sciendo Internal Medicine 2024 vol. XXI No. 3 - www.srmi.ro 91
10.2478/inmed-2024-0301

C ANCA ANTIBODIES AND INFECTIVE ENDOCARDITIS - FRIENDS OR FOES?

Luiza Buican[1], Silviu Stanciu[1,2], Mihaela Iordache[1], Diana Iancu[1,2], Ramona Constantin[1], Liviu Stan[1], Silviu Dumitrescu[1,3], Maria Magdalena Gurzun[1,2]
[1]"Dr. Carol Davila" Central Emergency University Military Hospital, Bucharest, Romania
[2]University of Medicine and Pharmacy, "Dr. Carol Davila", Bucharest, Romania
[3]University of Medicine and Pharmacy, "Titu Maiorescu", Bucharest, Romania
Corresponding author:
Silviu Stanciu, "Dr. Carol Davila" Central Emergency University Military Hospital, Bucharest, Romania,
e-mail: silviu.stanciu@umfcd.ro

Abstract
The differential diagnosis between granulomatosis with polyangiitis (GPA) and infective endocarditis (IE) is crucial. Both diseases show clinical similarities and serologic c-ANCA overlap. We present the case of a 45-year-old patient with inflammatory and anemic syndrome, c-ANCA positivity and initial respiratory and renal symptoms that raised the suspicion of GPA. Subsequent evolution revealed severe valve involvement and the presence of Streptococcus gallolyticus in blood cultures, confirming the diagnosis of infective endocarditis. Antibiotic treatment and surgical intervention were crucial for the patient's recovery. This case demonstrates the importance of imaging and microbiological examinations for the correct differentiation of these diseases and the importance of a multidisciplinary approach.
Keywords: *granulomatosis with polyangiitis, infective endocarditis, c-ANCA, endarteritis, renal involvement*

Rezumat
Diagnosticul diferențial între granulomatoza cu poliangeită (GPA) și endocardita infecțioasă (EI) este crucial, având în vedere similitudinile clinice și suprapunerea serologică a c-ANCA. Prezentăm cazul unui pacient de 45 de ani cu sindrom inflamator și anemic, pozitivitate c-ANCA și simptome respiratorii și renale inițiale, ce au ridicat suspiciunea de GPA. Evoluția ulterioară a evidențiat afectare valvulară severă și prezența Streptococcus gallolyticus în hemoculturi, confirmând diagnosticul de endocardită infecțioasă. Tratamentul antibiotic și intervenția chirurgicală au fost esențiale pentru recuperarea pacientului. Acest caz subliniază importanța investigațiilor imagistice și microbiologice în diferențierea corectă a acestor afecțiuni și necesitatea unei abordări multidisciplinare.
Cuvinte cheie: *granulomatoză cu poliangeită, endocardită infecțioasă, cANCA, endarterită, afectare renală.*

Internal Medicine

Clinical Cases

Introduction

Infective endocarditis and granulomatosis with polyangiitis (GPA) are two serious and potentially life-threatening diseases associated with systemic inflammation and damage. Although the clinical manifestations of these diseases may be similar, their therapeutic approaches and prognoses differ considerably, emphasizing the importance of accurate diagnosis. Anti-neutrophil cytoplasmic antibodies (ANCA), particularly c-ANCA anti-PR3, are important markers in the diagnosis of GPA, but can also occur in other diseases, including severe infections such as infective endocarditis[1].

c-ANCA antibodies are typically associated with granulomatosis with polyangiitis, a necrotizing vasculitis characterized by inflammation of small and medium-sized vessels, often involving the respiratory tract and kidneys. The presence of c-ANCA is an important serologic marker for the diagnosis of GPA[2]. However, recent studies and clinical cases have shown that c-ANCA antibodies can also be detected in patients with infective endocarditis, which is usually caused by Staphylococcus aureus or Streptococcus viridans[3].

