

Unexplained Bone Marrow Granulomas: Is Amiodarone the Culprit? A Report of 2 Cases

Surabhi Mukhopadhyay,^{1*} Sanjay Mukhopadhyay,² Naif Z. Abraham Jr.,³ Lee A. Jones,³ Leslie Howard,⁴ and Ajeet Gajra⁴

¹ Department of Medicine, SUNY Upstate Medical University, Syracuse, New York

² Department of Pathology, SUNY Upstate Medical University, Syracuse, New York

³ Department of Pathology, Veterans Affairs Medical Center, Syracuse, New York

⁴ Department of Medicine, Veterans Affairs Medical Center, Syracuse, New York

Granulomas in the bone marrow are usually caused by infectious or hematological diseases, and drugs are only rarely implicated as causative agents. Recent reports have drawn attention to the role of amiodarone in the etiology of bone marrow granulomas. We report two cases of amiodarone-induced bone marrow granulomas in patients being investigated for refractory anemia and pancytopenia, respectively. Since both patients had life-threatening arrhythmias, discontinuation of the drug followed by rechallenge was not possible. Both patients did well in spite of continued amiodarone therapy, indicating that the underlying hematological illnesses were unrelated to the granulomas. Amiodarone should be considered as a possible cause of bone marrow granulomas after the exclusion of other causes. Continued use of amiodarone after granuloma formation must be dictated by the underlying cardiac condition. *Am. J. Hematol.* 75:110–112, 2004. © 2004 Wiley-Liss, Inc.

Key words: amiodarone; bone marrow; granulomas

INTRODUCTION

Bone marrow granulomas are found in several settings, including mycobacterial and fungal infections, sarcoidosis and neoplasms. Drugs account for only 5% of cases [1]. We report 2 cases of bone marrow granulomas associated with amiodarone, a commonly used antiarrhythmic medication.

Patient 1

An 81-year-old man presented with a 4-year history of refractory anemia. The patient also had intractable atrial fibrillation, responsive only to amiodarone (200 mg/day for 2 years). His hemoglobin was 9.8 g/dl, hematocrit 30.3%, white blood count $4.95 \times 10^3/\mu\text{l}$, platelet count $166 \times 10^3/\mu\text{l}$, and reticulocyte count 0.9%. Red cells were normocytic and normochromic. Bone marrow biopsy revealed a normocellular marrow with 1% blasts, mild unilineage dyserythropoiesis, and scattered benign lymphoid aggregates. Numerous non-necrotizing granulomas were present (Fig. 1). Stains for acid-fast organisms and fungi were negative. The overall

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picture was consistent with myelodysplastic syndrome (refractory anemia). The patient was started on erythropoietin therapy with resolution of the anemia.

Chest radiographs and angiotensin-converting enzyme levels were normal. By exclusion, the bone marrow granulomas were attributed to amiodarone. In view of the patient's cardiac condition, amiodarone therapy was continued.

Patient 2

A 62-year-old man was found to have pancytopenia on routine investigations. He was being treated for non-sustained ventricular tachycardia with amiodarone

*Correspondence to: Surabhi Mukhopadhyay, M.D., SUNY Upstate Medical University, Department of Medicine, 750 East Adams Street, Syracuse, NY 13210. E-mail: mukhopsu@upstate.edu

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(200 mg/day for 2 years). Review of his hematological profile revealed that the onset of thrombocytopenia and leukopenia predated initiation of amiodarone therapy. His hemoglobin was 13.1 g/dl, hematocrit 36.9%, white blood count $3.6 \times 10^3/\mu\text{l}$, and platelet count $135 \times 10^3/\mu\text{l}$. Red cells were macrocytic and normochromic. Serum B₁₂ and folate levels were normal. Computed tomography revealed mild splenomegaly. Liver function tests and viral hepatitis markers were negative. Bone marrow biopsy showed a normocellular marrow with no increase in blasts. Multiple non-caseating granulomas were noted (Fig. 1), which were negative for acid-fast bacteria and fungi. The pancytopenia was attributed to hypersplenism, although the cause for splenomegaly was not evident. By exclusion, the bone marrow granulomas were attributed to amiodarone. In view of the history of ventricular tachycardia, amiodarone was not discontinued. Two years later, the patient's blood counts are stable.

