Received: 13 June 2023 | Revised: 9 July 2023 | Accepted: 22 July 2023

DOI: 10.1002/ccr3.7749

CASE REPORT

Clinical Case Reports Open Access WILEY

An unusual case of heart failure due to ANCA-negative vasculitis: A case report and focused review of the literature

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Key Clinical Message

Heart failure due to ANCA-negative vasculitis, is a rare potentially life-threatening manifestation of ANCA vasculitis. Therefore, physicians must always pay attention to this manifestation for proper disease diagnosis and treatment.

Abstract

Less than 10% of primary vasculitides cause cardiac dysfunction, with Takayasu's arteritis, polyarteritis nodosa, and eosinophilic granulomatosis with polyangiitis being the most common cases. However, any cardiac tissue can be affected by ANCA vasculitis. We present a case of heart failure with reduced ventricular ejection fraction due to ANCA negative-vasculitis.

KEYWORDS

anti-neutrophil cytoplasmic antibody-associated vasculitis, case reports, heart failure, HIV, vasculitis

1 | INTRODUCTION

Less than 10% of people with vasculitis experience cardiac impairment; however, all primary vasculitides can target the heart.[1] Regarding antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, both granulomatosis with polyangiitis (GP), microscopic polyangiitis (MP), and eosinophilic granulomatosis with polyangiitis (EGPA) can affect any cardiac tissue.[1]

Among ANCA-associated vasculitis, EGPA is the one that most frequently affects the heart.[2] Nevertheless, in EGPA, cardiac manifestations are more common in ANCA-negative patients. Eosinophilic myocarditis is the most common, but restrictive or dilated cardiomyopathy, pericarditis, coronary artery vasculitis, valvular defects, rhythm disturbances, left ventricular dysfunction, and intracardiac thrombosis, among other things, can also occur.[3] Heart involvement in GP and MP is seen in a small percentage of patients, with pericarditis and supraventricular arrhythmias being the most common cardiac manifestations, occurring in 1%–6% of patients.[1] Nevertheless, cardiac thrombosis is a less frequent manifestation, occurring in less than 1% of patients.[1]

2 | CASE DESCRIPTION

A 28-year-old man without a familiar history of cardiomyopathies or ethanol consumption, only with a medical history of HIV category A1 diagnosed 2 years

ago, who has been receiving antiretroviral therapy (ART) with tenofovir disoproxil fumarate plus emtricitabine and efavirenz since HIV diagnosis, presented to emergency room due to cough, hemoptysis, fatigue, palpitations, and dyspnoea in the previous 4 weeks. At admission, on auscultation tachycardia and gallop were present, and rales were detected in all lung fields in the lung exam. Also found were augmented jugular venous pressure with hepatojugular reflux, hepatomegaly, and lower limb edema.

At admission, the hemogram revealed a hemoglobin value of 13 grams per deciliter (g/dL), leukocytes of 20,450 per cubic millimeter (mm^3), with a neutrophil value of 16,237 per mm^3, eosinophils of 400 per mm^3, lymphocytes of 2679 per mm^3 and monocytes of 1134 per mm^3. The C reactive protein had an increased value of 100 milligrams per deciliter (mg/dL); creatinine value of 1.07 mg/dL and blood urea nitrogen test of 16 mg/dL. The urine test was transparent, with normal density, pH of 6, without proteinuria, leukocyturia, or hematuria, among others. The transthoracic echocardiogram showed a decreased left ventricular ejection fraction (LVEF) of 10%, and a left ventricular thrombus (LVT) of 40 by 38 millimeters (mm). The chest computed tomography (CT) showed right pleural effusion, multilobar alveolar occupancy suggesting diffuse alveolar hemorrhage (DAH) due to history of hemoptysis, pericardial effusion and the LVT (Figure 1). The contrast enhanced cardiac magnetic resonance (CMR) revealed a normal right atrium with an area of 22 cubic centimeters (cm^2); however, the left atrium was dilated with an area of 39 cm^2. Also, the right and left ventricles were dilated with augmented diastolic diameters of 45 and 75 mm, respectively, in the setting of dilated cardiomyopathy (DCM). It also revealed a LVEF of 18%, subendocardial fibrotic areas in the LV apex and with a diffuse pattern in the right ventricle (RV) with a 20% myocardial fibrosis burden. The contrast enhanced CMR also revealed a 40 by 38 mm apical mass that did not present enhancement at rest or late in relation to the LVT previously seen (Figure 2).