This serologic overlap between infective endocarditis and GPA can lead to considerable diagnostic confusion. In patients with infective endocarditis, strong immune activation and the presence of circulating immune complexes can lead to a false positive c-ANCA reaction. In addition, the systemic inflammation and severe vascular lesions seen in endocarditis may mimic some of the features of GPA, further complicating the differential diagnosis[1].

The differential diagnosis between infective endocarditis and granulomatosis with polyangiitis is crucial, as each condition requires specific treatment. Infective endocarditis is primarily treated with antibiotics and in certain cases requires surgery to repair or replace the affected heart valves. GPA, on the other hand, requires immunosuppressive therapy, including corticosteroids and cytotoxic agents, to control inflammation[4].

Careful clinical assessment in combination with laboratory and imaging studies is crucial to differentiate between these two entities. In suspected cases, repeated blood cultures are recommended to confirm the presence of active bacterial infection. Serial echocardiography may reveal vegetations or other endocardial lesions. In addition, tissue biopsy may be useful in cases of diagnostic uncertainty to identify the specific histopathologic features of the disease in question[5].

A stepwise diagnostic approach based on detailed clinical assessment and additional imaging is essential to ensure appropriate treatment and improve patient outcomes.

This article aims to provide a comprehensive overview of the role of c-ANCA antibodies in these diseases and thus contribute to a better understanding and management of these diseases in medical practice.

Case description

We present the case of a 45-year-old male patient with cardiovascular risk factors (hypertension, dyslipidemia) and no significant medical history. His symptoms started 5 months before his admission. He presented to a tertiary care center with cough, fever, and chills. Laboratory tests revealed leukocytosis, mild inflammatory syndrome, and mild anemic syndrome. Chest X-ray showed bilateral basal reticulonodular opacities and an accentuated interstitial lung pattern. He was diagnosed with interstitial pneumonia. Considering that the patient was stable, had no significant comorbidities and a low CURB-65 score, outpatient treatment was decided. He was treated with doxycycline for 10 days, which resulted in an initial favorable course and improvement of symptoms.

After his initial admission, the patient was admitted to the Department of Internal Medicine for further diagnostics to determine the etiology of the anemia.

He had no fever or chills, but reported fatigue and significant weight loss of approximately 8 kg over the previous 2 months. Laboratory tests revealed a mild hypochromic microcytic anemic syndrome (Hb =10.9 g/dL, MCV =78 fL, TIBC =209 µg/dL, serum iron =11 µg/dL, ferritin =1161 µg/L), an inflammatory syndrome (ESR =90 mm/1h, CRP =130 mg/L, fibrinogen =753 mg/dL, with negative procalcitonin), erythrocyturia and proteinuria (RBC =798, proteins >100 mg/dL, A/C ratio =555). The blood smear showed mild anisocytosis (microcytes), moderate hypochromia and erythrocyte rouleaux. The biological profile was extended to investigate the inflammatory syndrome and showed positivity for: cANCA (anti-PR3) - 18.9 U/mL - 3.5 times the normal limit, CIC (36.2 U/mL) and ANA. pANCA (anti-MPO), viral markers for hepatitis B and C, HIV and tumor markers were negative. Ultrasonography of the abdomen and pelvis showed hepatosplenomegaly. Endoscopy of the upper and lower digestive tract revealed no abnormalities.

Based on the biological markers, cANCA and ANA positivity, anemic and inflammatory syndrome, nephritic syndrome, and recent history of interstitial pneumonia, ANCA-positive vasculitis, specifically granulomatosis with polyangiitis, was suspected. The ENT examination showed no changes in the nasal mucosa. No specific treatment was initiated and the patient was discharged. He was referred to the nephrology department for a kidney biopsy for diagnostic confirmation.

