Le Infezioni in Medicina, n. 2, 226-232, 2025
doi: 10.53854/liim-3302-9

Aspergillus fumigatus endocarditis in an immunocompetent host aided by metagenomic next-generation sequencing assay: case report and literature review

Carlos E. Plazola[1,2], Aliya Rehman[3], Maria Morel[1,2], Christine Vu[2], Jose G. Castro[1,2], Folusakin Ayoade[1,2]

[1]Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, USA;
[2]Jackson Health System, Miami, USA;
[3]University of Maryland, Baltimore, USA.

Article received 5 February 2025 and accepted 5 May 2025

SUMMARY

Aspergillus fumigatus endocarditis is a rare but severe infection associated with high mortality, typically affecting immunocompromised individuals. Diagnosing fungal endocarditis can be challenging due to the often negative blood cultures and nonspecific symptoms. We present a case of *Aspergillus fumigatus* infective endocarditis in a 59-year-old immunocompetent man with no typical risk factors, diagnosed with the assistance of metagenomic microbial plasma cell-free DNA next-generation sequencing assay (Karius test). The patient presented with ocular symptoms and was found to have a heart murmur and a hypodense liver lesion, leading to suspicion of infective endocarditis. Blood cultures failed to reveal a pathogen, but elevated fungal biomarkers and the Karius test supported *Aspergillus fumigatus* as the causal agent. The patient received antifungal therapy with voriconazole and liposomal amphotericin B followed by surgical intervention for mitral valve replacement. The case exemplifies the difficulty in diagnosing *Aspergillus* endocarditis, as blood cultures are often negative and histological confirmation may be delayed. Molecular diagnostics, such as metagenomic microbial plasma cell-free DNA next-generation sequencing assay, significantly enhance pathogen detection in culture-negative cases.
However, although treatment with antifungal therapy and surgery can improve outcomes, the high mortality associated with *Aspergillus* endocarditis remains a critical concern, highlighting the need for further research and advancements in both diagnostic and therapeutic approaches.

Keywords: Aspergillus, fungal, endocarditis, DNA, molecular.

INTRODUCTION

Fungal endocarditis is a rare but serious condition with high morbidity and mortality rates. It accounts for less than 10% (approximately 1 to 3%) of all infective endocarditis cases, with *Aspergillus* spp. accounting for up to 30% of all cases (second only to *Candida* spp.) [1, 2]. This condition primarily affects immunocompromised patients and individuals with risk factors such as intravenous drug use, malignancy, and prosthetic valves. Diagnosis can be challenging as blood cultures are often negative, necessitating confirmation through histological and tissue culture methods. This highlights the increasing importance of molecular techniques like broad-range bacterial PCR and metagenomic sequencing for accurate

Corresponding author
Folusakin Ayoade
E-mail: fxa375@med.miami.edu

diagnosis. Managing fungal endocarditis remains difficult due to delayed detection and the limited effectiveness of antifungal therapy alone, contributing to its high fatality rates [3]. Here, we report a case of *Aspergillus fumigatus* infective endocarditis in an immunocompetent patient without typical risk factors, diagnosed with the assistance of metagenomic microbial plasma cell-free DNA next-generation sequencing assay.

