Aspergillus Pericarditis with Tamponade: Report of a Successfully Treated Case and Review

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We report a case of aspergillus pericarditis with tamponade complicating invasive pulmonary aspergillosis in a patient treated for acute lymphocytic leukemia. Prolonged antifungal therapy and aggressive surgical treatment cured the pericarditis, without relapse, despite the fact that the patient underwent autologous bone marrow transplantation. In a review of 28 other cases of aspergillus pericarditis, we found that this condition usually had occurred in severely immunocompromised patients and was always the result of contiguous dissemination of *Aspergillus* from the lung or myocardium. Tamponade was present in eight of 29 patients. *Aspergillus* antigen was detected in the pericardial fluid of all three patients whose fluid specimens were tested. Aspergillus pericarditis was diagnosed before death in 10 of 29 patients, all of whom had established premortem diagnoses of invasive aspergillosis at other sites and had received antifungal therapy. Three of the four survivors received combined medical and aggressive surgical therapies. The performance of echocardiography early during the course of invasive pulmonary aspergillosis, together with intensive combined therapies, might lower the high mortality associated with aspergillus pericarditis.

Invasive aspergillosis (IA) has become a common fungal infection in patients who have profound neutropenia for prolonged periods. The prevalence of IA is estimated to be as high as 70% among patients who have been granulocytopenic for 1 month [1]. IA is also being observed increasingly in patients with solid organ transplants, late-stage AIDS, and diabetes mellitus and in those who have received prolonged corticosteroid therapy. The most frequent sites of IA are the lungs and nasal sinuses, but dissemination occurs in 20%–30% of immunocompromised patients [2]. Cardiac involvement is uncommon and most often manifests as endocarditis or myocarditis [2]. Pericardial aspergillosis is rarely diagnosed before death and has been considered always fatal in neutropenic patients [3]. We report a case of pericardial aspergillosis with tamponade in which combined antifungal and surgical therapies were successful. We also review the cases of aspergillus pericarditis that have been previously reported in the literature.

Methods

We searched the French- and English-language literature from January 1969 to September 1996 with use of MEDLINE for cases of aspergillus pericarditis. We crossed the terms *Aspergillus* and *aspergillosis* with the terms *pericarditis, pericardium, hemopericardium, myocarditis,* and *pancarditis.* We also reviewed the published series and reviews on infectious pericarditis and IA in patients with AIDS, chronic granulomatous disease (CGD), leukemia, lymphoma, and solid organ and bone marrow transplants and in those receiving corticosteroid therapy. References cited in the articles reviewed were also scrutinized for potential additional cases.

A case could be evaluated when sufficient demographic information was available for the clear identification of an individual patient. We considered aspergillus pericarditis to be present in patients who had (1) evidence of clinical and/or macroscopic involvement of the pericardium during the course of histologically and mycologically confirmed IA, without any reported alternative cause of pericarditis; (2) a culture of pericardial tissue or fluid positive for an *Aspergillus* species, whether there were signs compatible with IA or a diagnosis of IA elsewhere; or (3) histological evidence of aspergillosis of the pericardium (i.e., when the report mentioned the presence of invading filamentous fungi after specific staining and when an *Aspergillus* species was isolated from another site).

The following data were also assessed, when available: age; sex; underlying conditions (leukopenia and neutropenia were defined as $<1{,}000$ leukocytes/mm^3 and <500 neutrophils/mm^3, respectively, for >1 week); clinical signs of pericarditis, including hypotension or shock when the report did not mention an alternative cause; electrocardiographic and echographic signs of pericardial involvement; macroscopic aspect of the pericardium and pericardial fluid; other localizations of IA; mycological features; the species of *Aspergillus* recovered; treatment of pericarditis and aspergillosis; outcome; and duration of evolution of the infection or of patient follow-up.

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Cases could not be evaluated when clinical or therapeutic series of purulent pericarditis or IA included cases of aspergillus pericarditis but did not contain sufficient information to identify individual patients or when histological or mycological proof of aspergillar involvement of the pericardium did not fulfill the criteria listed above.

Case Report

A 33-year-old woman who had had insulin-dependent diabetes mellitus since the age of 13 years presented on 8 January 1995 with weakness, headache, and back pain of 1 month's duration. On admission, the WBC count was 39.2×10^9/L with 20% neutrophils and 60% blast cells. Philadelphia chromosome–positive pre-B acute lymphocytic leukemia (ALL) was diagnosed on the basis of the results of bone marrow analyses. CSF findings were normal. Assays for antibodies to HIV and human T-lymphotropic virus type I were negative. ELISA for *Aspergillus* antigenemia [4] was negative.