At the current readmission to the Department of Internal Medicine, he complained of increasing weight loss, fatigue and dyspnea on exertion. He did not report fever and chills at home. General clinical examination revealed accentuated weight loss (~4 kg since last hospitalization) and diastolic murmur in the aortic region. Biology showed worsening of the anemic syndrome (Hb =9 g/dL) and thrombocytopenia (103 k/µL). Despite a slight accentuation of the inflammatory syndrome (CRP 145 mg/L, ESR 114 mm/1h), procalcitonin remained negative. A significant increase in c-ANCA/PR3 values to 13 times the normal value (c-ANCA =68 U/mL) and CIC (66 U/mL) as well as an increase in NT-proBNP was observed.

Granulomatosis with polyangiitis and cardiac involvement was considered as a possible

Internal Medicine

Clinical Cases

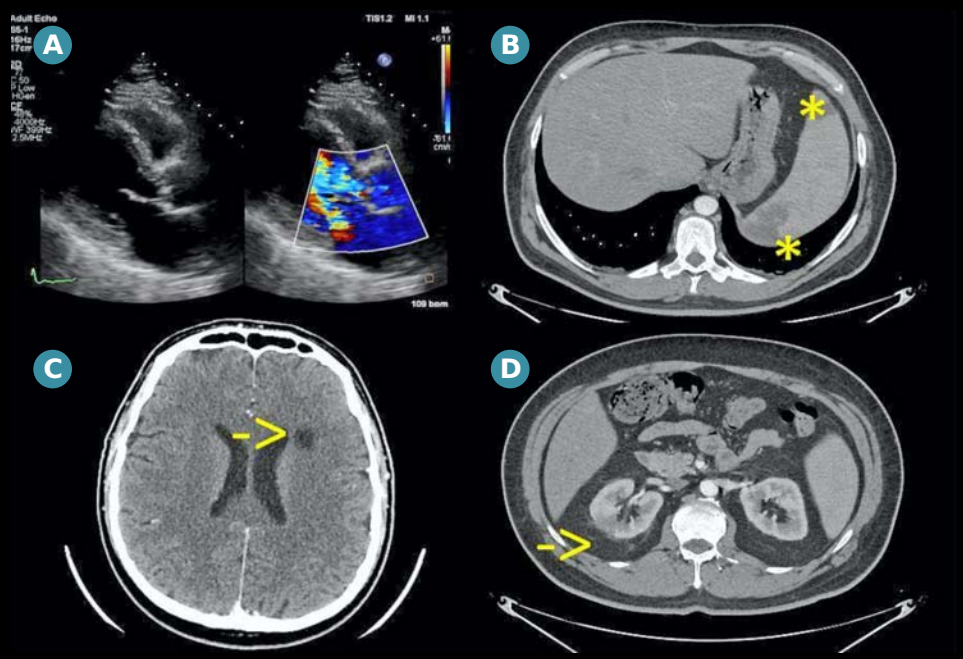

Figure 1. *Parasternal long axis 2D and color scan showing morphological changes at the level of the aortic valve and severe aortic regurgitation (A). The CT scan showed cerebral emboli (B) and splenic and renal abscesses (C, D)*

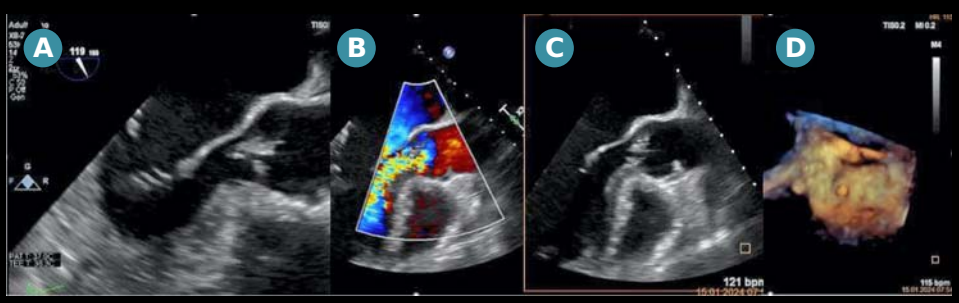

Figure 2. *The transesophageal examination shows morphological changes of the aortic valve in the longitudinal axis and a structure that is highly suggestive of attachment to the left aortic cusp (A), which causes severe aortic regurgitation (B). In addition, at the level of the anterior aortic wall, 3 cm from the aortic annulus, there is a small structure suggestive of endarteritis (C) also visible in 3 D (D)*

