CLINICAL PROBLEM SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Flipping the Switch

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In this Journal *feature, information about a real patient is presented in stages boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader regular type). The authors' commentary follows.*

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A 43-year-old woman presented to the primary care clinic with a 1-week history of dysuria and lower abdominal pressure. She reported no fevers, hematuria, or flank pain. She had reported similar symptoms several times over the previous 2 years in a different health care system. Each episode had been diagnosed as a urinary tract infection (UTI) with confirmation by culture (all cultures grew either *Escherichia coli* or *Enterococcus faecalis*) and had resolved after antimicrobial treatment.

The symptoms, culture data, and response to antibiotic agents are compatible with cystitis. Conditions with symptoms similar to those of UTIs include sexually transmitted infections (urethritis), vaginitis, and interstitial cystitis. Recurrent infections raise the question of reinfection or persistence. A recurrent or insufficiently eradicated infection should prompt clinicians to consider whether they are contending with the wrong diagnosis, wrong pathogen, wrong drug, or inadequate source control. The first three variables (e.g., diagnosis, microorganism, and antimicrobial agent) have been verified on the basis of culture data and treatment response. The patient may have an impaired immune system or may have an anatomical nidus (e.g., stone, cancer, or diverticulum) or physiological dysfunction (e.g., urinary stasis) that increases susceptibility to infections or makes complete eradication of infection challenging.

The patient's medical history included severe obesity that had been treated with a biliopancreatic diversion with a duodenal switch procedure 20 years earlier, nephrolithiasis (visualized on computed tomographic [CT] urography, with calcium phosphate and calcium oxalate stones identified on stone analysis), and iron-deficiency anemia. The patient was premenopausal. She had previously been treated with intravenous ferric gluconate infusions but had not received infusions in the past 6 months. Her only medication was a transdermal multivitamin patch; she preferred not to take supplements in pill form. She reported no tobacco smoking or illicit drug use. She drank alcohol twice a year. Her only international travel was a weeklong cruise to Jamaica several years earlier. She worked in an office. She was sexually active with one male partner.

Her temperature was 36.7°C, blood pressure 98/72 mm Hg, heart rate 73 beats per minute, respiratory rate 14 breaths per minute, and oxygen saturation 100 while she was breathing ambient air. The body weight was 68.2 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 27.6. There was mild tenderness in the suprapubic region and no costovertebral-angle

tenderness. The remainder of the physical examination was normal.

Her white-cell count was 10,300 per cubic millimeter, hemoglobin level 9.6 g per deciliter (unchanged from a recent value), and platelet count 190,000 per cubic millimeter. The mean corpuscular volume was 104 fl. The serum creatinine level was 0.8 mg per deciliter (70 μmol per liter), and the potassium level was 3.2 mmol per liter. Serum sodium, chloride, bicarbonate, and glucose levels were in the normal ranges. The serum albumin level was 3.4 g per deciliter. The serum ferritin level was 70 ng per milliliter (normal range, 7 to 271). Urinary dipstick analysis was positive for nitrites and leukocyte esterase; the urine pH was 6.0. Urine culture grew more than 100,000 colony-forming units of *E coli*. Her symptoms resolved with a 7-day course of cefuroxime.

There is no history of neurologic diseases or diabetes mellitus, which could predispose the patient to autonomic dysfunction and urinary retention. She has no history of infections to suggest a primary immunodeficiency or conditions associated with immunosuppression, such as cirrhosis. It is possible that her bariatric surgery could have caused malnutrition, owing to limited intake or malabsorption and associated micronutrient deficiencies, which could contribute to immunodeficiency; malnutrition may be overlooked when the body-mass index is normal or elevated. A CT scan would be helpful in determining whether nephrolithiasis is contributing to her recurrent infections.

The patient had additional UTIs caused by *E coli* and *E faecalis*. One year after her index primary care visit, CT urography revealed urothelial thickening and mild dilatation of the left renal collecting system and ureter with nonenhancing debris involving the majority of the left renal calyces (Fig. 1). Kidney size was normal. There was no perinephric fat stranding, bladder-wall thickening, or stones. Flexible ureteroscopy revealed pale, sloughing mucosa with patchy white plaques throughout both renal pelvicalyceal systems, with a greater plaque burden on the left side than on the right side (Video 1). During ureteroscopic biopsy of the left pelvicalyceal urothelium, scant fragments of keratinaceous debris were obtained, but there was insufficient tissue for further studies. The bladder urothelium was normal.