CASE DESCRIPTION

This is a 59-year-old man with a past medical history of hypertension and type 2 diabetes mellitus. He presented to the emergency room complaining of headache and painless loss of vision in the right eye and floaters in the left eye for one-day duration. He denied fever, chills, night sweats, or weight loss. Other reviews of systems were negative. Social history revealed that the patient was born and raised in the Miami, South Florida area of the United States where he lived with his wife. He worked as a waste disposal truck driver. He had three dogs but denied other animal exposure. He did admit to occasionally drinking a few beers weekly but otherwise denied tobacco use, recreational drug use, or recent travel. A physical exam revealed a 2/6 systolic murmur and ophthalmologic exam showed panuveitis, as well as inflammation and vitritis in the subretinal, retinal, and choroidal areas. Other parts of the physical examination were unremarkable. Vitreous bacterial cultures were taken from the right eye, and anterior chamber paracentesis of the left eye was performed to obtain samples for additional viral and parasitic testing. The patient subsequently received intravitreal vancomycin, ceftazidime, and voriconazole in both eyes. Initial laboratory results showed mild leukocytosis of 13,600 cells/mcL with an 81.4% neutrophil predominance. Kidney and liver function testing were also within normal limits. HIV and hepatitis C testing were negative. Computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed a hypodense lesion in the left liver lobe measuring 8 mm. The combination of ocular findings, heart murmur, and liver lesion were suggestive of infective endocarditis. He was empirically started on intravenous cefepime and vancomycin pending further infectious workup. The Infectious Diseases service was consulted and recommended switching cefepime to ceftazidime for better eye penetration. Blood cultures and further imaging were also ordered. Transthoracic echocardiogram showed a 0.9 cm mobile density on the anterior mitral valve tip, which was concerning for vegetation. Magnetic resonance imaging (MRI) of the brain with contrast showed findings consistent with

1) small bilateral cerebellar infarctions,
2) meningeal enhancements in the right sylvian, anterior interhemispheric fissures, and right frontal lobe, suggestive of meningitis,
3) right frontal subarachnoid hemorrhage and possible hemorrhagic meningitis.

On hospital day 2, the patient developed abdominal pain, and a CT of the abdomen and pelvis with intravenous contrast showed complete occlusion of the celiac artery with soft tissue attenuation surrounding the vessel measuring 3.3 x 2.6 cm, extending into the confluence of the splenic and hepatic artery as well as the left gastric artery, likely representing thrombosis with surrounding inflammatory changes. CT of the head with intravenous contrast showed a circumscribed hyper-density in the right sylvian fissure, concerning for a small aneurysm in the right M2 segment. A transesophageal echocardiogram (TEE) was also obtained which showed a mitral valve vegetation attached to A2, measuring 1 cm with moderate mitral valve regurgitation but no evidence of perforation or abscess formation. The Ophthalmology team meanwhile continued with bilateral intravitreal injections of ceftazidime, vancomycin, and voriconazole. On day 4 of the hospital course, intravenous ceftazidime was switched to meropenem, as eye findings were worsening. By day 5, blood cultures had not shown any significant microbial growth. *Bartonella* and *Coxiella* serum PCR and serologic testing were negative. *Brucella* IgG was positive but IgM was negative. *Histoplasma* urine antigen and cryptococcal serum antigen were both negative. On day 6, (1-3)-β-d-glucan (Fungitell) in the blood returned elevated at >500 pg/mL and serum *Aspergillus* galactomannan antigen returned at 1.40 (normal <0.5). At this time, metagenomic microbial plasma cell-free DNA next-generation sequencing assay from blood was ordered as fungal markers were elevated and blood cultures had shown no growth. On day 7, intravenous voriconazole was started. On day 8, digital subtraction angiography (DSA) showed a 2.8 x 2.4 mm M2/3 aneurysm at the bi-