Tuberculosis, histoplasmosis, cryptococcosis, aspergillosis, and acute infections due to aerobic bacteria, toxoplasmosis, cytomegalovirus, hepatitis B, hepatitis C, and Epstein–Barr virus were ruled out. Also ruled out were lupus, rheumatoid arthritis, cryoglobulinemia, and positive ANCA-associated vasculitis. Besides, a pleural and pericardial biopsy plus lobectomy from the subsegmental anterior segment of the right lower lobe was performed, which revealed DAH and pulmonary capillaritis (Figure 3). The pericardial and pleural biopsies only showed tissue congestion. In addition, a cardiac biopsy was performed, the result of which was normal.

The medical staff diagnosed ANCA-negative vasculitis. A course of intravenous methylprednisolone was administered for 3 days, followed by oral administration. Also, cyclophosphamide was administered due to the progression of DAH in a new CT. In the hospital, anticoagulation for the LVT was started with low molecular weight heparin after the administration of methylprednisolone and cyclophosphamide, and at discharge, it was continued with warfarin. Besides, standard heart failure medications with Sacubitril/valsartan, bisoprolol,

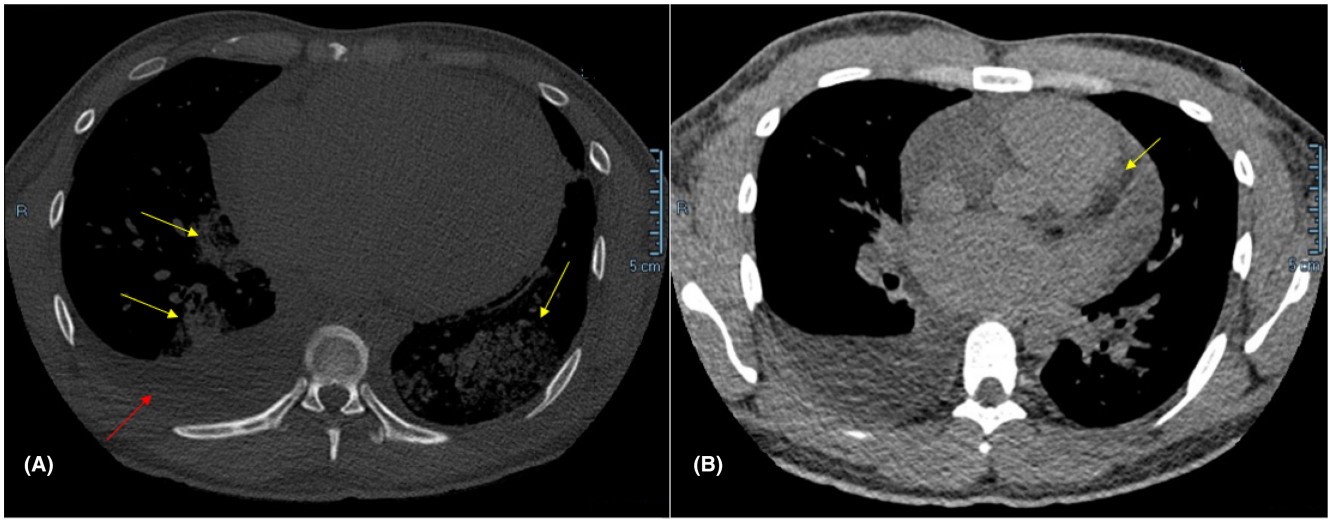

FIGURE 1 (A) CT showing right pleural effusion (red arrow) and multilobar alveolar occupancy (yellow arrows) suggesting diffuse alveolar hemorrhage (DAH) due to history of hemoptysis. (B) CT showing the LVT. CT, chest computed tomography; LVT, left ventricle thrombus.

