

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

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## Introduction:

Less than 10% of people with vasculitis experience cardiac impairment; however, all primary vasculitides can target the heart<sup>1</sup>. 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<sup>1</sup>.

Among ANCA-associated vasculitis, EGPA is the one that most frequently affects the heart<sup>2</sup>. 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<sup>3</sup>. 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% to 6% of patients<sup>1</sup>. Nevertheless, cardiac thrombosis is a less frequent manifestation, occurring in less than 1% of patients<sup>1</sup>.

## 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 two years ago, who has been receiving antiretroviral therapy (ART) with tenofovir disoproxil fumarate plus emtricitabine and efavirenz since HIV diagnosis, was consulted due to cough, hemoptysis, fatigue, palpitations, and dyspnoea in the previous four weeks. At admission, he was tachycardic; on auscultation, rales were detected in all lung fields, and gallop was also auscultated. Also found were augmented jugular venous pressure with hepatojugular reflux, hepatomegaly, and lower limb edoema.

The hemogram was normal. The transthoracic echocardiogram showed a decreased left ventricular ejection fraction (LVEF) of 10%, and a left ventricular thrombus (LVT) of 40 by 38 mm. The chest computed tomography (CT) showed bilateral pleural effusion, multilobar alveolar occupancy, diffuse alveolar haemorrhage (DAH), pericardial effusion and the LVT. The contrasted enhanced cardiac magnetic resonance (CMR) revealed a normal right atrium with an area of 22 cubic centimetres (cm<sup>2</sup>); however, the left atrium was dilated with an area of 39 cm<sup>2</sup>. Also, the right and left ventricles were dilated with augmented diastolic diameters of 45 mm 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 contrasted enhanced CMR also revealed a 40 by 38 mm apical

mass that does not present perfusion at rest or late enhancement in relation to the LVT previously seen. (Figure 1).

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 2). 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. Warfarin was started for the LVT.

During follow-up, after one 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.

## 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 <sup>4</sup>. 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<sup>4</sup>, as in our case. Besides, LVT has also been occasionally described in Takotsubo cardiomyopathy, amyloidosis, hypereosinophilic syndrome, and Chagas' disease <sup>4</sup>, being an infrequent manifestation of vasculitis, especially in ANCA-associated vasculitis <sup>1</sup>. 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 discharges EGPA.

Regarding pulmonary capillaritis, it is a histopathologic diagnosis that is not pathognomonic of a particular problem; it typically indicates the presence of a systemic vasculitis or collagen vascular disease, and hence, treatment should concentrate on the underlying condition that caused it, as in our case <sup>5</sup>.

In relation to heart failure in MP, it has been described with a prevalence between 6.8% <sup>6</sup> and 17.6%<sup>7</sup>. Additionally, 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<sup>8</sup>.

Respecting HIV and cardiomyopathy, prior to the development of ART, the patients suffered from cardiomyopathy with manifest left ventricular systolic dysfunction; however, after its development, the onset of cardiomyopathy had a more incisive course, being more frequently of ischemic aetiology and with a high prevalence of diastolic left ventricular dysfunction <sup>9</sup>. 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 <sup>9,10</sup>. However, cardiomyopathy due to mitochondrial toxicity with ART therapy was described mainly with zidovudine, zalcitabine, and didanosine, in the group of reverse transcriptase inhibitors <sup>10</sup>. Besides, defects in mitochondrial DNA replication and energetics have been reported with zidovudine <sup>11,12</sup>, clevudine and lodenosine <sup>13,14</sup>. Also, patients receiving ART with protease inhibitors had increased cardiovascular mortality and readmission rates at 30 days <sup>15</sup>. 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<sup>16,17</sup>. In addition, CMR imaging is the gold standard for LVT<sup>4</sup>. In our case, despite subendocardial LGE in the CMR, these results were not considered to be related to an ischemic aetiology 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<sup>18</sup>, nor 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 3 existing ones (GP, MP, and EGPA), MP was the most probable diagnosis since it presents pulmonary capillaritis more frequently than EGPA<sup>5</sup>, and the patient did not present chronic rhinosinusitis, asthma, or prominent peripheral eosinophilia leading to EGPA<sup>3</sup>. 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, which, like MP, is one of the most common disorders associated with pulmonary capillaritis<sup>5</sup>.

