, pulsus paradoxus, and hypotension; pericardial friction rub preceded the onset of tamponade in both patients. However, four patients had no clinical evidence of *Aspergillus* pericarditis.

Chest radiograph showed widening of the cardiac diameter in two of six patients (Fig. 1). Pleural effusions were also present in two of six patients and were related to pleural aspergillosis. Five patients had progressive pulmonary infiltrates, which pathologically corresponded to *Aspergillus* pneumonia. Pleural effusion and/or progressive pulmonary infiltrates preceded pericardial signs in Patients 3 and 5 (Fig. 1). Serial electrocardiograms were available in three patients (no. 2, 5, and 6), and all showed abnormalities. These consisted of inverted T waves in precordial leads in Patient 2 who had myocardial and visceral epicardial infection; sinus tachycardia, decreased voltage, and ST segment elevation in I, II, V<sub>3</sub> through V<sub>6</sub> in Patient 5 with large pericardial effusion; and sinus tachycardia with T wave inversion and ST segment depression in lateral leads

TABLE 2. Laboratory Features of *Aspergillus* Pericarditis

	Leukopenia (<1000/ mm <sup>3</sup> )	Chest radiograph	Electro- cardiogram	Echo- cardiogram	Cultures of <i>aspergillus</i>	Pericardio- centesis	Other cultures
Patient 1	-*	Widespread infiltrates	NSSTTC	N.D.	-	N.D.	-
Patient 2	+	Pulmonary edema	Inverted T waves in precordium	N.D.	Postmortem lung: <i>A. flavus</i>	N.D.	<i>Candida tropicalis</i> (CSF and skin lesion)
Patient 3	+	RLL infiltrates, widened cardiac diameter	NSSTTC	N.D.		N.D.	Gram-negative sepsis
Patient 4	+	Pleural effusions and lower lobe infiltrates	NSSTTC	N.D.	Nasopharynx, stool pleural effusions; postmortem lung: <i>A. flavus</i>	N.D.	<i>S. epidemidis</i> and gram-negative sepsis
Patient 5	+	Pleural effusion	Sinus tachycardia, decreased voltage, and ST elevation in I, II, V3-6.	Large pericardial effusion	Postmortem lung and pericardium: <i>A. flavus</i>	Serosanguinous fluid, negative culture	<i>S. epidemidis</i> and gram-negative sepsis
Patient 6	+	L.I.L nodule infiltrate	Sinus tachycardia, T wave inversion, ST depression	N.D.	Postmortem lung and kidney: <i>A. flavus</i>	N.D.	<i>S. epidemidis</i> sepsis

\* 1200 leukocytes/mm<sup>3</sup>.

N.D. = not done.

NSSTTC = nonspecific ST and T-wave changes.

PM. = Postmortem.

in Patient 6 who had a 2 cm diameter myoepicardial left ventricular free wall abscess. Echocardiography confirmed the presence of pericardial effusion in Patient 5 (Fig. 1) but was not performed in other patients.

Multiple cultures of blood, urine, sputum, stool, and CSF were obtained from these patients during their hospital course. Although, as noted in Table 2, other non-Aspergillus organisms were identified, Aspergillus was identified by culture during life in only one patient (no. 4) by thoracocentesis and culture of pleural fluid. Pericardiocentesis was performed in only one patient (no. 5) with removal of 120 ml of serosanguinous fluid. Gram stain and culture of this patient's pericardial fluid, soon before her death, grew no organisms. The pericardial fluid protein was 2.8 g/dl and glucose 392 mg/dl; serum total protein was 4.8 g/dl and serum glucose 318 mg/dl. Erythrocytes were too numerous to count, leukocytes measured 521/mm<sup>3</sup> with 76% polymorphonuclear neutrophil leukocytes and 24% monocytes. Although pericarditis was recognized, the clinical diagnosis of pericarditis resulting from Aspergillus infection was not established in any of the patients studied.