The CT urogram and ureteroscopic results showed an abnormal urothelium that could be the anatomical substrate for persistent or recurrent infection. Previous nephrolithiasis or bacterial UTIs could contribute to mucosal injury but are unlikely to cause diffuse urothelial damage. Tuberculosis or fungal infection is conceivable, although there are no risk factors (such as immunocompromise, travel, or preexisting structural urinary tract disease) and no other obvious foci (on the basis of symptoms and abdominal imaging) of these indolent infections. Squamous-cell carcinoma is also a consideration, although urothelial tumors typically arise in older patients and are associated with cigarette smoking or chemical exposures.

Bacterial and fungal cultures and cytologic testing of aspirated samples (from the left renal pelvis) and clean-catch urine samples were negative. Blastomyces antigen testing and nucleic acid amplification testing for *Neisseria gonorrhea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*, assessed in urine, were also negative. Polymerase-chain-reaction testing for *Ureaplasma parvum* in urine was positive. Serum testing for rapid plasma reagin and an interferon gamma

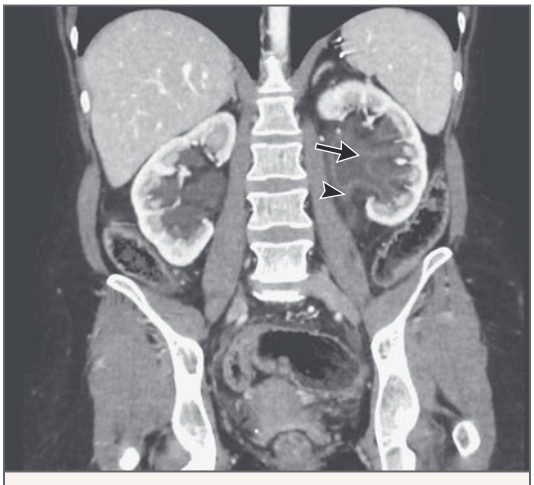

Figure 1. Urothelial Thickening and Enhancement of a Dilated Left Renal Collecting System and Upper Ureter.
A CT image that was obtained in the coronal view with the use of contrast material showed urothelial thickening and enhancement of a dilated left renal collecting system arrow) and upper ureter arrowhead). There was also urothelial thickening and edema on the right side. The right kidney contained multiple parapelvic cysts.

A video showing endoscopic evaluation of renal pelvicalyceal systems is available at NEJM org

release assay were negative, as were serologic tests for blastomyces, histoplasma, coccidioides, and schistosoma. Levels of IgG4, IgA, IgG, and IgM were normal. Testing for the human immunodeficiency virus was not done. Mycobacterial cultures of the urine were negative. The patient continued to have UTIs caused by *E coli* and *E faecalis*.

Given that two common bacterial uropathogens have been identified, I suspect that ureaplasma is a background commensal organism rather than a pathogen. The other results suggest that fungi, mycobacteria, and common sexually transmitted pathogens are not contributors to the urothelial abnormalities.

Percutaneous nephroscopy that was performed 7 months after the flexible ureteroscopy revealed white, pale, sloughing mucosa in the urothelial tract, which was débrided (Fig. 2). Histopathological assessment of a urothelial-biopsy sample showed extensive keratinizing squamous metaplasia (Fig. 3).

Squamous metaplasia of the urothelium usually arises from chronic infection (e.g., schistosomiasis) or mechanical irritation (e.g., a long-term indwelling urinary catheter). If the urothelium is replaced by keratinizing squamous cells that are then shed into the urine, the condition is called keratinizing desquamative squamous metaplasia. It is possible that the combined insults of repeated nephrolithiasis (preceding the current evaluation) and bacterial infection contributed to metaplasia in the renal collecting system. An alternative hypothesis is that the sloughing mucosa is the structural abnormality that has conferred a predisposition to stones or infections. Squamous metaplasia confers an increased risk of dysplasia and squamous-cell carcinoma in other tissues (e.g., the respiratory tract and cervix), but neither was identified in this more extensive biopsy specimen.