furcation of the angular M2 segment of the middle cerebral artery, concerning for mycotic aneurysm. On day 9, metagenomic microbial plasma cell-free DNA next-generation sequencing assay returned positive for *Aspergillus fumigatus*. Intravenous liposomal amphotericin B was then added to intravenous voriconazole for combination therapy due to concern for active metastasizing infection, while the Ophthalmology team continued administering intravitreal voriconazole to both eyes. While on intravenous voriconazole 350 mg twice daily, a serum trough returned at 3.3 ug/mL. During this time, Cardiothoracic surgery recommended no surgical intervention due to the inability to be placed on anticoagulants required for surgery, due to recent subarachnoid hemorrhage and increased bleeding risk. On day 28, the patient was considered less at risk for hemorrhagic conversion and cleared for surgery; he underwent mitral valve replacement with a bioprosthetic mitral valve. The patient developed acute kidney injury around the time of surgery, and so intravenous liposomal amphotericin B was discontinued. On day 31, mitral valve pathology revealed acute and chronic endocarditis with numerous septate, branching hyphae morphologically consistent with *Aspergillus* (Figure 1 and Figure 2). On day 37, the mitral valve culture grew *Aspergillus fumigatus* and this was sent out for antifungal susceptibility testing. On day 38, the patient underwent clipping of the middle cerebral artery aneurysm. A week later, antifungal susceptibilities returned with the following minimum inhibitory concentrations: amphotericin 2, voriconazole 0.25, posaconazole ≤0.03 and isavuconazole 0.5. On day 71, the patient underwent open repair of mycotic superior mesenteric artery aneurysm. On day 82, the patient developed prolonged QTc, and voriconazole and was subsequently switched to isavuconazole. Due to isavuconazole's long half-life, micafungin was also started for bridging purposes until a level could be obtained. A week later, isavuconazole trough returned 0.9 ug/mL and the dose was increased from 372 mg orally daily to twice daily. On day 114, the isavuconazole trough returned at 3.5 ug/mL, and micafungin was stopped. On day 165, the patient was discharged to a long-term acute care hospital

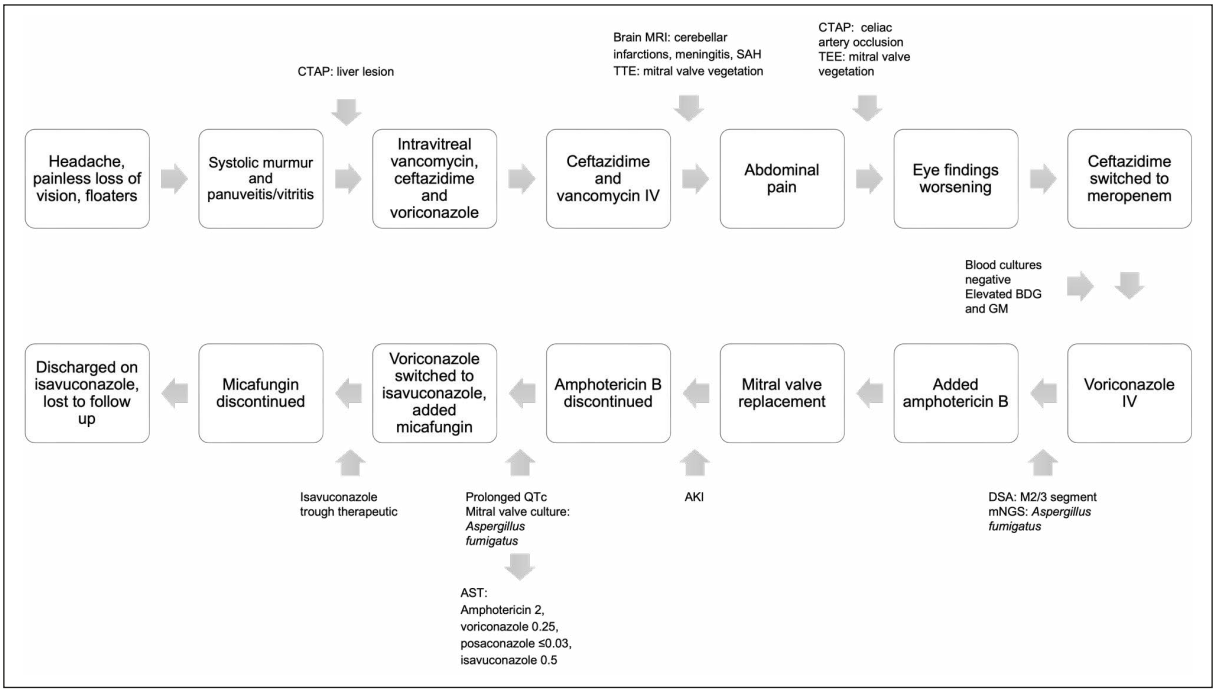

Figure 1 - The clinical course chronology. CTAP, computed tomography of the abdomen and pelvis; IV, intravenous; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; BDG, (1-3)-β-d-glucan; GM, *Aspergillus* galactomannan antigen; DSA, digital subtraction angiography; AKI, acute kidney injury; AST: antimicrobial susceptibility testing.

