To the editor:

Lenalidomide-induced diarrhea in patients with myeloma is caused by bile acid malabsorption that responds to treatment

There is an expanding armory of novel chemotherapeutic agents used in hematologic cancers, many of which cause problematic gastrointestinal (GI) side effects. These often mandate dose reduction or even cessation of treatment. Few studies have investigated the causes for this GI toxicity. At our institution, a gastroenterology-led multidisciplinary clinic offers patients with symptoms arising during/after cancer therapies review, investigation, and treatment using a detailed peer-reviewed algorithm.[1] This approach has identified and characterized a treatable physiological cause for GI toxicity from a chemotherapeutic or biological agent: namely, lenalidomide, a novel treatment of myeloma.

There is increasing evidence for the use of the immunomodulatory agent lenalidomide to treat myeloma for all disease stages. Continuous treatment until relapse is associated with longer progression-free survival and overall survival[2-5] but requires patients to remain on therapy long-term, and therefore optimal management of side effects is essential. Common toxicities include cytopenia, rash, and GI issues including diarrhea.[6] Diarrhea can severely impact quality of life and may lead to unnecessary discontinuation of therapy if not managed appropriately. Anecdotal reports suggest these patients might benefit from dietary modifications and/or bile acid sequestrants, but this has not been previously systematically investigated and diagnosed.

We report 12 consecutive patients (Table 1) referred to our clinic between April 2011 and November 2013 who developed progressive GI symptoms after starting lenalidomide. There was no significant difference in the symptom severity between patients taking different doses of lenalidomide (mean Bristol Stool Chart score: 25 mg group 6.6 vs 10-15 mg group 6.8, Student *t* test $P = .45$; mean frequency: 25 mg group 6.6 per day vs 10 mg group 4.9 per day, Student *t* test $P = .24$). For patients with preexisting erratic bowel function, patients' symptoms had deteriorated significantly with lenalidomide treatment leading to their referral.

Table 1. Patient characteristics

	Number of patients
Sex	
Male	5 (42%)
Female	7 (58%)
Age, median (range), y	66 (48-79)
Background bowel function	
Normal	5 (42%)
Lifelong intermittent loose stool	3 (25%)
Other GI history (not diarrhea)	4 (33%)
Time to deterioration of bowel function following lenalidomide commencement, median (range), mo	6 (1-15)
Dose of lenalidomide	
25 mg	5 (41%)
10-15 mg	7 (58%)
Symptoms	
Diarrhea*	12 (100%)
Urgency	11 (92%)
Fecal incontinence	7 (58%)
Abdominal cramps	5 (42%)

Data are presented as n (%) of patients unless indicated otherwise.

*Defined by Bristol Stool Chart (BSC) score 6 or 7. Median stool frequency: 6 episodes per day (range, 1-10).

All patients underwent investigations to exclude the presence of lactose intolerance, GI infection, dietary indiscretion, celiac disease, inflammatory bowel disease, colonic neoplasia, small intestinal bacterial overgrowth, pancreatic insufficiency, and bile acid malabsorption (BAM). A positive glucose hydrogen methane breath test result suggested possible bacterial overgrowth in 75% of patients, but the diarrhea did not respond to antibiotics.

^{75}Selenium homocholic acid taurine (SeHCAT) scanning is a noninvasive test for BAM with sensitivity of 90% to 98% and specificity of 100%.[7,8] It confirmed severe (<5% 7-day SeHCAT-retention) BAM in 9 patients, moderate (5% to 10%) BAM in 2 patients, and mild (10% to 15%) BAM in 1 patient. One patient had undergone SeHCAT scanning 2 years previously (43% retention) but after starting treatment with lenalidomide developed worsening diarrhea, and repeat scanning suggested lenalidomide-induced severe BAM (3% retention).

Following the diagnosis of BAM, patients were advised to reduce dietary fat intake (to 20% of total calories) or treated with colesevelam, a bile acid sequestrant, or both.[9] Two patients had resolution of diarrhea with a low-fat diet alone. Ten patients were given colesevelam (up to 6 × 625 mg in split doses with food, >4 hours before/after lenalidomide and other dose-critical medications). A total of 50% of patients reported bowel habit normalized, and the others reported a reduction in stool frequency and/or improvement in stool consistency. This response confirmed BAM as the cause of the diarrhea. No patient needed dose reduction or cessation of lenalidomide due to diarrhea.

We recommend that BAM should be considered as a cause of diarrhea in patients taking lenalidomide. Where appropriate, investigations for BAM should be carried out and a trial of bile acid sequestrant therapy initiated. In addition to improving symptoms and quality of life, this enables patients to continue on long-term treatment. Multicenter studies with large numbers of patients would enable further characterization of this side effect, and associated translational studies should be carried out to investigate the molecular mechanism whereby lenalidomide causes BAM. In addition, this case series emphasizes the importance of systematic investigation of GI toxicity of cancer treatments by an experienced gastroenterologist, as currently reversible causes are often missed.[10]

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