Urine samples were sent to a specialized laboratory. *U parvum* was grown on culture. The patient was treated with a prolonged course of doxycycline after the confirmation of antimicrobial susceptibility. Despite this therapy, she had additional symptomatic UTIs caused by *E coli*. A repeat ureteroscopy 5 months after the percutaneous nephroscopy revealed persistent extensive white plaques.

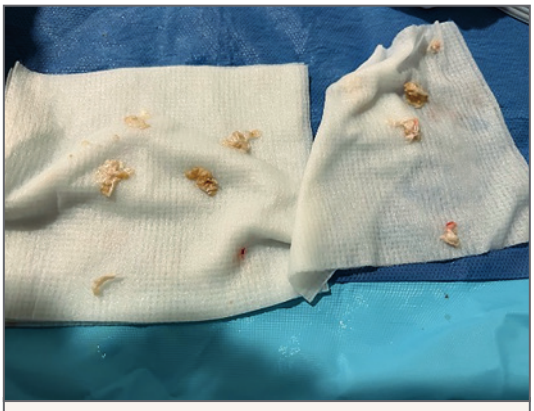

Figure 2. Gross Appearance of White Plaques Débrided from the Left Pelvicalyceal System during Nephroscopy.

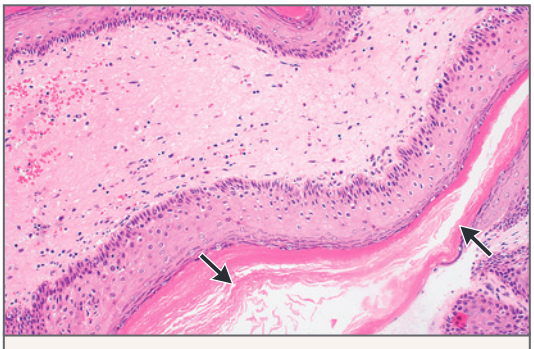

Figure 3. Histopathological Sample from the Left Renal Collecting System.

A histopathological assessment of a biopsy sample obtained from the left renal collecting system showed extensively keratinizing squamous metaplasia (arrows; hematoxylin and eosin staining).

The only definitive histologic finding to date is keratinizing squamous metaplasia. In the absence of a causative long-standing irritant or infection in the urinary tract, a primary epithelial abnormality warrants further consideration. Vitamin A has an essential role in epithelial integrity. Vitamin A deficiency causes squamous metaplasia in ocular, respiratory, and skin epithelial tissues. The patient's bariatric surgery may have led to vitamin A malabsorption that is insufficiently addressed by the transdermal vitamin patch.

Serum levels of copper, selenium, vitamin B_{12}, and

folic acid were normal. The serum zinc level was 51 μg per deciliter (7.8 μmol per liter; normal range, 55 to 150 μg per deciliter [8.4 to 23.0 μmol per liter]), the 25-hydroxyvitamin D level was 9 ng per milliliter (normal range, 30 to 100), the vitamin E level was less than 0.2 mg per deciliter (5 μmol per liter; normal range, 0.55 to 1.70 mg per deciliter [13 to 39 μmol per liter]), and the vitamin A level was less than 10 μg per deciliter (0.35 μmol per liter; normal range, 10 to 50 μg per deciliter [0.35 to 1.75 μmol per liter]).

On further questioning after the diagnosis of vitamin A deficiency, the patient reported problems with driving at night owing to difficulty seeing in the dark. She did not undergo a formal ophthalmologic assessment. She reported no pruritus, skin dryness, abdominal pain, or steatorrhea, and no abnormalities on skin examination were noted after the diagnosis.

There are deficiencies of multiple fat-soluble vitamins, presumably caused by postsurgical gastrointestinal malabsorption and insufficient supplementation. Severe vitamin A deficiency causing desquamative urothelial squamous metaplasia and resultant debris in the collecting system probably predisposed the patient to recurrent UTIs. Vitamin A deficiency also may explain her nighttime visual symptoms.