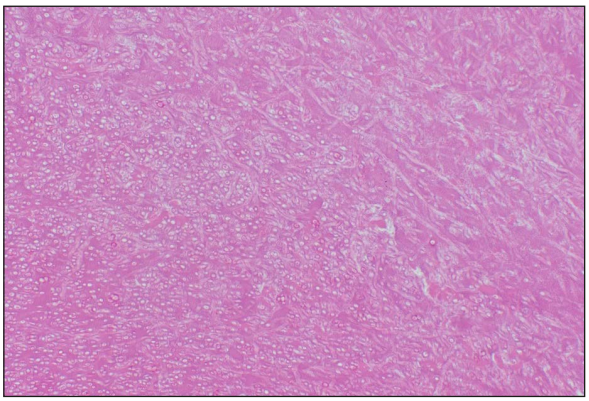

Figure 2 - Hematoxylin and eosin section slide of mitral valve tissue showing acute branching septate hyphae consistent with *Aspergillus fumigatus*.

with plans to continue prolonged isavuconazole treatment. Since then, the patient has been lost to follow up. The chronology of the clinical course is outlined in Figure 1.

SYSTEMATIC LITERATURE REVIEW

Methodology

We conducted a systematic PubMed review of cases published from 2000 to 2025 using the terms *Aspergillus fumigatus* and *endocarditis*. Inclusion was limited to patients aged ≥18 years with negative blood cultures. Seventeen cases met criteria. Data were extracted on immune status, prosthetic valve presence, affected valve, embolic events, fungal marker use, surgery, diagnostic method, treatment modification, and outcomes.

Results

The findings of the literature review are presented in Table 1. "Immunocompromise" status was reported in 10 cases (59%) [4-10], and prosthetic valves in 3 (18%) [11-13]. The mitral and tricuspid valves were most commonly involved (47% and 35%, respectively).

Embolic phenomena were seen in 11 cases (65%), commonly affecting the brain, lungs, or abdomi-

Table 1 - Retrospective review of 17 cases of culture-negative endocarditis caused by *Aspergillus fumigatus*.

Case	*Age/ sex*	*Immuno-compromise*	*Presence of prosthetic valve*	*Affected valve*	*Embolic phenomena*	*Non-invasive fungal markers*	*Valve surgery*	*Method of pathogen detection*	*Changes in therapies after pathogen detection*	*Outcome*
1	55/M	Kidney transplant on immuno-suppressants	No	Tricuspid	No	Elevated (1,3)-β-d-glucan (BDG), galactomannan test (GM)	No	Plasma metagenomic next-generation sequencing	Voriconazole	Left hospital voluntarily
2	42/M	No	Yes	Mitral	No	N/A	Yes	Polymerase chain reaction of mitral valve tissue	Voriconazole	Discharged on oral voriconazole
3	18/M	Myelodysplastic syndrome	No	Tricuspid	No	Elevated GM	Yes	Valve tissue culture	Voriconazole	Discharged on lifelong oral voriconazole
4	64/F	No	Yes	Mitral	No	N/A	Yes	Valve tissue culture	Voriconazole	Discharged
5	49/M	No	No	Mitral	Stroke, left-sided empyema, brain abscesses	N/A	Yes	Valve tissue culture	Amphotericin B	Hospice
6	39/M	No	No	Tricuspid (and papillary muscle)	Brain abscesses	Elevated GM	No	Brain tissue culture	Amphotericin B and voriconazole	Discharged on oral voriconazole for at least one year
7	71/M	Granulomatosis with polyangiitis on steroids	No	Mitral valve	Brain abscess	N/A	Yes	Brain and valve tissue culture	Amphotericin B and voriconazole	Discharged on oral voriconazole

