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CLINICAL PROBLEM-SOLVING

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

Inadequate Support

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Sanjay Saint, M.D., M.P.H., and Nathan Houchens, M.D.*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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CME
at NEJM.org**A 71-year-old man presented to the emergency department with a 6-month history of melena, easy bleeding and bruising, and lightheadedness.**

The time course and symptoms are suggestive of a disorder of hemostasis. Lightheadedness could be explained by anemia that arose from gastrointestinal blood loss. Disorders of hemostasis can usually be attributed to a quantitative or qualitative defect in platelets, a deficiency or an inhibitor of a coagulation factor, or a disruption in vascular integrity, such as that caused by vasculitis, amyloidosis, or scurvy. Gastrointestinal bleeding should not be attributed solely to a propensity to bleed, and the underlying abnormality causing melena, such as a peptic ulcer, arteriovenous malformations, or gastrointestinal cancer, must be sought out.

The patient reported 6 months of dark tarry stools, as well as 3 months of bleeding gums when brushing his teeth and 2 months of orthostatic lightheadedness and exertional dyspnea. In the past year, he had lost 4 kg of weight unintentionally. He reported no chest pain, abdominal pain, orthopnea, paroxysmal nocturnal dyspnea, leg edema, falls, or trauma.

Orthostasis and dyspnea could be explained by anemia, although dyspnea could also reflect a concomitant condition, such as angina. Mucosal bleeding of the gums and gastrointestinal tract is more characteristic of a platelet disorder than of a coagulopathy. Bleeding gums can also arise from gingivitis or gingival leukemic infiltration. Unintentional weight loss can arise from malnutrition (due to limited access to food, anorexia, disorders of mastication, or dysphagia), malabsorption, or a catabolic state induced by infection, cancer, autoimmunity, or endocrinopathy.

The patient's niece reported that he had had memory dysfunction for 3 years. During a visit to the emergency department 4 months before the current presentation, he had received a prescription for meloxicam for the treatment of back pain. At that time, the hemoglobin level was 13.1 g per deciliter. One month later, a large nontraumatic hematoma had developed on the left thigh, at which point the hemoglobin level was 10.8 g per deciliter.

The patient had hypertension, hyperlipidemia, an abdominal aortic aneurysm measuring 3.2 cm by 3.0 cm and an ascending thoracic aortic aneurysm measuring 4.0 cm by 3.7 cm (with the most recent measurements obtained 1 year before presentation), chronic kidney disease, chronic obstructive pulmonary disease, post-traumatic stress disorder, and vitamin D and vitamin B₁₂ deficiencies. Prolonged bleeding had occurred after a tooth extraction a few months earlier, but there was no other history of hemorrhage. The patient had never undergone a colonoscopy or surgery. His medications included amlodipine, aspirin, cyanocobalamin, lisinopril, meloxicam, omeprazole, prazosin, and rosuvastatin. There was no family history of bleeding disorders; there was a history of leukemia in his maternal grandmother.

The patient smoked one pack of cigarettes daily and had a 60-pack-year history of smoking tobacco. He had a 12-year history of alcohol use disorder but had stopped drinking alcohol 35 years earlier. He was a retired automotive plant worker and an army veteran. He was divorced and lived alone.

Prolonged bleeding after a tooth extraction and a large nontraumatic hematoma are characteristic of a bleeding disorder. Aspirin use and uremia can contribute to platelet dysfunction. The combination of back pain, anemia, and chronic kidney disease could signal multiple myeloma, whereas the smoking history increases the risk of cancer of the oropharynx, lung, stomach, or pancreas.

The unexplained vitamin D and vitamin B₁₂ deficiencies could have arisen from a malabsorptive disorder, such as celiac disease or Crohn's disease, or from a condition that limits nutrient intake, such as chronic mesenteric ischemia. However, the patient did not report abdominal pain, which often accompanies these conditions. Elderly people with cognitive impairment who live alone are at risk for nutritional deficiencies.

