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Case Report

Invasive aspergillosis in an immunocompetent patient: A retrospective case report and review of the literature

Xiaobing Zhang[1 #], Chuanling Hou[2 #], Yuhua Feng[1], Qi Zhang[3], Mingxia Yang[4], Xuebin Yu[1]

[1] *Department of Neurosurgery, Shaoxing People's Hospital, Zhejiang, 312000, China*
[2] *Department of Pathology, Shaoxing People's Hospital, Zhejiang, 312000, China*
[3] *Department of Ultrasonography, Shaoxing People's Hospital, Zhejiang, 312000, China*
[4] *Department of Radiology, Shaoxing People's Hospital, Zhejiang, 312000, China*

# Authors contributed equally to this work

Abstract

Introduction: Invasive aspergillosis (IA) is rare in immunocompetent patients. We present the case of a 44-year-old female with IA invading the lungs, mediastinum, heart, and brain, with a disease duration of 11 years.

Case presentation: The patient was initially diagnosed with lung aspergillosis that had invaded the mediastinum on October 8, 2008. Irregular uptake of itraconazole led to the aggravation of lung lesions. Echocardiography and enhanced magnetic resonance imaging revealed a large irregular mass in the left atrium and an enhanced 1-cm nodular lesion in the right frontal lobe respectively in 2016. The patient refused to undergo a biopsy of the cardiac mass. Oral itraconazole (200 mg, twice daily) was recommended for subsequent days. The intracranial lesion gradually enlarged, and a complete tumor resection of the right frontal lobe was performed on February 23, 2017. The patient's condition was well controlled with oral voriconazole by the end of follow-up until April 11, 2019. We conducted a search across multiple databases, including PubMed, Web of Science, Scopus, and Science Direct. We aimed to identify cases of aspergillosis that simultaneously invaded the lungs, heart, and brain. The details of these cases are summarized.

Results: Fourteen cases with available data met the requirements, and the mortality rate of these 14 cases was 100%.

Conclusions: IA can occur even in immunocompetent patients receiving antifungal therapy. Therefore, timely diagnosis and effective long-term antifungal treatments are crucial. Voriconazole is an effective antifungal drug that is used to treat cerebral aspergillosis.

Key words: Invasive aspergillosis; immunocompetent; intracardiac mass; intracranial lesion; voriconazole.

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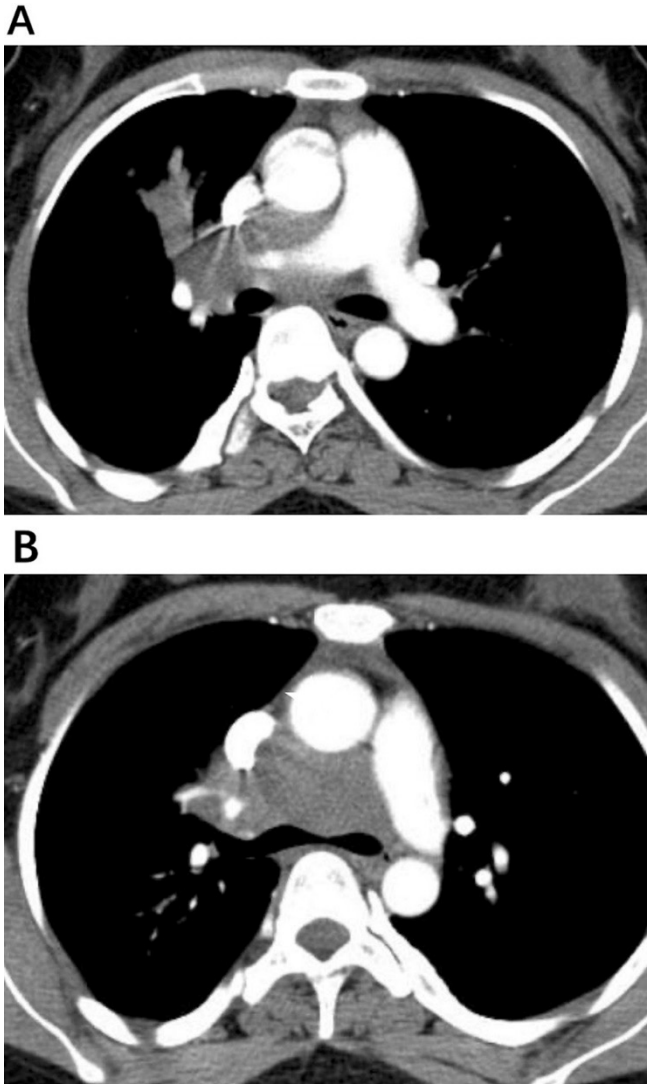
Introduction

Aspergillus fumigatus is ubiquitous in the environment [1]. Pulmonary aspergillosis is the most common type of aspergillosis, as *Aspergillus fumigatus* is small enough to enter the lung alveoli [2]. As most pathogens can be eliminated by the innate host immune system, aspergillosis often occurs in severely immunosuppressed patients such as organ transplant recipients [3-5], patients in the intensive care unit [6,7], and patients with hematological disease [8]. Aspergillosis, particularly invasive aspergillosis (IA), is rare in immunocompetent patients [9]. There are a few reports on IA that track the long-term evolution of a single patient who has already received antifungal therapy. Herein, we present the case of a patient with IA invading the lungs, mediastinum, heart, and brain, with a disease duration of 11 years. The patient's condition was well controlled with oral voriconazole at the end of the follow-up period. This is a rare case of IA in an immunocompetent patient who has received antifungal therapy with a long-term follow-up.

