CASE REPORT

Anagrelide-associated Cardiomyopathy and Heart Failure in a Patient with Essential Thrombocythemia: A Case Report and Literature Review

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Abstract:
Anagrelide is used worldwide to treat essential thrombocytemia (ET) by reducing platelet counts. Cardiomyopathy and heart failure (HF) are rare but serious complications associated with anagrelide use, although no cases were reported during Japanese Phase I to III studies. A 46-year-old, otherwise healthy, Japanese ET patient developed HF with reduced ejection fraction after 18 months of treatment with 1.0-3.5 mg of anagrelide daily. HF was stabilized with anagrelide withdrawal and guideline-directed HF therapy. The cardiac function returned to normal after six months. This case suggests that anagrelide can cause cardiomyopathy and HF in ET patients, regardless of nationality, comorbid cardiovascular conditions, or therapy duration.

Key words: anagrelide, heart failure, cardiomyopathy, essential thrombocytemia, myeloproliferative disease

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Introduction

Anagrelide is an oral imidazoquinazoline derivative that inhibits the maturation of megakaryocytes in the bone marrow. Since 1997, it has been widely used for the treatment of essential thrombocytemia (ET), a myeloproliferative disease (MPD). While anagrelide reduces platelet counts as effectively as hydroxyurea, several side effects limit its use. Cardiovascular complications, such as blood pressure changes, palpitations, tachycardia, arrhythmia, fluid retention, congestive heart failure, and angina pectoris, are the major adverse effects induced by anagrelide (1-3). It is also involved in rare but significant cardiac diseases that can potentially cause heart failure (HF), including acute coronary syndrome, coronary spastic angina, ventricular tachycardia, cardiac dysfunction, and inverted takotsubo syndrome (4-8).

Cases of cardiac dysfunction due to non-ischemic causes, known as non-ischemic cardiomyopathy (NICM), have been reported worldwide. However, no cases have yet been reported in Japan, even during phase III studies investigating the efficacy, safety, and tolerability of anagrelide (9). We herein report the details of a novel domestic case of anagrelide-associated NICM and overt congestive HF along with a literature review. It is the authors’ understanding that this is the first report that implicates a probable association between anagrelide and NICM in Japan.

Case Report

Three years ago, a 46-year-old Japanese man was diagnosed with ET with a JAK2 mutation. The patient had a history of chronic sinusitis and took 200 mg of clarithromycin daily. He drank a small amount of beer on weekdays but otherwise had no cardiovascular risk factors. Because he was non-symptomatic and his von Willebrand factor activity was reduced, aspirin treatment was withheld. His platelet count was initially 989×10³ cells/µL but gradually increased to 1,400×10³ cells/µL.

Approximately 20 months ago, mild left leg weakness occurred due to multiple cerebral infarctions. Cytoreductive therapy with 1 mg of anagrelide daily was initiated, with the...
dose increased to 2 mg daily after 2 weeks (Fig. 1). The patient occasionally complained of headache, palpitation, leg edema, and finger numbness, all of which were transient or self-limiting. The platelet counts fluctuated between 500 and 1,000×10^3 cells/μL, even after treatment.

Five months before referral to the authors’ cardiovascular department, the anagrelide dose was up-titrated to 3 mg daily, and 1 month before referral, it was increased to 3.5 mg daily. After the last treatment adjustment, the patient experienced palpitation and dyspnea on exertion. He spontaneously reduced the dose to 3 mg daily. Three days before referral, 20 mg of furosemide daily was prescribed by a local doctor due to suspected HF. The patient then presented to the authors’ cardiovascular department. His blood pressure was 119/75 mmHg, heart rate was 100 bpm, and oxygen saturation was 98%. His plasma brain natriuretic peptide (BNP) level was 98 pg/mL, serum troponin I was 12.1 pg/mL, and serum creatinine was 1.3 mg/dL.

Chest X-ray showed cardiomegaly. An electrocardiogram (ECG) revealed sinus tachycardia, left atrial overload, and left ventricular high voltage with non-specific ST-T changes (Fig. 2). On echocardiography, the left ventricle was enlarged to 55 mm, and its ejection fraction (EF) fell to 35% (Fig. 3, Supplementary material 1). Thus, HF with reduced
ejection fraction (HFrEF) was diagnosed.

Although guideline-directed medical therapy (GDMT) for HFrEF was started with a small dose of 0.625 mg bisoprolol daily, symptoms persisted. A few days later, the patient presented to the emergency department with orthopnea. His BNP level had increased to 518 pg/mL, and chest X-ray indicated cardiomegaly and mild pulmonary congestion (Fig. 4). His serum troponin I level was normal with 12.3 pg/mL. Anagrelide use was immediately discontinued, and furosemide was up-titrated to 40 mg daily against worsening HF. The patient was then admitted to the authors’ department for further treatment.