The temperature was 36.3°C, the heart rate 115 beats per minute, the respiratory rate 18 breaths per minute, the blood pressure 124/68 mm Hg, and the oxygen saturation 100% while the patient was breathing ambient air. The weight was 71.5 kg, and the body-mass index (the weight in kilograms

divided by the square of the height in meters) 24.0. He appeared ill. He had loose and missing teeth, caries, and oozing ulcerations of the gums. He had nonpalpable purpura on the torso, arms, and legs, as well as ecchymoses on the legs. The right ankle was swollen, without tenderness or limitation in the range of motion. Cranial nerves II through XII, muscle tone and bulk, sensation to light touch, and ambulation were normal. A rectal examination was not performed. The heart, lung, and abdominal examinations were normal.

The white-cell count was 4100 per cubic millimeter, of which 87.1% were neutrophils. The hemoglobin level was 8.1 g per deciliter, the mean corpuscular volume 92.6 fl, the red-cell distribution width 43.0 fl (normal range, 35.1 to 43.9), and the platelet count 124,000 per cubic millimeter. The serum creatinine level was 1.7 mg per deciliter (150 μ mol per liter), which was consistent with the patient's baseline value. The total bilirubin level was 0.8 mg per deciliter, and other results of serum liver-function tests, the albumin level, and the protein level were normal. The international normalized ratio was 1.2, the partial-thromboplastin time 27.0 seconds, and the fibrinogen level 606 mg per deciliter (normal range, 225 to 550).

The nontraumatic mucosal bleeding of the gums and skin reinforces the initial concern about a bleeding disorder. Nonpalpable purpura signifies bleeding without a component of vascular inflammation.

The patient's international normalized ratio is minimally elevated and the platelet count is slightly reduced, but neither value is sufficiently abnormal to explain the bleeding. Hemostatic disorders that are associated with a normal platelet count and normal results on coagulation studies include von Willebrand's disease, factor XIII deficiency, disorders of fibrinolysis, and disorders of vascular integrity. Connective-tissue disorders such as Ehlers-Danlos syndrome and infiltrative disorders such as amyloidosis can render blood vessels weak and susceptible to rupture. Vitamin C (ascorbic acid) deficiency can also disrupt the connective-tissue infrastructure of vessels. Scurvy, which often leads to periodontal degeneration, widespread bleeding, and generalized malaise, remains an important consideration; a dietary history and serum vitamin C

level should be obtained. It is important to obtain this level early in the hospitalization, since a few days of standard nutrition or multivitamin administration can quickly normalize blood levels.

The patient has chronic anemia (on the basis of the hemoglobin level of 10.8 g per deciliter obtained 3 months earlier) and acute anemia (on the basis of the melena, tachycardia, and further reduction in the hemoglobin level). Given the slightly low white-cell and platelet counts, review of a peripheral blood smear should be performed to look for evidence of a bone marrow disorder. Workups for anemia, gastrointestinal blood loss, and bleeding diathesis should be conducted in parallel.

The patient was admitted to the hospital. After the administration of 1 liter of intravenous crystalloid fluid, the heart rate decreased to 73 beats per minute. The next day, the patient reported worsening lightheadedness and fatigue. The hemoglobin level was 7.3 g per deciliter, and the platelet count 114,000 per cubic millimeter.

The serum iron level was 47 μg per deciliter (8 μmol per liter; normal range, 50 to 175 μg per deciliter [9 to 31 μmol per liter]), the total iron-binding capacity 368 μg per deciliter (66 μmol per liter; normal range, 250 to 450 μg per deciliter [45 to 81 μmol per liter]), the ferritin level 130.5 ng per milliliter (normal range, 21.8 to 275.0), the vitamin B₁₂ level 1195 pg per milliliter (882 pmol per liter; normal range, 213 to 816 pg per milliliter [157 to 602 pmol per liter]), and the folate level 4.6 ng per milliliter (10 nmol per liter; normal range, 7.0 to 31.4 ng per milliliter [16 to 71 nmol per liter]). The reticulocyte production index was 0.7%. The lactate dehydrogenase and haptoglobin levels were normal.

The erythrocyte sedimentation rate was 18 mm per hour (normal range, 0 to 15), and the C-reactive protein level 2.20 mg per liter (normal range, 0 to 0.50). Antibody tests for human immunodeficiency virus, *Treponema pallidum*, Epstein-Barr virus, and cytomegalovirus were negative. Review of a peripheral blood smear revealed normocytic anemia, mild thrombocytopenia, and mild leukopenia, with normal cell morphology.