Amphotericin B was administered to the five leukemia patients in doses ranging from 0.6 to 1.0 mg/kg/24 hrs. Two leukemic patients also received 5-fluorouracil. However, pericardial tamponade progressed in two patients despite administration of antifungal agents. Pericardiocentesis performed in one patient (no. 5) afforded only transient hemodynamic improvement

with systolic blood pressure rising from 90 to 160 mm Hg, only to decline to less than 90 mm Hg two days later. Pulsus paradoxus of 45 mm Hg was also temporarily reduced to 20 mm Hg but returned to the same level two days later. Both patients (nos. 3 and 5) died within one week after the onset of signs of pericardial constriction.

#### Postmortem Findings

Autopsies were performed on all patients. Pertinent postmortem findings are summarized in Table 3. Aspergillus pericarditis was present as visceral pericarditis and/or parietal pericarditis. Four patients had visceral pericarditis with extension of myocardial abscesses through the epicardium into the pericardial space (Fig. 2). Penetration of myocardial abscess into the pericardial space was the most common mechanism of spread of Aspergillus through the pericardium. A fifth patient (no. 5) had extension of organisms from contiguous pleural foci through the parietal pericardium and into the pericardial cavity but with no myocardial invasion (Fig. 3). Both contiguous pleural foci and myocardial abscesses penetrated the parietal and visceral pericardia, respectively, in another patient (No. 4). A patchy or diffuse fibrinous pericarditis was present in four patients (nos. 1, 3, 5, and 6). Single or multiple, raised, 1-25 mm nodules or plaques of Aspergilli involved one or both pericardial surfaces in all patients (Table 3). Four patients (nos. 1, 2, 4, and 6) had Aspergillus peri-