Case Presentation

A 33-year-old woman was admitted to the respiratory medicine department after a right lung mass was discovered during a routine medical examination on October 8, 2008. The patient had no other medical history. Tests for Hepatitis B virus yielded positive results, whereas other blood tests and physical examination results were normal. Chest computed tomography (CT) revealed a mass in the right hilum, with segmental pulmonary consolidation and mediastinal lymphadenopathy (Figure 1). A lung puncture biopsy conducted on October 13, 2008, revealed a granuloma with suspicious positive hyphae on periodic acid-Schiff (PAS) staining (Figure 2).

Figure 1. Chest CT: A mass located at the right hilum with segmental pulmonary consolidation(A) and mediastinal lymphadenopathy(B) was found on the CT. October 8, 2008. CT: computed tomography.



Therefore, fungal infection, particularly aspergillosis, was suspected. The patient was administered oral itraconazole (200 mg, twice daily). Furthermore, no additional tests were performed because the patient asked to be discharged. Oral itraconazole therapy was suggested; however, the patient did not take the medication regularly. The following day, the patient was intermittently hospitalized with oral itraconazole therapy for recurrent chest pain. A follow-up chest CT showed that the consolidation lesion had progressively enlarged, with nearly stable lymphadenopathy.

The patient was admitted to the thoracic surgery department on May 28, 2016. Physical examination revealed a grade II/VI systolic murmur in the upper left sternal border. Laboratory tests indicated an erythrocyte sedimentation rate of 34 mm/h, a rheumatoid factor of 22.8 IU/mL, and an elevated level of (1,3) β-D-Glucan at 1357.2 pg/mL. Galactomannan (GM) was not detected in the patient's serum samples. An electrocardiogram (ECG) showed premature atrial beats. Echocardiography was recommended on May 29, 2016. This procedure detected an enlarged left atrium with normal systolic function and a small pericardial effusion. Additionally, a large irregular hypoechoic mass measuring 74 × 68 × 50 mm was observed in the left atrium. Notably, the aortic base and pulmonary valves were surrounded by a homogeneous mass (Figure 3, A-B). The enhanced chest CT scan from May 29, 2016, showed an increase in the size of the right pulmonary consolidation compared to the initial imaging from October 8, 2008. However, this result was smaller than that obtained on October 19, 2015. Enhanced magnetic resonance imaging (MRI) of the mediastinum, conducted on May 31, 2016, revealed mediastinal lymphadenopathy with fibrous tissue hyperplasia and the presence of a left atrial mass (Figure 4, A-D). Additionally, an enhanced brain MRI was performed on June 4, 2016. An enhanced 1-cm nodular lesion with surrounding edema was observed in the right frontal lobe. A video-assisted thoracoscopic mediastinal tumor biopsy was performed on June 17, 2016. Pathological examination of the biopsy specimen revealed a chronic granulomatous inflammation. Acid-fast staining of the specimen was negative. PAS staining revealed the presence of fungal hyphae. The patient's family refused a biopsy of the cardiac mass. The patient was discharged on June 25, 2016, when the chest pain was relieved. Oral itraconazole (200 mg, twice daily) was recommended for the subsequent days. The patient was also treated with caspofungin (50 mg/day) between August 3, 2016, and March 11, 2016.

Figure 2. PAS staining of the lung puncture biopsy: PAS staining of the biopsy of the lung puncture disclosed suspicious positive hyphae. October 13, 2008. PAS: Periodic acid-Schiff.

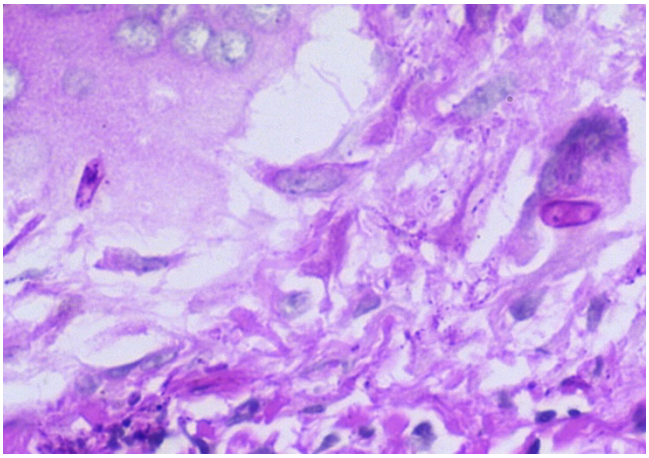


Figure 3. B-ultrasound of the heart: A large irregular hypoechoic density measuring 74 × 68 ×50 mm was shown at the left atrium (A and B). May 29, 2016. The mass disappeared with no signs of recurrence (C and D). April 9, 2019.