Continue >>>

>>> *Continue*

Case	*Age/ sex*	*Immuno-compromise*	*Presence of prosthetic valve*	*Affected valve*	*Embolic phenomena*	*Non-invasive fungal markers*	*Valve surgery*	*Method of pathogen detection*	*Changes in therapies after pathogen detection*	*Outcome*
8	29/M	Extra-nodal NK/T cell lymphoma nasal type) status-post SMILE regimen	No	Tricuspid valve and posterior wall of left ventricle	Lung, brain, cervical (intramuscular) and myocardial abscesses	Elevated BDG, GM	Yes	Gene analysis of cervical abscess and valve tissue culture	Amphotericin B and voriconazole	Discharged on oral voriconazole
9	66/M	No	No	Anterior papillary muscle and lateral wall of left ventricle	Renal and splenic infarcts, brain abscess	Elevated BDG, GM	Yes	Valve tissue culture	Voriconazole	Discharged on oral voriconazole
10	62/M	No	Yes	False aneurysm of the aortic annulus	Bilateral strokes	N/A	Yes	Tissue culture	Amphotericin B and voriconazole	Discharged on lifelong oral voriconazole, switched to posaconazole at 12 months due to side effects
11	58/M	Kidney transplant 8 months prior	No	Aortic valve (and interven-tricular septum)	Brain, lung and intramuscular abscesses	Elevated BDG, GM	No	Bronchoalveolar lavage and intramuscular abscesses culture	Amphotericin B and voriconazole	Expired
12	58/M	Chronic lymphocytic leukemia treated with chemotherapy	No	Left ventricular mass	No	N/A	No	Post-mortem myocardial biopsy	Voriconazole, imipenem, amikacin and trimethoprim-sulfamethoxazole	Expired
13	55/M	IgA vasculitis on steroids	No	Mitral valve	Endophthalmitis, left limb ischemia, brain abscesses	N/A	Yes	Sputum and left limb thrombus culture, cardiac biopsy	Amphotericin B and flucytosine	Expired
14	52/F	Recently diagnosed HIV infection	No	Mitral valve (and left atrium)	No	N/A	No	Bronchoalveolar lavage culture	Amphotericin B and voriconazole	Expired
15	34/M	Acquired immuno-deficiency syndrome	No	Mitral valve (interven-tricular septum)	Brain abscesses, purpuric skin lesions, pericardial effusion	N/A	No	Pericardial effusion, skin and lymph nodes cultures	N/A	Expired
16	70/F	B-cell chronic lymphocytic leukemia	No	Left ventricular mass	Brain abscesses	Elevated GM	Yes	Brain abscess and valve tissue culture	Voriconazole and micafungin	Expired
17	53/M	No	No	Tricuspid valve	Lung abscess	N/A	No	Post-mortem lung biopsy	N/A	Expired

N/A: does not apply.

nal organs [6-10, 13-17], findings echoed in our case. This supports the idea that *Aspergillus fumigatus* endocarditis should be suspected when unexplained emboli occur with negative blood cultures.

Non-invasive fungal markers especially (1-3)-βD-glucan and galactomannan were measured and elevated in 7 cases (41%) [4, 5, 7, 8, 10, 15, 16]. In our case, both markers were markedly elevated early in the clinical course and prompted further testing with metagenomic next-generation sequencing, which ultimately confirmed the diagnosis. This contrasts with the reviewed literature, where these markers were not consistently used, suggesting their diagnostic potential may be underutilized.