etiology. The diagnostic work-up included a cardiac examination and echocardiography on the first day of hospitalization. Transthoracic echocardiography revealed a left ventricle with normal dimensions and global and regional systolic function (end-diastolic dimension of the left ventricle of 50 mm and estimated ejection fraction of 55-60), normal-sized right ventricles and normal longitudinal function of the right ventricle. The aortic valve showed significant morphologic changes, with a maximum systolic velocity of 2.6 m/s and severe aortic regurgitation (Figure 1). In view of the recently diagnosed severe aortic regurgitation and inflammatory syndrome, further investigations by transesophageal echocardiography were recommended.

On the second day of hospitalization, the patient had a fever (39°C) and three blood samples were taken for cultures (during the first episode of fever and repeated at 30-minute intervals thereafter). A whole-body CT scan was performed, which showed a left frontal ischemic stroke sequence, chronic splenic and right renal infarcts (Figure 1). Transesophageal echocardiography showed a tricuspid aortic valve with marked morphologic changes. A 4.5/8.3 mm mass had adhered to the non-coronary cusp, causing valve leaflet flaccidity and severe aortic regurgitation. The ascending aorta was of normal size. At the level of the aortic wall, adjacent to the origin of the right coronary artery, a small, 5.5 mm structure with an echogenicity similar to that of an aortic cusp was visualized, suggesting endarteritis.

The clinical, biological and imaging findings supported the diagnosis of infective endocarditis with renal involvement. The diagnosis of granulomatosis with polyangiitis with cardiac involvement was therefore less likely. According to the ESC criteria6 , one major criterion and more than three minor criteria were fulfilled, confirming the diagnosis of definite infective endocarditis. Empirical antibiotic treatment with ceftriaxone (2 g/day) and vancomycin (1 g every 12 hours) and specific treatment for heart failure (ramipril, spironolactone, bisoprolol and furosemide) were initiated. The patient's condition remained stable, but the symptoms of heart failure and fever persisted. All three blood cultures were positive for Streptococcus gallolyticus spp gallolyticus after 3 days, confirming the diagnosis of infective endocarditis with Streptococcus gallolyticus. The infectious disease physician recommended targeted antibiotic treatment with ceftriaxone 2 g/day in combination with gentamicin 3 mg/kg/day.

The further development of the patient was not favorable. Despite a decrease in the inflammatory syndrome, he developed pancytopenia, which was related to the infection or the antibiotic treatment with vancomycin/gentamicin. In addition, the NT-proBNP level increased. Over the next few days, his clinical evolution was severe, with symptoms of heart failure, acute pulmonary edema and hemodynamic instability. According to the ESC guidelines, the patient had a class I indication for urgent surgical intervention. Emergency surgery was performed to remove the infectious tissue and replace the aortic valve with a size 21 Carbomedics Standard mechanical prosthesis.

After the operation, his clinical development was favorable, he could be extubated early and the drainage tube was removed after 48 hours. Antibiotic therapy was completed with ceftriaxone for up to 4 weeks. Biologically, hematologic indices and inflammatory markers normalized, but hematuria and proteinuria persisted, as did c-ANCA positivity. Postoperative transthoracic

echocardiography showed normal function of the mechanical aortic valve with a transprosthetic maximum and mean gradient of 31/18 mmHg without intra- or paravalvular leaks. The patient was discharged with the recommendation of reexamination one month after surgery and home medication with acenocoumarol, ramipril, furosemide, spironolactone, bisoprolol and empagliflozin.

