Lenalidomide-Induced Acute Interstitial Nephritis

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Key Words. Kidney failure • Acute • Lenalidomide • Multiple myeloma

Disclosures: Evan J. Lipson: None; Carol Ann Huff: Consultant/advisory role: Celgene, Amgen; Research funding/contracted research: Geron, Bristol-Myers Squibb; Danniele G. Holanda: None; Michael A. McDevitt: None; Derek M. Fine: None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

INTRODUCTION

Acute renal failure (ARF) in patients with multiple myeloma and other plasma cell dyscrasias is common, though the etiologies are varied. We report a case of acute interstitial nephritis (AIN) likely related to lenalidomide. This case highlights an adverse effect of lenalidomide rarely reported. It also underscores the utility of a renal biopsy in patients with plasma cell dyscrasias and ARF when the cause of that azotemia could be from one of many factors.

CASE PRESENTATION

A 62-year-old white woman with multiple myeloma was admitted to the hospital with a creatinine level of 6.7 mg/dl.

Seven months prior to admission, she was diagnosed with international stage I (Durie-Salmon stage III) IgG- κ multiple myeloma when her serum IgG level measured 6,010 mg/dl, her calcium was 12.2 mg/dl, a serum protein electrophoresis revealed a monoclonal spike of 4.4 g/dl, and a bone marrow biopsy showed 30% κ -restricted plasma cells. At diagnosis, her β -2 microglobulin measured 2.59 mg/l, her albumin was

3.6 g/d, her blood urea nitrogen (BUN) was 15 mg/dl, and her creatinine was 0.7 mg/dl. A 24-hour urine analysis revealed 178.5 mg protein (M-spike, 101.1 mg) and immunofixation positivity for IgG- κ and κ light chains. Her serum κ was 134.6 g/dl, λ was 7.52 g/dl and κ/λ ratio was 17.9. She was given zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ), 4 mg i.v. every 2–3 weeks, and bortezomib (Velcade®; Millennium Pharmaceuticals, Inc., Cambridge, MA) dosed at 1.3 mg/m² i.v. on days 1, 4, 8, and 11 in 21-day cycles. Dexamethasone was not prescribed out of the patient's concern for hyperglycemia and weight gain. Two months later, the patient's creatinine level rose to 1.4 mg/dl. Bortezomib was discontinued after three cycles because of minimal response and the development of grade 1 peripheral neuropathy. Her creatinine level returned to 0.9 mg/dl without intervention. She continued to receive zoledronic acid every 2–3 weeks.

Three months prior to admission, lenalidomide (Revlimid®; Celgene Corporation, Warren, NJ) was initiated at 25 mg orally daily for 21 days with dexamethasone, 40 mg orally

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Figure 1. Lab values and medication doses.

days 1–4 and 15–18 every 28 days. The patient tolerated cycle 1 well. Concurrently, she received two doses of zoledronic acid. During this time, her creatinine level rose from 0.9 mg/dl to 1.2 mg/dl but returned to 1.0 mg/dl prior to cycle 2.

Two weeks into the second cycle of lenalidomide and dexamethasone, the patient experienced fatigue, anorexia, mild diarrhea, and worsening of pre-existing vitiligo. Labs showed a serum creatinine level of 2.1 mg/dl and serum potassium level of 2.4 mEq/l. Lenalidomide was discontinued. It was restarted at a lower dose (15 mg/day $\times$ 3 weeks) after improvement in her creatinine level to 1.3 mg/dl. Zoledronic acid administration was decreased to every 4 weeks. One week after restarting lenalidomide at the lower dose, her renal function was preserved with a creatinine level of 1.2 mg/dl. Two weeks later, however, her creatinine level had risen to 6.7 mg/dl (Fig. 1).

She was admitted to the hospital. She reported mild rhinorrhea, oliguria, and back pain in the days leading up to admission and had taken one 800-mg dose of ibuprofen. There had been no change in her other medications.

On examination, her temperature was 36.7°C, heart rate was 56 beats per minute, blood pressure was 144/71 mmHg, and oxygen saturation was 95% on room air. A head, eye, ear, nose, and throat exam showed perioral vitiligo. Examination of the heart, lungs and abdomen was unremarkable. She had no rash and no costovertebral angle tenderness.