Chemotherapy with prednisone (80 mg/d), vincristine, idarubicin, and L-asparaginase was begun on 12 January and continued for 28 days. Mild aplasia in the absence of infection was recorded between 10 January and 3 February. Complete remission was achieved after the induction phase of chemotherapy. Consolidation therapy was begun on 21 February, and profound pancytopenia (neutrophil count, $<0.1 \times 10^9$/L) developed on 13 March. The patient's glycemia was well controlled by daily adjustment of insulin doses during the first 2 months of hospitalization.

Fever developed on 15 March and initially resolved with iv antibiotic therapy consisting of piperacillin/tazobactam and amikacin. High-grade fever reappeared on 20 March, in association with left upper-lobe pneumonia. Repeated cultures of blood, urine, bronchoalveolar lavage fluid obtained from the right upper lobe, and bronchial aspirates did not yield any pathogens. A high-resolution CT scan of the thorax revealed a round alveolar condensation of the left upper lobe, with a perilesional halo strongly suggestive of IA; right-base peripheral micronodules and mild right pleuritis were also present. The pericardium was considered normal. Treatment with iv amphotericin B (1.5 mg/[kg · d]) and granulocyte-colony stimulating factor (G-CSF; 300 mg/d) was begun. On 23 March a repeated ELISA for *Aspergillus* antigenemia was positive. The patient's condition worsened, with increasing dyspnea, hypoxemia, hypotension, and right ventricular cardiac incompetence. A chest roentgenogram showed bilateral pleural effusions, cardiomegaly, and diffuse interstitial pulmonary infiltrates. An electrocardiogram showed diffuse microvoltage. An echocardiogram revealed a circumferential pericardial effusion with tamponade.

The patient was admitted to the intensive care unit and underwent surgery for insertion of pleural and pericardial drains, which led to an improvement in her hemodynamic status. Although mycological cultures of pericardial and pleural fluids remained negative, both fluids contained *Aspergillus*-specific antigen, as assessed by latex agglutination [5] and ELISA. The patient recovered from neutropenia on 30 March and defervesced. Therapy with G-CSF and antibacterial drugs was withdrawn on 4 April. A repeated thoracic CT scan was obtained on 7 April and showed an air crescent sign within the left upper-lobe alveolar condensation. Thoracotomy with left upper lobectomy, pericardectomy, and pleuropericardial fenestration was performed on 14 April.

Histological examination of the left upper pulmonary lobe revealed two juxtapleural nodules with large areas of ischemic necrosis, polymorphic inflammation, and numerous arterial microthrombi. Grocott-Gomori methenamine–silver nitrate staining revealed septate and dichotomously branched hyphae colonizing the vascular walls and bronchi. Similar lesions were seen in the pericardium (figures 1A and 1B). Fungal and bacterial cultures of lung and pericardial specimens were negative.

After surgery, therapy with amphotericin B (total cumulative dose, 1.8 g) was switched to po itraconazole (loading dose, 200 mg t.i.d. for 1 week, then 200 mg b.i.d.). The antineoplastic chemotherapy was then continued, and aplasia did not recur. HLA (human leukocyte antigen) phenotyping was performed and revealed no match between the patient and her only brother. In November 1995, she underwent autologous bone marrow transplantation after receiving induction therapy with high-dose cyclophosphamide and etoposide and total body irradiation, which was followed by aplasia that lasted 3 weeks. No relapse of IA was observed during this aplastic period. Although complete remission was achieved, as assessed by the results of marrow smear analyses, she remained Philadelphia chromosome positive.

The itraconazole dose was tapered to 200 mg/d in December 1995. Serum itraconazole levels (determined with use of high-performance liquid chromatography) always remained >1,000 mg/L throughout follow-up. The patient became negative for *Aspergillus* antigen in August 1995 and remained negative thereafter (determined with use of ELISA and latex agglutination; last determination, January 1996). Findings on repeated thoracic CT scans were normal. In May 1996 the patient's ALL relapsed, her condition deteriorated rapidly, and she died of septic shock caused by *Escherichia coli*. Permission for autopsy was refused. At the time of death, there were no clinical or radiological signs of relapse of IA.

