

Severe pulmonary hypertension secondary to anagrelide treatment?

George Calcaianu*; Mihaela Calcaianu; Guillaume Barberet; Cyrille Mathien; Philippe Guiot

*George Calcaianu

Department of Pulmonogy, GHRMSA Mulhouse, France

Email: calcaianugeorge@gmail.com

Abstract

Some chemotherapeutic agents can induce pulmonary arterial hypertension (PAH). Dasatinib, a common treatment of chronic leukemia, was the most cited chemotherapy agent with a risk of developing PAH [1]. We report the case of a severe pulmonary hypertension (PH), complicated by cardiogenic shock, developing in a 77-year-old woman treated by anagrelide for an essential thrombocythemia.

During a ICU hospitalization for acute heart failure complicated with cardiogenic shock, we complete a right heart catheterization which showed a severe PH with mean pulmonary arterial pressure (mPAP) at 50 mmHg, cardiac index (CI) at 1,4 L/min/m² and pulmonary vascular resistance (PVR) at 995 dyne·second/cm⁵). Although she received an optimal treatment with vasopressives agents and NO support, associated to Sildenafil, the patient succumbed after a fatal cardiac arrest.

Keywords

pulmonary arterial hypertension (PAH); cardiogenic shock; anagrelide; ICU

Learning Objective

Anagrelide has been reported to develop reversible cardiomyopathy and the mechanism is not fully explained [2-4]. For the best of our knowledge, this report is the first reported case of a severe precapillary pulmonary hypertension secondary to anagrelide treatment

Introduction

Anagrelide is a chemotherapeutic agent used in the essential thrombocythemia that reduce the platelet count by a mechanism of inhibiting the maturation of platelets from megakaryocytes. Anagrelide is a potent inhibitor of cyclic adenosine monophosphate phosphodiesterase III which increases intracellular calcium levels in the cardiomyocytes and vascular smooth muscle cells. The common side effects of anagrelide include: headache, tachycardia and fluid retention [5].

There are some case reports regarding the cardiotoxicity due to anagrelide. These cases of congestive heart failure showed partial or complete improvement of symptoms or cardiac function after the withdrawal of anagrelide [2-4]. To our knowledge this article reports the first case of a possible severe pulmonary hypertension secondary to anagrelide and complicated with cardiogenic shock.

Case Presentation

77-year-old woman with a history of essential thrombocythemia treated by anagrelide for the last 5 years, with a total daily dose of 2 mg, developed pulmonary hypertension with systolic pulmonary pressure (sPAP) at 70 mmHg and tricuspid regurgitant velocity at 3,8 m/s in echocardiography, without any signs of pulmonary embolism or chronic thromboembolic pulmonary disease at V/Q lung scan. The initial laboratory evaluation is listed in Table 1.

At baseline, the subject was in function class 2, without any signs of right heart failure like peripheral edema or jugular turgescence.

Two months later she was hospitalized in the nephrology department for persistent diarrhea complicated with acute renal failure and dyspnea with signs of right heart failure (moderate peripheral edema and gain of weight). Her state was ameliorated by high doses of diuretic (500mg per day of iv. Furosemide). Her renal function was stabilized with a renal clearance at 20ml/min and she was discharged with indication for hemodialysis. Just few days after, her state continued to worsen with persistent diarrhea. She was re-hospitalized in the ICU with signs of dizziness, hypotension, water retention, severe edema of the lower limbs, ascites and oliguria. The laboratory data on admission: hemoglobin 11,5 g/dl, severe leukocytosis at 69000/ μ L, platelet count 652000/ mm^3 , urea 53,3 mmol/L, serum creatinine 560 μ mol/L with renal clearance at 9 ml/min and NTproBNP 27400 pg/mL (table 1). The arterial blood gases showed a severe metabolic acidosis with lactate acid at 5,6mmol/L. We didn't find any signs of infection with negative bacteriological analysis and very low inflammatory status with CRP at 8 mg/dL.

The electrocardiogram showed a normal sinus rhythm, with signs of right ventricle overload and the chest X-ray revealed a bilateral pleural effusion.

The respiratory status is rapidly worsening and the subject was intubated and mechanical ventilated. The hemodynamic data showed a hypovolemic shock with low cardiac index, measured by PICCO catheter, at 1,8 l/min/m² and high systemic vascular resistances (SVR); therefore, an inotropic support was insured with Noradrenaline and Dobutamine. Because of cardiorespiratory instability, a hemodynamic support with inhaled nitric oxide (NO) was initiated, which permitted to ameliorate the cardiac function and the hypoxemia. However, the subject remained dependent to inhaled NO with a sudden drop of the arterial pressure at the withdrawal of NO. In this situation, we installed a hemodynamic monitoring by a Swan-Ganz catheter that showed a severe pulmonary hypertension with mean pulmonary arterial pressure (mPAP) at 50 mmHg, pulmonary arterial wedge pressure (PAWP) at 7mmHg, high pulmonary vascular resistances (PVR) at 995dyn*s/cm⁵, high SVR at 1950 dyn*s/cm⁵, and a very low cardiac index at 1.4l/min/m², measured by dilution method (table 2).

The echocardiographic evaluations showed an important right heart failure with a paradoxical septal motion, right ventricle dilation, major tricuspid insufficiency and a moderate pericardial effusion (1,8 cm). The left ventricle ejection fraction was preserved at 50%.

After a multidisciplinary discussion, we decided to start a treatment with specific pulmonary vasodilators and therefore Sildenafil 20 mg t.i.d was initiated. The echocardiographic reexamination, 1 week after the initiation of Sildenafil treatment, showed a slight improvement of the right ventricle

functions which permitted to withdraw the inhaled NO and to diminish the inotropic support by Noradrenaline and Dobutamine. Despite a slight improvement, few days later, the subject had a cardiac arrest, which was non-resuscitable.

Discussion

Anagrelide is an agent that inhibits phosphodiesterase 3 with increasing intracellular cAMP and Calcium levels that can produce cardiovascular adverse effects like cardiomyopathy with worsening in ventricular function and congestive heart failure, arrhythmias or myocardial infarction. Diarrhea remains the most important gastrointestinal side effect [5] and probably in this case the anagrelide treatment was the only cause of this symptom.

Among the adverse effects cited by the manufacturer of anagrelide was the pulmonary hypertension, without any other details (D. Parker, Shire Richwood Inc., personal communication, June 2000).

Although the exact mechanism of the pulmonary hypertension due to anagrelide is not fully known, the increased intracellular calcium levels in the pulmonary vascular smooth muscle cells can produce a chronic vasoconstriction with a vascular tissue remodeling.

Our diagnosis algorithm excluded a septic shock in the absence of any signs of infection and a very low inflammatory syndrome (CRP at 8 mg/dL). The other causes of pulmonary hypertension were excluded. We didn't notice a history of drug induced PAH, there was no clinical sign of connective tissue disease, and chronic thromboembolic disease was excluded by a V/Q lung scan.

Tables

Table 1: Initial laboratory evaluation

Test	Value 2 months before ICU admission	Value at ICU admission	Normal value
Hemoglobin	9,9 g/dL	11,5 g/dL	13,5-18 g/dL
Leucocytes	16100/ μ L	69000/ μ L	4000-10000/ μ L
Platelets	427000/ μ L	652000/ μ L	150000-450000/ μ L
Sodium	146 mEq/L	125 mEq/L	137-145 mEq/L
Potassium	3,7 mEq/L	4,7 mEq/L	3,6-5 mEq/L
Urea	21,6 mmol/L	41,4 mmol/L	2,5-6,4 mmol/L
Creatinine	126 μ mol/L	403 μ mol/L	59-104 μ mol/L
AST	15 UI/L	1062 UI/L	5-35 UI/L
ALT	14 UI/L	1562 UI/L	7-56 UI/L
Total bilirubin	7 μ mol/L	21 μ mol/L	1-17 μ mol/L
NT pro-BNP	2080 pg/mL	37071 pg/mL	<194 pg/mL
D-dimer	234 μ g/mL	445 μ g/mL	<500 μ g/mL
C-reactive protein	26 mg/L	8 mg/L	0-3 mg/L
Lactic acid level		5,66 mmol/L	0,6-2,4 mmol/L

Table 2: Right heart catheterization in ICU.

MAP (mmHg)	78
HR (beat/min)	79
PAWP (mmHg)	7
sPAP (mmHg)	78
dPAP (mmHg)	36
mPAP (mmHg)	50
CI (l/min/m ²)	1,4
SVR (dyne·second/(cm ⁵))	1951
PVR (dyne·second/(cm ⁵))	995

Abbreviations: MAP: mean arterial pressure, HR: heart rate, PAWP: pulmonary arterial wedge pressure, sPAP: systolic pulmonary arterial pressure, dPAP: diastolic pulmonary arterial pressure, mPAP: mean pulmonary arterial pressure, CI: cardiac index, SVR: systemic vascular resistance, PVR: pulmonary vascular resistance.

Conclusion

In conclusion, for the best of our knowledge, this report is the first reported case of a severe precapillary pulmonary hypertension secondary to anagrelide treatment. The hemodynamic state was worsened by a hypovolemic shock due to a persistent diarrhea which could be also a side effect of anagrelide.

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Authors Information: George Calcaianu^{1*}; Mihaela Calcaianu²; Guillaume Barberet²; Cyrille Mathien²; Philippe Guiot²

¹Department of Pulmonogy, GRHSA Mulhouse, France

²Department of Intensive Care Unit, GHRMSA Mulhouse, France

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