



RESEARCH ARTICLE

FUNGAL ENDOCARDITIS OF THE RIGHT SIDE HEART: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE A CASE REPORT AND LITERATURE REVIEW

Coulibaly Fatimatou Zahra¹, Berrag Kaoutar¹, Mohamed Abidi¹, Dindane Tarek² and Abidi Khalid^{2,3}

1. Department Of Medical Intensive Care Chu Ibn Sina Rabat (Morocco).
2. Professor of Intensive Care.
3. Head of the Medical Intensive Care Unit at CHU Ibn Sina Rabat.

Manuscript Info

Manuscript History

Received: 18 July 2024

Final Accepted: 20 August 2024

Published: September 2024

Abstract

Infective endocarditis is defined as an infection of one or more heart valves by bacteria, more rarely by intracellular germs or yeasts. Involvement of the parietal endocardium is less common. Infective endocarditis is rare but serious (1). Even rarer is fungal endocarditis of the right side of the heart. We report here the case of a female 48-year-old patient with Crohn's disease under immunosuppressive therapy admitted to intensive care for management of a febrile disorder of consciousness. Biological and radiological investigations revealed a vegetation of the tricuspid valve and candida fungemia, indicating a diagnosis of fungal endocarditis of the right heart. The patient was put on fluconazole 800mg/day with a good initial course, followed by a worsening of her clinical and biological condition in connection with pulmonary empyema and a nosocomial infection with multi-resistant *Acinetobacter baumannii*, which compromised her prognosis. The patient died in multiple organ failure. Certain risk factors, such as intravenous drug use, immunodepression and intravenous catheters, predispose to both right heart and fungal endocarditis. The clinical presentation is not very different from that of the left heart, but special methods are needed to detect it. Treatment is essentially based on antifungal agents and surgery.

Copyright, IJAR, 2024,. All rights reserved.

Introduction:-

Fungal endocarditis is rare; however, its incidence is undoubtedly underestimated due to difficulties in identifying the microorganism responsible. (2)

Endocarditis of the right heart is equally rare, accounting for 5% to 10% of all infective endocarditis (IE). They are either associated with a primary left-sided location (IE in an interventricular septal defect or complicated by perforation of the interventricular septum), or are exclusively localised to the valve orifices of the right heart, tricuspid more often than pulmonary (3). They may occur in patients with pacemakers, defibrillators, central venous catheters or congenital heart disease.

The epidemiology of fungal endocarditis has changed radically in recent decades. Reported mainly among intravenous drug users or following cardiac surgery in the years 1965-1995,

Corresponding Author:- Coulibaly Fatimatou Zahra

Address:- Department Of Medical Intensive Care Chu Ibn Sina Rabat (Morocco).

fungal endocarditis now mainly affects immunocompromised patients and/or those with a central venous line, undergoing prolonged broad-spectrum antibiotic therapy or parenteral nutrition (4).

We report here the case of a 48-year-old patient with Crohn's disease under immunosuppressive therapy admitted to the intensive care unit for management of a febrile disorder of consciousness due to fungal endocarditis of the right heart.

Patient and Observation:-

Mrs TR, 48 years old, was admitted to the intensive care unit with haemodynamic instability related to a state of septic shock with pulmonary and digestive origins. She was being treated for relapsing Crohn's disease with corticosteroids and immunosuppressants. The septic shock was brought under control by broad-spectrum dual antibiotic therapy, with a good clinical and biological outcome. The patient was transferred to her original department, gastroenterology. A week later, she was readmitted to intensive care with tonic-clonic convulsions complicated by a febrile disorder of consciousness. It should also be noted that the patient had kept a central venous line for the administration of antibiotics. On admission, she was unconscious with a GCS of 11, febrile at 39°C, with a dull facies and respiratory distress. The patient's haemodynamic status was correct, and cardiac auscultation revealed no murmur. The osteoarticular and mucocutaneous examinations were unremarkable. She no longer had any diarrhoea associated with the relapse of her Crohn's disease. A brain scan was performed in response to the disturbance of consciousness, and was found to be unremarkable. Given the respiratory distress, a TTE (transthoracic echocardiography) was performed to look for signs of pulmonary embolism. There was no evidence of acute pulmonary heart disease, but there was a vegetation measuring 13 mm at the level of the tricuspid valve without tricuspid insufficiency (see Figure 1).