On admission, he was afebrile, and his severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test was negative. Intensified diuresis with furosemide quickly resolved the symptoms, with the patient’s condition improving from New York Heart Association class IV to class II within a few days. Examinations to identify the cause of the cardiac dysfunction were subsequently conducted. The patient was taking no other potentially hazardous agents besides anagrelide, such as herbal compounds or illicit drugs. There was no family history of specific cardiac conditions, such as cardiomyopathy and sudden cardiac death. Cardiac computed tomography (CT) showed normal coronary arteries with no fibrosis in the left ventricle wall (Fig. 5). Serum biomarkers involved in cardiac diseases were also normal, including thyroid hormone, angiotensin-converting enzyme, soluble interleukin-2 receptor, free light chains, and rheumatic factor. Along with these tests, GDMT was resumed. In addition to diuretics, cardioprotective drugs were sequentially initiated and increased in a phased manner: bisoprolol 0.3125 mg/day, perindopril 2.0 mg/day, dapagliflozin 10 mg/day, and esaxerenone 1.25 mg/day. As platelet counts markedly increased to 1,203×10^3 cells/μL after anagrelide withdrawal, 500 mg of hydroxyurea, a classical cytotoxic agent, was prescribed daily.

The patient was discharged 15 days after admission, with his EF improved to 42% and exercise tolerance as high as 4.16 metabolic equivalents. Following discharge, the patient had an uneventful course and did not develop any complications. ET was well controlled with hydroxyurea. Six months after discharge, an ECG only showed flat T waves with no signs of sinus tachycardia, left atrial overload, or left ventricular high voltage (Fig. 6). His left ventricle size had normalized to 44 mm, and his EF had recovered to 53% on echocardiography, indicating almost complete reverse cardiac remodeling (Supplementary material 2).

**Discussion**

Although the exact mechanism remains unknown, anagrelide is thought to suppress thrombopoietin-induced megakaryopoiesis and reduce the platelet count by specifically inhibiting the expression of GATA-1 and GOF-1, both of which are downstream of JAK2 signaling (10). In addition, anagrelide also inhibits phosphodiesterase (PDE) III in a distinct and independent manner from megakaryopoiesis inhibition. Undegraded cyclic adenosine monophosphate due to PDE III inhibition triggers an increase in intracellular calcium levels in cardiomyocytes and smooth muscle cells, thereby leading to positive inotropic and chronotropic effects on the heart and relaxation of muscular arteries. PDEs have been reported to stimulate transmitter release from sympa-
Cardiac CT findings. Cardiac computed tomography (CT) images depicting neither atherosclerotic changes in the coronary arteries nor late enhancement in the myocardium: a) left anterior descending artery, b) left circumflex artery, and c) right coronary artery.

Electrocardiogram after discharge. An electrocardiogram taken six months after discharge exhibits only flat T waves.

Anagrelide has been shown to stimulate sympathetic nerves and enhance the sympathetic tone in animal models (11). These effects are considered to contribute to the adverse reactions associated with anagrelide use.

Clinical studies have reported several adverse events, some of which appear to be related to cardiovascular PDE III inhibition. Initial observational studies examining the use of anagrelide for MPDs, including ET, with a variable ratio ranging from 58% to 85%, have consistently reported headache, flatulence, palpitation, and edema (1-3, 12). Later studies specifically focused on ET patients also reported these events with comparable incidences, although a large-scale international retrospective study indicated that the frequency of palpitation and tachycardia were higher in ET patients than in non-ET patients (9, 13-21). As exemplified by the present case, common cardiovascular adverse effects are palpitation (32.6±16.7%), tachycardia (18.9±7.1%), and edema or fluid retention (16.4±8.9%). Of note, edema was usually tolerable and was not associated with HF. Its mechanism is unknown, but similar to calcium channel blockers, selective arterial dilatation that causes intracapillary hypertension and extravasation of fluids is presumed to be the primary cause (22).

There are several other uncommon but potentially fatal cardiovascular adverse events. HF and cardiomyopathy are rarely reported, with their incidences ranging from 0% to 3.5% and 0% to 0.5%, respectively (12, 14, 15, 18-20, 23). Sporadic cases of HF and/or cardiomyopathy associated with the use of anagrelide have also been reported (7, 8, 24-29) (Table). Accordingly, the American Heart Association has stated that anagrelide may cause or exacerbate HF through direct myocardial toxicity (30). However, the patient characteristics, such as age, sex, and primary disease, as well as the dosage and duration of anagrelide use are too diverse to identify individuals that may be susceptible to anagrelide toxicity. According to previous reports, specific findings on an ECG, echocardiogram, CT, or magnetic resonance imaging (MRI) have not yet been described. Consequently, anagrelide-associated cardiomyopathy and probable anagrelide-induced cardiomyopathy are retrospectively diagnosed by the exclusion of other cardiomyopathies and patient recovery from HF and/or cardiac function normalization following anagrelide withdrawal. Considering that reverse cardiac remodeling by GDMT with beta-blockers and renin-angiotensin-aldosterone inhibitors often takes time (from months to years), the temporal proximity between the discontinuation of anagrelide therapy and the
improvement of HF and the cardiac function strongly suggested that the drug was the causative agent in the present case.