The cultures of the surgical specimens were sterile.

One month after surgery, a significant decrease in c-ANCA levels, normalization of NT-proBNP levels, and a marked decrease in hematuria and proteinuria were observed. The nephrologist did not recommend a renal biopsy but recommended follow-up of the patient and diagnosed limited renal involvement related to infective endocarditis.

Discussion

Granulomatosis with polyangiitis is a vasculitis affecting small and medium-sized blood vessels and characterized by c-ANCA/PR3 specificity, with particularly marked involvement of the respiratory and renal systems[7]. It can also affect the heart. The most common cardiac manifestations are valvular heart disease such as non-infective endocarditis and perforations[8]. The cardiac manifestation of granulomatosis with polyangiitis primarily affects the aortic valve, leading to valve regurgitation[9].

There are several cases of ANCA-positive endocarditis in the literature with a wide range of clinical manifestations, which makes the differential diagnosis between infective and non-infective ANCA-positive endocarditis difficult. Both entities may have similar cardiac, renal and pulmonary involvement. Subacute bacterial endocarditis is mainly associated with c-ANCA positivity and rarely with p-ANCA and ANA[10].

Distinguishing between infective endocarditis and non-infective endocarditis can be difficult, especially when the classic signs of infection are absent.

In the present case, the patient had no classic signs of infection, which typically occur in the later stages of the disease. The differential diagnosis between infective endocarditis and granulomatosis with polyangiitis was difficult due to the overlapping clinical symptoms and inflammatory markers without classic signs of infection. The strong positivity of c-ANCA raised the suspicion of GPA, but subsequent findings (valvular vegetations and positive blood cultures) clearly pointed to the diagnosis of infective endocarditis.

The involvement of c-ANCA in bacterial endocarditis remains unclear. However, the infectious process may induce c-ANCA production, possibly through polyclonal B-cell activation. Sustained vascular injury by a bacterial antigen may activate endothelial

cells, induce expression of cytoplasmic enzymes by polymorphonuclear cells, and lead to expression of autoantibodies[11]. Our patient had a prolonged infectious disease, so the ongoing inflammatory process may have led to c-ANCA positivity.

Other causes leading to elevated c-ANCA in suspected GPA should not be overlooked. ANCA may be positive in infections (tuberculosis, hepatitis B/C), hematologic or non-hematologic malignancies as well as in the ingestion of certain substances (sulfasalazine, cocaine)[12]. In infective endocarditis, the positivity of these antibodies is low in contrast to GPA.

The literature indicates that c-ANCAs may be useful in the early diagnosis of IE and in some cases they may be used in disease surveillance, as c-ANCA positivity is associated with an unfavorable prognosis[13]. On the other hand, c-ANCAs may complicate the diagnosis of infective endocarditis, as they have limited specificity and only occur in some cases of infective endocarditis.

Some studies that included patients with infective endocarditis and positive ANCA concluded that their survival rate was lower. In addition, the duration of the disease was longer in these patients and the kidneys were more frequently affected. Furthermore, there is data to suggest that in many cases patients were initially misdiagnosed as having vasculitis[14].

In addition, infective endocarditis with c-ANCA positivity is more frequently associated with male gender, anemia, thrombocytopenia and gram-positive bacteria[3].

In the case presented by us, a differential diagnosis was essential in view of the different treatment approaches for the two diseases. The treatment of granulomatosis with polyangiitis (GPA) and infective endocarditis (IE) differs due to the different nature of these diseases. GPA requires immunosuppression to control the autoimmune inflammation and prevent relapses. High-dose glucocorticoids and immunosuppressants such as cyclophosphamide or rituximab are used to induce remission, followed by maintenance of remission with azathioprine, methotrexate or mycophenolate mofetil[15]. Regular monitoring of organ function and infection prophylaxis are essential for the long-term treatment of GPA.