Results

Unevaluable Cases

Aspergillus pericarditis was not mentioned as a distinct entity in early reviews of infective pericarditis [6]. When aspergillus pericarditis was specifically cited in large series before 1980 [7–13], individual patients could not be identified, and these cases were not included in the present review. In such series, aspergillus pericarditis was always documented after death,

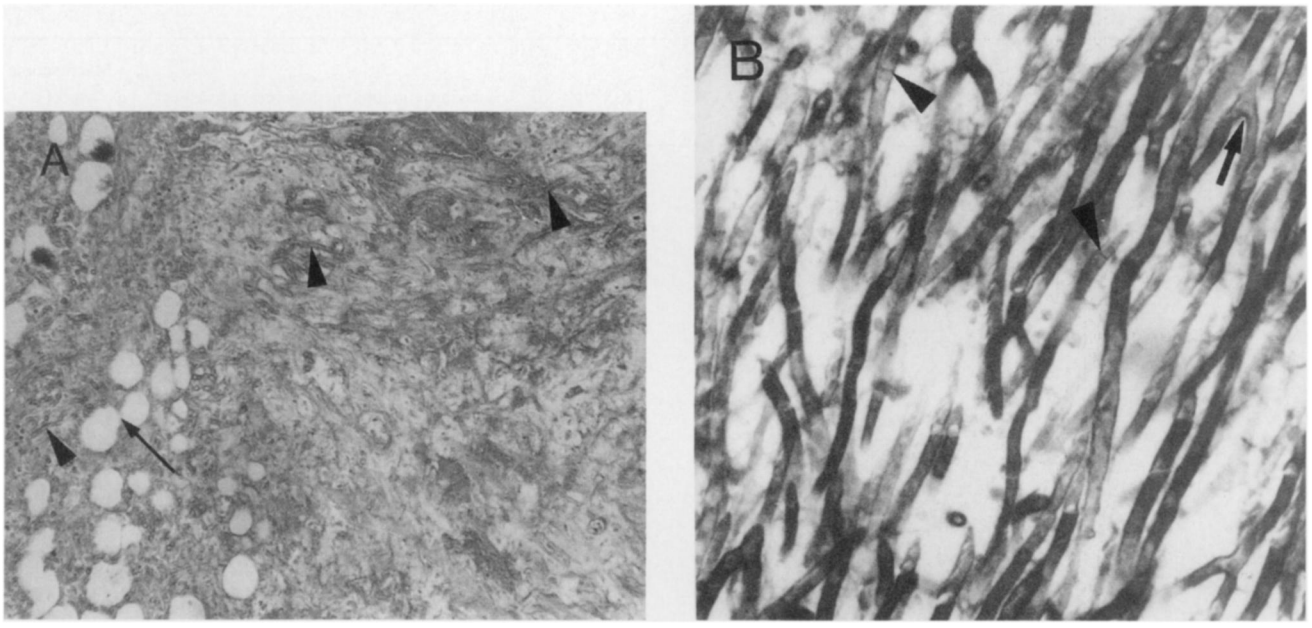

Figure 1. *A,* The pericardium of a patient with aspergillus pericarditis is enlarged due to an edematous inflammatory reaction, which is situated between connective and adipose (*arrow*) tissues and is infiltrated by numerous hyphae (*arrowheads*) (hematoxylin-eosin staining; original magnification, ×30). *B,* Under high magnification with Grocott-Gomori methenamine–silver nitrate staining, *Aspergillus* hyphae are large, regular, and septated (*arrowheads*), with dichotomous branching at 45° angles (*arrow*) (original magnification, ×250).

most often in immunocompromised hosts; death was attributed to tamponade in only one case [12].

Two other cases were not included in the present review because they did not fulfill the criteria listed above [3], and 19 other cases were not included because data or complete histological and/or mycological reports were lacking [14–20]. Among these latter cases, two leukemic children had pneumopericardium that responded favorably to treatment with amphotericin B and pericardial drainage [17, 18].

Evaluable Cases

Twenty-nine cases of aspergillus pericarditis, including our case, were described in greater detail and could be adequately evaluated. These cases are summarized in table 1. The first isolated case was published in 1955 [21].

Evidence in support of aspergillus pericarditis. Aspergillus pericarditis was documented by culture of pericardial tissue or pericardial fluid alone for six patients (21%), by histology alone for 10 (34%), and by both histology and culture for 11 (38%). The two patients described in [23] had no histological or mycological evidence of aspergillus pericarditis, but IA was confirmed at other sites, and there was no other probable cause of pericarditis.