TEE (transesophageal echocardiography) confirmed the diagnosis, demonstrating a large cauliflower-like vegetation attached to the tricuspid septal valve measuring 13x8 mm suggesting fungal endocarditis (see Figure 2). Biological tests revealed an inflammatory syndrome, with high C-reactive protein (CRP : 136 mg/l), and leukopenia. Procalcitonin was positive. Renal function tests were normal, and blood cultures were positive for yeasts, which could not be identified due to a lack of suitable media. In front of this body of argument, the diagnosis of infective endocarditis was made according to the modified Duke's criteria (two major criteria: vegetation and blood cultures, and one minor criterion: fever).

A probabilistic parenteral antifungal therapy based on fluconazole (800 mg/dr) was instituted and well followed. The initial outcome was favourable 24 hours after introduction of the antifungal agent, with apyrexia lasting 4 days, correction of the disorder of consciousness with a GCS of 15 and a considerable reduction in the biological inflammatory and infectious syndrome.

On day 5, the patient's clinical condition worsened (fever of 40° and drowsiness), as did her biological condition. Investigation (chest CT scan, blood cultures) revealed a left mid-lobe pneumonia caused by white staphylococcus. This led to the introduction of a major antistaphylococcal drug (Zyvoxid), with no clinical improvement but a discreet fall in CRP from 130 to 97 mg.

This was followed by a further rise in CRP with persistent clinical deterioration and a syndrome of multisystemic failure with impaired renal, hepatic and haematological function, with disseminated intravascular coagulation and a septic shock.

Multiple blood cultures and bacteriological examination of the central catheter revealed multi-resistant *Acinetobacter baumannii* bacteremia.

The patient was put on colistin and tigecycline without improvement. After 2 weeks of relentless treatment, the patient died.

Patient consent:

Given the fatal outcome for the patient, we were unable to obtain her consent.

Discussion:-

Scientific discussion of the strengths and limitations associated with this case report:

Fungal endocarditis of the right heart is a very rare pathology deserving attention both because of the seriousness of the prognosis and the difficulty of its therapeutic management. Very few cases have been reported in the literature, despite the fact that management is a real challenge for the practitioner. This case report also highlights the need to be extremely vigilant in monitoring venous and arterial access routes, especially when patients are immunocompromised. This case report is limited by the absence of certain diagnostic tests in our facility.

Epidemiology :

As mentioned above, fungal endocarditis is a rare infection. Two reviews have brought together 270 cases published in English-language literature between 1965 and 1995 and 152 cases between January 1995 and June 2000. In an epidemiological survey carried out in France in 1999 in six regions representing 26% of the French population, out of 390 cases of definite endocarditis, only one case of fungal endocarditis, caused by *Aspergillus* sp., was reported. However, their frequency is very probably underestimated, due to the difficulty of identifying the microorganism responsible and the relative lack of knowledge about these rare and often rapidly fatal infections. (4) The most frequent fungal microorganisms are represented by the *Candida* (53% of cases), more rarely by the *Aspergillus* (24%), with *Histoplasma capsulatum* var. *capsulatum* endocarditis being much rarer (6%). (2)

Fungal endocarditis predominantly affects men (sex ratio between 2.0 and 2.2). The mean age of onset is 40 years, with extremes ranging from one week to 84 years. (2) In our case, the patient was a 48-year-old woman.

Risk factors:

Valvular anomalies are the main risk factor and are found in 64% of patients (history of valve surgery in 54% of patients, history of bacterial endocarditis in 13% of patients, rheumatic fever, non-rheumatic heart disease, mitral valve prolapse). Seven cases of *Candida* sp. endocarditis in pacemakers have also been reported.