In contrast, treatment of IE focuses on eradication of the bacterial infection through aggressive antibiotic therapy and, if necessary, surgical intervention. Intravenous empiric antibiotics such as ceftriaxone and vancomycin are administered until blood culture results are available, and treatment is adjusted based on the sensitivity of the identified pathogen. Surgical intervention is often required to repair or replace the affected valve, especially in cases of severe heart failure, large vegetations, uncontrolled infections or recurrent septic emboli[6].

A special feature in this case was the presence of the filamentous mass on the aortic wall, which is a rare finding. In the literature, there are only a few case reports of isolated vegetations on the aortic wall, which usually result from a local development due to continuity of the infectious process at the level of the aortic valve and resemble worm-like vegetations[16]. These can lead to complications due to embolization, either in the systemic circulation, resulting in ischemic infarcts in the target organs (e.g., brain, kidneys, spleen) or at the coronary artery level leading to myocardial infarction[17]. Other complications include acute aortic valve insufficiency with severe hemodynamic consequences as well as aneurysm and rupture of the aortic wall, whereby chronic

inflammation and infection can weaken the aortic wall[18].

The most important predictors of long-term mortality in infective endocarditis are age, comorbidities, endocarditis affecting two consecutive valves, recurrence of IE, and heart failure[19]. In our case, the patient had a favorable outcome thanks to proper diagnosis and treatment.

Long-term treatment includes general infection prevention measures (good oral and skin hygiene), antibiotic prophylaxis and drug therapy, including anticoagulant treatment and maintenance of the INR target.

Conclusion

This case illustrates the complexity of the differential diagnosis between infective endocarditis and ANCA-positive vasculitis. Despite the presence of c-ANCA and severe inflammatory symptoms, imaging and microbiologic studies were critical in confirming infective endocarditis.

Prompt antibiotic treatment and appropriate surgical intervention led to a favorable outcome. This demonstrates the importance of a multidisciplinary approach in the management of patients with complex clinical presentations.

References

1. McAdoo SP, Densem C, Salama A, Pusey CD. Bacterial endocarditis associated with proteinase 3 anti-neutrophil cytoplasm antibody. NDT Plus. 2011 Jun;4(3):208-210.

2. Dewan R, Trejo Bittar HE, Lacomis J, Ocak I. Granulomatosis with Polyangiitis Presenting with Coronary Artery and Pericardial Involvement. Case Rep Radiol. 2015;2015:516437.

3. Van Gool IC, Kers J, Bakker JA et al. Antineutrophil cytoplasmic antibodies in infective endocarditis: a case report and systematic review of the literature. Clin Rheumatol 2022:41: 2949–2960.

4. Ying CM, Yao DT, Ding HH, Yang CD. Infective endocarditis with antineutrophil cytoplasmic antibody: report of 13 cases and literature review. PLoS One. 2014 Feb 25;9(2):e89777. doi: 10.1371/journal. pone. 0089777. PMID: 24587028; PMCID: PMC3934949.

5. Bele D, Kojc, N., Perše, M. et al. Diagnostic and treatment challenge of unrecognized subacute bacterial endocarditis associated with ANCA-PR3 positive immunocomplex glomerulonephritis: a case report and literature review. BMC Nephrol 21, 40 (2020). https://doi.org/10.1186/s12882-020-1694-2

6. Victoria Delgado, Nina Ajmone Marsan, Suzanne de Waha & Co, ESC Scientific Document Group , 2023 ESC Guidelines for the management of endocarditis: Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM), European Heart Journal, Volume 44, Issue 39, 14 October 2023, Pages 3948–4042, https://doi.org/10.1093/eurheartj/ehad193

7. Shue, Lisa & Chow, Maggie & Cohen, Brandon & Peng, David. (2019). Explosive Granulomatosis with Polyangiitis Mimicking Infective Endocarditis. Internal Medicine: Open Access. 09. 10.4172/2165-8048. 1000302.