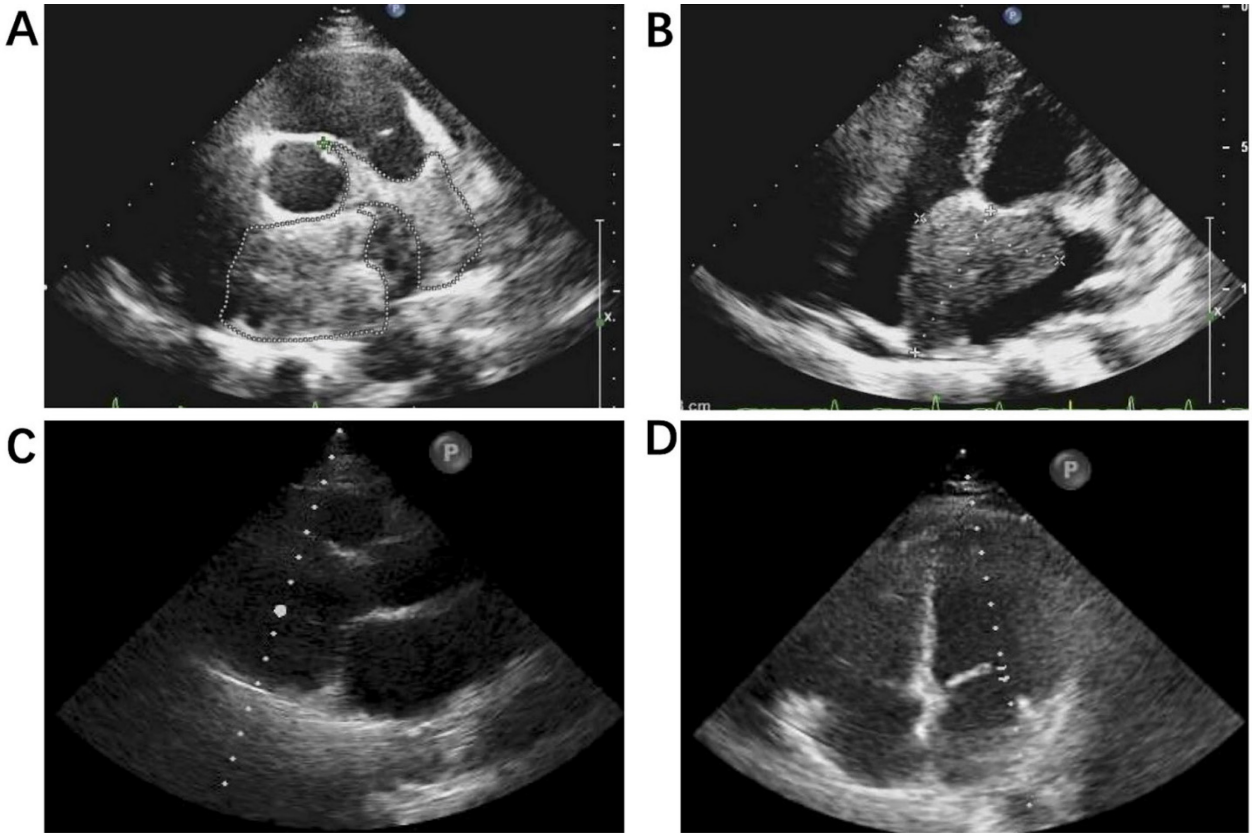


Figure 4. MRI of the chest and heart: Enhanced MRI revealed the left atrium mass was directly connected to mediastinal lymphadenopathy (A -D). May 31, 2016. The intracardiac mass disappeared and absorption of the chest lesion was observed on CT (E and F). April 9, 2019. MRI: magnetic resonance imaging; CT: computed tomography.

