Reversible Fanconi syndrome due to lenalidomide

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Case report

The patient is a 69-year-old male who presented to the emergency department complaining of severe fatigue and weakness. He had a history of IgG λ MM diagnosed ~2.5 years ago after presenting with back pain and was found to have vertebral metastases. A bone marrow exam revealed marked interstitial monoclonal λ plasma cell infiltrate. The patient was initially treated with radiation to his spine, followed by a course of thalidomide and dexamethasone. He developed steroid-induced myopathy and his chemotherapy was changed to bortezomib. He also developed fatigue and vomiting on this medication and was noted to have rising free serum λ chains. His regimen was changed to doxorubicin, carmustine, cyclophosphamide and melphalan. He received two cycles but had progression of disease with rising λ chains and prolonged thrombocytopenia. Subsequently, he failed the stem cell collection and was deemed poor candidate for high-dose stem cell transplantation. He was started on oral cyclophosphamide and prednisone and was able to tolerate this therapy well with stable light chain disease for ~1 year. He was given a brief chemotherapy holiday but was started on lenalidomide 15 mg daily once his serum λ chains began to rise. At the time lenalidomide was initiated the patient’s serum creatinine was stable at 1.7 mg/dl (0.6–1.3 mg/dl), free serum λ chains 28.5 mg/dl (0.57–2.63 mg/dl). Of note, the patient was also receiving monthly zoledronic acid for treatment of bone disease for 26 months. Three weeks after lenalidomide was started the patient presented to the hospital with fatigue, weakness, orthostatic symptoms, thirst and polyuria. His upright and supine blood pressures were 83/45 and 110/79, respectively. The laboratory data revealed acute renal failure, hypernatremia, hypokalemia, hypophosphatemia, hyperuricemia and metabolic acidosis with serum pH of 7.29 and anion gap of 7 (Table 1). The serum λ light chains were 5.76 mg/dl. Urinalysis showed pH of 7.0 and glucosuria with normal serum glucose level. Twenty-four hour urine collection revealed 1.8 g of protein. Urine osmolality was 128 mOsm/kg. The patient’s urine output was noted to be 6.1 l in the first 24 h after admission. Fractional excretion of sodium was 4.33% and fractional excretion of phosphate was 65.5%. Twenty-four hour potassium excretion was calculated to be 70 mEq. He underwent...
Table 1. Laboratory data

| Variables                  | Treatment with lenalidomide started | At presentation | Two months after discontinuation of lenalidomide | Normal values |
|----------------------------|-------------------------------------|-----------------|-------------------------------------------------|---------------|
| Free λ light chains (mg/dl)| 28.5                                | 5.76            | 33.25                                           | 0.57–2.63     |
| Serum sodium (mEq/l)       | 141                                 | 147             | 142                                             | 136–144       |
| Serum potassium (mEq/l)    | 3.6                                 | 2.7             | 4.4                                             | 3.5–5.1       |
| Serum bicarbonate (mg/dl)  | 2.4a                                | 0.8             | 3.4                                             | 2.5–4.2       |
| Serum uric acid (mg/dl)    | 1.9b                                | 1               | 2                                               | 3.8–8.5       |
| Serum creatinine (mg/dl)   | 1.7                                 | 2.7             | 2                                               | 0.6–1.3       |
| Serum glucose (mg/dl)      | 107b                                | 89              | 95                                              | 70–99         |
| Urinary glucose (mg/dl)    | Negativeb                           | 100             | Negative                                        | Negative      |

aValue was obtained 7 months prior to the initiation of lenalidomide.
bValue was obtained 8 months prior to the initiation of lenalidomide.

hydration with aggressive electrolyte and bicarbonate supplementation. His electrolyte abnormalities improved and urine output decreased over the next several days. He was discharged home 12 days after admission but required oral potassium, phosphorus and bicarbonate supplementation. At two-month follow-up, he was able to discontinue oral supplementation as the electrolyte abnormalities resolved. His renal function improved and the glucosuria also resolved (Table 1). However, his serum λ light chains started to rise (Table 1).