Our patient was free of any pre-existing valvular anomaly and had a strictly normal transthoracic ultrasound ten days before the diagnosis of infective endocarditis.

She did, however, have a right external jugular line for the administration of vasoactive drugs and broad-spectrum antibiotics for her condition of septic shock. In addition, as mentioned above, she was on immunosuppressants for her Crohn's disease.

Intravenous drug use is also a major risk factor, occurring in 3.9% to 13% of patients with fungal endocarditis. Fungi account for 12-20% of endocarditis in drug addicts, with *C. parapsilosis* accounting for 52% and *Candida albicans* for less than 15% of the microorganisms responsible. However, in a French series involving four drug-addicted patients with *Candida* sp. endocarditis, all were infected with *C. albicans*. Three cases of *Aspergillus* sp. endocarditis, linked to contamination of injected substances by *Aspergillus* spores, have also been reported in drug addicts, two of whom were also infected with HIV. Infections in drug addicts are facilitated by the use of lemon juice, talc powder, plastic syringes, cotton or paper, all of which act as reservoirs for fungal agents.

The increased use of broad-spectrum antibiotic treatments, together with technological advances over the last 30 years such as prolonged central intravenous catheterisation, dialysis, immunosuppression, organ and bone marrow transplants, cardiovascular surgery, parenteral nutrition, undoubtedly explain to a large extent the rise in the incidence of fungal endocarditis observed in recent years (5,6). In patients who have received prior antibiotic therapy, *C. albicans* and *C. glabrata* are the most frequently found agents, accounting for around 2/3 of cases. The mechanism of infection is then essentially linked to catheter colonisation or, particularly in neutropenic patients, to episodes of translocation with a digestive starting point and fungemia. This was probably the case of our patient. In solid organ transplant patients, fungal microorganisms account for 28% of cases of endocarditis, and are mainly observed in the early phase (within 30 days of surgery). These endocarditis cases are essentially linked to *Aspergillus fumigatus* and are characterised by a very high degree of local regional aggressiveness, with invasion of the non-valvular endocardium. (2,7)

Clinical presentation:

The clinical signs of fungal endocarditis do not differ from those of bacterial endocarditis. However, fungal endocarditis usually presents acutely. The clinical signs most frequently encountered are fever, modification of a

pre-existing murmur or the appearance of a new regurgitant murmur, the existence of peripheral emboli, focal or diffuse neurological signs, heart failure and dyspnoea indicative of pulmonary septic emboli. The presence of peripheral signs (Roth's spots, purpura, splenomegaly or Osler's false panaris) is unusual. However, an eye fundus examination is necessary, to look for Roth's spots, which could support the suspicion of diagnosis, and for ocular embolic localisations of the infection. The existence of skin lesions such as papules, pustules or nodules should also point to a fungal aetiology. Complications are frequent in this context. Of the 152 cases of fungal endocarditis observed between 1995 and 2000, complications were reported in 100 patients, with some patients presenting with several complications. The most frequent complications were embolic disease (61 patients), congestive heart failure (16 patients) and sepsis (16 patients). Large vessel emboli are a feature of fungal endocarditis, as the valvular vegetations are large and friable. Mycotic aneurysms are more common in fungal endocarditis than in bacterial endocarditis. Complications frequently involve the central nervous system: in the literature review by Ellis et al. of 270 patients, 47 patients presented with focal neurological signs, and 24 presented with non-focal signs, such as confusion, convulsions or consciousness disorders. (8)

Our patient had suffered convulsions complicated by a febrile disorder of consciousness without motor deficit, which led to her admission to intensive care. She subsequently presented with a cavitary image at the base of the left lung suggestive of an abscess due to a probable pulmonary infarction.

Multiple septic pulmonary embolisms are very common. They may be complicated by pulmonary infarction, pulmonary abscess, pneumothorax and purulent pleural effusion. Right heart failure is rare. *Staphylococcus aureus* is the most frequently implicated micro-organism, with an increase in the prevalence of methicillin-resistant strains. The prevalence of polymicrobial infections is also increasing. Transthoracic echocardiography is generally used to diagnose tricuspid IE because of the anterior location of the valve and the often large size of the vegetations, but transoesophageal echocardiography is more effective for analysing the pulmonary valve, abscesses and lesions in the left heart (9).

