

# Anagrelide Treatment and Congestive Heart Failure in the COVID-19 Era: A Case Report

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## Abstract

**Background:** This case report emphasises the importance of differential diagnosis in dilated cardiomyopathy and the frequent misdiagnosis of congestive heart failure in the COVID-19 era.

**Case presentation:** A patient with Polycythemia Vera (PV) and no history of cardiac disease developed dyspnoea and radiological signs of pulmonary congestion. He was then treated as a suspected COVID-19 patient. However, echocardiogram showed biventricular dysfunction and severely reduced Left Ventricular Ejection Fraction (LVEF) (22%) without regional wall motion abnormalities. We hypothesised drug-related cardiotoxicity.

**Conclusion:** Particular attention should be paid to patient admitted to Emergency Department (ED) with respiratory symptoms and clinical signs of congestion in order to correctly differentiate COVID-19 related respiratory disease from cardiogenic dyspnoea. Cardiotoxicity should always be ruled out in dilated-hypokinetic cardiomyopathy.

**Keywords:** Anagrelide • Congestive heart failure • Cardiotoxicity • Cardiogenic dyspnoea • COVID-19

**Abbreviations:** CVAEs: Cardiovascular Adverse Events • ED: Emergency Department • ET: Essential Thrombocythemia •

JAK-2: Janus kinase 2 • LVEF: Left Ventricular Ejection Fraction • MPN: Myeloproliferative Neoplasms • PV: Polycythemia Vera • RVEF: Right Ventricular Ejection Fraction

## Introduction

Anagrelide-associated cardiomyopathy has been widely reported in literature. The potential mechanisms underlying cardiotoxicity are probably related to the inhibition of cyclic adenosine monophosphate phosphodiesterase 3 exerted by anagrelide, which results also in positive inotropic, lusitropic and vasodilatory effects (with consequent sympathetic activation) and may result in congestive heart failure, with echocardiographic phenotype of variably dilated and hypokinetic cardiomyopathy. Similarly to that observed in tachycardia-induced cardiomyopathy, this condition is characterized by partial or complete reversibility after drug discontinuation.

## Case Report

An 80-year-old male was admitted to S. Orsola Hospital, Bologna, for persistent dry cough, worsening dyspnoea, weight gain (4-5 kilograms in the last 10 days) and bilateral leg swelling. At admission in the Emergency Department (ED) hemodynamic was stable and the electrocardiogram showed sinus rhythm at 95 bpm, nonspecific ST-T wave abnormalities, monomorphic isolated ventricular ectopic beats. Laboratory findings included white blood cells 14980/mm<sup>3</sup>, haemoglobin 11.7 g/dL, platelet count 196000/mm<sup>3</sup>, creatinine 1.27 mg/dL, aspartate aminotransferase 38 U/L, alanine aminotransferase 42 U/L, brain natriuretic peptide 1731 pg/mL, C-reactive protein 1.86 mg/dL, D-dimer 2.14 mg/l. High-resolution computed tomography of chest showed