Underlying conditions. Well-defined underlying conditions predisposing to IA were present in 21 cases (72%: hematologic malignancies were present in 16, all but two of which were associated with leukopenia and/or neutropenia, and four of which were secondary to allogeneic bone marrow transplantation; heart transplantation was present in one; CGD was present in two; and AIDS was present in three). Additional risk factors were present in most of these cases: corticosteroid treatment in eight, graft-versus-host disease in two, and insulin-dependent diabetes mellitus in one.

In two cases of chronic aspergillus mediastinitis [25, 28], the underlying condition was not clearly diagnosed, but allergic bronchopulmonary aspergillosis (ABPA) might have been present. Among the patients described in table 1, two of the first four were unusual because their underlying conditions remained unknown even after autopsy [21, 23]. However, all three patients had been treated with corticosteroids. Zimmerman [22] described the case of a neonate with IA involving the pericardium; the only predisposing factor in this case was steroid treatment for suspected adrenal insufficiency. Aspergillus pericarditis developed in one patient after coronary bypass and open-chest cardiac resuscitation were performed; the only other underlying factor was a short-term high-dose steroid regimen [39]. Liver cirrhosis was the only underlying condition in one patient [40].

Signs and symptoms. The clinical onset of IA was acute in 26 (90%) of 29 cases and subacute in the two cases of granulomatous mediastinitis [25, 28]; the only reported case of constrictive aspergillus pericarditis developed 6 years after cure of Hodgkin's disease, in the absence of any other underlying condition [36]. Pericardial involvement was symptomatic in 17 (59%) of the 29 patients. Tamponade or arterial hypoten-

Table 1. Analysis of 29 assessable cases of aspergillus pericarditis.

Reference	Sex/age (y)	Underlying condition(s)	Clinical signs of pericarditis	EKG signs of pericarditis	Echocardiographic findings	Macroscopic aspect of pericardium	Macroscopic aspect of pericardial fluid
[21]	F/24	Acute leukemia? steroid therapy	None	Yes	ND	Abscesses	NA
[22]	M/22 d	Steroid therapy	NA	NA	ND	Normal	Clear
[23]	M/13	Steroid therapy	NA	NA	ND	Fibrinous exudate	NA
[23]	M/36	NA	NA	NA	ND	Fibrinous exudate	NA
[24]	M/44	AML, steroid therapy, leukopenia	NA	NA	ND	Fibrinous exudate, abscesses	Hemorrhagic
[25]	M/25	ABPA?	Cardiac constriction	Yes	ND	Fibrosis, granuloma	No effusion
[26]	M/41	Lymphoma, AML, steroid therapy	Tamponade	Yes	ND	Fibrinous exudate, abscesses	Purulent
[27]	F/38	AML, allogeneic BMT, steroid therapy	Chest pain, pericardial friction rub, tamponade	Yes	Pericardial effusion	Fibrinous exudate	Serosanguineous
[28]	M/33	Tuberculosis? ABPA?	NA	NA	Pericardial mass	Fibrosis, granuloma	No effusion
[29]	M/6	CGD	NA	NA	NA	NA	NA
[3]	F/16	Myelomonocytic leukemia, steroid therapy, leukopenia	Tamponade	Yes	ND	Nodules	NA
[3]	F/16	AML, leukopenia	Hypotension	No	ND	Nodules	NA
[3]	F/27	CML, steroid therapy, leukopenia	Pericardial friction rub, tamponade	Yes	Large pericardial effusion	Fibrinous exudate, nodules	Serosanguineous
[3]	F/29	AML, steroid therapy, leukopenia	No	Yes	ND	Fibrinous exudate, nodules	NA
[30]	F/48	AML, leukopenia, steroid therapy	Chest pain, pericardial friction rub	None	NA	NA	NA
[31]	M/31	Lymphoma, neutropenia	None	None	Normal	Fibrinous exudate	Purulent
[32]	M/40	CML, allogeneic BMT	Pneumopericardium, tamponade	NA	NA	Fibrinous exudate, infarction	NA
[33]	M/41	Heart transplant	NA	NA	NA	NA	NA
[34]	M/44	AIDS, neutropenia	None	NA	Pericardial effusion	NA	NA

Table 1. (*Continued*)

