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Scurvy: A Disease not to be Forgotten

Massimo Montalto, MD, PhD; Enrica Porceddu, MD; Erika Pero, MD; Andrea Lupascu, MD; Antonella Gallo, MD; Clara De Simone, MD, PhD; Eleonora Nucera, MD, PhD; Arianna Aruanno, MD; Igor Giarretta, MD; Roberto Pola, MD, PhD; and Raffaele Landolfi, MD, PhD

Abstract

An 18-year-old man presented to our hospital with muscular pain, diffuse petechiae, spontaneous thigh ecchymosis, edema and pain of the right knee, bilateral pretibial subcutaneous nodules, and gingival hypertrophy and hemorrhage. His history was positive for a mixed anxiety-depressive disorder and a restrictive diet caused by self-diagnosed food allergies. Skin lesions appeared like hyperkeratotic papules with coiled hairs and perifollicular hemorrhages. A diagnosis of scurvy was made upon demonstration of low serum levels of ascorbic acid. An allergy evaluation found cross-reactivity between pollens and food, related to the presence of panallergens. Moreover, we found that our patient was also affected by celiac disease. In conclusion, scurvy should be considered in the differential diagnosis of patients with petechiae and ecchymosis, especially when food restriction, malabsorption, or psychiatric disorders are present. (*Nutr Clin Pract.* 2021;36:1063–1067)

Keywords

anxiety disorders; celiac disease; food allergy; scurvy; vitamin C

Introduction

Scurvy is a well-known disease that has existed since the dawn of human history. The first reports of scurvy and the related therapy can be found in Papyrus of Ebers (1550 BC), but the first systematic description of the disease is attributed to Hippocrates.[1] Scurvy became a severe problem during the great explorations of the 15th and the 16th century, when mariners and explorers were constrained to a diet lacking in fresh fruits and vegetables.[1]

Vitamin C, or ascorbic acid, is an organic water-soluble compound that plays an important role in human and animal physiology. Whereas most animals can synthesize vitamin C by themselves, humans must rely on diet to obtain it. Foods containing vitamin C are fresh fruit and vegetables. A diet poor in these foods may lead to vitamin C deficiency and possibly to scurvy. Indeed, although scurvy is usually considered a disease of the past, it is still present.

The main role of ascorbic acid concerns collagen synthesis. Collagen is a triple helix–structured protein that represents the main component of connective tissue. The formation of the triple helix requires the hydroxylation of prolyl and lysyl residues of the procollagen. Ascorbic acid is involved in this reaction as a cofactor together with α-ketoglutarate, molecular oxygen, ferrous iron, and a reducing agent.[2] The altered collagen synthesis causes blood-vessel fragility, leading to rupture of the blood vessels with ecchymosis, petechiae, subcutaneous nodules, bleeding gums, and hemarthrosis. Ascorbic acid is also involved in catecholamine synthesis (hydroxylation of dopamine in noradrenaline), iron absorption, and carnitine biosynthesis and has antioxidant functions.[3,4]

The vitamin C recommended dietary allowance is 90 mg and 75 mg for adult males and females, respectively. Intestinal vitamin C absorption is regulated by an active dose-dependent transporter, which decreases absorption when the doses increase.[5] The human body content of vitamin C is ~1500 mg.[6] Vitamin C is particularly concentrated in leukocytes as well as the brain, adrenal cortex, spleen, liver, and pancreas.[7] Vitamin C is excreted and reabsorbed at the renal level. Alcohol has been found to increase the urinary

From the Department of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli, Istituto di Ricovero e Cura a Carattere Scientifico – Università Cattolica del Sacro Cuore, Roma, Italy.