Less clinical experience of anagrelide in Japan was reflected by the drug lag issue in Japan. It was approved in 2014 in Japan, 17 years later than in the United States and 9 years later than in Europe. As a result, less clinical experience has been accumulated among Japanese ET patients than among patients in other countries. Despite this limitation, Japanese Phase I, II, and III studies have consistently demonstrated that no critical cardiovascular events occurred after one year of treatment with anagrelide (9, 31). Specifically, in a Japanese single-arm Phase III study examining the efficacy, safety, and feasibility of anagrelide use among 53 ET patients who were at a high risk of developing thrombotic or hemorrhagic events, there were no cases of overt HF, ischemic heart disease, or fatal arrhythmia. However, the rates of palpitation (37.7%), peripheral edema (26.4%), and drug discontinuation (15.1%) were all comparable to prior studies (9). Given these results, the Japanese manufacturer of anagrelide states on the product information that although HF and cardiomyopathy are considered serious cardiovascular side effects, they have only been reported in foreign studies. The Japanese package insert also refers to HF and cardiomyopathy as having unknown frequencies.

Table. List of Cases with ANA-associated Heart Failure and/or Cardiomyopathy.

| Ref | Age | Sex | Diagnosis | ANA dose (mg/day) | Onset | Recovery | HU therapy |
|-----|-----|-----|-----------|-------------------|-------|----------|------------|
| (7) | 48  | F   | PV        | N/A, 6.0          | 25    | N/A      | 6 months   |
| (8) | 75  | F   | ET        | 1.5, 1.5          | 45    | 6 weeks  | N/A        |
| (24) | N/A | F   | PV        | N/A, N/A          | 30    | 60 months| N/A        |
| (24) | N/A | F   | ET        | N/A, N/A          | 25    | 6 months | N/A        |
| (24) | N/A | F   | PV        | N/A, N/A          | 20    | 36 months| 1 year     |
| (24) | N/A | F   | ET        | N/A, N/A          | 30    | 13 months| 3 months   |
| (24) | N/A | F   | PV        | N/A, N/A          | 35    | 10 months| 1 month    |
| (24) | N/A | F   | ET        | N/A, N/A          | 10    | 11 months| 1 month    |
| (25) | 35  | M   | ET        | N/A, 8.0          | N/A   | 4 years  | N/A        |
| (26) | 50  | M   | ET        | 1.0, 5.0          | 18    | 2 years  | 50 months  |
| (27) | 30  | F   | ET        | N/A, 2.0          | 40    | 2 years  | 55 days    |
| (28) | 67  | M   | CMPD      | N/A, 2.0-3.0      | 32    | 10 years | 55 months  |
| (29) | 52  | M   | ET        | N/A, 3.0          | 18    | 25 months| 3 months   |
| (Present case) | 46 | M   | ET        | 1.0, 2.0-3.0      | 35    | 19 months| 53 months  |

*Hydroxyurea was prescribed either as first-line therapy before ANA, as combination therapy with ANA, or as second-line therapy after ANA withdrawal.

*Time interval from ANA introduction to onset of heart failure and/or cardiomyopathy.

*Time interval from ANA withdrawal to recovery of cardiac function.

ANA: anagrelide, Ref: reference, HU: hydroxyurea, EF: ejection fraction, M: male, F: female, N/A: not available, PV: polycythemia vera, ET: essential thrombocythemia, CMPD: chronic myeloproliferative disease

The drug dose may be more important than patient characteristics. According to data collected from 13 European countries, the median induction dose of anagrelide was 1.0 mg/day, and the median maintenance dose was 1.5 mg/day. These doses are consistent with those used in previous Japanese studies (9, 21, 32). Some cases, including the current case, exhibited manifestation of HF after dose escalation to more than 3 mg/day (7, 25, 26). However, an observational study from Italy indicated that only the induction dose, not the maintenance dose, significantly differed between cases with and without adverse cardiovascular events during anagrelide treatment (18). Therefore, there are still many questions regarding dose, timing, and the mode of escalation that could affect the development of cardiovascular adverse events.

Tortorella et al. reported that there were no specific findings of or practical ways to screen anagrelide-associated cardiomyopathy and HF (19), suggesting that we should keep in mind cardiac toxicity due to anagrelide and possible HF development during anagrelide use. Practically, the early and simple diagnosis of HF based on physical examinations, chest X-ray findings, and BNP levels would be prioritized over elaborate examinations for cardiomyopathy with MRI, strain echo, and biopsies. Management of anagrelide-associated cardiomyopathy and HF should focus on clinical decisions, such as an early and simple HF diagnosis, stop-
ping or changing drugs for ET, initiation of HF treatment, early consultation with the cardiovascular department, and the regular evaluation of the cardiac function. This case suggests that anagrelide can cause cardiomyopathy and HF in Japanese ET patients who are otherwise healthy and free from cardiovascular disease. This experience may serve as rationale supporting the cautious follow-up of patients on anagrelide therapy, regardless of nationality, comorbid cardiovascular conditions, or therapy duration.

The patient provided his written informed consent to publish his case, including the publication of images.

The authors state that they have no Conflict of Interest (COI).

Masafumi Sugawara and Sho Okada contribute equally to the work.

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