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Aspergillus pericarditis: a case report and literature review

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Abstract

Aspergillus pericarditis is a condition characterized by nonspecific clinical features, making diagnosis challenging. Although relatively uncommon, it is associated with a low diagnostic yield and high mortality. We herein present a case of *Aspergillus* pericarditis alongside a review of similar cases from the literature. This report underscores the importance of enhancing clinicians' awareness of *Aspergillus* pericarditis and emphasizes the need for prompt diagnosis and early initiation of treatment to improve patient outcomes.

Keywords

Aspergillus, pericarditis, isavuconazole, blood galactomannan antigen test, case report, antifungal therapy

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Introduction

Invasive aspergillosis is a fatal opportunistic infection that primarily affects immunosuppressed patients. The lungs are the most common site of *Aspergillus* infection, accounting for 70% of cases, with subsequent dissemination to other organs via the bloodstream.[1] The most common cardiac fungal infections are caused by *Candida* (62%), followed by *Aspergillus* and algae (12%).[2] Cardiac *Aspergillus* infections are rare and typically present as myocarditis or endocarditis, with only a few cases of isolated pericardial involvement reported.[3] Risk factors for cardiac *Aspergillus* infection include organ transplantation,

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granulocyte deficiency, AIDS, chronic granulomatous disease, and the use of steroids or immunosuppressive drugs.[4] The absence of specific signs and symptoms complicates the timely diagnosis of *Aspergillus* pericarditis. This diagnostic delay contributes to a poor prognosis, high mortality, and a low rate of positive biopsy diagnoses, which are often confirmed only postmortem.[2] In this study, we report a case of pericardial *Aspergillus* infection complicated by pulmonary *Aspergillus* ball formation following surgery and provide a literature review of similar cases to enhance clinicians' understanding and management of *Aspergillus* pericarditis.

Clinical data

The reporting of this study conforms to the CARE guidelines.[5] We have de-identified all patient details, and the patient provided written informed consent to publish this report.

The patient was a woman in her 50s who was admitted to the hospital with a 2-week history of coughing and chest tightness. Two weeks prior to admission, she had developed a cough with minimal white mucous sputum production, accompanied by chest tightness and shortness of breath following physical activity. Initially, these symptoms were not taken seriously because there was no fever, chest pain, or blood in the sputum, and the cough did not produce yellow or purulent sputum. However, the symptoms progressively worsened.

A chest computed tomography scan performed after the onset of symptoms revealed a suspected right upper lung carcinoma, right lower pulmonary aspergillosis, enlargement of the right upper lung hilum, and a small amount of pericardial effusion. The patient was admitted to the hospital for further evaluation and diagnosis.

At the beginning of the year, the patient underwent a single-incision thoracoscopic procedure involving resection of nodules in the right upper and lower lobes of the lung, along with lymph node dissection. Postoperative pathology showed the following:

1. Right lower lung: Bronchiolar dilatation in the lung tissues, numerous hyphae in the lumen of the bronchioles, lymphoid hyperplasia in the surrounding lung tissues, and numerous lymph follicles, suggesting fungal infection of the lungs.
2. Right upper lung: Invasive adenocarcinoma with adherent growth as the main type. The tumor measured $2 \times 2 \times 1.5$ cm, with no infiltration of cancerous tissue at the lung margin or metastasis to lymph nodes in groups 2 and 4 (0/3).

The patient did not receive radiotherapy or antifungal treatment after surgery. Eight years earlier, she had been diagnosed with nephrotic syndrome based on increased urinary foam at a local hospital and had since been taking Bering capsules, with no history of long-term glucocorticoid or immunosuppressant use.

On examination, superficial lymph nodes throughout the body were not palpable or enlarged. Two surgical incisions, approximately 2 cm in size, were observed on the right chest wall and appeared to have healed well. On auscultation, breath sounds in both lungs were coarse yet clear, with no evident dry or wet rales. The patient's heart rate was 124 beats per minute, and no abnormal murmurs were detected. Abdominal examination revealed no notable abnormalities, and the lower limbs were not swollen.