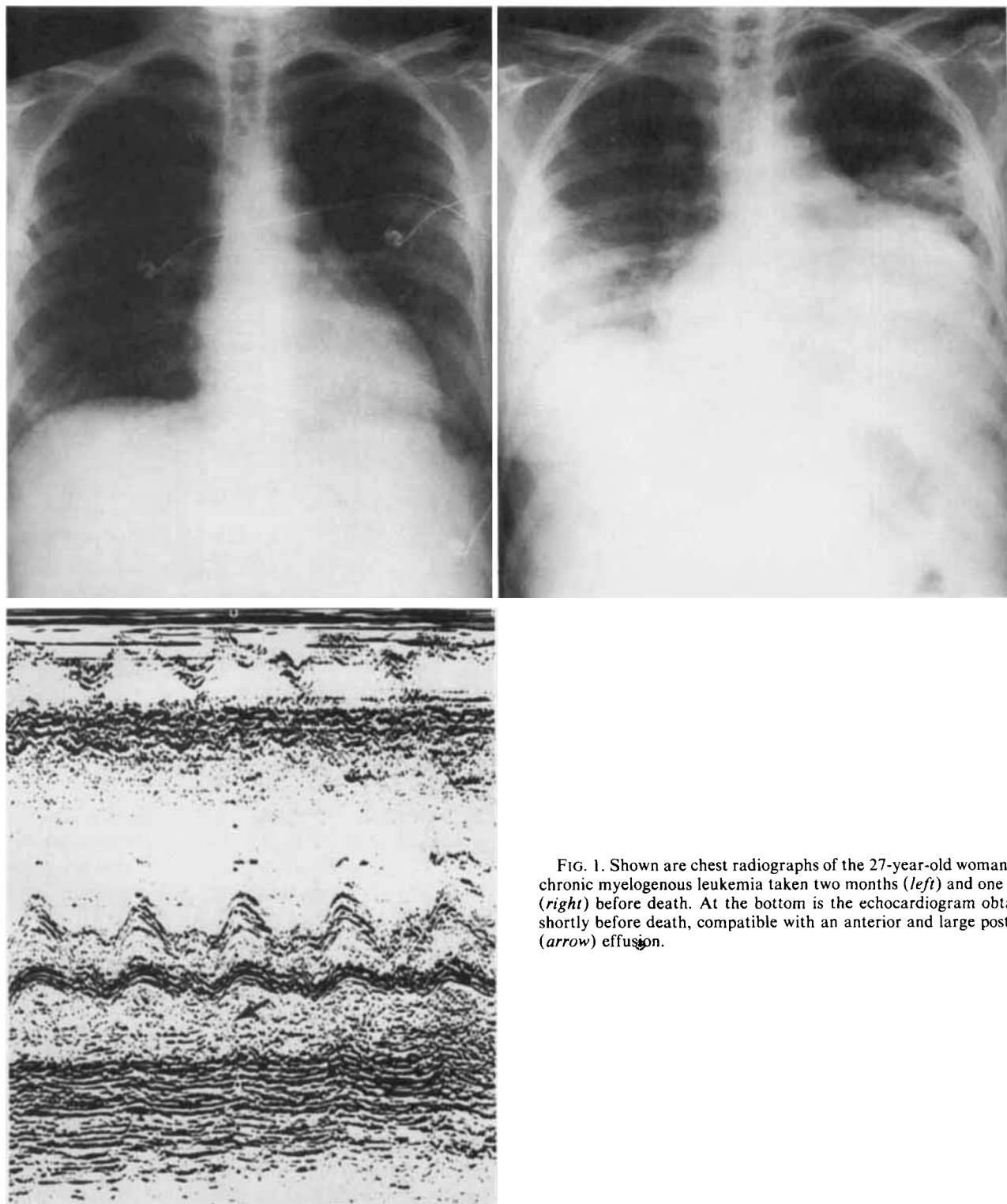


FIG. 1. Shown are chest radiographs of the 27-year-old woman with chronic myelogenous leukemia taken two months (*left*) and one week (*right*) before death. At the bottom is the echocardiogram obtained shortly before death, compatible with an anterior and large posterior (arrow) effusion.

carditis with involvement of endocardium, myocardium, and pericardium. Tense serosanguinous pericardial effusions of 600 ml and 1000 ml were present in the two patients (nos. 3 and 5) who suffered pericardial tamponade. Gram stain of 12 cc of the postmortem pericardial fluid of Patient 5 revealed septate angular branching hyphae of *Aspergillus*. Four patients had

positive postmortem cultures. *Aspergillus flavus* was cultured each time. The pericardial surface was cultured directly in only patient (no. 5) and grew *A. flavus*. Pericardia of granulocytopenic patients demonstrated unchecked proliferation of organisms with scant inflammatory response in a fibrinous exudate.

All patients had invasive pulmonary aspergillosis.

TABLE 3. Pertinent Pathologic Findings in *Aspergillus* Pericarditis

	Pericardial effusion (cc) (>50 cc)	Parietal pericardium	Visceral pericardium and myocardium	Pancarditis	Pleural aspergillosis	Extracardiac involvement by aspergillus	Immediate cause of death
Patient 1	—	+	+	+	+	Lungs, brain, eyes, liver, spleen, thyroid, intestines, peritoneum	Pulmonary septic emboli
Patient 2	—	—	+	+	—	Lungs, brain, eyes, kidneys, spleen, thyroid, skin, intestines, spinal cord	Pulmonary hemorrhage
Patient 3	1000	—	+	—	+	Lungs, larynx, kidneys, bladder, esophagus, stomach, vagina	Pericardial tamponade
Patient 4	—	+	+	+	+	Lungs	Pulmonary aspergillosis
Patient 5	600	+	—	—	+	Lungs	Pericardial tamponade
Patient 6	—	—	+	+	+	Lungs, brain, kidneys, esophagus, and breast	Pulmonary aspergillosis

Two patients nos. 4 and 5) with pleural aspergillosis had clinical histories of unilateral pleuritic pain and pleural effusion. Two patterns of extracardiac involvement were present. Four patients had widespread dissemination. Aspergillus infections in the other two were confined to the heart, lungs, pleurae, and pericardia; extension of contiguous pleural foci into parietal pericardium occurred in both.

The lungs were apparent sources of infection in all patients. Four patients died from pulmonary aspergillosis and its thromboembolic complications. Cardiac tamponade was the cause of death in two patients (nos. 4 and 6).

