IDCases 19 (2020) e00694

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Aspergillus fumigatus endocarditis in a splenectomized patient with no risk factors

Aggarwal Abhimanyu*, Hogan Karen, Paez Armando

Division of Infectious Diseases, Baystate Medical Center/University of, Massachusetts Medical School, Baystate, MA, USA

ARTICLE INFO

Article history:
Received 11 December 2019
Received in revised form 28 December 2019
Accepted 28 December 2019

Keywords:
Aspergillus fumigatus
Invasive aspergillosis
Infective endocarditis
Splenectomy
Fungal endocarditis

ABSTRACT

Aspergillus endocarditis is a rare cause of culture-negative fungal endocarditis, after *Candida* endocarditis. Typical risk factors include intravenous drug use, immunosuppression, prior cardiac surgery or presence of prosthetic heart valves, hematopoietic stem cell or solid organ transplantation. Common presentations include signs and symptoms consistent with endocarditis but with negative bacterial blood cultures. Here, we present a case report of a 49-year-old male without known risk factors for fungal endocarditis who presented with a stroke and found to have *Aspergillus* endocarditis. Despite surgical intervention and antifungal treatment, the outcome was fatal. This underscores the difficulty in diagnosing *Aspergillus* endocarditis and its poor prognosis, necessitating the need for early diagnosis and intervention.

Introduction

Aspergillus sp. is a mold that is ubiquitous worldwide and found in soil, water, food and air, and is particularly common in decaying vegetation. Associated syndromes can range from colonization such as fungal ball, to allergic responses such as allergic bronchopulmonary aspergillosis, to semi-invasive or invasive infections such as pulmonary aspergillosis. In rare cases, in the presence of risk factors such as intravenous drug use, immunocompromised patients or prosthetic heart valves, invasive aspergillosis can present as infective endocarditis as well, the most common species involved being *Aspergillus fumigatus*.

Case report

A 49-year-old otherwise healthy male sustained a motor vehicle accident causing splenic laceration, traumatic brain injury, multiple rib fractures and pelvic fracture, and required a series of 14 intraabdominal, transthoracic and intracranial surgeries within a span of two months. Computed tomography (CT) chest noted an isolated 6 mm right lower lobe pulmonary nodule. He never smoked cigarettes but smoked marijuana. He eventually needed splenectomy, tracheostomy and gastrostomy tube placement, and long term rehabilitation. During this hospitalization, he did not receive any prolonged antibiotic treatment and only received one week of antibiotic therapy. He initially received vancomycin and piperacillin-tazobactam that was later switched to cefepime for suspected ventilator acquired pneumonia with endotracheal aspirate culture growing *Acinetobacter baumanii*. He was not discharged on any antibiotic regimen. Six months post-hospital discharge, he was sent to the emergency department of a local hospital for sudden altered mentation and inability to follow commands. He was noted to have right facial droop and right arm weakness. Significant lab results showed elevated white blood cell count of 18,800/mm^3 with 86.5 % neutrophils with remainder blood work being unremarkable. Electrocardiography showed sinus tachycardia but no other conduction abnormalities or ischemic changes. Magnetic resonance imaging (MRI) brain demonstrated subacute left middle cerebral artery distribution ischemic stroke in the insular cortex and portion of the frontoparietal cortex. Transthoracic echocardiogram demonstrated 1.2 cm × 1.3 cm vegetation in the anterior leaflet of native mitral valve but with normal left ventricular function and no regional wall motion abnormality consistent with endocarditis. Three sets of blood cultures were negative. He was transferred to our facility for cardiac surgery evaluation. Cardiac surgery did not recommend any immediate surgical intervention. He was discharged with a left upper extremity PICC line to complete a total of six weeks of intravenous vancomycin, ciprofloxacin and ampicillin/sulbactam treating for culture-negative mitral valve endocarditis. Repeat echocardiogram was recommended prior to finishing the course of antibiotics. At the time of hospital discharge, he was noted to

* Corresponding author at: Baystate Medical Center, 759 Chestnut street, S4426, Springfield, MA, 01199, USA.
E-mail addresses: Abhi.aggarwal@outlook.com (A. Aggarwal), Karen.Hogan@baystatehealth.org (K. Hogan), Armando.paez@baystatehealth.org (A. Paez).

https://doi.org/10.1016/j.idcr.2020.e00694

be alert, awake, could speak in full sentences and moderate resolution of right-sided hemiparesis.