High-dose vitamin A (100,000 IU by mouth daily for 4 days, then 50,000 IU daily) was prescribed, as were oral vitamin D, calcium, zinc, iron supplements, and a multivitamin. Four months later, the serum vitamin A level was 23 μg per deciliter (0.80 μmol per liter), and ureteroscopy revealed a substantial reduction in white plaques and sloughing mucosa. Ureteroscopy that was conducted after 15 months of vitamin A supplementation revealed resolution of the urothelial abnormalities, and the vitamin A level at that time was 13 μg per deciliter (0.45 μmol per liter). Although the patient's vitamin A level had decreased from the previous year, she reported taking oral vitamin A supplementation as prescribed. After 2 years of treatment, she had not had any subsequent UTIs.

COMMENTARY

The time between this patient's first UTI and identification of the cause of recurrent UTIs — keratinizing desquamative squamous metaplasia — was approximately 4 years. Keratinizing desquamative squamous metaplasia due to vitamin A deficiency occurred after a bariatric operation that had been performed 20 years earlier, with subsequent insufficient nutritional supplementation.

Clinicians often rely on visual assessments of adiposity, muscle mass, or frailty to make inferences about nutritional status, but these conclusions are often inaccurate.[1] Patients who undergo bariatric surgery often have preexisting nutritional deficiencies from insufficient dietary intake of micronutrients; common deficiencies include thiamine, folate, vitamin B_{12}, iron, vitamin D, calcium, and fat-soluble vitamins.[2] Such patients are also at risk for several nutritional deficiencies postoperatively, including deficiencies in vitamin C, thiamine, vitamin B_6, riboflavin, vitamin A, vitamin D, and vitamin B_{12}.[3]

Patients who undergo operations that induce malabsorption by means of anatomical alterations, such as the biliopancreatic diversion with duodenal switch (Fig. 4)[4] and Roux-en-Y gastric bypass, are at higher risk for nutritional deficiencies than those who undergo restrictive bariatric procedures, such as sleeve gastrectomy or gastric banding.[5] Vitamin A deficiency after biliopancreatic diversion with duodenal switch often coexists with deficiencies of zinc, copper, iron, and other fat-soluble vitamins.[2] At least one nutritional deficiency develops within 4 years after the procedure in 70 of patients,[3] and in one retrospective study, reoperation (usually a lengthening of the common limb) occurred in approximately 10 of patients because of protein-calorie malnutrition.[5]

Guidelines advise that patients who undergo bariatric surgery should undergo laboratory monitoring for deficiencies in vitamin B_{12}, folic acid, iron, 25-hydroxyvitamin D, and vitamin A; symptoms or examination findings that are compatible with deficiencies of copper, zinc, selenium, or thiamine should trigger relevant laboratory testing.[3,5] Patients who undergo biliopancreatic diversion with duodenal switch should receive indefinite, high-dose vitamin A supplementation as well as supplementation with protein, calcium, thiamine, vitamin B_{12}, vitamin D, zinc, iron, and folic acid at higher doses than are contained in a typical oral multivitamin.[3] Data from randomized, controlled trials comparing transdermal multivitamin patches with oral supplementation are lacking; however, limited observational data