### Discussion

In recent years infections due to *Aspergillus* have increased. Early reviews of nontuberculous infective pericarditis did not even describe *Aspergillus* as a cause.<sup>1</sup> However, the spectrum of purulent pericarditis has changed considerably since the advent of antibiotics and immunosuppressive agents<sup>2,3</sup> and now includes *Aspergillus* as an uncommon, albeit lethal cause of pericarditis.<sup>7-9</sup> Other fungi that have also been described as causes of pericarditis include *Histoplasma capsulatum*,<sup>10</sup> *Coccidioides immitis*,<sup>11</sup> *Blastomyces*,<sup>12</sup> and *Candida*.<sup>13</sup> Early reports described *Aspergillus* pericarditis as nodular lesions on the parietal or visceral pericardial surfaces<sup>14,15</sup> or as a fibrinous pericarditis,<sup>16,17</sup> but electrocardiographic changes of pericarditis were described with no other clinical documentation for peri-

cardial infection.<sup>14</sup> An immunocompromised patient who had clinically overt and fatal *Aspergillus* pericarditis with cardiac tamponade was later reported.<sup>7</sup> Subsequent studies of large patient populations with aspergillosis also cite pericardial invasion in the spectrum of disease.<sup>4,5</sup>

Leukopenia, leukemia, cytotoxic agents, and corticosteroids predisposing patients to disseminated aspergillosis have been well described<sup>4,5,18-20</sup> and not surprisingly are similar to those seen in the patients studied here with *Aspergillus* pericarditis (Table 1). Although postthoracotomy bacterial pericarditis has become a bigger problem,<sup>21</sup> the frequency of *Aspergillus* pericarditis has increased in a different clinical setting: the immunocompromised patient.

The most common mechanism of invasion of the pericardial space in our patients was rupture of a myocardial abscess into the pericardial space. The organism also extended from a contiguous pleural focus through the parietal pericardium in two patients with clinically evident pleural aspergillosis. *Aspergillus* pericarditis caused pericardial tamponade in two patients; pulmonary aspergillosis was the more overwhelming problem and cause of death in the other four patients. Successful therapy of invasive aspergillosis depends upon early diagnosis and prompt antifungal therapy.<sup>22</sup> *Aspergillus* precipitins<sup>5</sup> and surveillance nose cultures<sup>23</sup> may aid in early recognition. Pulmonary infiltrates, pleuritic pain, and pleural effusion due to *Aspergillus* all preceded cardiac tamponade. Once clinical evidence of pericarditis appeared, a rapidly deteriorating course of tam-