Three days following hospital discharge, he presented again to the local ED with altered sensorium and leukocytosis at 28,000/mm^3, with otherwise unremarkable blood work. He was transferred back to our facility where repeat MRI brain showed increased restricted diffusion in the periphery of prior stroke distribution, presumably an evolution of prior stroke, but no new lesions. He was continued on vancomycin, gentamicin and ceftriaxone. Repeat transthoracic and transesophageal echocardiogram demonstrated enlarged mitral valve vegetation of the size 2.1 cm × 2.2 cm. Repeat blood cultures were drawn as well as *Bartonella* and *Coxiella* antibodies were sent that later returned negative. The patient underwent mitral valve replacement with placement of bioprosthetic valve the following day. Intra-operative findings were described as "extensive replacement of entire mitral valve with what appeared to be fungus with vegetation extending into both papillary muscles requiring extensive debridement" (Fig. 1). Postoperatively, he was started on liposomal amphotericin B dosed at 5 mg/kg/day. Histopathology of the valve specimen showed acute-angle branching septate hyphae, suspected to be a mold (Fig. 2). Tissue fungal culture grew *Aspergillus fumigatus* (Fig. 3). Post-operatively, he developed shocked liver with aspartate transaminase 3955 U/L and alanine transaminase 2141 U/L. He developed postoperative fevers and persistently elevated white blood cell count. His respiratory status worsened with development of left-sided empyema, which was drained with pleural fluid culture eventually growing *Aspergillus fumigatus*. Repeat MRI brain showed development of right parietal leptomeningeal enhancement compatible with meningitis and new extensive bilateral cerebral ring enhancing lesions consistent with small abscesses, likely embolic in nature. Further evaluation for extent of aspergillosis was done and several non-healing fractures in the pelvic area were noted. One of them had the largest lucency in right iliac bone which was aspirated under CT-guidance but returned negative for the fungal infection. Patient's family eventually decided to pursue hospice care and shortly thereafter, the patient expired.

Discussion

Aspergillus is a saprophytic sporulating mold, with most species reproducing asexually but a sexual form has been identified for some pathogenic species, including *Aspergillus fumigatus*. A distinguishing characteristic of *Aspergillus fumigatus* is its ability to grow at 50OC. Each conidial head produces several conidia which upon disturbance by environment or strong air releases them into air, and their small size keeps them suspended in air and virtually all humans inhale it at some point in their lifetime [1].

Aspergillus fumigatus is the most frequent species associated with invasive infections. Patients with prolonged and profound immunosuppression are at high risk for invasive aspergillosis. Factors associated with poor host pulmonary defense mechanisms predispose to enlargement and germination of inhaled conidia resulting in maturation into hyphal forms with subsequent vascular invasion and eventual dissemination. Despite its nature of vascular invasion and that *Aspergillus fumigatus* can grow in BACTEC culture vials. For unclear reasons, blood culture of patients with invasive aspergillosis is frequently negative [2].

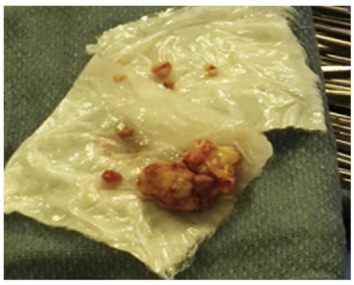

Fig. 1. Excised fungating lesion of the mitral valve.

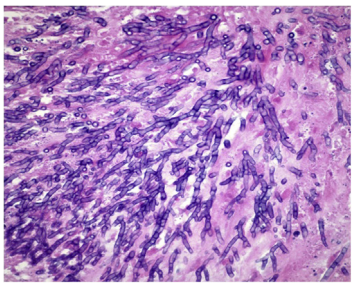

Fig. 2. Acute-angle branching septate hyphae as seen under 100x magnifications on Gomori methenamine silver (GMS) staining.

Fig. 3. Fungal culture growth in microbiology laboratory.