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<sup>19</sup>. Our patient also received management of his heart failure in accordance with current European and American guidelines<sup>20,21</sup>. 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.

## Conclusion

In patients with DAH and pulmonary capillaritis associated with cardiac pathologies with negative ANCAS 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

Porrás Bueno Cristian Orlando: Wrote and reviewed the manuscript and was involved in data acquisition and analysis.

Saldarriaga Giraldo Clara Ines: Conceived and designed the study and reviewed the manuscript.

Roncancio Villamil Gustavo Eduardo: Conceived and designed the study and reviewed the manuscript.

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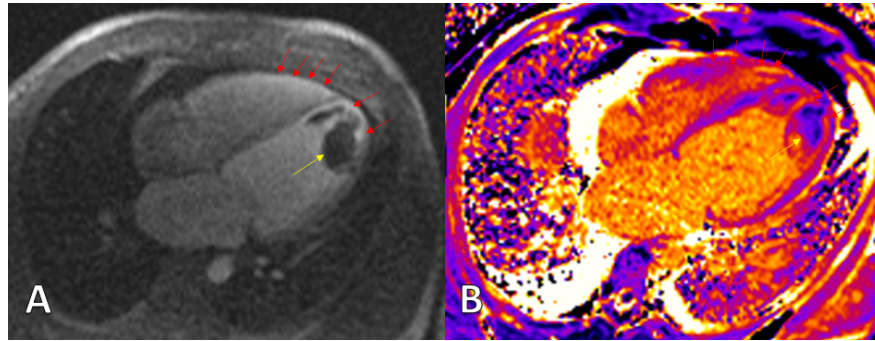
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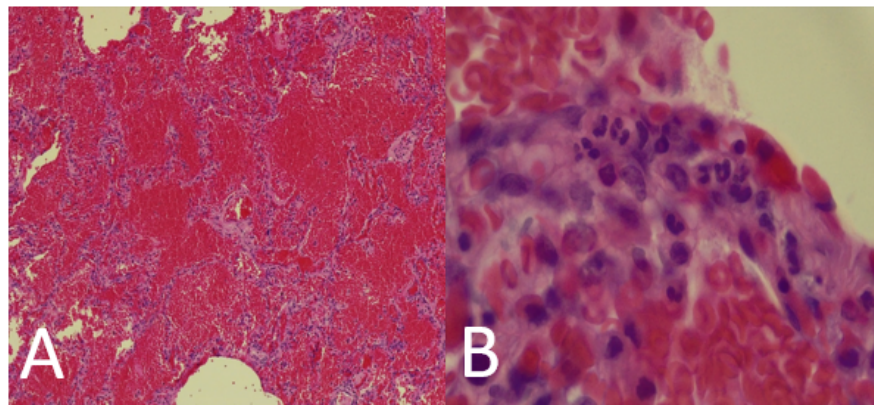
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## Figures



**Figure 1.** A) CMR with late gadolinium enhancement 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. Abbreviations: DCM: Dilated cardiomyopathy. CMR: Cardiac magnetic resonance. LV: Left ventricle. RV: Right ventricle.



**Figure 2.** A. At 10x magnification, pulmonary histopathology stained with H&E, showing multiple intra-alveolar haemorrhages with the presence of hemosiderophages in relation to DAH. B. At 100x magnification (H&E), oedematous walls with polymorphonuclear cells, reactive endothelial cells, and type II pneumocyte hyperplasia in relation to pulmonary capillaritis. Abbreviations: H&E: Haematoxylin and eosin. DAH: Diffuse alveolar haemorrhage.