Labs revealed a WBC of 5,250 cells/mm³, hematocrit of 26.6%, and platelet count of 249,000 cells/mm³. A differential showed 3% eosinophils. An extended metabolic panel was normal, with the exception of a creatinine level of 6.7 mg/dl, CO₂ of 18 mEq/l, and BUN of 41 mg/dl. Her urine was hazy, with a specific gravity of 1.005, pH of 5.0, 1+ protein, no glucose, bilirubin, or ketones present, trace hemoglobin pigments, negative leukocyte esterase, negative nitrite, one RBC per high power field (hpf), four WB cells/hpf, and no epithelial cells. A renal ultrasound showed echogenic kidneys compatible with renal parenchymal disease. No hydronephrosis was seen. A chest x-ray was clear. Her serum M protein declined from 3.4 g/dl prior to lenalidomide and dexamethasone to 1.06 g/dl after two cycles of treatment. A 24-hour urine analysis showed 640 mg protein with an M spike of 33 mg/dl. Her serum κ was 92.5 mg/l, λ was 24.1 mg/l, and κ/λ ratio was 3.84.

Lenalidomide was discontinued. A renal biopsy was performed and it was consistent with acute and early chronic drug-induced interstitial nephritis (Fig. 2).

The patient was treated with a steroid taper. Over the next 4 months her serum creatinine level returned to 1.2 mg/dl.

DISCUSSION

We present what is perhaps the first case of biopsy-proven lenalidomide-induced AIN. Although determining a cause of renal failure is often not straightforward, many elements

Figure 2. Renal biopsy consistent with acute and early chronic drug-induced interstitial nephritis. **(A):** A mixed interstitial infiltrate of lymphoplasmacytic cells, predominantly eosinophils. Moderate tubular injury was also noted, with tubular cell swelling, vacuolization, focal simplification of tubules with bland casts, and reactive and regenerative changes. (Masson Trichrome; 160 $\times$) **(B):** Interstitial nephritis with eosinophils in the medullary parenchyma. (H&E; 64 $\times$)

in this case point to lenalidomide as the major contributor. First, the time course of the patient's renal failure and subsequent improvement in kidney function along with the results of her renal biopsy are most consistent with a drug reaction. Possible offending agents included lenalidomide, zoledronic acid, and ibuprofen [1].

Zoledronic acid is a known nephrotoxin [2–5]. However, the mechanism of ARF associated with zoledronic acid is reported as tubular necrosis, not interstitial nephritis. Additionally, our patient had received multiple doses of zoledronic acid, both alone and in combination with other therapy, in the months leading up to her admission and had not experienced any ill effects. Although zoledronic acid (and hypercalcemia) may have contributed to her mild fluctuations in creatinine, it likely does not explain her severe renal impairment.

While ibuprofen is a well-known cause of interstitial nephritis, our patient had only taken one dose immediately prior to admission. Moreover, she had used ibuprofen in the preceding months without problems, making this an unlikely cause of her renal failure.

Lenalidomide possesses immunomodulatory properties. The timing of our patient's renal failure—during the second and third cycles of lenalidomide—argues for an immune-based reaction. We postulate that, during the first cycle of lenalidomide, the patient's immune system was “primed” for activity against the drug. It was then reactivated during the second cycle. This pattern of a more rapid and fulminant course of renal failure is well described in AIN resulting from drug exposures [6]. Intriguingly, the precise mechanism of action of lenalidomide remains unknown, but in patients with multiple myeloma and myelodysplastic syndrome treated with lenalidomide, significant T-cell activation and immune stimulation have been ob-

served and are thought to be part of the antitumor effects [7–10].

Another point that this case illustrates nicely is the utility of a renal biopsy. Initially, our suspicion was that the patient was suffering from “myeloma kidney.” She had no rash or fever, her peripheral eosinophil count was normal, and her admission urinalysis was relatively unremarkable. Though these are considered “classic” features of interstitial nephritis, it is important to note that the absence of these features is well described in AIN [11]. Therefore, AIN should always remain in the differential diagnosis of ARF in the presence of new or ongoing drug therapy. Only after her biopsy did it become clear that her treatment, not her disease, was responsible for her ARF. This changed our management considerably, because the patient received glucocorticoids and is no longer receiving lenalidomide.

Overall, the rarity of reports of lenalidomide-induced renal failure may indicate that a combination of factors may be necessary for toxicity, including a predisposition to AIN, underlying kidney damage from myeloma proteins, concomitant use of bisphosphonates, and some level of nonsteroidal anti-inflammatory drug use. Further study and observation are necessary to assess these potential confounders.

AUTHOR CONTRIBUTIONS

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