More commonly, the invasive aspergillosis involves the lungs and rarely causes endocarditis. Most cases of *Aspergillus* endocarditis have been reported to affect prosthetic valves. There is paucity of literature about infections affecting native valves. Reported risk factors for *Aspergillus* endocarditis include intravenous drug use, immunosuppression, prior cardiac surgery or prosthetic heart valves, hematopoietic stem cell or solid organ transplantation. Kalokhe et al. published a review of 53 cases of *Aspergillus* endocarditis reported between 1950 and 2010, of which 50 cases were left-sided endocarditis and in 11 cases, diagnosis was established post-mortem [3]. In 2016, another series of 14 case reports of *Aspergillus fumigatus* endocarditis was published where except for one case with positive blood culture, all had negative blood cultures [4]. All published reports had variable outcomes regardless of surgical intervention.

Aspergillus endocarditis is difficult to diagnose particularly in patients who do not have traditional risk factors for this infection such as our case. In the case presented above, after going through several surgeries including splenectomy and acute illness after the accident, the patient was in a relative immunocompromised state. Perhaps, *Aspergillus fumigatus* invasive infection occurred. Source could also have been an undiagnosed pelvic infection given open fracture contaminated from the environment. A biopsy of one of the non-healing fractures of right ilium was performed that was negative for fungal growth but sensitivity of this is low. Another possibility is respiratory colonization with *Aspergillus fumigatus* or subclinical infection given the presence of pulmonary nodules. Development of empyema with positive pleural fluid culture may support this but fungal pulmonary septic emboli cannot be ruled

out either although that would require lesions on tricuspid/pulmonary valve which was not noted in his case. In any case, the suspicion for *Aspergillus* endocarditis was low and diagnosis was established intraoperatively. It is unclear if his asplenia contributed to his risk of invasive aspergillosis. Mehrotra et al. presented a case report of chronic pulmonary aspergillosis in a splenectomized patient but no definitive evidence of increased risk of Aspergillosis in patients undergoing splenectomy [5] and no conclusive evidence on our review of literature too. At least 2 case reports of *Aspergillus* endocarditis did not have definite risk factors for this infection [6,7]. Variable presentations of *Aspergillus* endocarditis have also been reported [8,9].

Molecular diagnosis of *Aspergillus* infection utilizes serum galactomannan assay that has been shown to be an accurate marker for diagnosis of invasive aspergillosis in certain patient subpopulation, and was noted to be having 78.4 % sensitivity, 87.5 % specificity, 27 % positive predictive value and 98.6 % negative predictive value [10]. Some case reports have utilized this combined with *Aspergillus* PCR testing with not much significant additional benefit [11]. Other fungal markers of infection such as beta-D glucan although sensitive, they are not specific for *Aspergillus* [11].

A review of 270 cases of fungal endocarditis between 1965–1995, showed recurrence rate of 30 % of cases despite improved diagnostic technology and treatment options [12]. Surgical intervention remains the corner stone of treatment of fungal endocarditis including *Aspergillus* endocarditis. Fungal endocarditis has been a "standalone indication" for surgical intervention due to bulky nature of vegetations and subsequent increased risk of relapse and emboli [2]. In 2012 UK guidelines, *Aspergillus* endocarditis has a separate category where "surgical valve replacement is mandatory for survival". Most case reports on *Aspergillus* endocarditis have documented the use of amphotericin B but the liposomal formulation of amphotericin B has less nephrotoxic potential and more propensity to work on biofilms, which can be somewhat beneficial particularly in cases where surgery is not feasible. With the landmark trial published in 2002, voriconazole emerged as a primary choice of fungicidal drug against *Aspergillus* endocarditis [13]. Current IDSA guidelines recommend voriconazole or lipid formulation Amphotericin B as the initial therapy for *Aspergillus* endocarditis and consideration for lifelong antifungal therapy after surgical replacement [14]. Even with surgery, the long term survival is limited. Mortality rates have approached 96 % in patients with *Aspergillus* endocarditis treated only with medical therapy.

CRediT authorship contribution statement

Aggarwal Abhimanyu: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Hogan Karen:** Data curation, Formal analysis, Writing - review & editing. **Paez Armando:** Data curation, Formal analysis, Writing - review & editing, Supervision.