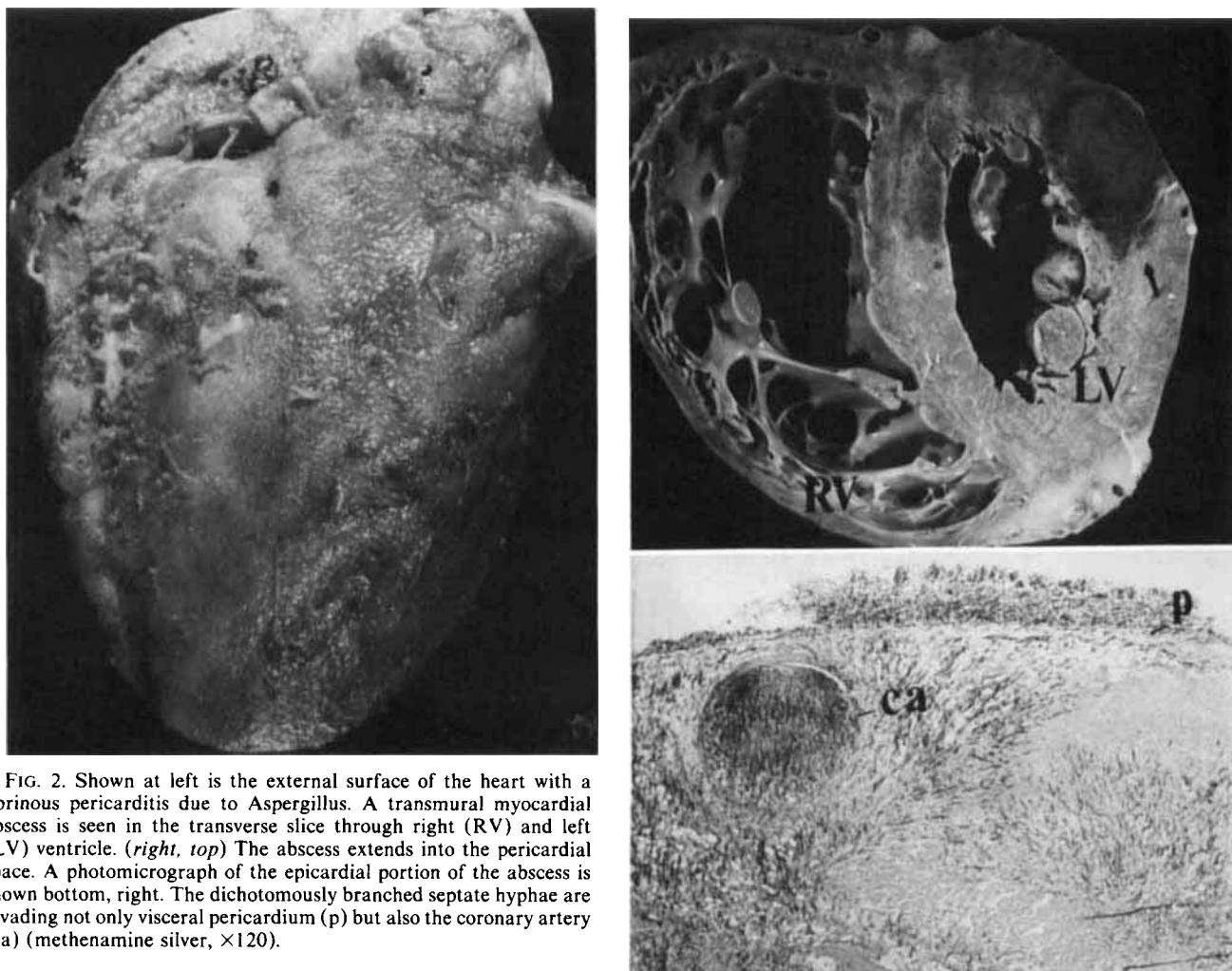


FIG. 2. Shown at left is the external surface of the heart with a fibrinous pericarditis due to *Aspergillus*. A transmural myocardial abscess is seen in the transverse slice through right (RV) and left (LV) ventricle. (right, top) The abscess extends into the pericardial space. A photomicrograph of the epicardial portion of the abscess is shown bottom, right. The dichotomously branched septate hyphae are invading not only visceral pericardium (p) but also the coronary artery (ca) (methenamine silver,  $\times 120$ ).

ponade usually followed within one week in our patients and in others.<sup>7,8</sup> Early identification and treatment of preceding pulmonary aspergillosis before progression to clinically overt pericarditis with progressive hemodynamic deterioration seem especially important, since resolution of pulmonary aspergillosis in the immunocompromised patient is possible.<sup>24</sup>

The diagnosis of *Aspergillus* pericarditis is difficult. Electrocardiographic<sup>25</sup> and echocardiographic<sup>26</sup> changes of pericarditis in a patient with pulmonary or disseminated *Aspergillus* infection suggests an etiology. Large *Aspergillus* pericardial plaques (Fig. 3A) might be detectable by two-dimensional echocardiography, but only one patient studied here had had an echocardiogram. Diagnostic and therapeutic pericardiocentesis would be necessary in the pancytopenic patient in whom *Aspergillus* pericarditis is suspected. Pericardial effusions caused tamponade and death in two of our patients (nos. 3 and 5). Pericardial fluid was scant in the other four patients, in whom *Aspergillus* pneumonia was the cause of death, and a clinical diagnosis of *Aspergillus* pericarditis would have been considerably more difficult in them.

The physical features of the pericardial fluid of *Aspergillus* pericarditis have been described as clear and straw-colored,<sup>27</sup> serosanguinous,<sup>8</sup> and grayish-green purulent<sup>7</sup>; however, biochemical studies, cell counts, and Gram stains were not previously reported on these fluids. Although three previously described cases of *Aspergillus* pericarditis have had culture positive pericardial fluid either premortem<sup>8</sup> or postmortem,<sup>7,27</sup> this organism can be missed. *Aspergillus* was not cultured antemortem from pericardial fluid obtained in Patient 5, but shortly thereafter at autopsy, culture-positive pericardial vegetations were obtained. Gram stain of the spun sediment of pericardial fluid also may reveal the gram-positive branched hyphae.