Echocardiography:

The echocardiographic characteristics of fungal endocarditis remain difficult to specify, due to the absence of large series reported in the era of trans-oesophageal echocardiography, the sensitivity of which has been shown to be better than that of transthoracic echocardiography (10). Of the 102 patients described between 1995 and 2000 for whom ultrasound data were specified, at least 44 benefited from trans-oesophageal ultrasound. Vegetations were visualised in 83 patients (81.4%), described as voluminous in 42 patients (50.6%), 35 of whom had endocarditis of a native valve and seven of whom had endocarditis of a prosthesis. Vegetations were described as mobile in 16 patients (19.3%). The discovery of myocardial abscesses was unusual (5.9% of patients). (5). The aortic valve is most frequently affected, and it is interesting to note that among 36 patients with risk factors for right heart endocarditis (intravenous drug use, central line, total parenteral nutrition), pulmonary or tricuspid involvement was noted in only eight patients (22%) (8).

Our patient underwent both echocardiographic modalities. It was the TEE that characterised the cauliflower-like vegetations suggesting fungal endocarditis.

Biology:

One of the major criteria in the diagnosis of infective endocarditis is blood culture. However, previous studies have highlighted the variable sensitivity of blood cultures in diagnosing fungal endocarditis. In particular, germs such as *histoplasma*, *mucor* and *aspergillus* rarely grow on conventional culture media. Blood cultures that remained negative despite genuine candida endocarditis were reported in 32% of cases in a 1974 study. In these patients, the diagnosis of certainty was made post-mortem at autopsy. The advent of the lysis centrifugation technique has improved the rate and speed of detection of fungal microorganisms. (10) In addition, new blood diagnostic tools such as the detection of galactomannan antigen (invasive aspergillosis), mannan and anti-mannan antibodies (candidemia), and β 1-3 D glucan (any invasive mycosis) could also partly compensate for the lack of sensitivity of blood cultures and reduce the diagnostic delay.

In our patient, only the routine blood culture on broth allowed the detection of a candida after 05 days, without specification of type due to lack of availability in our facility.

The other tests were non-specific and enabled evaluation of both the infectious and inflammatory syndrome and secondary localisations. They are as follows :

- haemogram, platelets and search for haemolytic anaemia.
- Inflammatory work-up: CRP, protein electrophoresis.
- Immune assessment: circulating immune complexes.
- Urea and creatinine, search for haematuria and proteinuria, ECG.
- BNP to assess left ventricular impact (not systematic).

Extension Assessment:

A lumbar puncture in the case of meningeal syndrome, a cerebral CT or MRI scan in the case of cerebral embolism, an ultrasound or abdominal/pelvic CT scan, particularly in the case of renal embolism, a pulmonary angiogram and pulmonary ventilation and perfusion scintigraphy in the case of IE of the right heart.

Even in the absence of warning signs, brain imaging (CT or MRI) and an abdominal/pelvic CT scan are now recommended to rule out any subclinical embolisms.

Treatment:

Treatment is essentially based on parenteral antifungal therapy. The development of new systemic antifungal agents over the last 15 years has led to tangible progress: 1) echinocandins, fungicidal against most yeasts, have improved the prognosis of *Candida* sp, including on valve prosthesis, even in the absence of surgery; 2) voriconazole, a fungicide on *Aspergillus* sp., has demonstrated its superiority over amphotericin B in invasive aspergillosis, even though the prognosis of *Aspergillus* endocarditis remains highly dependent on surgical possibilities. (4) Yeasts are responsible for the formation of very large vegetations, which are less accessible to anti-infective treatment and almost always require surgical treatment. The prognosis also depends on the patient's condition: diabetes, immunodepression, pre-existing heart failure.