Discussion

To date, no cases implicating lenalidomide as a causative agent of FS have been reported.

Our patient exhibited cardinal features of the FS. He had evidence of severe proximal dysfunction with glucosuria, despite normal serum glucose level, urinary phosphate wasting with high fractional excretion of phosphate in the setting of hypophosphatemia and renal sodium, and potassium wasting. The patient also had impaired bicarbonate reabsorption manifesting as non-anion gap metabolic acidosis with high urinary pH. Concentrating defect was also present with polyuria and low urinary osmolality resulting in hypernatremia due to free water loss. The apparent diabetes insipidus was likely nephrogenic and resulted from severe hypokalemia which causes decreased responsiveness of collecting duct to antidiuretic hormone [6,7].

The causal relationship between the lenalidomide and development of FS in our patient is very likely. There is strong temporal association between initiation of lenalidomide and development of FS. In addition, FS had resolved several weeks after the discontinuation of the agent.

While FS is a well-established complication of MM, 96% of MM causing FS occurs in setting of κ light chain disease [3]. Monoclonal light chains are incompletely digested in lysosomes of proximal tubules and serve as nidus of crystal formation which in turn causes renal injury by interfering with apical membrane transporters [3,8].

Our patient exhibited partial response to the lenalidomide with evidence of significant decline in serum free λ light chain counts (Table 1). Given that our patient had λ light chain disease and that he had diminished tumor burden probably resulting in lesser amount of toxic light chains delivered to proximal tubes we postulate that MM is a less likely cause of Fanconi syndrome in our patient.

Acquired FS has been reported as a side effect of many medications. Among the anti-cancer agents ifosfamide is the most frequent offender. The ifosfamide-induced FS is more common in children and is frequently reversible, though chronic renal damage with persistent electrolyte abnormalities has been reported [2]. Pamidronate, a bisphosphonate used for treatment of metastatic bone disease, has also been reported to cause FS [9]. Our patient received zoledronic acid. Although also a bisphosphonate, it has not been reported as a causative agent of FS.

In conclusion, we report the first case of lenalidomide-induced FS. As lenalidomide is gaining a wider role in the treatment of MM and other hematologic malignancies, it is important to be aware of FS as a potential complication of the therapy. Recognizing FS may be difficult in this patient population as symptoms of FS such as generalized weakness, fatigue and bone or back pain may be attributed to MM itself. Discontinuation of the offending drug appears to lead to relatively rapid resolution of the syndrome. Partial or complete oncologic remission and λ light chain disease may help to exclude MM as a cause of FS.

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Conflict of Interest Statement. None declared.

References
1. Korbet SM and Schwartz MM. Multiple myeloma. J Am Soc Nephrol 2006; 17: 2533–2545
2. Izzedine H et al. Drug-induced Fanconi’s syndrome. Am J Kidney Dis 2003; 41: 292–309
3. Lacy MQ and Gertz MA. Acquired Fanconi’s syndrome associated with monoclonal gammopathies. Hematol Oncol Clin North Am 1999; 13: 1273–1280
4. Richardson PG et al. New drugs for myeloma. Oncologist 2007; 12: 664–689
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5. Rao KV. Lenalidomide in the treatment of multiple myeloma. *Am J Health Syst Pharm* 2007; 64: 1799–1807

6. Hoorn EJ and Zietse R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat Clin Pract Nephrol* 2007; 3: 171–175

7. Sands JM and Bichet DG. Nephrogenic diabetes insipidus. *Ann Intern Med* 2006; 144: 186–194

8. Messiaen T et al. Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. *Medicine (Baltimore)* 2000; 79: 135–154

9. Buysschaert M et al. Pamidronate-induced tubulointerstitial nephritis with Fanconi syndrome in a patient with primary hyperparathyroidism. *Nephrol Dial Transplant* 2003; 18: 826–829

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