Method of detecting aspergillar pericardial involvement	Other localization(s) of aspergillosis	*Aspergillus* species	Diagnosis of invasive aspergillosis	Treatment of pericarditis and aspergillosis (dosage)	Outcome/duration of follow-up
Culture	Brain, lungs, myocardium, endocardium	NA	Postmortem histology and culture	None	Died/31 d
Culture	Brain, pleura	*A. sydowi*	Postmortem histology and culture	None	Died/30 d
NA	Brain, lungs, pleura, myocardium	NA	Postmortem histology and culture	None	Died/16 d
NA	Brain, lungs, bronchi, myocardium, thyroid, kidneys	NA	Postmortem histology and culture	None	Died/3 mo
Histology	Lungs, myocardium, thyroid, kidneys, spleen, liver	*A. fumigatus*	Postmortem histology and culture	No	Died/4 d
Histology	Lungs, pleura, mediastinum	*A. fumigatus*	Pulmonary biopsy	No	Died/7 y
Culture	Brain, lungs, bronchi, myocardium, endocardium, spleen, thyroid, kidneys, psoas muscle	*A. fumigatus*	Postmortem histology and culture	No	Died/13 d
Histology, culture	Lungs, pleura, myocardium, thyroid, kidneys, intestines	*A. niger*	Histology and culture of pericardial and pulmonary biopsy specimens	Pericardial drainage, AmB (total dose, 750 mg)	Died/NA
Histology, culture	Left lung, pleura, mediastinum	*A. flavus*	Histology and culture of pericardial and pulmonary biopsy specimens	AmB (total dose, 2 g); AmB (total dose, 5 g); ketoconazole	Relapsed Improved Stabilized/NA
Histology, culture	Brain, lungs, kidneys, thyroid, spleen	*A. fumigatus*	Histology and culture of pericardial and pulmonary biopsy specimens	Granulocyte transfusions, AmB (2 mg/[kg · d])	Died/NA
Histology	Brain, eyes, spinal cord, myocardium, endocardium, kidneys, thyroid, skin, spleen, intestines	*A. flavus*	Postmortem histology and culture	AmB (NA)	Died/NA
Histology	Lungs, pleura, myocardium, endocardium	*A. flavus*	Postmortem histology and culture	AmB (NA)	Died/NA
Histology, culture	Lungs, pleura	*A. flavus*	Postmortem histology and culture	Pericardiocentesis; AmB (NA); 5-FC (NA)	Died/NA
Histology	Brain, lungs, myocardium, endocardium, kidneys, esophagus, breast	*A. flavus*	Postmortem histology and culture	AmB (dose NA)	Died/NA
Histology	Lungs, pleura, coronary arteries, spleen, peritoneum	NA	Pleural fluid culture; postmortem histology	AmB (0.6 mg/[kg · d])	Died/NA
Histology	Lungs, coronary arteries	*A. fumigatus*	Postmortem histology and culture	None	Died/NA
Histology, culture	Lungs, pleura	*A. fumigatus*	Sputum culture, histology and culture of pericardial biopsy specimen	Pericardial drainage, AmB (NA)	Died/10 d
Culture	Lungs	*A. fumigatus*	Sputum, bronchoaspirate and pericardial fluid culture	Itraconazole (200 mg/d for at least 4 mo)	Cured/4 mo
Culture	Brain, meninges, lungs	*A. fumigatus*	Histology and culture of lung biopsy specimen	AmB (total dose, 590 mg)	Died/43 d

Table 1. *(Continued)*

Reference	Sex/age (y)	Underlying condition(s)	Clinical signs of pericarditis	EKG signs of pericarditis	Echocardiographic findings	Macroscopic aspect of pericardium	Macroscopic aspect of pericardial fluid
[35]	M/34	CML, allogeneic BMT, GVHD	Chest pain	None	NA	"Green plaques"	NA
[36]	F/26	Hodgkin's disease	Pericardial constriction	NA	NA	Fibrosis	No effusion
[37]	M/41	ALL, allogeneic BMT, GVHD	Chest pain, pericardial friction rub	NA	Pericardial effusion	ND	Purulent
[38]	M/11	CGD	Chest pain	NA	NA	NA	NA
[39]	M/68	Cardiac surgery, steroid therapy	Pericardial friction rub	NA	NA	Necrosis	NA
[40]	F/38	Cirrhosis	Tamponade	NA	Pericardial effusion	Fibrinous exudate	Serosanguineous
[41]	M/29	AML, neutropenia	Chest pain, pericardial friction rub, pneumopericardium	Yes	Air and fluid in the pericardial space	Abscesses, infarction	NA
[42]	M/49	AIDS	Tamponade	Yes	Pericardial effusion	Fibrinous exudate	Serosanguineous
[43]	M/47	AIDS	Pneumopericardium	NA	NA	Abscesses	NA
[PR]	F/33	ALL, neutropenia, diabetes	Tamponade	ND	Large circumferential pericardial effusion	Fibrinous exudate, abscesses, infarction	Clear