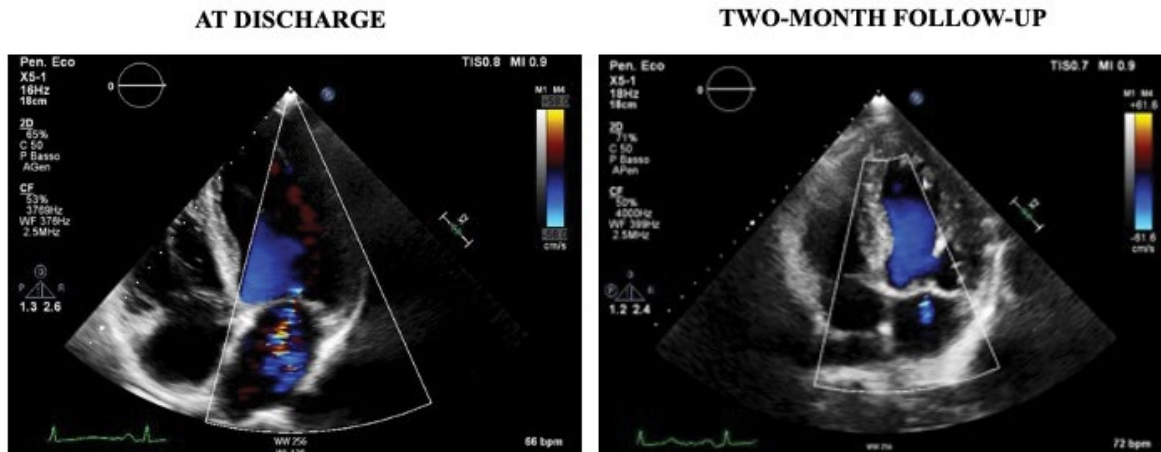
bilateral pleural effusion (maximal depth 6.5 cm on the right vs 2.5 cm on the left side) with bilateral basal ground glass opacities attributable to pulmonary atelectasis and marked cardiomegaly. CT pulmonary angiography excluded pulmonary embolism. The patient had a history of Polycythemia Vera (PV) with documented Janus kinase 2 (JAK-2) gene mutation treated with phlebotomy and hydroxyurea (for concomitant thrombocytosis), the latter one replaced by anagrelide (1.5 mg/day) nine months before hospital admission for suspected cutaneous side effect of hydroxyurea (basal cell carcinomas which were exerted). Past medical history also included high blood pressure, benign prostatic hyperplasia, intraductal papillary mucinous neoplasm, right ankle and right knee replacement surgery. Five months before admission he was screened with echocardiogram, which documented left ventricular hypertrophy with normal Left Ventricular Ejection Fraction (LVEF) without regional wall motion abnormalities.

According to the hospital protocol for newly admitted patients, a routine nasopharyngeal swab for COVID-19 was taken; due to the presence of suggestive symptoms (dry cough), radiological aspects and blood tests (lymphopenia and eosinopenia, elevated D-dimer and interleukin-6) the patient was referred to a dedicated ward for patients with high clinical suspicion of COVID-19 infection. In order to exclude other potential diseases, and in presence of clinical and radiological signs of heart failure, the patient underwent echocardiogram that revealed biventricular dysfunction with mildly dilated left ventricle, severely reduced left ventricular ejection fraction (LVEF) (22%) without regional wall motion abnormalities, tricuspid annular plane systolic excursion mildly reduced (17 mm). Moderate to severe functional mitral regurgitation (effective regurgitant orifice area 0.14 cm<sup>2</sup>, regurgitant volume 22 mL), and mild tricuspid regurgitation with pulmonary hypertension (estimated systolic pulmonary artery pressure 55 mmHg) were also found. In order to completely exclude SARS-CoV2 infection and potentially related myocarditis, a second nasopharyngeal swab was repeated after 24 hours that resulted negative as the previous one. The subsequent diagnostic work up included: firstly, coronary angiography, showing non-significant stenosis of the left main and the three main epicardial vessels, with critical stenosis of the first diagonal branch (small caliber) and of the first obtuse marginal artery, which

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**Figure 1.** End-systolic volume and functional mitral regurgitation at discharge and after two-month follow-up.

were not judged to be responsible of the severe biventricular dysfunction. Then, cardiac magnetic resonance confirmed biventricular dilation (left ventricular end-diastolic volume 150 ml/m<sup>2</sup>, right ventricular end-diastolic volume 144 ml/m<sup>2</sup> and severe biventricular dysfunction (LVEF 27%, RVEF 24%), with diffuse increase in T1 and T2 relaxation times (myocardial edema).

Perfusion imaging showed absence of perfusion deficits, whereas areas of intramyocardial late gadolinium enhancement (fibrosis) were found in the inferior and superior right ventricle-left ventricle insertion regions. Available data permitted to exclude SARS-CoV2 related myocarditis, as well as severe ischemic heart disease. Alternative potential causes of rapid onset biventricular dysfunction were then to be found. Anagrelide was reported to be a potential cause of heart failure through the inhibition of phosphodiesterase 3, resulting in chronic positive inotropic, lusitropic and vasodilatory effects. Due to the high clinical suspicion of causative effect in the patient's myocardial dysfunction, the drug was discontinued at admission and replaced after a few days with hydroxyurea (1500 mg/day) after hematologic consultation. Furthermore, heart failure treatment with bisoprolol (up titrated to 5 mg/day), valsartan (up titrated to 40 mg twice daily), furosemide (75 mg/day), canrenone (25 mg/day) was administered and acetylsalicylic acid (150 mg/day) was started.