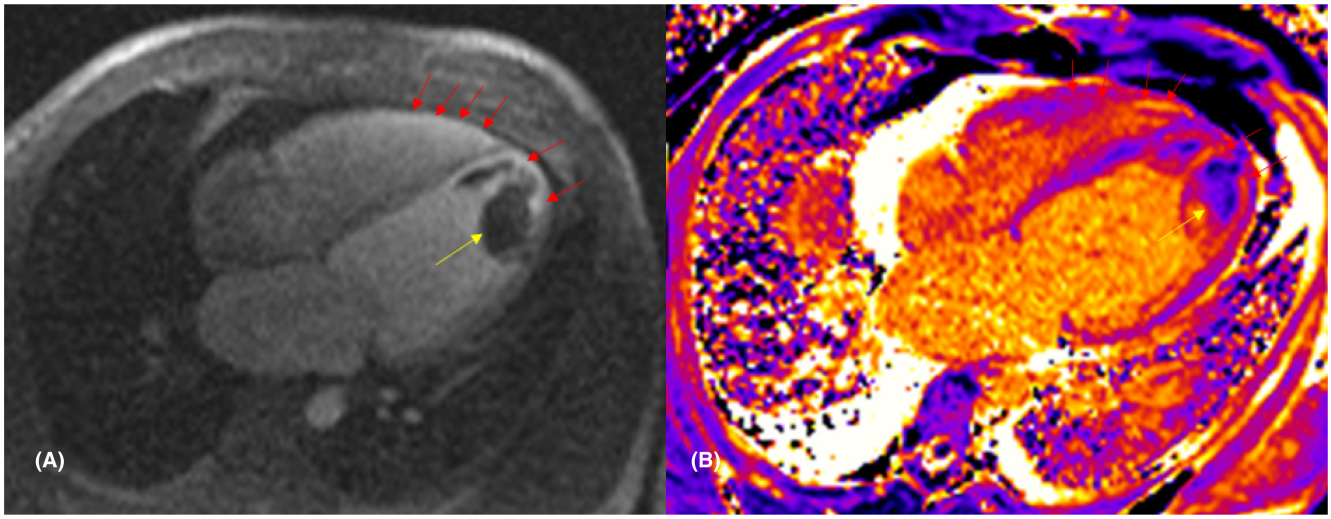

FIGURE 2 (A) CMR with late gadolinium ehnancement revealing DCM in the LV with subendocardial fibrotic areas in the LV apex and with a diffuse pattern in the RV (red arrows), as an LV thrombus (yellow arrow). (B) CMR in T1 mapping showing the same findings. DCM, dilated cardiomyopathy; CMR, cardiac magnetic resonance; LV, left ventricle; RV, right ventricle.

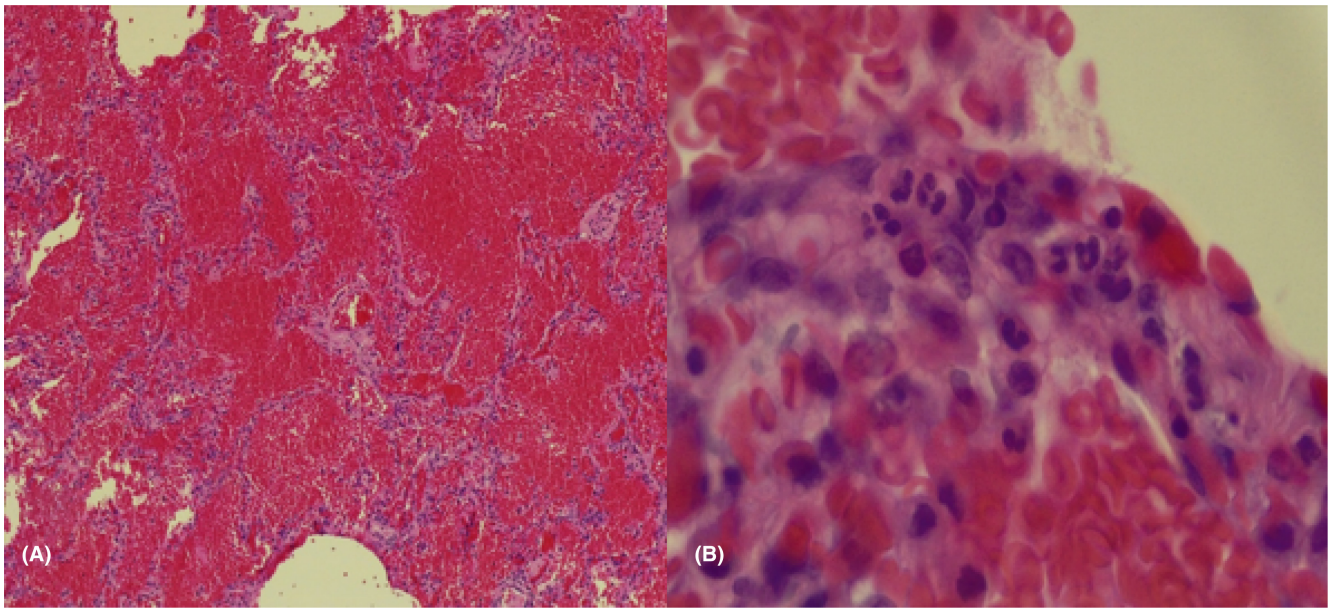

FIGURE 3 (A) At 10× magnification, pulmonary histopathology stained with H&E, showing multiple intra-alveolar hemorrhages with the presence of hemosiderophages in relation to DAH. (B) At 100× magnification (H&E), edematous walls with polymorphonuclear cells, reactive endothelial cells, and type II pneumocyte hyperplasia in relation to pulmonary capillaritis. H&E, hematoxylin and eosin; DAH, diffuse alveolar hemorrhage.

spironolactone and empaglifozin was initiated before the discharge.