Declaration of Competing Interest

There were no conflicts of interest in preparation of this case report.

Acknowledgments

Peter Hassiotis, MBA, MT (ASCP) from Microbiology Laboratory, Baystate Health

References

[1] Latge JP, Chamilos G. Aspergillus fumigatus and Aspergillosis in 2019. Clin Microbiol Rev 2019;33(December (1)), doi:http://dx.doi.org/10.1128/cmr.00140-18.
[2] Tattevin P, Revest M, Lefort A, Michelet C, Lortholary O. Fungal endocarditis: current challenges. Int J Antimicrob Agents 2014;44(October (4)):290–4, doi:http://dx.doi.org/10.1016/j.ijantimicag.2014.07.003.
[3] Kalokhe AS, Rouphael N, El Chami MF, Workowski KA, Ganesh G, Jacob JT. Aspergillus endocarditis: a review of the literature. Int J Infect Dis 2010;14 (December (12)):e1040–7, doi:http://dx.doi.org/10.1016/j.ijid.2010.08.005.
[4] Rofael R, Turkistani Y, McCarty D, Hosseini-Moghaddam SM. Fungal mobile mass on echocardiogram: native mitral valve Aspergillus fumigatus endocarditis. BMJ Case Rep 2016;2016(December (8)), doi:http://dx.doi.org/10.1136/bcr-2016-217281.
[5] Mehrotra A, Lieberman J, Legro IR, Cross S, Lanfranco J. Chronic pulmonary aspergillosis in a patient with splenectomy. Am J Med 2018;131(April (4)), doi:http://dx.doi.org/10.1016/j.amjmed.2017.10.040 e141-e2.
[6] Marinelli T, Kidd S, Shaw D, Rowe E. Aspergillus fumigatus endocarditis in an indigenous Australian male without classic risk factors. Med Mycol Case Rep 2018;22(December):61–4, doi:http://dx.doi.org/10.1016/j.mmcr.2018.09.005.
[7] Ikediobi U, Sutton RE. Aspergillus fumigatus native valve infective endocarditis in an otherwise healthy adult. JMM Case Rep 2016;3(February (1))e005018, doi:http://dx.doi.org/10.1099/jmmcr.0.005018.
[8] Vassiloyanakopoulos A, Falagas ME, Allamani M, Michalopoulos A. Aspergillus fumigatus tricuspid native valve endocarditis in a non-intravenous drug user. J Med Microbiol 2006;55(May (Pt 5)):635–8, doi:http://dx.doi.org/10.1099/jmm.0.46398-0.
[9] Pavlina AA, Peacock JW, Ranginwala SA, Pavlina pm, Ahier J, Hanak CR. Aspergillus mural endocarditis presenting with multiple cerebral abscesses. J Cardiothorac Surg 2018;13(October (1)):107, doi:http://dx.doi.org/10.1186/s13019-018-0796-4.
[10] Imbert S, Gauthier L, Joly I, Brossas JY, Uzunov M, Touafek F, et al. Aspergillus PCR in serum for the diagnosis, follow-up and prognosis of invasive aspergillosis in neutropenic and nonneutropenic patients. Clin Microbiol Infect 2016;22(June (6))e1–8, doi:http://dx.doi.org/10.1016/j.cmi.2016.01.027562.
[11] Hatlen TJ, Filler SG, Bayer A, Shah S, Shodhan S, Van TT. Aspergillus endocarditis diagnosed by fungemia plus serum antigen testing. Med Mycol Case Rep 2019;23(March):1–3, doi:http://dx.doi.org/10.1016/j.mmcr.2018.10.004.
[12] Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965-1995. Clin Infect Dis 2001;32(January (1)):50–62, doi:http://dx.doi.org/10.1086/317550.
[13] Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347(August (6)):408–15, doi:http://dx.doi.org/10.1056/NEJMoa020191.
[14] Patterson TF, Thompson [56_TD$DIFF][49_TD$DIFF]3rd GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of america. Clin Infect Dis 2016;63(August (4)):e1–e60, doi:http://dx.doi.org/10.1093/cid/ciw326.