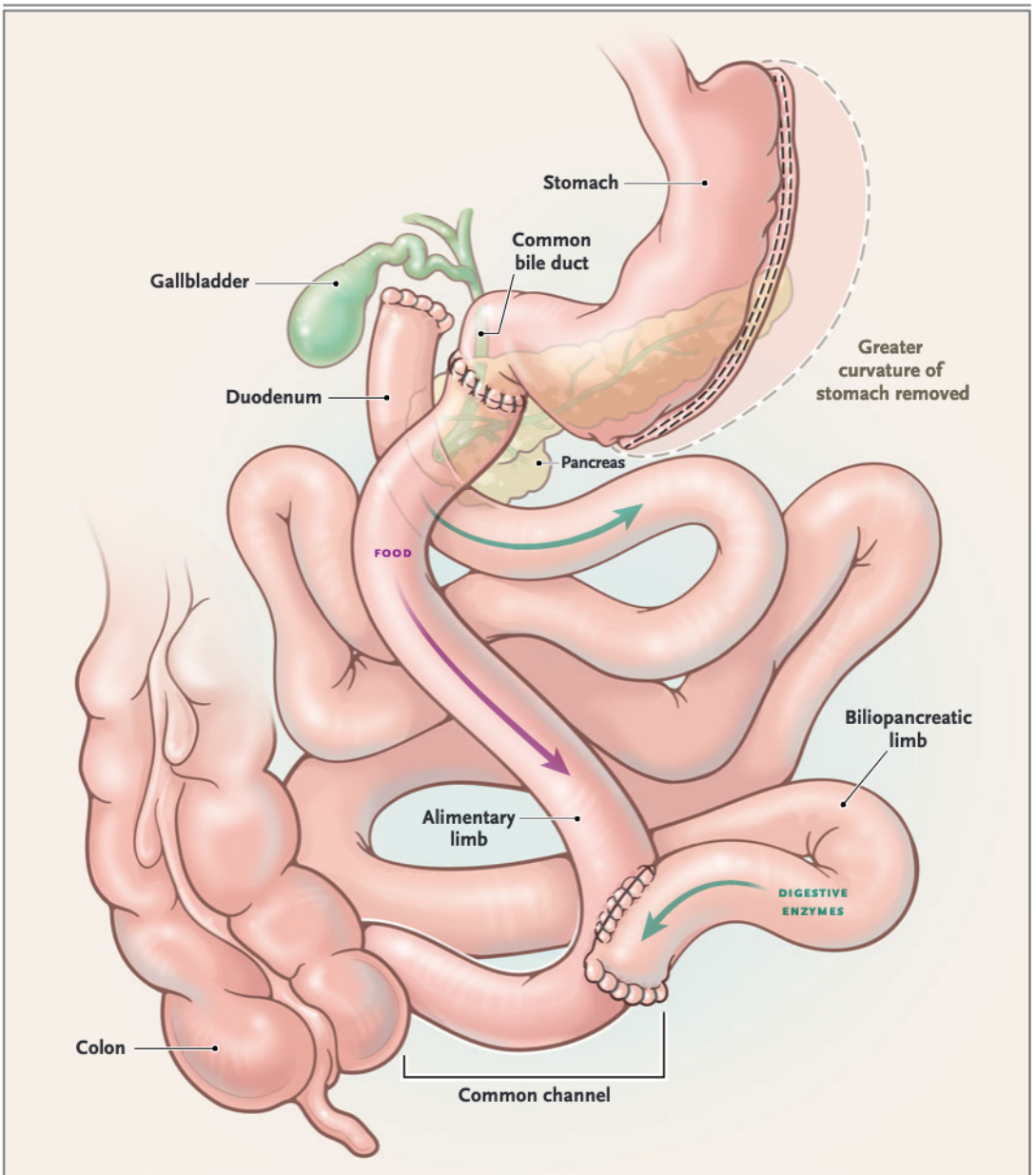

Figure 4. Biliopancreatic Diversion with Duodenal Switch.

In a biliopancreatic diversion with duodenal switch procedure, a portion of the greater curvature of the stomach is removed. The duodenum is then divided, and the intestinal tract is rerouted to create a long limb of bowel that contains only digestive enzymes and another long limb that contains only food. There is a short segment of distal bowel (50 to 100 cm) where food and digestive enzymes mix. This situation leads to a reduced surface area for absorption. Adapted from DeMaria.[4]

have shown micronutrient deficiencies in patients using patches after bariatric surgery.[6] This patient had elected to use a transdermal patch to decrease the burden of taking multiple supplement pills.

Keratinizing desquamative squamous metaplasia is a pathologic adaptation of the urinary tract in which the native urothelial lining transforms to squamous epithelium with prominent keratin deposition. This form of metaplasia impairs urothelial integrity, leading to mucosal sloughing. The resulting keratinaceous debris (plaques) can

lead to urinary stasis or obstruction. Keratinizing desquamative squamous metaplasia also generates chronic genitourinary inflammation characterized by urothelial-cell apoptosis, an impairment of urothelial-cell barrier integrity, macrophage recruitment, and the production of proinflammatory cytokines.[7]

Urothelial keratinizing desquamative squamous metaplasia can be idiopathic or related to existing genitourinary pathologic conditions, such as chronic infection (particularly genitourinary tuberculosis), stone disease, encrusting pyelitis (encrustations in the wall of the pelvicalyceal system that develop in response to a chronic trigger, such as urea-splitting bacteria or a long-term urinary catheter), and malakoplakia (a rare inflammatory condition characterized by macrophage dysfunction and plaque development in patients with immunocompromise).[8] Keratinizing desquamative squamous metaplasia may be mistaken for nephrolithiasis or cancer on imaging studies but not on endoscopy.