In the literature reviewed by Mellis and al, the combination of surgery and antifungal treatment resulted in better survival at 20 months than in the group of patients treated with antifungal agents alone, i.e. 57% versus 41% respectively, with a statistically significant difference. (8)

For endocarditis of the right heart, according to the 2015 ESC recommendations, the surgical indications are (IIa, C):

- right heart failure secondary to severe tricuspid insufficiency with an inadequate response to diuretic therapy;
- IE due to micro-organisms that are difficult to eradicate (e.g. fungi) or bacteremia persisting for at least 7 days (e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*) despite adequate antibiotic therapy;
- vegetations on the tricuspid valve larger than 20 mm which persist after recurrence of pulmonary embolism (11).

These latest recommendations also made it a point of honour to set up an "endocarditis team". They stipulate that patients with complicated IE such as infective endocarditis with heart failure, abscess, embolic and/or neurological complication, or congenital heart disease, should be referred early and managed in a reference centre with cardiac surgery facilities. Patients with uncomplicated IE may be initially managed in a centre other than a referral centre, but which must be in regular communication with the referral centre, and have consultations with the IE team. When necessary, the patient should receive consultations at the centre of reference.

The characteristics of the centre of reference are: immediate access to diagnostic tests, including TTE, TEE, CT, MRI and nuclear imaging, as well as immediate access to cardiac surgery, particularly in the case of complicated infective endocarditis. Various specialists must be present on site (the IE team), including cardiac surgeons, cardiologists, intensive care anaesthetists, infectiologists and microbiologists. As required, specialists in valvular disease, congenital heart disease, pacemaker removal, echocardiography and other cardiac imaging techniques, neurologists, neurosurgeons and interventional neuroradiologists will also be present. The role of the IE team is to discuss cases, make surgical decisions and define the type of follow-up. The IE team chooses the type, duration and follow-up of antibiotic treatment, according to a standardised protocol that follows current recommendations. It must participate in national and international registers, publicly communicate its centre's mortality and morbidity figures, and be involved in quality improvement and other programmes. Follow-up should be organised by consulting the patient at a frequency that depends on his clinical state (ideally at 1, 3, 6 and 12 months after discharge, since the majority of events occur during this period). (11)

We don't have a reference centre in our country, but we can set up a team within our hospital structure. This is a great prospect for the future.

In our patient's case, she did not have right heart failure or vegetations >20mm, but she had fungal infective endocarditis. This was an indication for surgery, but given the highly disturbed inflammatory balance, the immunodepression and the nosocomial infection (*Acinetobacter baumannii* bacteraemia) responsible for haemodynamic instability, she could not be operated on and her outcome was fatal.

Conclusion:-

Very few articles in the literature deal with our subject. The few papers on case series of fungal endocarditis date back more than twenty years. Endocarditis of the right heart is also little covered in the literature, and the latest recommendations of the European Society of Cardiology devote only a short paragraph to it. Which just goes to show how complex the subject is.

A meta-analysis of large groups of patients suffering from fungal endocarditis of the right heart should be carried out in order to refine both diagnostic methods and therapeutic management.

Finally, it is vital to set up an endocarditis team that takes account of local realities.