On admission auxiliary examination, routine blood tests showed a leukocyte count of 5.53×10^9/L, hemoglobin level of 108 g/L, and platelet count of 211×10^9/L. The neutrophil and lymphocyte counts and ratios were normal. The sedimentation rate was elevated at 27 mm/hour. The C-reactive protein and procalcitonin levels were within

the reference ranges. The (1-3)-β-D glucan antigen test (G test) was 201.9↑, while the blood galactomannan antigen test (GM test) was negative (0.3). Serum tumor markers (alpha-fetoprotein, β2-microglobulin, carcinoembryonic antigen, neuron-specific enolase, squamous cell carcinoma antigen, and ferritin) and autoimmune antibodies (anti-nuclear antibody, anti-dry syndrome A and B antibodies, anti-double-stranded DNA antibody, anti-Sm antibody, anti-Jo-1 antibody, and anti-neutrophil cytoplasmic antibody) were all within the reference ranges.

Cardiac ultrasound revealed normal atrial diameters, ventricular wall thickness, and valve morphology. The left ventricular ejection fraction was 68%, and the maximal depth of pericardial effusion at the apex was approximately 1.5 cm. Ultrasound findings suggested pericardial effusion.

Pericardiocentesis and drainage were performed to investigate the cause of the pericardial effusion. The effusion appeared as bloody turbid fluid, and routine laboratory tests indicated exudative fluid with a cell count of 54,000, a mononuclear cell ratio of 70%, a lobulated nucleated cell ratio of 30%, a lactate dehydrogenase level of 1287 u/L, a glucose level of $<$2.22 mmol/L, and a protein level of 62 g/L. Adenosine deaminase, carcinoembryonic antigen, and X-pert tests were normal.

Pathological examination of the pericardial effusion revealed mesothelial cells and chronic inflammatory cells, with no evidence of tumor cells. Acid-fast staining was negative, and bacterial and fungal cultures yielded negative results. The pericardial effusion GM test was positive (1.98↑).

The patient's prior surgical specimens (right upper lung and right lower lung) were reanalyzed. The right lower lung specimen contained an *Aspergillus* ball, while the right upper lung specimen showed invasive lung adenocarcinoma of the adherent type. Given the patient's history of pulmonary *Aspergillus* ball resection, positive pericardial GM test, and subsequent exclusion of other potential causes of pericardial effusion (e.g., tumors, tuberculosis, and connective tissue diseases), *Aspergillus* pericarditis was suspected.

After obtaining the patient's consent, we treated her with oral isavuconazole at a dose of 200 mg every 8 hours for the first 48 hours, followed by 200 mg daily. Upon improvement of the cough and chest tightness, the pericardial drainage tubes were removed. The patient was discharged from the hospital with a prescription for sequential oral administration of voriconazole tablets. At the 1- and 2-month follow-ups, the patient reported no discomfort, and no significant pericardial effusion was observed on re-examination.

Literature review

We searched PubMed using the keywords "Aspergillus, pericarditis" and "Aspergillus pericardial aspergillosis," which led to the identification of 27 cases of *Aspergillus* pericarditis. Of these, 26 were case reports and 1 was a comparative study. The earliest reported case was published in 1979. Among the 24 cases with available demographic data, 10 patients were female and 16 were male, with ages ranging from 30 months to 78 years.

There were 11 reported deaths, 6 of which were identified through autopsy. Sixteen cases were attributed to pulmonary *Aspergillus* dissemination, and 8 patients presented with pericardial tamponade, including 4 fatalities. Among the 26 cases, 2 involved myocarditis, 5 involved endocarditis, and 5 involved total heart inflammation.