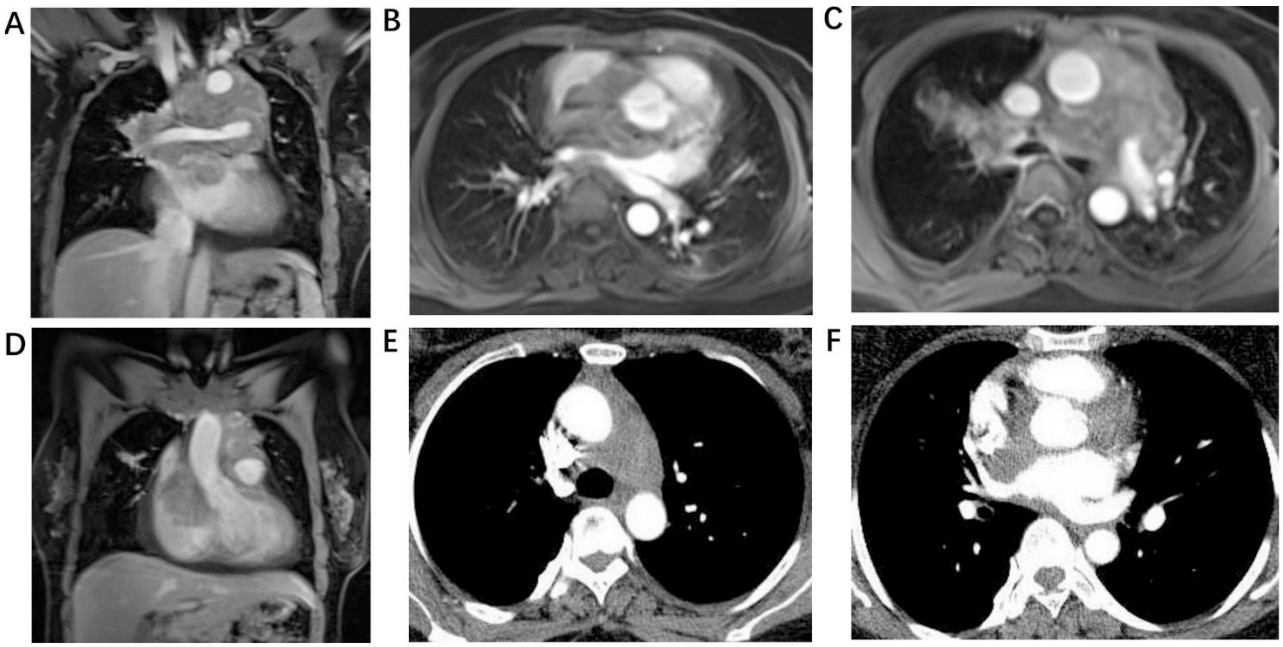
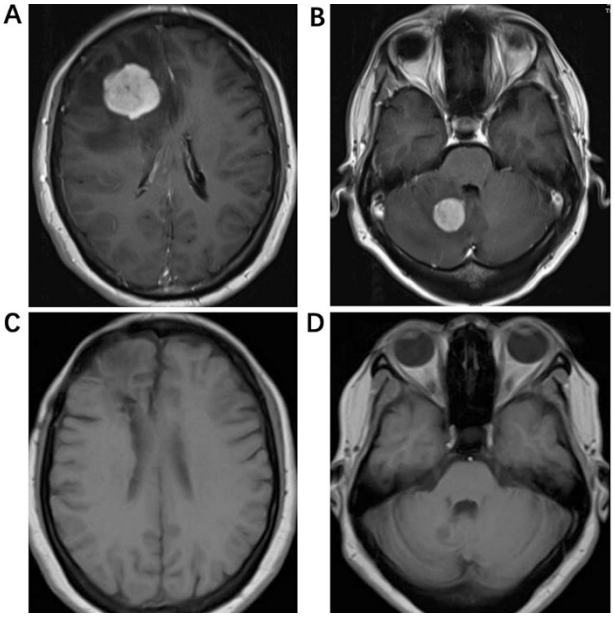
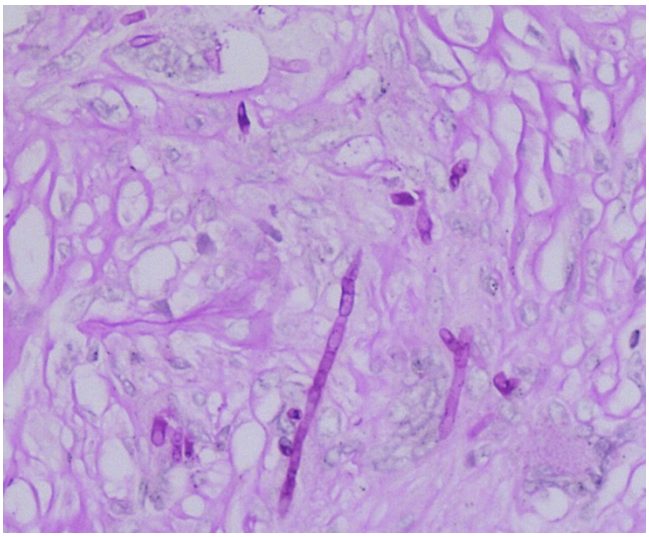


Figure 5. MRI of the brain. Enhanced mass of the right frontal lobe (A) and right cerebellum (B) on the MRI. February 18, 2017. MRI disclosed no recurrence of the right frontal lobe mass (C). April 11, 2019. The tumor of the right cerebellum decreased in size and remained stable (D). April 11, 2019. MRI: magnetic resonance imaging.



She was readmitted to the neurosurgery department on February 15, 2017, with symptoms of headache, vomiting, and epileptic seizures. Physical examination revealed a grade II/VI systolic murmur at the upper left sternal border, and mild gait unsteadiness. The irregular hypoechoic density observed on echocardiography on February 17, 2017, along with the right lung consolidation lesion and mediastinal lymphadenopathy detected on the enhanced chest CT from the same date, showed nearly no change compared with the results from May 29, 2016. On February 18, 2017, an MRI of the brain revealed enhanced masses in the right frontal lobe and right cerebellum, measuring 30 and 18 mm in diameter, respectively (Figure 5, A-B). A complete tumor resection of the right frontal lobe was performed on February 23, 2017. During surgery, the tumor was found to be gray-white with a tough texture, clear boundaries with surrounding tissues, and insufficient blood supply. Chronic granulomatous inflammation was observed, and PAS staining showed positive hyphae (Figure 6). A diagnosis of IA involving the lungs, mediastinum, heart, and brain was made. Voriconazole (200 mg), administered twice daily, was recommended because of its resistance to itraconazole. The patient's symptoms gradually subsided after treatment. Regular treatment with 200 mg of oral voriconazole should be administered twice daily. In addition, follow-up

Figure 6. PAS staining of the brain tumor: PAS staining of the brain tumor showed positive hyphae. February 23, 2017. PAS: Periodic acid-Schiff.



imaging, including enhanced chest/head CT/MRI and echocardiography, was suggested on the subsequent days until April 11, 2019.

Over the subsequent days, there was a consistent improvement in the imaging results. The hypoechoic density of the heart completely disappeared on June 13, 2017, with no signs of recurrence until April 9, 2019 (Figure 3, C-D). Furthermore, a chest CT scan conducted on August 21, 2017, showed increased absorption of the right hilar lesion and mediastinal lymphadenopathy. Subsequent scans revealed no changes in these conditions until April 9, 2019 (Figure 4, E-F). Brain MRI conducted on June 13, 2017, showed no recurrence of the mass in the right frontal lobe. Additionally, the tumor in the right cerebellum, which decreased in diameter to 13 mm, remained stable until April 11, 2019 (Figure 5, C-D).

