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A case of DRESS (drug reaction with eosinophilia and systemic symptoms) with acute interstitial nephritis secondary to lenalidomide

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Abstract

Acute kidney injury is commonly observed in patients with multiple myeloma and other plasma cell dyscrasias. The pathophysiologic causes, however, are varied. We report a case of a severe 'drug reaction with eosinophilia and systemic symptoms' syndrome associated with acute interstitial nephritis in a patient with multiple myeloma likely related to the administration of lenalidomide. This disease entity requires prompt recognition and cessation of the offending drug and often treatment with high-dose corticosteroids.

Keywords

Lenalidomide, drug reaction, nephritis

Introduction

Lenalidomide is an immunomodulatory drug that is currently being increasingly utilized for the treatment of patients with a variety of hematologic disorders including relapsed or refractory multiple myeloma (MM), and low or intermediate risk myelodysplastic syndromes (MDS).^{1,2} The drug is typically administered orally, 25 mg/day (MM) or 10 mg/day (MDS), on days 1 through 21 in repeated 28-day cycles (combined with dexamethasone for MM). There is sparse information in the medical literature reporting an association between AIN and this medication. This is, to our knowledge, the first case report of a severe drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome related most likely to lenalidomide use.

Case report

A 65-year-old woman with MM was admitted to our hospital for evaluation and management of AKI with a creatinine level of 8.1 mg/dl. She complained of a one-week history of progressive pruritic erythematous rash, dry cough and two days of episodic high fevers.

Three months prior to admission, she was diagnosed with Durie-Salmon stage III IgG-kappa MM when her calcium was 13 mg/dl, a serum protein electrophoresis (SPEP) revealed a monoclonal spike of 5 g/dl, and a bone marrow biopsy showed 45% kappa-restricted plasma cells. At diagnosis, her beta-2 microglobulin measured 3.6 mg/l, her albumin was 3.2 g/dl, her blood urea nitrogen (BUN) was 13 mg/dl, and her creatinine was 1.0 mg/dl. A 24-h urine analysis revealed 208.5 mg protein (M-spike, 95.1 mg) and immunofixation positivity for IgG-kappa and kappa light chains. For the first cycle, she was given bortezomib, which was dosed at 1.3 mg/m² intravenously (IV) on days 1, 4, 8, and 11 in 21-day cycles. Dexamethasone was also administered at a dose of 40 mg/day once a week. Her creatinine level after the first cycle was 0.9 mg/dl. She started to complain of tingling and numbness in upper and lower extremities which was attributed to the

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bortezomib therapy. A decision was made to switch her therapy to lenalidomide and dexamethasone.

She started her first cycle of her new regimen and this time lenalidomide was initiated at 25 mg orally daily for D1–D14 (bortezomib was omitted) in addition to her prior dosing regimen of dexamethasone. The patient tolerated the cycle well. Two weeks into the second cycle of lenalidomide and dexamethasone, the patient started to experience fatigue, anorexia and diffuse pruritic erythematous rash. Laboratory tests showed a serum creatinine level of 8.1 mg/dl and serum potassium level of 5.0 mEq/l. Chemotherapy was discontinued and she was immediately admitted to the hospital. She also reported oliguria. She was not on any other medications at the time. On examination, her temperature was 101.7°F, heart rate was 75 beats per minute, blood pressure was 100/71 mmHg, and oxygen saturation was 95% on room air. A head, eye, ear, nose, and throat examination showed palpable bilateral cervical and axillary lymphadenopathy. Examination of the heart, lungs and abdomen was unremarkable. She had a severe erythematous macular rash involving her face and trunk without any mucous membrane involvement. Laboratory tests revealed a white blood cell (WBC) of 12,500 cells/microliter (mcL), hematocrit of 28%, and platelet count of 375,000 cells/mm³. A differential showed 8% eosinophils (1000 cells/mcL). An extended metabolic panel was normal, with the exception of mild transaminitis aspartate aminotransferase (AST) 200 U/L, alanine aminotransferase (ALT) 163 U/L, lactate dehydrogenase (LDH) level of 400 U/L, creatinine level of 8.1 mg/dl with estimated glomerular filtration rate (eGFR) of 6 mL/min/1.73 m², serum phosphate (7 mg/dl), serum bicarbonate (CO₂) of 15 mEq/l, and BUN of 50 mg/dl. Her serum calcium (9 mg/dl) and serum uric acid (4 mg/dl) were unremarkable. Antinuclear antibody testing and viral polymerase chain reaction testing for Hepatitis A, B and C, Human Herpes Virus-6 and 7, Epstein-Barr virus and Cytomegalovirus were all negative. Blood cultures including cultures for Chlamydia and Mycoplasma species were also negative. Her urine analysis revealed eosinophiluria and WBC casts. A renal ultrasound showed normal sized kidneys without any evidence of parenchymal disease. A chest X-ray was clear. Urine cultures were negative. A renal ultrasound and a computed tomography (CT) scan of the abdomen without intravenous contrast were negative for any pathology. A skin biopsy of the rash revealed a mild perivascular lymphocytic infiltrate, consistent with a medication-induced hypersensitivity reaction. A renal biopsy was also done that revealed a lymphocytic infiltrate in the peritubular areas of the interstitium confirming the diagnosis of interstitial nephritis. There was no evidence of myeloma involvement in the kidney biopsy.