Three patients showed no signs of immunodeficiency, while the remaining 23 had various immunodeficiency conditions. These included 12 cases of hematologic malignancies, 3 cases of chronic granulomatous

disease, 2 cases of acquired immunodeficiency syndrome, 2 cases of organ transplantation, 1 case involving chemotherapy for solid tumors, 2 instances of glucocorticoid use, and 1 case of multivisceral necrotizing fasciitis.

The main clinical manifestations were fever, chest pain, and dyspnea. Cardiac examinations were nonspecific, with tachycardia being the most commonly observed finding and pericardial friction rubs being noted in a few cases. Echocardiography frequently revealed pericardial effusion or thickening of the pericardium, while electrocardiograms showed tachycardia, low voltage, or no significant abnormalities. In one instance, laboratory analysis of pericardial effusion revealed a reddish, exudative appearance with an elevated cell count (4035), predominantly multinucleated cells (92%), a high lactate dehydrogenase level (1969 IU/L), and a protein concentration of 3.8 g/dL.[6]

The diagnosis was primarily based on pericardial fluid culture and autopsy findings. Commonly used therapeutic agents included amphotericin B, voriconazole, caspofungin, itraconazole, or combination therapy. The duration of antifungal treatment in successfully treated cases ranged from 3 months to 2 years. In addition to drug therapy, four patients underwent simultaneous pericardiectomy.

Discussion

Cardiac *Aspergillus* infections can be classified into *Aspergillus* myocarditis, endocarditis, and pericarditis, depending on the site of infection. Myocarditis is the most common, accounting for 83% of cases, while endocarditis and pericarditis each account for 17%.[7] These infections may occur in isolation or coexist with other cardiac infections, and cases of total carditis have also been reported. Myocarditis is typically asymptomatic, although it may occasionally present with conduction abnormalities, which are often identified through biopsy.[7] Advances in diagnostic techniques have facilitated the use of myocardial biopsy for the *in vivo* diagnosis of myocarditis.[8] Endocarditis, however, may present with fever, embolic events, or a heart murmur, and echocardiography can reveal valvular abnormalities such as redundancies.[7]

Pericarditis cases are often secondary to *Aspergillus* pneumonia[9,10] and commonly present with symptoms such as chest pain, hypotension, cardiac tamponade, or pericardial friction sounds.[3] Electrocardiographic findings in *Aspergillus* pericarditis are typically nonspecific, including tachycardia, widespread hypotension, or normal readings. Echocardiography usually reveals pericardial effusion or pericardial thickening. Previous reports,[6] including the present case, have shown that *Aspergillus* pericardial effusion often appears as a bloody exudate. Routine laboratory analysis typically demonstrates an increased cell count, lactate dehydrogenase level, and protein content, along with low glucose levels—features similar to bacterial infections causing effusions in plasma cavities. However, while the literature indicates that lobulated nucleated cells are usually predominant in *Aspergillus* pericarditis, the present case showed a predominance of mononuclear cells. This difference may reflect the prolonged duration of pericardial effusion in this patient. In rare instances, *Aspergillus* pericarditis may manifest as pericardial pneumoperitoneum, likely due to lung lobe necrosis near the heart creating a connection between the bronchus and the pericardium.[11] This phenomenon is similar to the development of bronchopleural fistulae caused by pulmonary aspergillosis.

Clinically, the diagnosis of *Aspergillus* infections is challenging because of the lack of specific symptoms and signs. This limitation contributes to poor prognosis, high mortality, and a low positive rate of biopsy

diagnoses, with many cases only being confirmed postmortem.[2] Technological advancements have improved the positive rate of pericardial fluid culture. However, in patients with a history of pulmonary *Aspergillus* infection or immunodeficiency, *Aspergillus* infection should not be ruled out based on a negative culture result. A negative culture does not exclude the possibility of infection and should not be considered evidence against the use of antifungal therapy.[12] A positive *Aspergillus* antigen test offers a reliable suspected diagnosis, with specificity and sensitivity exceeding 95%.[13] Notably, the literature indicates that *Aspergillus* antigen testing has not yielded false-positive results for other filamentous organisms, with the exception of a single case involving disseminated pseudoconjugate infection.[14] Therefore, antifungal therapy should be initiated promptly following a positive *Aspergillus* antigen test to maximize the likelihood of successful treatment.