Review of the Literature

A comprehensive literature search was conducted to identify cases of aspergillosis that simultaneously invaded the lungs, heart, and brain. The search was conducted using several databases, including PubMed, Web of Science, Scopus, and ScienceDirect. Fourteen cases with available data met these requirements [10-23]. The details of these cases are listed in Table 1. In this group of fourteen patients, twelve had immunodeficiency, two had unfortunately experienced drowning incidents, and one had quadriplegia due to hemorrhage from a cervical vascular malformation, which necessitated the use of high-dose corticosteroids. The mortality rate of these fourteen patients was 100%.

Table 1. Literature review of cases of aspergillosis invading the lungs, heart, and brain simultaneously in an individual.

First author, yr.	Sex, age	Location	Related primary disease	Pathology or Smear	Culture	GM	Autopsy	Treatment	Outcome
Walsh TJ, 1983, [10]	M, 9	Lungs/heart/brain/kidney/ spleen/pancreas/thyroid	Hepatic Failure	NA	N (sputum)	NA	Yes	None	Fatal
Henochowicz S, 1985, [11]	M, 32	Lungs/heart/brain	AIDS	N (CSF/blood)	N (CSF/blood)	NA	Yes	Amphotericin B	Fatal
Brems JJ, 1988, [12]	M, 42	Lungs/heart/brain/ gastrointestinal mucosa	Liver transplantation	NA	P (sputum)	NA	Yes	Amphotericin B	Fatal
Woods GL, 1990, [13]	F, 30	Lungs/heart/brain/kidney	AIDS	N (BAL/CSF)	NA	NA	Yes	Amphotericin B	Fatal
Ter Maaten JC, 1995, [14]	M, 62	Lungs/heart/brain/kidney/ adrenal gland	Drowning	P (lung)	P (sputum)	NA	Yes	Amphotericin B + flucytosine	Fatal
Riesenfeld EP, 2000, [15]	M, 44	Lungs/heart/brain/kidney/ thyroid	Cervical Arteriovenous Malformation (quadriplegia, treated with high-dose corticosteroids)	NA	P (sputum), N (blood)	NA	Yes	None	Fatal
Marcinkowski M, 2000, [16]	M, 1	Lungs/heart/brain/ adrenal gland	DiGeorge syndrome	N (colon)	N (blood/CSF/hematoma of the abdominal wall)	NA	Yes	None	Fatal
Kobayashi M, 2000, [17]	F, 31	Lungs/heart/brain/trachea/ esophgus/stomach/ thyroid gland	HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count)	NA	P (sputum)	NA	Yes	None	Fatal
Nenoff P, 2002, [18]	M, 64	Lungs/heart/brain/ subcutaneous	Hypoblastic myelodysplastic syndrome/acute myeloid leukaemia	P (BAL/corium and subcutis)	P (skin tissue/BAL)	P (BAL)	NA	Amphotericin B	Fatal
Yamamoto N, 2002, [19]	M, 39	Lungs/heart/brain/kidney/ parietal/liver	Chronic eosinophilic pneumonia	P (lung/brain), N(CSF)	N (lung/CSF/brian/blood)	N (CSF/ blood)	Yes	Amphotericin B	Fatal
Saito T, 2009, [20]	F, 63	Lungs/heart/brain	Good-pasture syndrome	NA	N (blood)	N (blood)	Yes	Fosfluconazole	Fatal
Li P, 2011, [21]	F, 72	Lungs/heart/brain/kidney	Drowning	NA	N (sputum)	NA	Yes	Voriconazole	Fatal
McCarter SJ, 2019, [22]	M, 79	Lungs/heart/brain/muscles/ subcutaneous	B-cell lymphma/leukemia	P (subcutaneous nodule), N (pericardial fluid)	P (subcutaneous nodule/ deeper tissue), N (pericardial fluid/blood)	N (blood)	None	Voriconazole + caspofungin	Fatal
Hardie R, 2020, [23]	F, 41	Lungs/heart/brain	Systemic Lupus Erythematosus	N (lung/BAL)	N (lung/BAL/ blood)	P (blood)	Yes	Caspofungin	Fatal

M: male; F: female; AIDS: Acquired Immune Deficiency Syndrome; NA: Data not available; N: Negative; P: Positive; GM: Galactomannan; CSF: Cerebrospinal Fluid; BAL: Bronchoalveolar lavage; CSF: Cerebrospinal Fluid; BAL: Bronchoalveolar lavage.

Discussion

Aspergillosis, particularly IA, is rare in immunocompetent patients [9]. The lungs are the most common initial sites of aspergillosis. IA typically affects the skin, kidneys, heart, and the brain. This condition occurs when *Aspergillus fumigatus* invades the small pulmonary vessels [24]. The mortality ranges from 30% to 50% [25]. In this case, although the young female carried Hepatitis B virus, her liver function was normal. Based on her medical history and clinical test results, we concluded that she was an immunocompetent patient. Reports on IA in immunocompetent patients receiving antifungal therapy are rare.

IA was diagnosed based on the biopsy and imaging results of a mediastinal tumor, lung consolidation, and brain tumor. We believe that this is a rare case of cardiac aspergillosis. This was based on MRI and echocardiographic findings, which revealed that the mediastinal mass was directly connected to the left atrial intracardiac mass. This suggests a direct invasion of the endocardium by the mediastinal mass. However, histological evidence was absent because the patient refused to undergo a biopsy. Patients with cardiac aspergillosis may die from a complete heart block (CHB) [24], cardiac tamponade [25], or septic shock [26]. CHB reflects an inflammatory response to the mass and may be a harbinger of the mass embolization [26]. In this case, long-term antifungal therapy before and after the onset of cardiac aspergillosis played an important role in patient survival. Therefore, a timely diagnosis and effective antifungal treatment are crucial.