DISCUSSION

Drugs are a rare cause of bone marrow granulomas. Only a few isolated reports exist in the literature [2]; the implicated drugs include ibuprofen (2 cases), phenytoin (2 cases), allopurinol (1 case), and sulfasalazine (1 case). In contrast, amiodarone is increasingly being recognized as a potential cause of bone marrow granulomas (6 cases) [3–6]. The dose of amiodarone in the cases reported so far ranged from 100 to 200 mg/day for 6–8 months. Granulomas were discovered incidentally in all 6 cases. The indications for bone marrow biopsy included myeloma, myelofibrosis, pyrexia of unknown origin, and thrombocytopenia. Follow-up bone marrow biopsies after discontinuation of amiodarone were performed in only three of these cases. All three showed reduction or disappearance of the granulomas, providing evidence that amiodarone was involved in their causation [3,4]. The clinical significance of amiodarone-induced bone marrow granulomas in the literature as well as in our cases is unclear. In the first case, anemia predated the institution of amiodarone. Whether the granulomas contributed to worsening of the anemia is a matter of speculation. In the second case, thrombocytopenia and leukopenia predated the use of amiodarone. No worsening of the blood counts was noted in spite of continuation of the drug over the next 2 years, indicating that amiodarone was not involved in the causation of pancytopenia in this patient.

Definitive proof of causation in cases of suspected drug-induced disease can be obtained by observing disappearance of disease on withdrawal of the drug followed by relapse on re-challenge with the drug. However, given the seriousness of the underlying con-

ditions for which amiodarone is administered, these maneuvers are neither medically advisable nor ethically sound. We therefore chose to continue the drug in both of our patients. Other authors have reported a similar approach to this vexing problem [6].

The pathogenesis of granuloma formation by amiodarone is unclear. Amiodarone inhibits phospholipases, leading to accumulation of phospholipids in several organs, most notably the liver and lung [7]. A similar mechanism may be applicable in the bone marrow, where granuloma formation may plausibly occur due to an immunological reaction to built-up lipid.

To summarize, amiodarone must be considered as a potential cause of bone marrow granulomas when more common causes have been excluded. Whether amiodarone-induced granulomas are an incidental finding or contribute to the main hematological illness remains unclear, although we favor the former hypothesis. Pending further addition to the scant literature on this subject, the continued use of amiodarone after granuloma formation must be dictated by the underlying cardiac condition.

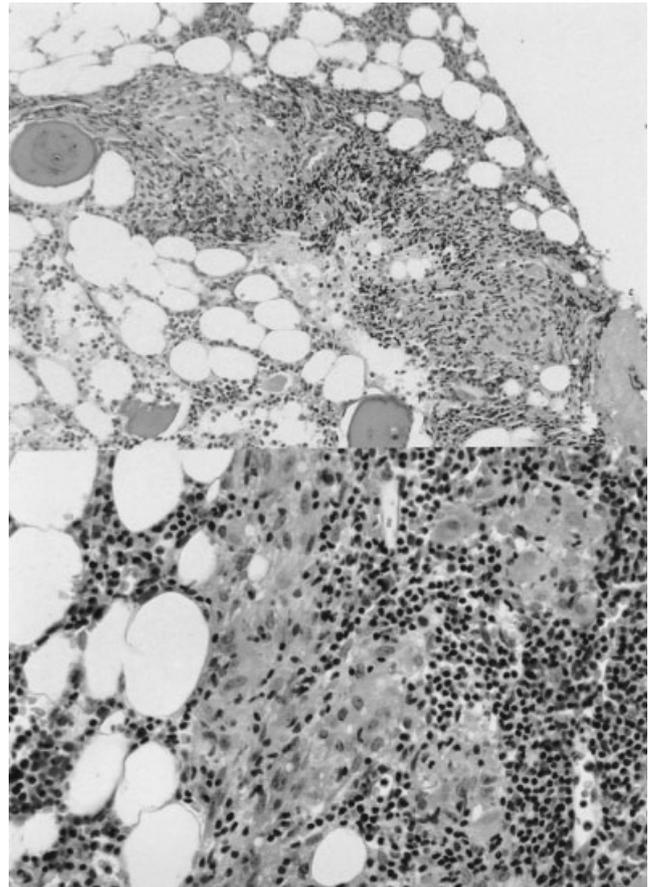


Fig. 1. (Top) Bone marrow biopsy of patient 1 showing non-caseating granulomas (original magnification 20 \times). (Bottom) High-power view of non-caseating granulomas in bone marrow of patient 2 (original magnification 40 \times).

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