NOTE. ABPA = allergic bronchopulmonary aspergillosis; ALL = acute lymphocytic leukemia; AmB = amphotericin B; AML = acute myeloid leukemia; BAL = bronchoalveolar lavage; BMT = bone marrow transplant; CGD = chronic granulomatous disease; CML = chronic myelogenous leukemia; EKG = electrocardiogram; 5-FC = 5-fluorocytosine; GVHD = graft versus host disease; NA = data not available; NC = not cultured; ND = not done.

sion due exclusively to pericardial disease was reported in nine cases (31%). Pneumopericardium was present in three cases, including one with tamponade [32, 41, 43]. Thus, definite clinical, radiographic, electrocardiographic, or echocardiographic signs of pericardial involvement were reported in 18 cases, but only one patient was clearly described as having had no signs of pericarditis [31]; these data were not available for the other 10 cases.

Exploratory interventions. Exploratory interventions were performed before death for 12 patients (41%): pericardiocentesis was performed for five; pericardectomy or pericardial biopsy was performed for four, and both procedures were performed for three. These explorations led to the diagnosis of aspergillus pericarditis during life for 10 patients, all of whom had established premortem diagnoses of IA at sites other than the pericardium and all of whom had received antifungal therapy. In two cases, pericardiocentesis performed before death was not contributive: in one case because the results of direct examination and culture were negative, and in the other because positive results of fungal cultures and tests for specific antigens were obtained only after the patient's death [40].

Histological and mycological data. The pericardial fluid was reported to be purulent in three cases, clear and straw-colored in two cases, and hemorrhagic or serosanguineous in five cases. No pericardial effusion was present in three cases; the presence of pericardial effusion and histological findings were not mentioned in 16 cases. The most frequent macroscopic finding was a fibrinous exudate covering the whole pericardium in association with multiple small abscesses. Results of histological examinations of premortem pericardial tissue were positive for the six patients for whom such results were reported.

On premortem direct examination, pericardial fluid was positive for *Aspergillus* in three of the five cases in which the result was reported. Premortem cultures of pericardial fluid or pericardial tissue were positive in 10 cases. *Aspergillus*-specific antigens were detected in pericardial fluid in all three cases

Table 1. (*Continued*)

Method of detecting aspergillar pericardial involvement	Other localization(s) of aspergillosis	*Aspergillus* species	Diagnosis of invasive aspergillosis	Treatment of pericarditis and aspergillosis (dosage)	Outcome/duration of follow-up
Histology	Brain, lungs, myocardium, endocardium, kidneys, bladder, liver, spleen, intestines, diaphragm	*A. fumigatus*	Postmortem histology and culture	AmB (NA)	Died/2 w
Histology, culture	Mediastinum	*A. fumigatus*	Histology and culture of pericardial biopsy specimen	Pericardectomy, itraconazole (400 mg/d for at least 4 mo)	Improved/4 mo
Culture	Lungs	*A. fumigatus*	Culture of pericardial fluid and BAL fluid	Pericardial drainage, AmB (NA)	Died/NA
Histology, culture	Lung, skin	*A. fumigatus*	Culture of pericardial fluid and skin abscesses	Miconazole iv (NA), AmB (NA), pericardectomy	Died/NA
Histology, culture	Pleura, diaphragm, peritoneum, coronary arteries	*A. fumigatus*	Postmortem histology and culture	None	Died/10 d
Histology, culture, *Aspergillus* antigen in pericardial fluid	Lungs, kidneys	*A. fumigatus*	Postmortem histology and culture	Pericardial drainage	Died/5 d
Histology	Lungs, bronchi, pleura	*A. fumigatus*	Culture of BAL fluid, antigenemia	AmB (1 mg/[kg · d]), itraconazole (400 mg/d)	Died/2 mo
Histology, culture, *Aspergillus* antigen in pericardial fluid	Lungs, myocardium, kidney	*A. fumigatus*	Culture of BAL fluid and pericardial fluid	Pericardial drainage, itraconazole (600 mg/d)	Died/11 d
Histology, culture	Lungs, pleura, myocardium	*A. fumigatus*	Culture of pleural fluid	NA	Died/NA
Histology, *Aspergillus* antigen in pericardial fluid	Lungs, pleura	NC	Antigenemia, histology of pericardium and lung	AmB (total dose, 1.8 g) Pericardectomy, itraconazole (400 mg/d for 12 mo)	Cured/1 y

tested: two cases from the literature (the technique of detection was not specified [40, 42]) and in the present report (by latex agglutination and ELISA).