## Discussion

Anagrelide, an imidazoquinolin, inhibits megakaryopoiesis and more selectively reduces platelet production in humans. It is a drug with specific platelet-lowering activity, primarily used in essential thrombocythemia (ET), registered as a second-line drug in ET in Europe for hydroxyurea intolerant or refractory patients [1] and in some countries as first-line therapy; in USA it is licensed by FDA for thrombocythemia in Myeloproliferative Neoplasms (MPN) [2]. The exact anagrelide mechanism of action is unclear, although it is known to be a cyclic adenosine monophosphate phosphodiesterase 3 inhibitor; as a consequence, it may have actions in common with drugs such as amrinone, milrinone and enoximone, known for their positive inotropic effects and for their adverse impact on mortality when used over the long term in patients with heart failure [3]. Similarly, anagrelide exerts positive inotropic, lusitropic and vasodilatory effects (with consequent sympathetic activation): these properties may contribute to Cardiovascular Adverse Events (CVAEs), mostly palpitations, which in some cases lead to the treatment discontinuation [4].

Anagrelide-associated cardiomyopathy was first reported in 2000 [5]. Therefore, in a retrospective analysis from the Mayo Clinic Rochester database [6] 11 patients were described with echocardiogram confirming idiopathic hypokinetic cardiomyopathy with severely reduced LVEF that post-dated (median period of 9 years) a diagnosis of either PV or ET (9 females; age range 46-78 years; 7 PV and 4 ET). Anagrelide therapy (median dose of 2 mg/day) was temporally associated with cardiomyopathy in 6 of the 11 patients, all of whom experienced symptomatic and/or objective echocardiographic improvement after drug discontinuation. Other cases of anagrelide-associated

hypokinetic cardiomyopathy with severely reduced LVEF have been described: after 10 years of treatment (2 to 3 mg/day) [7], and after 2 years of treatment (3 mg/day) [8], both reversible after drug discontinuation. Wong et al. [9] reported a successful rechallenge with anagrelide in a patient who developed anagrelide-associated hypokinetic cardiomyopathy after 17 months of treatment (5 mg/day); the treatment was discontinued temporarily and was successfully restarted at a lower dose (1 mg/day) with gradual improvement of symptoms and cardiac function (LVEF from 18% to 50%). This case illustrates that rechallenge with anagrelide could be an option in patients with anagrelide-associated cardiomyopathy who otherwise have limited treatment options.

Finally, clinical presentation with Takotsubo cardiomyopathy, have been described during anagrelide treatment - which was identified as the only potential responsible for intensive inotropic stimulation and sympathetic hyperactivation in the described clinical scenarios [10]. Our patient was then longitudinally observed: 2-month follow-up after anagrelide suspension and heart failure treatment starting showed clinical improvement to NYHA II functional capacity and echocardiographic improvement to LVEF 45% with only mild mitral regurgitation (Figure 1). Therefore, particular attention should be paid to patient admitted to ED with respiratory symptoms and clinical signs of congestion in order to correctly differentiate COVID-19 related respiratory disease from cardiogenic pulmonary edema.

## Conclusion

Our clinical report strengthens available literature data suggesting that long standing positive inotropic, lusitropic and vasodilatory effects (with consequent sympathetic activation) exerted by anagrelide may result in congestive heart failure, with echocardiographic finding of variably dilated and hypokinetic cardiomyopathy, characterized by partial or complete reversibility after drug discontinuation and heart failure treatment. The reversible nature of anagrelide-associated dilated-hypokinetic cardiomyopathy appears to be similar to that observed in tachycardia-induced cardiomyopathy. Concomitant conditions, such as coronary artery disease, may increase myocardial vulnerability, but this was not a frequent condition in published case reports. Prospective studies are needed to assess whether serial echocardiographic follow-up of patients treated with anagrelide could reduce the risk of this serious side effect and whether it could be dose-dependent.

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