In the present case, the patient had a history of lung cancer surgery and pulmonary *Aspergillus* ball resection, with pericardial effusion observed postoperatively. Despite multiple laboratory tests, the cause of the pericardial effusion could not be clearly identified and was suspected to be *Aspergillus* pericarditis. Although the pericardial effusion culture tested negative for *Aspergillus*, the pericardial GM test returned positive results. The resolution of pericardial effusion during follow-up after antifungal therapy confirmed the diagnosis of *Aspergillus* pericarditis. This case highlights that a positive pericardial GM test may be more sensitive and clinically meaningful than a blood GM test because the blood GM test in this patient was negative. During follow-up, GM testing can be used to monitor for recurrence. However, the conversion of the *Aspergillus* antigen alone is not sufficient grounds for discontinuing antifungal therapy. A previous case report demonstrated that stopping antifungal medication after *Aspergillus* antigen conversion led to recurrence of the infection, multiorgan dissemination, and eventual death. This underscores the importance of continuing antifungal therapy until the infection is fully resolved and clinical stability is achieved.[15]

Previous literature recommends voriconazole as the first-line treatment for *Aspergillus* pericarditis, demonstrating good effectiveness.[16] For refractory cases that do not respond adequately to voriconazole, alternative antifungal agents such as amphotericin B, echinocandins, or combination therapies are suggested. Posaconazole, a triazole derivative, is another effective option, with studies showing favorable outcomes.[17] However, echinocandins are not recommended as initial monotherapy for aspergillosis because of their limited efficacy in this context. Isavuconazole, a third-generation azole antifungal drug, has been approved for the treatment of invasive trichosporonosis and invasive aspergillosis in adults in recent years. To date, there have been no previously reported cases of *Aspergillus* pericarditis treated with isavuconazole. In this case, we demonstrated for the first time that isavuconazole is effective in treating *Aspergillus* pericarditis, with good safety and tolerability. This represents a novel contribution to the management of this condition.

In some cases, antifungal therapy combined with surgical interventions, such as resection of lung lesions and pericardiectomy, may improve treatment outcomes and reduce the risk of recurrence.[9] In this case, the patient's favorable prognosis can be attributed, in part, to the combined approach of lung lesion resection and voriconazole antifungal therapy. However, there are no established guidelines regarding the optimal duration of antifungal therapy. The available literature reports treatment durations ranging from 3 months to 2 years. We recommend

tailoring the duration of therapy based on the patient's age, overall condition, immunodeficiency status, and recovery of liver and kidney function. Adverse reactions should be closely monitored throughout the course of antifungal therapy, and signs of recurrence should be carefully assessed following drug cessation.

Because of its rarity, diagnosing *Aspergillus* pericarditis remains a challenge. The disease often presents with nonspecific symptoms, and current diagnostic tests have limited accuracy. This diagnostic difficulty contributes to the high mortality rate associated with the condition. For high-risk patients, clinicians should maintain a high index of suspicion and prioritize timely diagnosis and treatment to improve outcomes.

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Author contributions

Yuan Xie and Yanli Gu (co-first authors): Conceptualization, methodology, software, investigation, formal analysis, and drafting of the manuscript.
Liang Chen (corresponding author): Conceptualization, writing – review and editing.

Consent for publication

The patient provided written informed consent to publish this report.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Declaration of conflicting interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

We have fully de-identified the patient's information in this article. The data contain no identifiable personal information, sensitive details, or commercial interests, and do not pose any risk of harm. Therefore, we believe this case report meets the criteria for exemption from ethical review in accordance with the relevant submission requirements.

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