Pathogen detection was most commonly achieved via tissue culture (13/17, 76%), while molecular diagnostics (polymerase chain reaction or mNGS) were used in 3 cases (18%) [4, 7, 11].

DISCUSSION

Aspergillus fumigatus endocarditis is an uncommon but serious condition with high mortality. While traditionally associated with immunocompromise, indwelling devices, intravenous drug use, or prosthetic valves, our case and others show it can also occur in immunocompetent individuals. Environmental exposures, such as handling organic waste, may also increase risk [18, 19].

Diagnosis is challenging due to nonspecific symptoms and frequent embolic phenomena [1]. Blood cultures are often negative, and histology or tissue cultures, while diagnostic, are invasive and not always feasible. As a result, non-invasive fungal markers like serum (1-3)-β-D-glucan and galactomannan, along with molecular tools such as mNGS, have become increasingly recommended in culture-negative endocarditis. Our patient's diagnosis was supported by early elevation of both serum markers and confirmed by mNGS (Karius test) [20-22].

In our case, mNGS provided the first definitive identification of *Aspergillus fumigatus*, enabling early, targeted therapy. This combined approach, using both fungal markers and molecular testing, was uncommon in the reviewed literature but played a pivotal role in our case. Wider adoption may improve outcomes by helping clinicians recognize and treat culture-negative *Aspergillus fumigatus* endocarditis earlier.

Treatment remains challenging. Despite optimal care, including surgery and antifungal therapy, mortality may approach 80% [23]. In our review, 10 patients underwent valve surgery, of whom 8 survived. Overall mortality was 41% (7/17), with worse outcomes in patients lacking surgery or facing delays in diagnosis [8, 9, 17].

Antifungal therapy was modified or initiated based on pathogen identification in 88% of the cases reviewed (15/17) [4-8, 10-16]. Though current guidelines are cautious about combination therapy, retrospective data suggest potential benefit in reducing mortality [6, 24]. This was reflected in our case, where combination therapy was used in the setting of disseminated infection and was adjusted based on antifungal susceptibility testing.

Aspergillus fumigatus endocarditis remains a rare but daunting clinical challenge. Symptoms are often vague, and blood cultures are typically negative, delaying diagnosis and treatment. Our case, alongside those reviewed, highlights the importance of early use of molecular diagnostics, especially mNGS [4, 25], and non-invasive fungal markers. Together, these tools can enable faster identification and initiation of appropriate therapy.

Outcomes vary widely, with highest mortality seen in those without surgery or with late diagnosis. Some cases are only identified post-mortem, underscoring the need for high clinical suspicion and early use of advanced diagnostics in culture-negative endocarditis. Continued progress in diagnostic and therapeutic strategies will be critical to improving outcomes in this life-threatening condition.

Conflicts of interest
None.

Funding
This work was not by specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

[1] Ellis ME, Al-Abdely H, Sandridge A et al. Fungal endocarditis: evidence in the world literature, 1965-1995. *Clin Infect Dis*. 2001; 32(1): 50-62.