During follow-up, after 1 month, the patient experienced symptom resolution. Besides, the control echocardiogram showed an improvement of the LVEF with a new value of 25%. It also showed improvement in LVT, evidencing a decrease in their measurements to 29 by 33 mm. Furthermore, the new chest CT showed improvement in the lung involvement previously evidenced.

3 | DISCUSSION

Although LVT can occur both in ischaemic and non-ischaemic cardiomyopathies, the vast majority of them are diagnosed after myocardial infarction, especially when an anterior apical scar and reduction of systolic function are developed.[4] However, although limited data is available on the epidemiology of LVT in patients affected by non-ischemic heart diseases, within this subgroup, DCM is

the most common underlying cardiomyopathy,[4] as in our case. Besides, LVT has also been occasionally described in Takotsubo cardiomyopathy, amyloidosis, hypereosinophilic syndrome, and Chagas' disease,[4] being an infrequent manifestation of vasculitis, especially in ANCA-associated vasculitis.[1] In our case, the most probable diagnosis was MP with negative ANCA serology due to the presence of DAH, pulmonary capillaritis, DCM, heart failure, and LVT. The absence of eosinophilia, asthma, chronic rhinosinusitis, or other manifestations allowed EGPA to be ruled out.

Regarding pulmonary capillaritis, it is a histopathologic diagnosis which has been highly associated with GP, MP and systemic lupus erythematosus. However, our patient did not meet diagnostic criteria for SLE.[5] Taking the above into account, the most probable diagnosis would be an ANCA-negative vasculitis of the MP or GP type due to the strong association described between this pulmonary finding and these diseases. Besides, our patient did not present granulomatous inflammation of the upper and lower airways or pauci-immune necrotizing glomerulonephritis, which are typically seen in GP. Therefore, the most probable diagnosis would be MP. Also, other conditions as anti-glomerular basement membrane disease, Henoch-Schönlein purpura, EGPA, Cryoglobulinemia, Behçet disease, IgA nephropathy, idiopathic pulmonary fibrosis, antiphospholipid antibody syndrome and propiltiuracile has been associated less frequently with pulmonary capillaritis,[5] but also, all these conditions were ruled out in our patient.

In relation to heart failure in MP, it has been described with a prevalence between 6.8%[6] and 17.6%.[7] In addition to, heart involvement in GP is uncommon, although pericarditis and cardiomyopathy are the most frequent cardiac pathologies, whereas arrhythmias, coronary arteritis, cardiac thrombus, valve lesions, and intracardiac masses are less frequently seen.[8]

Regarding HIV-related cardiomyopathy, prior to the development of ART, the patients suffered from cardiomyopathy with manifestation of left ventricular systolic dysfunction; however, after its development, the onset of HIV-related cardiomyopathy has manifested late and is less frequent, being more frequently of ischemic etiology and with a high prevalence of diastolic left ventricular dysfunction.[9] Our patient was in category A1 and had been adhering to ART (tenofovir disoproxil fumarate, emtricitabine, efavirenz) since HIV diagnosis, which made an HIV-related cardiomyopathy unlikely.

Also, while ART generally appears to help the HIV-related cardiomyopathic process by reducing viral effects on the myocardium, some antiretroviral drugs may have long-term negative myocardial effects, including mitochondrial toxicity.[9,10] However, cardiomyopathy due to mitochondrial toxicity with ART therapy was described mainly with zidovudine, zalcitabine, and didanosine, in the group of reverse transcriptase inhibitors.[10] Besides, defects in mitochondrial DNA replication and energetics have been reported with zidovudine,[11,12] clevudine and lodenosine.[13,14] Also, patients receiving ART with protease inhibitors had increased cardiovascular mortality and readmission rates at 30 days.[15] In our case, the patient was not receiving any of these reverse transcriptase inhibitors with potential cardiotoxicity, and he was not receiving protease inhibitors, so ART cardiotoxicity was very unlikely.