On further questioning, the patient reported that he had been drinking 1 liter of tonic water

daily for several months to alleviate leg cramps, but there had been no improvement.

The hypoproliferative normocytic anemia is probably multifactorial, arising from acute gastrointestinal bleeding, internal bleeding (involving the skin), malnutrition (including folate deficiency), and chronic kidney disease. The test results indicate adequate iron and vitamin B₁₂ stores. The normal iron stores suggest that either the melena had been intermittent rather than continuous during the 6-month course or the time frame reported by the patient was inaccurate, perhaps because of his cognitive impairment. The normal bilirubin, lactate dehydrogenase, and haptoglobin levels and the normal erythrocyte morphology rule out hemolysis. The normal cellular morphology in the peripheral blood indicates a reduced probability of a myelophthisic process or leukemia.

It would be helpful to know the timing and precipitants of the leg cramps. Nighttime leg discomfort could reflect restless legs syndrome, pain with exertion could suggest claudication, and paroxysms of pain could point to radiculopathy or neuropathy. Vitamin C deficiency can lead to myalgias, and coexisting nutrient deficiencies such as inadequate thiamine can lead to neuropathy. Quinine is generally not effective for the treatment of leg cramps and poses a risk of thrombocytopenia and microangiopathy, but it is still widely used and widely available, both in pills and in tonic water.

Folate supplementation and empirical vitamin C supplementation were initiated. On hospital day 2, the patient underwent esophagogastroduodenoscopy and colonoscopy, which revealed multiple nonbleeding angiodysplastic lesions, as well as patchy erythematous mucosa throughout the gastrointestinal tract. Biopsy specimens of the erythematous mucosa were obtained. On hospital day 3, the patient's hemoglobin level decreased to 6.5 g per deciliter.

The angiodysplasias or the mucosal irregularities would explain the melena and anemia, which may be compounded by bleeding at the biopsy sites. The use of aspirin and meloxicam could be contributing to the mucosal injury. The biopsy

results may reveal an inflammatory or infiltrative disorder leading to malabsorption and bleeding.

An acquired deficiency of von Willebrand factor not only increases the predisposition to bleeding from angiodysplastic lesions but also may contribute to their formation. A qualitative and quantitative assessment of von Willebrand factor is indicated in patients with mucosal bleeding and angiodysplastic lesions who have normal results on coagulation studies and a relatively preserved platelet count. An acquired von Willebrand's syndrome can arise in the context of lymphoproliferative disorders, plasma-cell dyscrasias, myeloproliferative neoplasms, autoimmune diseases, and cardiovascular diseases (e.g., aortic stenosis). However, the examination, peripheral blood smear, and levels of inflammatory markers in this patient are not suggestive of these disorders.

Further physical examination that was focused on the skin revealed sparse corkscrew hairs and perifollicular hemorrhages on the chest.

Vitamin C is essential for synthesis of the collagen that forms the structural foundation of the vessel wall. This patient's isolation and cognitive impairment are risk factors for malnutrition and scurvy, which is characterized by purpura, gum disease, corkscrew hairs, and perifollicular hemorrhages. Orthostasis, lightheadedness, dyspnea, and leg pain can all arise from vitamin C deficiency or associated anemia. The patient could also have coexisting nutritional deficiencies that can cause neurologic syndromes (e.g., dementia or neuropathy).

On further questioning, the patient reported that his diet lacked fruits, rarely included vegetables, and mainly consisted of "tater tots" (fried potatoes).

The activity and level of factor VIII were normal, as were the activity (ristocetin cofactor level) and antigen level of von Willebrand factor. Serum levels of vitamin A, copper, and zinc were normal. The serum vitamin C level, for which a blood specimen was sent for analysis early in the hospitalization, was undetectable; serum manganese and thiamine levels were low. Examination of biopsy specimens of erythematous mucosa in the

stomach, duodenum, terminal ileum, and descending colon revealed no abnormalities. A registered dietitian recommended high-protein supplemental shakes, increased fruit and vegetable intake, a meal plan, and enrollment in a meal assistance program.