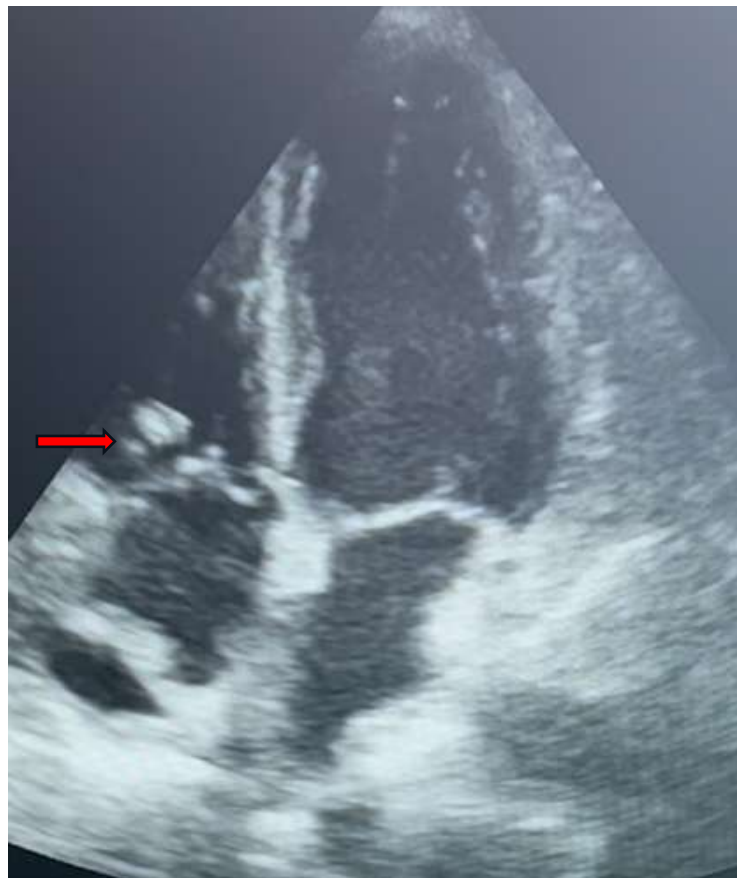


Figure 1:- On this TTE in an apical four-cavity section, the red arrow indicates a big vegetation attached to the ventricular face of the septal cusp of the tricuspid valve. There was no significant tricuspid regurgitation associated.



Figure 2:- TEE (transesophagealechocardiography) confirmed the diagnosis, demonstrating a large cauliflower-like vegetation attached to the tricuspid septal valve measuring 13x8mm suggesting fungal endocarditis

Conflicts of interest:

The authors declare no conflicts of interest.

Authors' contributions:

COULIBALY FATIMATOU ZAHRA: principal author, who managed and wrote the patient's data. KAOUTAR BERRAG: co-author who analysed the patient's data. MOHAMED ABIDI: co-author who managed the patient. ABIDI KHALID and TAREK DINDANE supervised the management of the patient. All authors have read and accepted the final manuscript.

References:-

1. FRON JB. RecoMédicales. 2021. Endocardite infectieuse. Disponible sur: <https://recomedicales.fr/recommandations/endocardite/>
2. Lefort A, Gantier JC, Lortholary O. Endocardites fongiques. Réanimation. 1 mai 2004;13.
3. Carozza A, De Santo LS, Romano G, Della Corte A, Ursomando F, Scardone M, et al. Infective endocarditis in intravenous drug abusers: patterns of presentation and long-term outcomes of surgical treatment. J Heart Valve Dis. janv 2006;15(1):125-31.
4. Fillâtre P, Revest M, Tattevin P. Les endocardites fongiques: mise au point. Réanimation. 1 mai 2016;25(3):348-60.
5. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. Chest. juill 2002;122(1):302-10.
6. Rubinstein E, Lang R. Fungal endocarditis. Eur Heart J. avr 1995;16 Suppl B:84-9.
7. Paterson DL, Dominguez EA, Chang FY, Snyderman DR, Singh N. Infective endocarditis in solid organ transplant recipients. Clin Infect Dis Off Publ Infect Dis Soc Am. mars 1998;26(3):689-94.
8. Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965-1995. Clin Infect Dis Off Publ Infect Dis Soc Am. janv 2001;32(1):50-62.

9. Delahaye F, De Gevigney G. Endocardites infectieuses : formes particulières (coeur droit, prothèse valvulaire, dispositif électronique intracardiaque). Presse Médicale. 1 mai 2019;48(5):549-55.
10. Melgar GR, Nasser RM, Gordon SM, Lytle BW, Keys TF, Longworth DL. Fungal prosthetic valve endocarditis in 16 patients. An 11-year experience in a tertiary care hospital. Medicine (Baltimore). mars 1997;76(2):94-103.
11. Delahaye F. Recommandations de la Société européenne de cardiologie sur l'endocardite infectieuse. Réalités cardiologiques. janv 2016;2, 5, 6, 11.