Regarding CMR, it allows the assessment of ventricular function and the analysis of myocardial tissue, which can help, as in our case, to reveal or rule out underlying aetiologies of heart failure like ischaemic cardiomyopathy, myocarditis, hypertrophic and DCM, cardiac amyloidosis, and sarcoidosis, among others.[16,17] In addition, CMR imaging is the gold standard for LVT.[4] In our case, despite subendocardial late gadolinium enhancement (LGE) in the CMR, these results were not considered to be related to an ischemic etiology because the involvement was biventricular, suggesting two coronary territories in a patient who did not have a medical history of risk factors for coronary artery disease in young people such as smoking, dyslipidemia, diabetes mellitus, arterial hypertension, or obesity, among others.[18] In addition, he did not present angina with moderate or high-intensity physical activity in his medical history.

These considerations, together with the finding of DAH, guided the medical team to consider and rule out systemic conditions such as tuberculosis, fungal, viral, and bacterial infections, as well as autoimmune conditions such as rheumatoid arthritis, cryoglobulinemia, anti-glomerular basement membrane disease, and Chagas disease, as previously mentioned; the finding of pulmonary capillaritis was the one that finally led us to consider systemic vasculitis, ruling out those that compromise large and medium vessels due to clinical and laboratory findings, as well as anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgA vasculitis and urticarial hypocomplementary vasculitis within those of small vessels. Also, Behçet and Cogan syndromes were ruled out.

Thus, a negative ANCA vasculitis was diagnosed; of the three existing ones (GP, MP, and EGPA), MP was the most probable diagnosis since it presents with pulmonary capillaritis more frequently than EGPA,[5] and the patient did not present with chronic rhinosinusitis, asthma, or prominent peripheral eosinophilia leading to EGPA.[3] Besides, as we described above, our patient did not present granulomatous inflammation of the upper and lower airways or pauci-immune necrotizing glomerulonephritis, which are typically seen in GP, which, like MP, is one of the most common disorders associated with pulmonary capillaritis.[5]

Regarding incidence of cardiac involvement due to ANCA negative vasculitis, it has been described that in the

group of patients with EGPA ANCA negative, they have more commonly cardiomyopathy or myocarditis than those with positive ANCA.[19] It has not been extensively researched how the heart is affected by MP, however, in a cohort of 132 Chinese patients with ANCA vasculitis, most of whom (97%) had MP, cardiac involvement was present in 26 (20%) of patients, with nine of them with chronic heart failure and cardiomyopathy.[6] Also, pericardial and myocardial involvement, aortic incompetence, and rhythm disturbances were described.[6]

Concerning GP cardiac involvement, in a cohort of 517 North American GP patients followed up for more than 8 years revealed cardiac involvement in only 3.3%, with various forms of cardiac involvement described as pericarditis, cardiomyopathy, conduction defects, ischemic heart disease, and valvular involvement.[20] With regard to ANCA positivity or negativity in GP, no specific preference for cardiac involvement has been described. Besides the presence of cardiac involvement at initial assessment also has been described as in our case, and it portends a greater risk of relapse in patients with GP.[21]

Finally, regarding ANCA vasculitis management, our patient was in a severe disease state, for which he received an intravenous pulse of glucocorticoids followed by high-dose oral glucocorticoids plus cyclophosphamide as remission induction therapy, according to the American College of Rheumatology guidelines.[22] Our patient also received management of his heart failure in accordance with current European and American guidelines.[23,24] He presented an improvement in the LVEF with a new value of 25% in the control echocardiogram. He also presented an improvement in the LVT, evidencing a decrease in their measurements, and also an improvement in the lung involvement previously evidenced in a new chest CT.

4 | CONCLUSION

In patients with DAH and pulmonary capillaritis associated with cardiac pathologies with negative ANCA serology, the diagnosis of ANCA-negative vasculitis should be considered, especially in MP or GP, when granulomatous inflammation of the upper and lower airways or pauci-immune necrotizing glomerulonephritis is present. However, when conditions such as peripheral eosinophilia, chronic rhinosinusitis, and asthma are present, it would point to an EGPA.

AUTHOR CONTRIBUTIONS

Porras Bueno Cristian Orlando: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; writing – original draft; writing – review and editing. **Saldarriaga Giraldo Clara Inés:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Roncancio Villamil Gustavo Eduardo:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Alvarez Barreneche Maria Fernanda:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing.

FUNDING INFORMATION

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Orlando PBC, Ines SGC, Eduardo RVG, Fernanda ÁBM. An unusual case of heart failure due to ANCA-negative vasculitis: A case report and focused review of the literature. *Clin Case Rep*. 2023;11:e7749. doi:10.1002/ccr3.7749