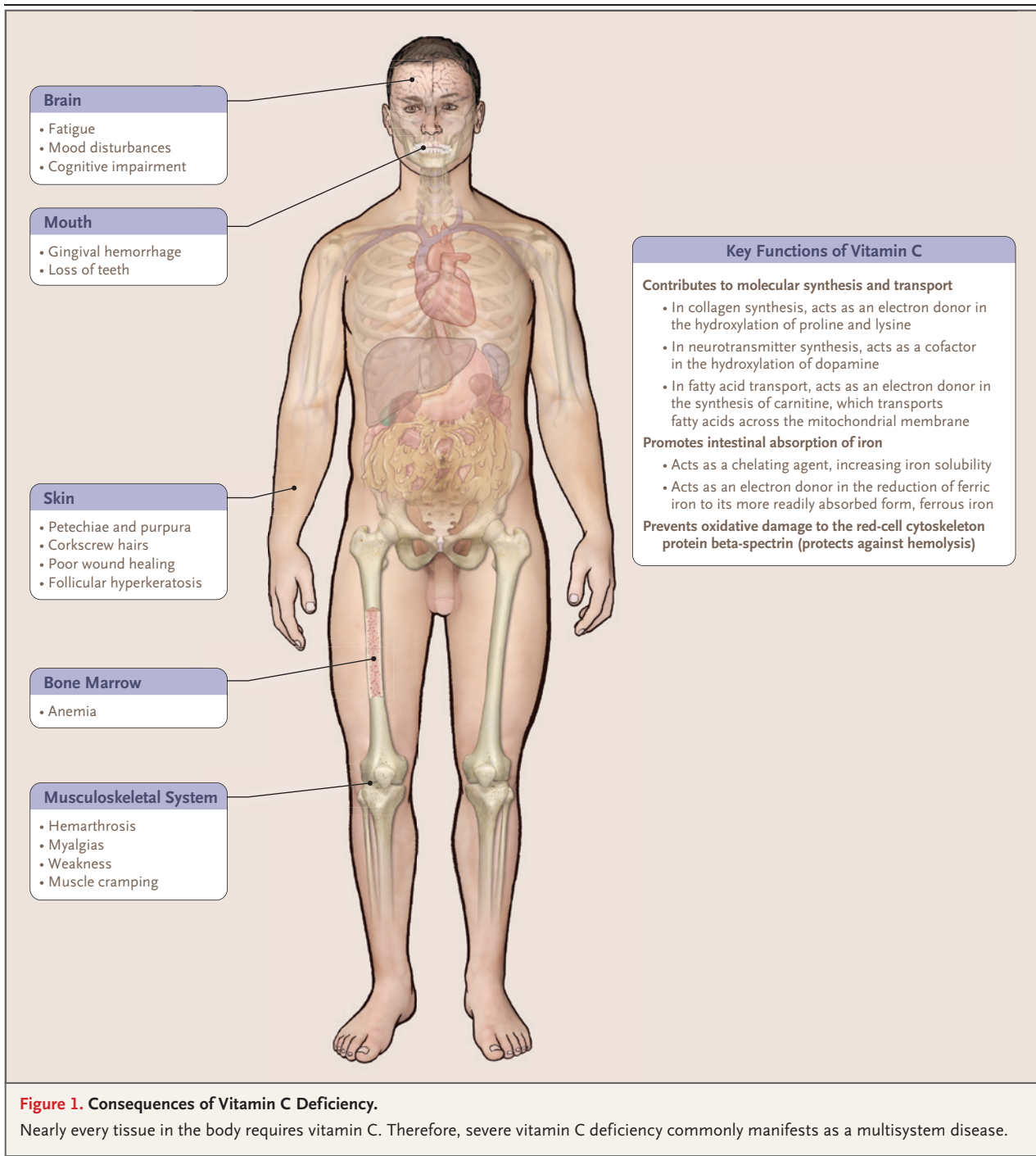
After 4 days of vitamin C supplementation, the patient's bruising and petechiae began to resolve. He was discharged and instructed to continue taking vitamin C (1000 mg daily), folate (1 mg daily), and a multivitamin and to discontinue meloxicam, aspirin, and tonic water. Three months after discharge, he reported that he had a balanced diet and was adhering to his regimen of nutritional supplements. At that time, the melena, bruising, and bleeding had resolved and the hemoglobin level had increased to 12.9 g per deciliter. One year later, three of his teeth were extracted with minimal bleeding. He reported decreased confusion and improved memory.