There is a theoretical risk of keratinizing desquamative squamous metaplasia leading to squamous-cell carcinoma, but a direct causal relationship has not been shown. Percutaneous renal surgery is recommended to remove adherent keratin plaques (which cannot be extracted through a ureteroscope) and obtain biopsy samples to rule out cancer.[9] Current recommendations emphasize treatment of the underlying cause and monitoring (e.g., annual CT imaging) to ensure that endothelial changes do not progress to cancer.[10,11]

Vitamin A is a fat-soluble vitamin that occurs in multiple chemical forms. It is a transcription factor ligand with roles in gene regulation for morphogenesis, differentiation, and proliferation, which collectively are responsible for the integrity of epithelial tissue. Damage to epithelial tissues can serve as a portal of entry for infection.[12] Vitamin A deficiency causes metaplasia and keratinization of the corneal and conjunctival epithelium, leading to ulceration, scarring, and blindness. Vitamin A is also integral to phototransduction, the process by which retinal rod and cone cells convert light into electrical signals. Vitamin A is essential for the formation and maturation of keratinocytes, which are epithelial cells that produce the structural protein keratin; deficiency leads to abnormal keratinocyte differentiation and skin hyperkeratosis (thickening of the outermost layer) and dryness. Vitamin A deficiency commonly manifests as eye disease (ranging from dryness to blindness) and dermatologic disorders (often xerosis or pruritus).

Vitamin A deficiency has been shown to induce keratinizing desquamative squamous metaplasia in the urothelial tracts of animal models[13]; we are aware of one case of urothelial keratinizing desquamative squamous metaplasia in a human that resulted from vitamin A deficiency and resolved with vitamin A treatment.[14] In our patient, high-dose vitamin A supplementation led to substantial plaque reduction and resolution of her UTIs, results suggesting that severe vitamin A deficiency was the primary cause of her keratinizing desquamative squamous metaplasia with possible contributions from recurrent UTIs and nephrolithiasis.

Recurrent urinary tract infections are typically managed with antibiotic agents and behavioral strategies and adjunctive regimens (e.g., vaginal estrogen for atrophic vaginitis), usually without an extensive evaluation. In this patient, evaluation was pursued after a multiyear history of frequent recurrent UTIs and revealed sloughing mucosa with plaques throughout both renal pelvicalyceal systems; this finding led to testing for chronic infections and cancer and ultimately to the identification of severe vitamin A deficiency.

Care fragmentation and uncertain primary responsibility of postsurgical bariatric care among multiple clinicians contributed to inadequate vitamin supplementation and diagnostic delay in this case. The patient's primary care physician and bariatric surgeon worked in two different health systems with distinct electronic medical records, and her urology and infectious disease specialists were in a third health system with yet another electronic medical record, which complicated the reconciliation of medications. There is considerable variation across systems and practices with regard to primary responsibility for nutritional management in patients who have undergone bariatric surgery, and time constraints can limit the ability of one clinician to ensure that all elements of care outlined in guidelines are addressed.[15] Postsurgical bariatric care requires frequent laboratory testing and multiple encounters with the health care team to review and respond to results; care restrictions that were associated with the coronavirus disease 2019 pandemic made the situation more challenging for this patient. This case highlights the impor-

tance of clearly defined and coordinated nutritional care pathways after bariatric surgery and the hazards of fragmented care.

Bariatric procedures such as biliopancreatic diversion with duodenal switch are associated with enduring medical and psychological benefits, but they can induce occult or overt malnutrition, including micronutrient deficiencies. This case reminds us how close attention to postoperative nutritional supplementation and coordination of care can flip the switch.

Disclosure forms provided by the authors are available with the full text of the article at NEJM.org.

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