Systemic fungal infections are difficult to treat.<sup>28</sup> Even as amphotericin B was administered in our patients, pericarditis and pericardial tamponade progressed in two patients. Amphotericin B may not penetrate well into a fibrinous pericardial sac where mesothelium and blood vessels have been destroyed. Intrapericardial instillation of amphotericin B is likely the best means of ensuring adequate levels in pericardial fluid, but a chemical pericarditis may ensue as a com-

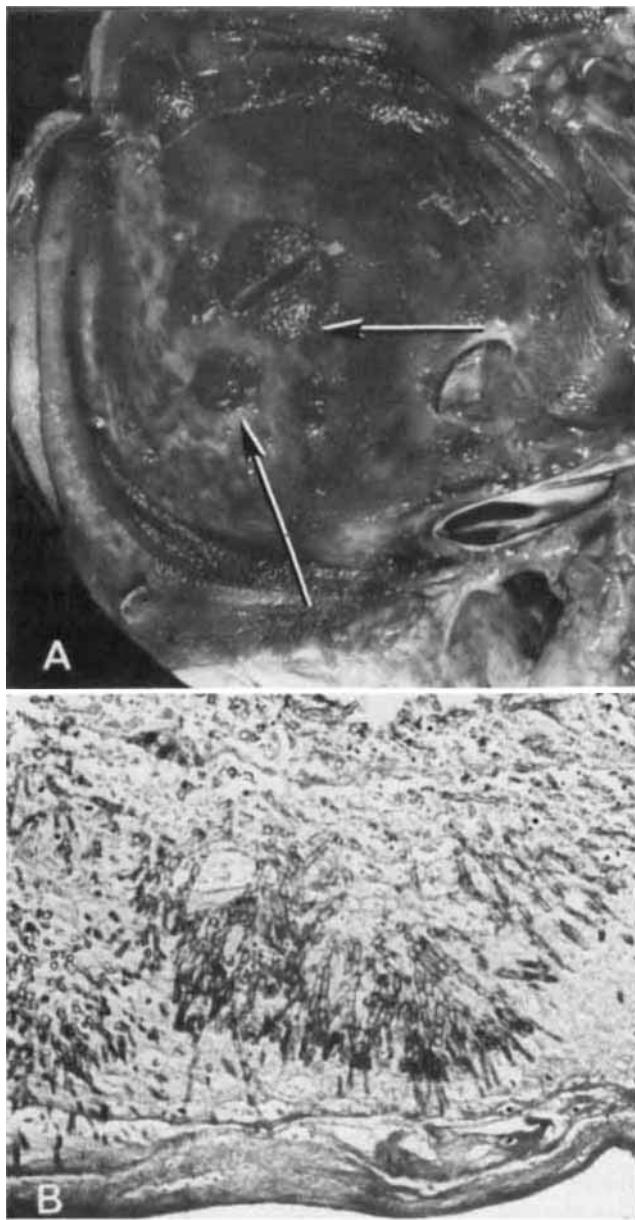


FIG. 3. Shown in A is parietal pericardium with massive colonies of *Aspergillus flavus* forming nodules, which protrude into pericardial cavity. B is a photomicrograph of the parietal pericardium containing the fungus (methenamine silver B,  $\times 400$ ).

plication. Pericardiocentesis only transiently temporized hemodynamic instability. Pericardectomy may be the only definitive means of eliminating the infective foci.<sup>8</sup>

Aspergillus pericarditis is a difficult clinical problem that is likely to increase in frequency among the debilitated and immunocompromised patients who are susceptible to systemic fungal infections. The presence of pulmonary aspergillosis should warrant more careful auscultatory, radiographic, electrocardiographic, and sonographic assessment of changes suggesting Aspergillus pericarditis, which may progress rapidly to tamponade. Aspergillus pericarditis is an uncommon, but

potentially preventable and treatable life-threatening complication of invasive aspergillosis in the immunosuppressed patient.

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