Early diagnosis should be made based on the clinical manifestations, laboratory tests, and imaging findings. The presence of characteristic clinical manifestations usually depends on the site of the infection [6,9]. Culture and microbiological examination are important for diagnosis. Abundant fungal hyphae can be detected using needle aspiration biopsy, surgery, and other methods [27,28]. PAS staining helps determine the fungal morphology. Our diagnosis relied particularly on the biopsy results, including those of mediastinal tumors, lung consolidation, and brain tumors. However, no

histological evidence of an intracardiac mass was found. In other cases, cardiac aspergillosis is confirmed by histopathological findings followed by surgical removal of the intracardiac mass or autopsy [6,26]. Galactomannan (GM) and (1,3) β-D-Glucan, which are both isolated from the cell wall of Aspergillus, are used diagnostically. Test of GM and (1,3) β-D-Glucan can be performed in bronchoalveolar lavage fluid and serum [29]. The GM test was negative in our cases because the assay has low sensitivity and high specificity [30]. DNA detection in specimens can also be used for diagnosis [31]. Different imaging tests, such as ultrasonic examination, CT, and MRI, are suggested according to the clinical symptoms.

Although long-term antifungal treatment is recommended, no uniform criteria for drug withdrawal have been established yet. The generally recommended treatment duration is ≥ six months [32,33]. Itraconazole and voriconazole were the drugs of choice [34]. The therapy should be changed in case of drug resistance or toxicity. In our case, the patient was resistant to itraconazole, whereas voriconazole had a dramatic effect, which was proven by a decrease in cerebellar lesions and the disappearance of the intracardiac mass. Amphotericin B, posaconazole, and caspofungin are alternative drugs [34]. For patients with cerebral aspergillosis, the ability of drugs to penetrate the blood-brain barrier is key [35], and the hematogenous dissemination pattern displays a worse prognosis than dissemination from the paranasal sinuses [36]. The concentrations of voriconazole in both the brain tissue and cerebrospinal fluid surpassed those of amphotericin B, itraconazole, and caspofungin. This suggests that voriconazole may be an effective antifungal treatment for patients with cerebral aspergillosis [37]. This finding is consistent with the therapeutic effects observed in the present case. Caspofungin may be an option for the treatment of cerebral aspergillosis; however, further clinical studies are needed [38]. Compared with voriconazole, isavuconazole, a novel triazole agent, has proven to be effective in treating invasive mold disease with fewer side effects [39].

In this case, surgery on the right frontal lesion was performed for the diagnosis. Surgery is considered only if the drug therapy is ineffective or unfeasible. However, for patients with cardiac aspergillosis, early surgical intervention is recommended to prevent embolic complications and valvular decompensation [33]. In our case, surgery for cardiac mass was not performed because the patient refused surgery. Long-term antifungal therapy and timely switching of the drug to voriconazole may have contributed to the patient's survival.

Conclusions

IA can occur even in immunocompetent patients receiving antifungal therapy. Therefore, timely diagnosis and effective long-term antifungal treatment are crucial. Antifungal drugs must be changed over time in cases of drug resistance or toxicity. Voriconazole is an effective antifungal drug used to treat cerebral aspergillosis. The current case is interesting because the patient had a normal immune function, a long disease duration, and a good prognosis. This finding differs from that of other reported cases. This case provides new insights into disease research.

Acknowledgements

We appreciate the patient for her consent for this publication. Written informed consent for the publication of the patient's data was obtained from the patient.

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Ethical Approval

This is a case report and review study. The Shaoxing People's Hospital Research Ethics Committee has confirmed that no ethical approval is required.

Authors' Contributions

Xiaobing Zhang and Chuanling Hou were responsible for data collection, review of literature, and drafting of manuscript. The clinical data was collected by Yuhua Feng. Mingxia Yang and Qi Zhang interpreted and prepared the radiographic and ultrasound data respectively. Xuebin Yu provided the idea, drafted the manuscript and reviewed the manuscript. All authors contributed to the writing of the final manuscript. All authors read and approved the final manuscript.

References

1. Van de Veerdonk FL, Gresnigt MS, Romani L, Netea MG, Latge JP (2017) Aspergillus fumigatus morphology and dynamic host interactions. Nat Rev Microbiol 15: 661-674. doi: 10.1038/nrmicro.2017.90.
2. Barnes PD, Marr KA(2006) Aspergillosis: spectrum of disease, diagnosis, and treatment. Infect Dis Clin North Am 20: 545-561. vi. doi: 10.1016/j.idc.2006.06.001.
3. Gavalda J, Len O, San Juan R, Aguado JM, Fortun J, Lumbreras C, Moreno A, Munoz P, Blanes M, Ramos A, Rufi G, Gurgui M, Torre-Cisneros J, Montejo M, Cuenca-Estrella M, Rodriguez-Tudela JL, Pahissa A, RESITRA (Spanish Network for Research on Infection in Transplantation) (2005) Risk factors for invasive aspergillosis in solid-organ transplant