The *Aspergillus* species responsible for IA were *A. fumigatus* (n = 17, 59% of cases), *A. flavus* (n = five, 17%), and *A. sydowi* and *A. niger* (n = one each, 3%). The *Aspergillus* species was not reported in four cases, and fungal cultures of sites outside the pericardium were negative in one case (the present report).

Other localizations of IA. Concomitant pulmonary localization of IA was present in 25 (86%) of 29 cases, and aspergillus pleural effusion was present in 13 (45%) of cases. The myocardium or coronary arteries were involved in 15 cases (52%), but the former localization was the only specific lesion contiguous to pericarditis in one case. Aspergillus pericarditis was never the only intrathoracic localization of aspergillosis. IA had disseminated outside the thorax in 17 (59%) of the 29 cases.

Treatment and outcome. Ten patients (34%) did not receive any treatment for IA, which was diagnosed at autopsy. Treatment was not mentioned in one case report from a radiological series. Antifungal therapy (amphotericin B and/or itraconazole) was instituted in 19 cases (66%) or combined with pericardectomy or pericardial drainage in eight cases (28%). Improvement, stabilization, or cure was documented for only four patients ([28, 33, 36] and the present report); two of these patients had subacute infections, and three of them received combined medical and aggressive surgical treatment. Pericardial involvement was one of the immediate causes of death for 11 (50%) of 22 patients for whom it was specified.

Discussion

Despite the fact that fungal cultures of pericardial tissue and pericardial fluid from our patient remained negative (she

received a cumulative dose of 1.8 g of amphotericin B before surgery), we clearly documented the presence of aspergillus pericarditis with tamponade. Indeed, our patient presented with well-known underlying conditions favoring the development of IA (i.e., a hematologic malignancy complicated by prolonged neutropenia and corticosteroid therapy), as well as with necrotizing pneumonia and CT scan findings and perioperative features strongly suggestive of IA, the presence of numerous invading hyphae in the lung and pericardium, persistent *Aspergillus* antigenemia, and, finally, the presence of *Aspergillus*-specific antigen detected by two different methods in both pericardial and pleural fluids.

Our case also underlines the difficulty in obtaining a culture-confirmed diagnosis of IA for patients at such high risk. Deep infections due to *Pseudallescheria boydii* and *Fusarium* species can be histologically misdiagnosed as IA, but, to the best of our knowledge, these fungi have never been reported to cause pericarditis and have also not been reported to cause false positivity for *Aspergillus* antigen by either of the two methods now routinely available. Recently developed assays for the detection of *Aspergillus* antigen (ELISA [44] and latex agglutination [5, 45]) can provide important guidance for the decision to initiate antifungal therapy before fungal culture results are available, but these assays are not available worldwide. Their specificities and positive predictive values are estimated to be >95% [5, 44, 45].

To the best of our knowledge, false-positive detection of *Aspergillus* antigen has never been reported in cases of human infections caused by other filamentous fungi, except in one recently reported case of disseminated *Trichoderma pseudokoningii* infection [46]. False positivity due to airborne contamination in the laboratory [47] was unlikely in our case because antigen was persistently detected by use of the two methods in two different laboratories. Estimates of the sensitivities of these tests are diverse, varying from 27.5% to 98% for latex agglutination [5, 45, 48] and from 82.5% to 95% for ELISA [4, 44, 48], and the sensitivities of these tests seem to be lower for bone marrow transplant recipients [48]. It should be noted that specific antigen was also detected in the pericardia of two other patients [40, 42].

Aspergillus pericarditis usually complicates the course of acute IA in patients with various types of immunodeficiencies. In all but one case, including ours, aspergillus pericarditis was due to the contiguous spread of the infection from the myocardium, the adjacent lung(s), or both.

Bronchopulmonary or myocardial aspergillosis was present in all cases summarized in table 1. Myocardial infection was not detected echocardiographically or during exploratory surgery in our patient, and the pulmonary aspergillosis was localized near the heart. Aspergillus pericarditis may rarely present as pneumopericardium [32, 41, 43]. This unusual complication of pulmonary IA, as suggested by the histological report of Müller et al., may result from necrosis of the lower lobe of the left lung, leading to communication between the bronchus and the pericardial space [32]. This description is similar to the pathophysiology of bronchopleural fistula complicating pulmonary IA [49]. Simultaneous pneumothorax and pneumopericardium have been reported in one case [43].