8. Shelton A, Parikh S, Mims C, Quintero-Del-Rio A. A challenging case of granulomatosis with polyangiitis with

cardiac involvement: a rare case report. AME Case Rep. 2022 Nov 21;7:8. doi: 10.21037/acr-22-29. PMID: 36817711; PMCID: PMC9929659.

9. Borowiec A, Rosinska M, Kowalik I & Co, Cardiac valvular involvement in granulomatosis with polyangiitis in long-term observation. Rev Port Cardiol. 2024 Mar;43(3):97-103. English, Portuguese. doi: 10.1016/j.repc.2023.08.008. Epub 2023 Dec 19. PMID: 38122897.

10. Chun-Mei Ying ,Dong-Ting Yao ,Hui-Hua Ding,Cheng-De Yang, Infective Endocarditis with Antineutrophil Cytoplasmic Antibody: Report of 13 Cases and Literature Review, PLOS ONE 9(2): e89777. https://doi.org/10.1371/journal.pone.0089777

11. Langlois V, Lesourd A, Girszyn N, Ménard JF, Levesque H, Caron F, Marie I. Antineutrophil Cytoplasmic Antibodies Associated With Infective Endocarditis. Medicine (Baltimore). 2016 Jan;95(3):e2564. doi: 10.1097/MD.0000000000002564. PMID: 26817911; PMCID: PMC4998285.

12. Robert SC, Forbes SH, Soleimanian S, Hadley JS. Complements do not lie. BMJ Case Rep. 2011 Dec 1;2011:bcr0820114705. doi: 10.1136/bcr.08.2011.4705. Erratum in: BMJ Case Rep. 2011 Dec 13;2011:null. PMID: 22674942; PMCID: PMC3229323.

13. Zhou Z, Ye J, Teng J, et alClinical characteristics of infective endocarditis in patients with antineutrophil cytoplasmic antibody or antiphospholipid antibody: a retrospective study in ShanghaiBMJ Open 2020;10:e031512. doi: 10.1136/bmjopen-2019-031512

14. Ai S, Liu X, Chen G, Zhang Y, Bai X, Qin Y, Miao Q, Li X. Characteristics and Diagnostic Challenge of Antineutrophil Cytoplasmic Antibody Positive Infective Endocarditis. Am J Med. 2022 Nov;135(11):1371-1377. doi: 10.1016/j.amjmed.2022.06.015. Epub 2022 Jul 9. PMID: 35820459.

15. Hellmich B, Sanchez-Alamo B, Schirmer JH, et alEULAR recommendations for the management of ANCA-associated vasculitis: 2022 updateAnnals of the Rheumatic Diseases 2024;83:30-47.

16. Falkenberg B, Dalén M, Ivert T. Migration of worm-shaped vegetation into the left coronary ostium. Ann Thorac Surg. 2014 May;97(5):1809. doi: 10.1016/j.athoracsur.2013.09.103. PMID: 24792280.

17. Ferreira, Ana & Baptista, Rui & Monteiro, Sílvia & Pego, M.. (2016). A rare aortic wall vegetation. Revista Portuguesa de Cardiologia. 35. 10.1016/j. repc. 2015.09.025.

18. Moaref AR, Mollazadeh R, Zamirian M, Sharifkazemia MB. Rapid progression of aortic wall vegetation. J Am Soc Echocardiogr. 2008 Mar;21(3):297.e1-2. doi: 10.1016/j.echo.2007.08.036. Epub 2007 Oct 1. PMID: 17904809.

19. Durante-Mangoni E, Giuffrè G, Ursi MP, Iossa D, Bertolino L, Senese A, Pafundi PC, D'Amico F, Albisinni R, Zampino R. Predictors of long-term mortality in left-sided infective endocarditis: an historical cohort study in 414 patients. Eur J Intern Med. 2021 Dec;94:27-33. doi: 10.1016/j.ejim.2021.08.011. Epub 2021 Aug 31. PMID: