

ANAGRELIDE-INDUCED PERICARDIAL EFFUSION IN A PATIENT WITH ESSENTIAL THROMBOCYTHEMIA

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Abstract

We present a rare case of anagrelide-induced pericardial effusion that is presented with tamponade physiology in a patient with essential thrombocythemia. After cautiously weighing the risks and benefits of further invasive interventions following an unsuccessful pericardiocentesis, the decision was to stop anagrelide while managing the pericardial effusion medically.

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Abstract

Pericardial effusion leading to cardiac tamponade can occur due to a multitude of etiologies, one of which is medication adverse effects. In patients with comorbid conditions, this can prove to be a challenge in its co-management along with the primary disease. We present a rare case of anagrelide-induced pericardial effusion that is presented with tamponade physiology in a patient with essential thrombocythemia. After cautiously weighing the risks and benefits of further invasive interventions following an unsuccessful pericardiocentesis, the decision was to stop anagrelide while managing the pericardial effusion medically. Therefore, managing pericardial effusion should be tailored to each patient individually through shared-decision making.

Key Clinical Message:

- Pericardial effusion leading to cardiac tamponade can occur due to a multitude of etiologies, one of which is medication adverse effects
- In ET patients on anagrelide with pericardial effusion, a drug-induced etiology should be considered as an adverse reaction
- In our case the decision to continue or to stop anagrelide while managing the pericardial effusion should be tailored to each patient individually through shared decision making.

Keywords : pericardial effusion, anagrelide, essential thrombocythemia, adverse effect

Introduction:

The pericardium normally houses between 10 - 50 milliliters of plasma ultrafiltrate. If and once fluid accumulates above such physiologic amount, pericardial effusion sets in by definition. The ramifications that could follow are ultimately governed by the rate of accumulation of the fluid, whether incremental over a prolonged period of time, or swift over a short one. Eventually, this may lead to cardiac tamponade as defined by an intra-pericardial pressure exceeding pressures of the intra-cardiac chambers, causing life-threatening derangements in hemodynamics [1]. Transthoracic Echocardiogram (TTE) remains the gold standard modality in diagnosing cardiac tamponade with the sign of early diastolic right ventricular (RV) collapse exhibiting 100% specificity [2]. However, essential focus should be placed on correlating the patient's clinical status and assessing for the presence of hypotension, jugular venous distention (JVD) and distant heart sounds in order to make appropriate clinical decisions. There are multiple, distinguishable etiologies that may introduce the development of pericardial effusion and a possible cardiac tamponade sequelae, but one that is often overlooked, underestimated, and substituted with an idiopathic label is the adverse effect of medications [3]. Throughout literature, only a handful of medications have been implicated as triggers of such pericardial disease. In clinical trials as well as prospective and retrospective studies, the platelet reducing agent anagrelide has been shown to cause cardiovascular adverse events such as heart failure (HF), myocardial infarction, cardiomyopathy, arrhythmia, pericarditis, and although rare, pericardial effusion. Anagrelide is used for the treatment of essential thrombocythemia (ET), polycythemia vera and myeloproliferative disorders [4-6]. There has been one case reported of pericardial effusion after the introduction of anagrelide in an essential thrombocythemia patient [7]. We present a case of an 84-year-old female with anagrelide-induced pericardial effusion progressing to cardiac tamponade.

Case Presentation:

An 84-year-old female with a history of ET, factor V Leiden, hypertension and bilateral lower extremity venous insufficiency complicated by multiple ulcers presented to the emergency department (ED) after a fall secondary to a syncopal episode. She was ambulating in her apartment at the nursing home when she lost consciousness. In the preceding weeks, the patient had been experiencing intermittent, pleuritic chest pain, palpitations, in addition to resting and exertional shortness of breath. She denied orthopnea, paroxysmal

nocturnal dyspnea, cough, hemoptysis, fever, unintentional weight loss, recent viral illness or sick contacts, tuberculosis exposure, malignancies, and autoimmune disease. Further history revealed that the patient's pleuritic chest pain, palpitations and shortness of breath started after the patient's hematologist switched to anagrelide from hydroxyurea because it was likely impeding the healing of her venous ulcers. The dose of anagrelide was gradually increased to 1 mg twice daily, worsening the patient's aforementioned symptoms. Her other medications included candesartan 16 mg daily and warfarin 5 mg daily.

Initial vital signs consisted of blood pressure 137/81 mm Hg, heart rate 76 beats per minute, respiratory rate 18 respirations per minute, oxygen saturation of 100% on room air, and temperature 97.6° F (36.4° C). Her physical examination was only notable for 3+ bilateral lower extremity edema and multiple venous stasis ulcers, with evidence of JVD and crackles. Laboratory findings included white blood cell count $34.01 \times 10^3/\text{mL}$, hemoglobin 9 g/dL, platelet count $916 \times 10^3/\text{mL}$, potassium 5.4 mmol/L, troponin 0.039 ng/mL, and NT-pro B-type natriuretic peptide 982 pg/mL. Her admission chest radiograph was unremarkable. However, electrocardiogram (ECG) showed new-onset atrial fibrillation with rapid ventricular response (**Figure 1A**) which resolved with administration of 500 mL of intravenous normal saline. A bedside echocardiogram showed a large pericardial effusion. The patient was admitted to the cardiac care unit for further care. TTE confirmed the large pericardial effusion and revealed tamponade physiology including abnormal respirophasic variation, free wall inversion and early diastolic right ventricular collapse (**Figure 1B-C**).

The patient remained hemodynamically stable without any clinical signs of cardiac tamponade. Her oxygen requirement consistently ranged from 2 L nasal cannula to being in room air throughout her hospitalization. Malignancy, tuberculosis and autoimmune workup was negative. As a result, in the absence of common causes, the patient's pericardial effusion was attributed to anagrelide and the medication was therefore stopped after consulting hematology. Given the high risk of tamponade, pericardiocentesis was offered and later attempted, but proved to be challenging due to increased pericardial clotting and anatomical variance with high risk for RV puncture. Right heart catheterization ruled out constrictive and restrictive patterns, and showed elevated left and right pressures. She continued to have mild, intermittent shortness of breath as well as pleuritic chest pain, both of which were symptomatically managed with nebulized ipratropium bromide/albuterol, supplemental oxygen and pain control as needed. Repeat TTE showed a mildly improved, but persistent pericardial effusion, without tamponade physiology. Given the likelihood of re-accumulation, a pericardial window was offered, but after multiple multidisciplinary discussions concerning her goals of care and previous attempt, the patient declined and decided to be discharged back to her nursing home.

Discussion:

The etiology of pericardial effusion and cardiac tamponade is often idiopathic. Cubero et al states the three major causes of large pericardial effusions were idiopathic pericarditis, tuberculous, and neoplastic origin in descending order of incidence. Similar results were found in Sagristà-Sauleda et al, attributing the most common cause of large pericardial effusions to idiopathic pericarditis, followed by iatrogenic, and malignant with the latter having the highest likelihood of becoming cardiac tamponade [9,10]. Among the majority of data pertaining to etiology, drug-induced pericardial effusion seems to be either excluded or dismissed under the umbrella of idiopathic.

Management of pericardial effusion and cardiac tamponade is case-dependent and essentially remains the same with either pericardiocentesis, pericardial window or pericardiectomy. However, rare etiologies in certain clinical scenarios may warrant a different approach to management. The progression of a pericardial effusion into a cardiac tamponade could impose catastrophic clinical outcomes, especially in patients with co-morbid conditions such as malignancy that may hinder any invasive intervention and augment the hemodynamic instability of cardiac tamponade [11,12]. Markiewicz et al found that predictors of long-term survival relied on the prognosis of the primary illness, regardless of the treatment modality. This poses a challenge since the majority of pericardial effusion and cardiac tamponade cases are attributed to an idiopathic etiology, as previously mentioned.

The diagnosis of cardiac tamponade continues to rely on echocardiography, which apart from identifying the

specific signs, also aims to evaluate the size, distribution, presence of intrapericardial adhesions or clot, the feasibility of pericardiocentesis, and the evolution of the pericardial effusion. Sanjay et al concluded that the sensitivity, specificity and positive predictive value of RV diastolic collapse is 93%, 100% and 100%, respectively. On the other hand, Rifkin et al states that although sensitivity of RV diastolic collapse increased in relation to the severity of cardiac tamponade, its specificity remained higher and constant at 88% whether the tamponade was early, moderate or severe. RV collapse takes place in early diastole, and as the cardiac tamponade progresses, it could span the entirety of diastole [15-17]. Although our patient's echocardiography showed tamponade physiology, the classic Beck's triad of muffled heart sounds, presence of JVD, and hypotension did not completely manifest and the patient's only recurrent complaint was shortness of breath requiring minimal oxygen supplementation by nasal cannula. However, decompensation risk remained very high. In practice, the clinical symptoms and signs of cardiac tamponade are a good compass of suspicion, but they are not reliable without echocardiographic confirmation, especially since they could be present in other overlapping conditions such as acute or chronic obstructive airway disease, pulmonary embolism, tension pneumothorax, large pleural effusions, effusive constrictive pericarditis, RV infarction, restrictive cardiomyopathy, extreme obesity, or tense ascites. In addition, the combination of classic and non-classic cardiac tamponade signs and symptoms are most likely to be absent in gradually developing cardiac tamponade [18]. Thus, given our patient's sustained and relative hemodynamic stability, her pericardial effusion most likely developed in a gradual manner over days to weeks following the change in her ET regimen by the introduction of anagrelide, allowing the pericardium to stretch and accommodate the large effusion. The only identifiable event was the discontinuation of hydroxyurea and the initiation of anagrelide three weeks prior to presentation, which is consistent with enough lead-time for a gradual, large pericardial effusion to develop and be reflected with the patient's progressive feeling of being unwell since the change. It is important to note that the patient had previously been placed on an anagrelide trial with an intolerant outcome described by the patient as pleuritic chest pain, shortness of breath and palpitations. The recent switch to anagrelide was a re-trial by the patient's primary hematology team in an attempt to reevaluate tolerability in order to reduce her sustained, hydroxyurea-refractory thrombocytosis at the time.

Pericardial effusion was reported as a rare adverse reaction of anagrelide during its trials. Its incidence among its current users is unknown and the mechanism behind it is unclear [13]. In conditions indicated to receive anagrelide such as our patient's ET, management of drug-induced cardiovascular events becomes a challenge in the setting of withdrawing the insulting medication. ET is known to put patients at risk for both thromboembolic as well as bleeding events. The thromboembolic events stem from abnormalities in platelet morphology, including its membrane, as well as derangements in arachidonic acid metabolism, and the bleeding nature of the disease is a result of qualitative platelet dysfunction as well as acquired Von Willebrand disease secondary to diminished large Von Willebrand multimers [8, 13].

Thus, at baseline, ET patients are at a higher risk for cardiovascular thromboembolic events in addition to a low threshold of bleeding, potentially complicating the course of, in our case, pericardial effusion and demonstrating an obstacle in the face of required invasive procedures. In chronic, stable pericardial effusions of large volume as well as cardiac tamponade, a complete benefit versus harm stratification that addresses both the myeloproliferative disorder and the cardiovascular pathology must be considered before initiating a medical decision concerning either one. Our case represents a complex scenario with multidisciplinary collaboration that could become more frequent as anti-platelet aggregation therapies become the dominantly preferred approach to hematologic disorders in patients at risk of cardiovascular disease and its escalation.

Conclusions

In ET patients on anagrelide with pericardial effusion, a drug-induced etiology should be considered as an adverse reaction since it can precipitate to cardiac tamponade; therefore, the decision to continue or to stop anagrelide while managing the pericardial effusion should be tailored to each patient individually through shared-decision making.

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Authors Contribution:

Conceptualization: David Song; **Writing - original draft preparation:** David Song, Jawad Shabani, Vikash Jaiswal, Kusum; **Writing - review and editing:** , David Rubinstein; **Funding acquisition:** None

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Figure Legend

Figure 1A-C. [A] ECG showing new atrial fibrillation without ischemic changes or low voltage. [B] subcostal view of TTE showing large pericardial effusion and free wall inversion [C] Transmitral doppler showing abnormal respirophasic variation

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