COMMENTARY

Scurvy is a multisystem illness caused by vitamin C deficiency that has been known since the times of ancient Egypt and Greece. It was recognized more widely in the Age of Sail (from the mid-16th century to the mid-19th century), when large numbers of sailors and soldiers who lacked basic nutritional provisions developed tooth decay, bruising, and lassitude and often died from massive hemorrhage.¹ A small study by Scottish naval surgeon James Lind published in 1753 showed that consumption of citrus fruits both prevented and cured scurvy.²

Scurvy occurs infrequently in the United States and other industrialized nations because of the wide availability of fruits, vegetables, and fortified foods.³ However, in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States, low vitamin C levels were identified in 5 to 17% of participants.⁴ Groups at risk for scurvy include persons with psychiatric illnesses who have eating disorders or selective eating habits, infants who consume only pasteurized milk, children with autism spectrum disorder, persons with alcohol use disorder, and isolated elderly persons with poor nutrition.⁵⁻⁸

Nearly all tissues in the body require exoge-



nous vitamin C as a cofactor for biosynthetic reactions that drive collagen synthesis and energy production (Fig. 1). Vitamin C is required for hydroxylation of proline residues on procollagen

molecules, which support the triple-helix structure of collagen that underpins the integrity of skin, vessels, mucous membranes, and bone. Disruption in collagen formation from vitamin C

deficiency causes microfractures in bone, perifollicular hemorrhages, ecchymoses, hemarthroses, petechiae, and gingival bleeding. Vitamin C is also a cofactor for enzymes involved in the biosynthesis of carnitine, which plays an essential role in the release of energy through beta-oxidation by facilitating the transport of fatty acids into mitochondria. This impairment in carnitine synthesis may account for the weakness, fatigue, and muscle cramping that occur in patients with scurvy.⁹

Anemia is commonly identified in patients with scurvy and is often caused by decreased erythrocyte production, hemolysis, and blood loss.⁷ Vitamin C facilitates the absorption of nonheme iron and may protect against oxidation of tetrahydrofolate and resultant decreased folate levels. Therefore, vitamin C deficiency can lead to iron and folate deficiencies (which compound the underlying deficiencies from malnutrition). In addition, the antioxidant property of vitamin C has been implicated in maintaining the red-cell cytoskeleton protein beta-spectrin, which is crucial to the structure and integrity of the cell. The loss of beta-spectrin can contribute to nonimmune hemolysis in patients with vitamin C deficiency.¹⁰ This patient's anemia was probably due to the combination of acute gastrointestinal blood loss from angiodysplasia, internal bleeding, and diminished erythrocyte production caused by folate deficiency.

The pathophysiological mechanisms underlying the hematologic manifestations of scurvy are understood better than the mechanisms underlying the neuropsychiatric sequelae. Vitamin C functions as a modulator of neurotransmitter synthesis and release.¹¹ Some studies have

suggested that the psychiatric symptoms caused by scurvy precede the physical manifestations and can occur with less severe total body vitamin C deficits than those associated with the physical manifestations.^{12,13} Scurvy has been associated with mood disturbances, depression, cognitive impairment, and delusions.^{12,14} These neuropsychiatric findings quickly resolve with the administration of 1 g of oral vitamin C daily.^{12,13} Both thiamine and vitamin C deficiencies could have contributed to the patient's longstanding memory dysfunction and cognitive deficits, which abated with sustained vitamin C supplementation (and with the administration of a subtherapeutic dose of thiamine in the multi-vitamin).

This patient presented with melena, non-traumatic ecchymoses, and anemia, findings that pointed to a bleeding diathesis. The normal results on coagulation studies and mild thrombocytopenia suggested that the bleeding was caused by impaired vascular integrity. The findings of perifollicular hemorrhages and corkscrew hairs implicated scurvy, which was confirmed by the serum vitamin C level and the dramatic response to vitamin replacement therapy. This case emphasizes the importance of obtaining a thorough dietary history in vulnerable populations. The development of scurvy in this isolated elderly patient with cognitive impairment exemplifies how inadequate social support can lead to inadequate tissue support.

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

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