In light of the clinical presentation, the patient was diagnosed with DRESS with acute interstitial nephritis. During the hospitalization, the patient became delirious. The CT of the head was negative. The altered mental status was attributed to uremic encephalopathy. The patient was emergently dialysed. She was also given hydrocortisone 40 mg IV every 8 h for two days followed by prednisone 80 mg PO daily. Three days later, her rash and mental status started to gradually improve. Her renal function was better and the creatinine level decreased to 3 mg/dl. In light of clinical improvement with steroids, the nephrologist stopped the dialysis treatments. On day 8 of hospitalization, her clinical condition was dramatically better and her renal function had completely normalised. Serum creatinine performed a week later was 1.2 mg/dl.

One month later, she resumed her treatment for MM with subcutaneous bortezomib and dexamethasone and has so far tolerated two cycles of this therapy without any clinical adverse events.

Discussion

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic hypersensitivity response characterized by a maculopapular erythematous eruption that typically develops 2–6 weeks following initiation of the culprit drug.³ The classical findings include fever, lymphadenopathy, multisystem organ failure and eosinophilia or atypical lymphocytosis. The term DRESS was first introduced in 1996 by Bocquet et al.⁴ This is the first case report of DRESS syndrome with multiple organ systems affected, including skin, hematological, liver, brain and kidneys secondary to lenalidomide. Foti et al. reported a similar case report of HHV-6 associated DRESS induced by lenalidomide.⁵

In our patient, there was no evidence of HHV-6 reactivation as confirmed by undetectable viral copies of the virus and it is most likely that lenalidomide was the sole major offending agent. It is unlikely that bortezomib was the offender because she tolerated her 1st cycle well and she was clinically stable with normal renal function until lenalidomide was introduced into her regimen three weeks later. Moreover, when she was re-challenged with bortezomib, she did not experience any side effects. The time course of the patient's renal failure and subsequent improvement in kidney function after elimination of the culprit drug are most consistent with a severe drug reaction secondary to lenalidomide.

More interestingly, the precise mechanism of action of lenalidomide remains unknown, but in patients with MM and myelodysplastic syndrome treated with lenalidomide, significant T-cell activation and immune stimulation have been observed and are thought to be

part of the antitumor effects.⁶ This may also be the pathophysiologic explanation for this severe hyper-immune drug-induced hypersensitivity syndrome that was witnessed in our patient.

Recognizing patients with this syndrome is imperative, as mortality approaches 10%.⁷ The main treatment of this disease entity is to immediately and strictly stop the administration of the offending drug(s). Supportive care with symptomatic treatment using H1 and H2 receptor antagonists and systemic corticosteroids are necessary when internal organ involvement is present.⁸

Conclusion

We report a case DRESS syndrome with AIN that occurred during the first course of lenalidomide therapy for multiple myeloma. It appears to be a reversible condition as long as the culprit drug is discontinued in a timely and immediate fashion. Health care professionals including oncologists, pharmacists, etc. should all be made aware of this potential association given the increased frequency of lenalidomide usage. Recognition of this condition will result in early detection which will result in early treatment and management.

Conflict of interests

The authors report that they do not have any conflict of interests.

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