recipients: a case-control study. Clin Infect Dis 41: 52-59. doi: 10.1086/430602.
4. Singh N, Paterson DL (2005) Aspergillus infections in transplant recipients. Clin Microbiol Rev 18: 44-69. doi: 10.1128/CMR.18.1.44-69.2005.
5. Neofytos D, Chatzis O, Nasioudis D, Boely Janke E, Doco Lecompte T, Garzoni C, Berger C, Cussini A, Boggian K, Khanna N, Manuel O, Mueller NJ, van Delden C (2018) Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study. Transpl Infect Dis 20: e12898. doi: 10.1111/tid.12898.
6. Singh G, Kalyan S, Kataria SP, Sharma J, Parmar P, Gilotra M, Sen R (2017) Disseminated invasive aspergillosis in a prolonged stay in the intensive care unit. Autops Case Rep 7: 17-21. doi: 10.4322/acr.2017.010.
7. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, Lagrou K, Verweij PE, Van de Veerdonk FL, Gommers D, Spronk P, Bergmans DCJJ, Hoedemaekers A, Andrinopoulou ER, van den Berg CHSB, Juffermans NP, Hodiamont CJ, Vonk AG, Depuydt P, Boelens J, Wauters J, Dutch-Belgian Mycosis study group (2018) Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 6: 782-792. doi: 10.1016/S2213-2600(18)30274-1.
8. Pagano L, Caira M, Picardi M, Candoni A, Melillo L, Fianchi L, Offidani M, Nosari A (2007) Invasive Aspergillosis in patients with acute leukemia: update on morbidity and mortality--SEIFEM-C Report. Clin Infect Dis 44: 1524-1525. doi: 10.1086/517849.
9. Latgé JP, Chamilos G (2019) Aspergillus fumigatus and Aspergillosis in 2019. Clin Microbiol Rev 33: e00140-18. doi: 10.1128/CMR.00140-18.
10. Walsh TJ, Hamilton SR (1983) Disseminated aspergillosis complicating hepatic failure. Arch Intern Med 143: 1189-91.
11. Henochowicz S, Mustafa M, Lawrinson WE, Pistole M, Lindsay J Jr (1985) Cardiac aspergillosis in acquired immune deficiency syndrome. Am J Cardiol 55: 1239-40. doi: 10.1016/0002-9149(85)90679-4.
12. Brems JJ, Hiatt JR, Klein AS, Hart J, E1-Khoury G, Winston D, Millis JM, Busuttil RW (1988) Disseminated aspergillosis complicating orthotopic liver transplantation for fulminant hepatic failure refractory to corticosteroid therapy. Transplantation 46: 479-481. doi: 10.1097/00007890-198809000-00038.
13. Woods GL, Goldsmith JC (1990) Aspergillus infection of the central nervous system in patients with acquired immunodeficiency syndrome. Arch Neurol 47: 181-184. doi: 10.1001/archneur.1990.00530020087020.
14. Ter Maaten JC, Golding RP, Strack van Schijndel RJ, Thijs LG (1995) Disseminated aspergillosis after near-drowning. Neth J Med 47: 21-24. doi: 10.1016/0300-2977(94)00102-f.
15. Riesenfeld EP, Shan Y, Pietropaoli AP (2000) Pathologic quiz case: infection in a patient with a cervical arteriovenous malformation. Arch Pathol Lab Med 124: 466-468. doi: 10.5858/2000-124-0466-PQCIIA.
16. Marcinkowski M, Bauer K, Stoltenburg-Didinger G, Vogel M, Versmold H (2000) Fatal aspergillosis with brain abscesses in a neonate with DiGeorge syndrome. Pediatr Infect Dis J 19: 1214-1216. doi: 10.1097/00006454-200012000-00023.
17. Kobayashi M, Ito M, Hotchi M (2000) An autopsy case of HELLP syndrome with disseminated aspergillosis. Nihon Ishinkin Gakkai Zasshi 41: 103-107. doi: 10.3314/jjmm.41.103.
18. Nenoff P, Kliem C, Mittag M, Horn LC, Niederwieser D, Haustein UF (2002) Secondary cutaneous aspergillosis due to Aspergillus flavus in an acute myeloid leukaemia patient following stem cell transplantation. Eur J Dermatol 12:93-98.
19. Yamamoto N, Miyara T, Kawakami K, Kaneshima H, Akamine M, Uezu K, Kouguchi Y, Tohyama M, Touyama M, Ishimine T, Nakamoto A, Higa F, Tateyama M, Saito A (2002) A case of disseminated aspergillosis with smoldering adult T-cell leukemia. Kansenshogaku Zasshi 76: 460-465. doi: 10.11150/kansenshogakuzasshi1970.76.460.
20. Saito T, Shime N, Itoh K, Fujita N, Saito Y, Shinozaki M, Shibuya K, Makimura K, Hashimoto S (2009) Disseminated aspergillosis following resolution of Pneumocystis pneumonia with sustained elevation of beta-glucan in an Intensive Care Unit: a case report. Infection 37: 547-550. doi: 10.1007/s15010-009-8108-5.
21. Li P, Cao EH, Zhao BL, Sun HM, Li MM, Xu J, Song Y, Shi Y (2011) Invasive aspergillosis after near-drowning: case reports and review of the literature. Zhonghua jie he he hu xi za zhi 34: 657-662.
22. McCarter SJ, Vijayvargiya P, Sidana S, Nault AM, Lane CE, Lehman JS, Wilson JW, Parikh SA, Nowakowski GS, Al-Kali A (2019) A case of ibrutinib-associated aspergillosis presenting with central nervous system, myocardial, pulmonary, intramuscular, and subcutaneous abscesses. Leuk Lymphoma 60: 559-561. doi: 10.1080/10428194.2018.1494271.
23. Hardie R, James-Goulbourne T, Rashid M, Sullivan J, Homsi Y (2020) Fatal disseminated aspergillosis in a patient with systemic lupus erythematosus. Case Rep Infect Dis 2020: 9623198. doi: 10.1155/2020/9623198.
24. Kohli U, Sahu J, Lodha R, Agarwal N, Ray R (2007) Invasive nosocomial aspergillosis associated with heart failure and complete heart block following recovery from dengue shock syndrome. Pediatr Crit Care Med 8: 389-391. doi: 10.1097/01.PCC.0000269397.95479.3C.
25. Han KH, Kim JH, Shin SY, Jeong HY, Chu JM, Kim HS, Kim D, Shim M, Cho SH, Kim EK (2014) A case of invasive pulmonary aspergillosis with direct invasion of the mediastinum and the left atrium in an immunocompetent patient. Tuberc Respir Dis (Seoul) 77: 28-33. doi: 10.4046/trd.2014.77.1.28.
26. Tabandeh M, Bahramali E, Savand Roomi Z, Salari S, Radpey M, Shamsolvaezin N (2020) Intra-cardiac aspergilloma in a normally structured heart: A case report. J Cardiol Cases 21: 165-168. doi: 10.1016/j.jccase.2019.12.006.
27. Segal BH, Walsh TJ (2006) Current approaches to diagnosis and treatment of invasive aspergillosis. Am J Respir Crit Care Med 173: 707-717. doi: 10.1164/rccm.200505-727SO.
28. Pushker N, Meel R, Kashyap S, Bajaj MS, Sen S (2011) Invasive aspergillosis of orbit in immunocompetent patients: treatment and outcome. Ophthalmology 118: 1886-1891. doi: 10.1016/j.ophtha.2011.01.059.
29. Lamoth F (2016) Galactomannan and 1,3-β-d-Glucan Testing for the Diagnosis of Invasive Aspergillosis. J Fungi (Basel) 2: 22 doi: 10.3390/jof2030022.
30. Arastehfar A, Carvalho A, Houbraken J, Lombardi L, Garcia-Rubio R, Jenks JD, Rivero-Menendez O, Aljohani R, Jacobsen ID, Berman J, Osherov N, Hedayati MT, Ilkit M, Armstrong-James D, Gabaldón T, Meletiadis J, Kostrzewa M, Pan W, Lass-Flörl C, Perlin DS, Hoenigl M (2021) Aspergillus