[2] Antinori S, Ferraris L, Orlando G et al. Fungal endo-

carditis observed over an 8-year period and a review of the literature. *Mycopathologia*. 2014; 178(1-2): 37-51.
[3] Pasha AK, Lee JZ, Low SW et al. Fungal Endocarditis: Update on Diagnosis and Management. *Am J Med*. 2016; 129(10): 1037-1043.
[4] Li X, Li D, Han D. Rapid diagnosis of Aspergillus fumigatus endocarditis using mNGS assay: A case report and review of the literature. *Diagn Microbiol Infect Dis*. 2024; 108(3): 116171.
[5] Kalokhe AS, Rouphael N, El Chami MF et al. Aspergillus endocarditis: a review of the literature. *Int J Infect Dis*. 2010; 14(12): e1040-7.
[6] Aldosari MA, Alghamdi MH, Alhamdan AA et al. Native valve fungal endocarditis caused by Aspergillus fumigatus: management dilemma. *Oxf Med Case Reports*. 2020; 2020(3): omz147.
[7] Hiroshima Y, Kurumisawa S, Aizawa K, Fukushima N, Kawahito K. Successful treatment of Aspergillus mural endocarditis in malignant lymphoma using a combined antifungal and surgical approach: a case report. *Surg Case Rep*. 2020; 6(1): 128.
[8] Chevalier K, Barde F, Benhamida S et al. Invasive aspergillosis and endocarditis. *Rev Med Interne*. 2021; 42(10): 678-685.
[9] García CG, García-Fernández MA, Sarnago Cebada F. Aspergillus endocarditis. *Echocardiography*. 2005; 22(7): 623-624.
[10] Pavlina AA, Peacock JW, Ranginwala SA et al. Aspergillus mural endocarditis presenting with multiple cerebral abscesses. *J Cardiothorac Surg*. 2018; 13(1): 107.
[11] Museedi AS, Nashawi M, Ghali A et al. Prosthetic mitral valve Aspergillus fumigatus endocarditis. *IDCases*. 2020; 21: e00891.
[12] Abuzaid AA, Zaki M, Tarif H. Atypical early Aspergillus endocarditis post prosthetic mitral valve repair: a case report. *Heart Views*. 2015; 16(1): 30-33.
[13] Lennard K, Bannan A, Grant P et al. Potential benefit of combination antifungal therapy in Aspergillus endocarditis. *BMJ Case Rep*. 2020; 13(6): e234008.
[14] Aggarwal A, Hogan K, Paez A. Aspergillus fumigatus endocarditis in a splenectomized patient with no risk factors. *IDCases*. 2020; 19: e00694.
[15] Marinelli T, Kidd S, Shaw D et al. Aspergillus fumigatus endocarditis in an indigenous Australian male without classic risk factors. *Med Mycol Case Rep*. 2018; 22: 61-64.
[16] Zhao Y, Wu X, Wang X et al. Severe fever with thrombocytopenia syndrome complicated with aspergillus endocarditis and multiple organ infarctions after glucocorticoid treatment in an immunocompetent man: a case report. *BMC Infect Dis*. 2025; 25(1): 116.
[17] Vohra S, Taylor R, Aronowitz P. The tell-tale heart: Aspergillus fumigatus endocarditis in an immunocompetent patient. *Hosp Pract (1995)*. 2013; 41(1): 117-121.
[18] Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. *Chest*. 2002; 122(1): 302-10.
[19] Sabino R, Veríssimo C, Viegas C et al. The role of occupational Aspergillus exposure in the development of diseases. *Med Mycol*. 2019; 57(Supplement. 2): S196-S205.
[20] Hatlen TJ, Filler SG, Bayer A et al. Aspergillus endocarditis diagnosed by fungemia plus serum antigen testing. *Med Mycol Case Rep*. 2018; 23: 1-3.
[21] Imbert S, Gauthier L, Joly I 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(6): 562.e1-8.
[22] Zeng X, Liang Y, Wang H et al. Detection of pathogens from venous or arterial blood of patients with left-sided infective endocarditis by metagenomic next-generation sequencing: A prospective study. *Clin Chim Acta*. 2024; 552: 117698.
[23] Ikediobi U, Sutton RE. Aspergillus fumigatus native valve infective endocarditis in an otherwise healthy adult. *JMM Case Rep*. 2016; 3(1): e005018.
[24] Meshaal MS, Labib D, Said K et al. Aspergillus endocarditis: Diagnostic criteria and predictors of outcome, A retrospective cohort study. *PLoS One*. 2018; 13(8): e0201459. Erratum in: *PLoS One*. 2018; 13(8): e0203103.
[25] Mitchell SL, Simner PJ. Next-Generation Sequencing in Clinical Microbiology: Are We There Yet? *Clin Lab Med*. 2019; 39(3): 405-418.