The two cases of granulomatous mediastinitis reported by Hunt et al. [25] and Cooper et al. [28] can be separated from the others cited above. Indeed, the disease evolved over several years; the patients were immunocompetent; aspergillus infection was very extensive, involving the whole left lung and the mediastinum; and the tissular reaction was fibrous and granulomatous, without dissemination outside the thorax. Evidence of ABPA was found in both cases. Such progression of disease may represent either chronic necrotizing pulmonary aspergillosis [50] or, more probably, secondary invasion of tissues during the course of ABPA. The latter has rarely been described with invasion of the lungs [51] or wider dissemination potentially facilitated by steroid treatment [52, 53].

Aspergillus pericarditis was diagnosed before death in only 10 of the 29 reported cases that we could evaluate. This lack of diagnosis may partially explain the poor prognosis associated with aspergillus pericarditis. However, pericarditis was considered to be one of the immediate causes of death for only 11 patients. In most of the other cases reported in the literature, aspergillus pericarditis seems rather to have been part of a widely disseminated fungal infection, discovered only at autopsy. Thus, the frequency of pericardial localization may be underestimated in cases of IA. Systematic echocardiographic study during the course of pulmonary IA could allow better estimation of the prevalence of this complication and probably facilitate improved care of patients because of earlier diagnosis.

When clinical, radiological, electrocardiographic, or echocardiographic symptoms of pericardial involvement were present, the appearance of tamponade usually followed quickly, as in our patient. We report herein the first case of aspergillar tamponade for which treatment was successful. Thus, IA should be considered and empirical antifungal therapy urgently administered when a neutropenic patient develops a pericardial effusion. In this setting, early examination of the pericardium or pericardial fluid by means of fungal culture and testing for *Aspergillus* antigen should also be performed, as these procedures were contributive in most of the cases in which they were performed.

Antifungal treatment, even when combined with surgery, has been ineffective in all but two acute cases of pericardial aspergillosis ([33] and the present report). However, the diagnosis was usually made very late in the course of the disease, and most cases were reported before the generalization of intensive care medicine. The most important factor associated with cure or attenuation of IA is recovery from immunosuppression [1, 54]. Thus, our patient's recovery from neutropenia, possibly accelerated by treatment with G-CSF, with achievement of complete remission of the leukemia, were probably determinants in her cure. Absence of myocardial involvement was perhaps another good prognostic factor for patients who were

cured or whose conditions improved. Indeed, myocardial involvement was not noted in any of these patients, as compared with 11 of the 25 patients who died with well-documented pericardial aspergillosis. Another favorable prognostic factor seemed to be the chronicity of the progression of IA in the other two successfully treated patients who were evaluated [28, 36].

Surgical resection of residual localized pulmonary lesions of aspergillosis after recovery from neutropenia must be considered to prevent secondary bleeding or relapse during a subsequent episode of neutropenia [36, 55]. Because aspergillosis did not recur in our patient during two later episodes of aplasia, her case suggests that such a procedure could also be relevant for patients with pericardial aspergillosis. Indeed, three of the four patients described in the literature whose conditions improved or who were cured were aggressively treated with a combination of antifungal treatment and pericardial surgery ([28, 36] and the present report); the fourth patient [33] underwent pericardial drainage, but pericardial surgery was not mentioned and thus most likely was not performed.

The fact that our patient did not relapse can also be explained by the administration of long-term itraconazole therapy, which was continued until her death; serum drug levels were always maintained at >1,000 mg/mL. Reactivation of fungal infections occurs in more than half of acute leukemia patients during subsequent granulocytopenic episodes, probably because of the persistence of *Aspergillus,* especially in cavitary or poorly vascularized areas [56]. Different preventive therapies have been proposed [57], including long-term itraconazole therapy, with or without iv amphotericin B during aplastic episodes [58], or antifungal therapy alone during aplastic episodes, consisting of either high doses of amphotericin B and 5-fluorocytosine [59] or itraconazole [60, 61]. With such secondary prophylaxis, bone marrow transplantation was successful without relapse of aspergillus infection in a few cases ([60, 61] and the present report).

In conclusion, aspergillus pericarditis usually complicates the course of acute pulmonary IA and remains a life-threatening condition. The diagnosis of aspergillus pericarditis must be considered rapidly when a severely immunocompromised patient develops pericarditis. Detection of *Aspergillus* antigens in pericardial fluid may be an important diagnostic clue. Aspergillus pericarditis with tamponade can be successfully managed if diagnosed early and treated with an aggressive combined medical and surgical approach. Long-term itraconazole therapy may prevent relapse of pericardial IA during subsequent episodes of neutropenia, including those due to autologous bone marrow transplantation.

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