fumigatus and aspergillosis: from basics to clinics. Stud Mycol 100: 100115. doi: 10.1016/j.simyco.2021.100115.
31. Heng SC, Morrissey O, Chen SC, Thursky K, Manser RL, Nation RL, Kong DC, Slavin M (2015) Utility of bronchoalveolar lavage fluid galactomannan alone or in combination with PCR for the diagnosis of invasive aspergillosis in adult hematology patients: a systematic review and meta-analysis. Crit Rev Microbiol 41: 124-134. doi: 10.3109/1040841X.2013.804033.
32. Alastruey-Izquierdo A, Cadranel J, Flick H, Godet C, Hennequin C, Hoenigl M, Kosmidis C, Lange C, Munteanu O, Page I, Salzer HJF, on behalf of CPAnet (2018) Treatment of chronic pulmonary aspergillosis: current standards and future perspectives. Respiration 96: 159-170. doi: 10.1159/000489474.
33. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE (2016) Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis 63: e1-e60. doi: 10.1093/cid/ciw326.
34. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, Ullmann AJ, Dimopoulos G, Lange C, European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society (2016) Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J 47: 45-68. doi: 10.1183/13993003.00583-2015.
35. Schwartz S, Thiel E (2009) Cerebral aspergillosis: tissue penetration is the key. Med Mycol Suppl 1: S387-393. doi: 10.1080/13693780802537953.
36. Serris A, Benzakoun J, Danion F, Porcher R, Sonneville R, Wolff M, Kremer S, Letscher-Bru V, Fekkar A, Hekimian G, Pourcher V, Bougnoux ME, Poirée S, Ader F, Persat F, Cotton F, Tattevin P, Gangneux JP, Lelièvre L, Cassaing S, Bonneville F, Houze S, Bretagne S, Herbrecht R, Lortholary O, Naggara O, Lanternier F, CEREAL study group (2022) Cerebral aspergillosis in the era of new antifungals: The CEREALS national cohort study Nationwide CEREbral Aspergillosis Lesional study (CEREALS). J Infect 84: 227-236. doi: 10.1016/j.jinf.2021.11.014.
37. Schwartz S, Ruhnke M, Ribaud P, Corey L, Driscoll T, Cornely OA, Schuler U, Lutsar I, Troke P, Thiel E (2005) Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 106: 2641-2645. doi: 10.1182/blood-2005-02-0733.
38. Ullmann I, Aregger A, Leib SL, Zimmerli S (2022) Caspofungin cerebral penetration and therapeutic efficacy in experimental cerebral aspergillosis. Microbiol Spectr 10: e0275321 doi: 10.1128/spectrum.02753-21.
39. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR 3rd, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann AJ (2016) Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 387: 760-9. doi: 10.1016/S0140-6736(15)01159-9.

Corresponding author
Xuebin Yu, MD
No. 568 Zhongxing Road, Shaoxing,
Zhejiang province, China.
Tel: 86-18757539180
Email: yuxuebinok@126.com

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