CASE REPORT

Anagrelide-Induced Pneumonitis: 
Case Report and Review of the Literature

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INTRODUCTION

Anagrelide, a phospholipase A₂ inhibitor that inhibits megakaryocyte proliferation, is used in the management of thrombocytopenia and myeloproliferative disorders. Several adverse reactions, including dyspnea, have been attributed to this drug. However, reports of serious pulmonary toxic effects are rare. We report a case and review the literature on anagrelide-induced pneumonitis to illustrate the morbidity associated with this reaction.

CASE REPORT

A middle-aged patient was admitted to hospital for a cerebrovascular event. On day 12 of the hospital stay, the patient was referred to the respirology service with increasing dyspnea of 1 week's duration. On examination, the patient was febrile and dyspneic, with partial pressure of oxygen of 62 mm Hg on room air. The patient had no orthopnea or paroxysmal nocturnal dyspnea, but mild peripheral edema was present. On auscultation, the patient had crackles in both lung bases with normal heart sounds. Chest radiography revealed extensive bilateral parenchymal disease. Chest computed tomography revealed bilateral ground glass opacities. Bronchoscopy and biopsy performed on day 13 revealed mild interstitial pneumonitis with alveolar hemorrhage, possibly related to drug toxicity. The bronchoscopy revealed no vasculitis, granulomas, fungus, or malignancy; similarly, the results of bacterial culture and culture for Pneumocystis jiroveci were also negative. The patient's medical history was significant for polycythemia rubra vera, Budd-Chiari syndrome, invasive squamous carcinoma on the dorsum of the hands and left foot, and peptic ulcer disease. Medications at the time of consultation were anagrelide 0.5 mg 3 times daily, hydroxyurea 1000 mg twice daily, dalteparin 14 000 units once daily, clopidogrel 75 mg once daily, acetylsalicylic acid 81 mg once daily, ramipril 2.5 mg once daily, metoprolol 37.5 mg twice daily, simvastatin 20 mg once daily, nitroglycerin patch 0.4 mg applied once daily, furosemide 20 mg IV once daily, ciprofloxacin 400 mg IV twice daily, nystatin suspension 500 000 units “swish and swallow” 4 times daily, zopiclone 5–7.5 mg at bedtime as needed, acetaminophen 325–650 mg every 4 h as needed, and saliva substitute as needed.

The patient had been taking anagrelide since 2005. The drug was briefly discontinued 4 days before the hospital admission because of worsening pulmonary edema but was restarted on the day of admission because of thrombocytosis (platelet count 1033 x 10⁹/L; normal 150–400 x 10⁹/L). Four days after anagrelide was restarted, the patient began to complain of dyspnea, becoming increasingly dyspneic over the following week and ultimately requiring oxygen (4 L/min) to maintain oxygen saturation greater than 90%. The temporal relation between reinstitution of anagrelide and the pulmonary symptoms, as well as previous reports of pulmonary toxicity associated with anagrelide, led to discontinuation of the anagrelide on day 14. All other medications were continued as described above. Steroids were not initiated, because the patient had Clostridium difficile colitis. However, 1 week later, on day 20, prednisone 50 mg PO daily was started, since only limited improvement had been achieved with conservative management. At that time, the patient still needed supplemental oxygen at 3-4 L/min. On day 23 (3 days after initiation of prednisone), oxygen saturation was 96% on oxygen 2 L/min, and oxygen therapy was discontinued 2 days later. The patient began ambulating

*Patient demographic information that was not deemed pertinent to the understanding of this case has been omitted for reasons of patient confidentiality.
Spencer and Lawrence described a patient whose condition had previously been stabilized on anagrelide. The patient experienced hypersensitivity pneumonitis after streptococcal pneumonia. The patient’s condition improved within 3 days once the anagrelide was stopped and prednisone 60 mg daily was started.

Tirgan and others presented a case of anagrelide-induced pulmonary fibrosis in a patient with polycythemia rubra vera. After 1 year of therapy, cough and dyspnea on exertion developed, with progressive pulmonary changes evident on radiography. Open-lung biopsy demonstrated interstitial changes consistent with drug-induced disease. The patient’s condition improved with prednisone therapy.

The patient described here had a presentation similar to that reported by Raghavan and others, albeit of milder severity. Our patient also responded quickly to exogenous corticosteroid administration. To our knowledge, this is the first report of a patient who had been previously stabilized on anagrelide reacting to the drug after it was withdrawn for a few days and restarted. The Naranjo score of 7 suggests a probable adverse reaction. Other drug-related causes, such as hydroxyurea, were excluded because of the temporal relation between the initiation of anagrelide and the onset of symptoms, as well as the patient’s recovery once the anagrelide was discontinued.

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The pathophysiology of anagrelide-induced pneumonitis is not understood. If it is a hypersensitivity reaction, as has been suggested by some, it is unclear why our patient had previously tolerated use of the drug. Spencer and Lawrence speculated that a “double hit” was responsible for pneumonitis in their patient. In that case, the patient was predisposed to lung injury by the use of anagrelide, and pneumonitis developed once streptococcal pneumonia had become established. The patient described here did not experience a “second hit” of this type to induce the pneumonitis, but may have been sensitized to the drug during the short period during which the drug was discontinued.

DISCUSSION

Anagrelide has been associated with several serious toxic effects, including stroke, heart failure, myocardial infarction, pancreatitis, pleural effusion, and pulmonary hypertension; however, pneumonitis has been reported only rarely. Four other cases of anagrelide-induced pneumonitis have been published.

A retrospective analysis of 3660 patients treated with anagrelide revealed 2 cases of pneumonitis and death related to respiratory failure. Details of the diagnostic and therapeutic work-up for these patients were not reported. The patient described here did not progress to respiratory failure, probably because of the short course of treatment and the rapid implementation of and response to corticosteroid therapy.

Raghavan and others reported a case of severe hypersensitivity pneumonitis to anagrelide in a 60-year-old woman, who experienced progressive dyspnea 1 week after anagrelide was initiated. Chest computed tomography revealed extensive ground glass attenuations, and the patient eventually required endotracheal intubation and mechanical ventilation for respiratory failure. Biopsy results were not presented in the published report. The anagrelide was stopped, and the patient was then treated with methylprednisolone and experienced marked improvement over the next 48 h.

CONCLUSIONS

This report suggests that anagrelide-associated pneumonitis may occur even in patients who have previously tolerated the drug. Health care professionals should be diligent in assessing patients with dyspnea who are taking anagrelide. Dyspnea, extensive ground glass opacities on computed tomography, and pneumonitis on bronchoscopy are characteristic of this adverse reaction.
References

LETTER TO THE EDITOR

Tribute to Scott Walker

As a colleague and a past Associate Editor of CJHP, I was delighted to read “A Tribute to Scott Walker”, written by two of the Journal’s current Associate Editors.1

I was privileged to work with Scott for many years, first at Sunnybrook Medical Centre and then, as an Associate Editor, on the Journal. The tribute in the January–February issue praised Scott for his commitment and loyalty to the Journal, and I would echo those sentiments. What truly stood out for me in terms of Scott’s tenure as the CJHP Editor was his integrity as the leader of the editorial team. Whenever a difficult issue arose related to manuscripts, advertising, or revenues, Scott always seemed to do the right thing, even in the face of considerable contrary opinion. Regardless of the situation, he always took the “high road” in his dealings with professional colleagues, authors, and agencies. His dedication, commitment, professionalism, and integrity made us proud to be able to work with him on the editorial team.

Yes, indeed, CSHP and its Journal owe much to Scott, and I am pleased to add my voice to his much deserved tribute.

Reference

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