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Corresponding Author:
Massimo Montalto, MD, PhD, Department of Internal Medicine, Fondazione Policlinico, Istituto di Ricovero e Cura a Carattere Scientifico, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168 Rome RM, Italy
Email: massimo.montalto@unicatt.it

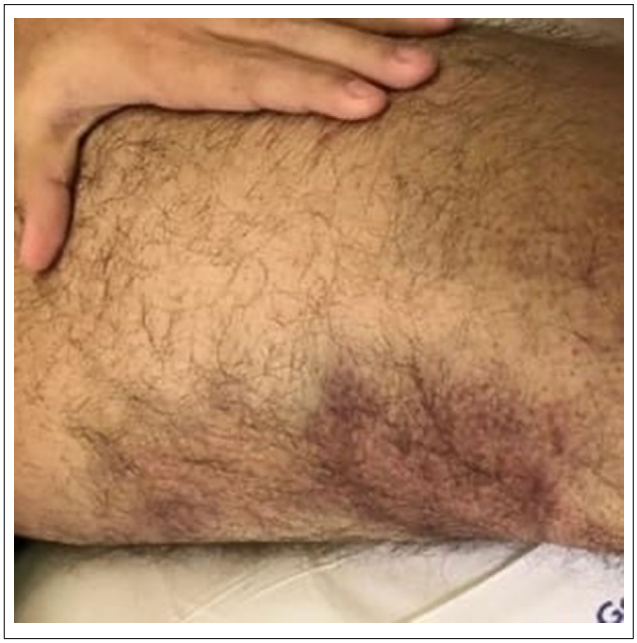

Figure 1. Spontaneous large ecchymosis of the thighs.

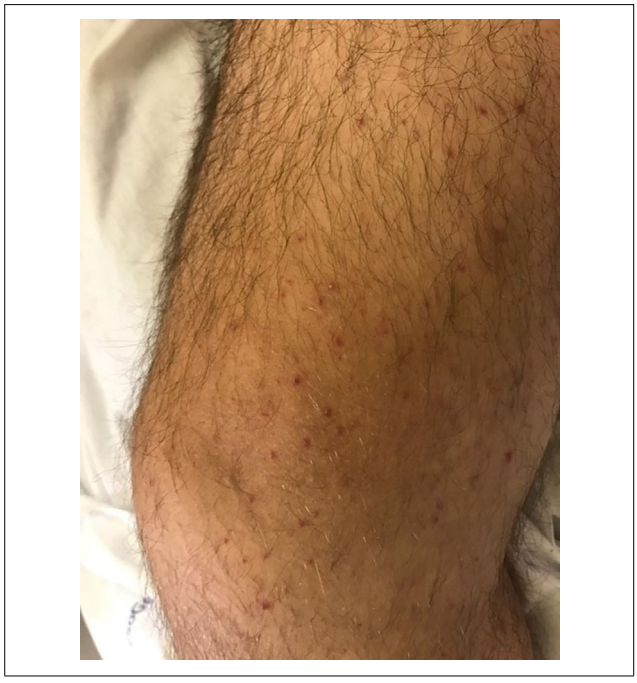

Figure 2. Diffuse petechiae into the 4 limbs.

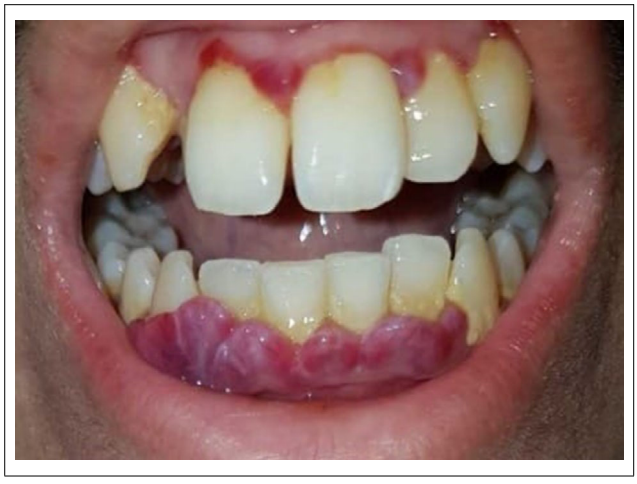

Figure 3. Acute periodontitis with gingival hypertrophy and frequent gingival bleeding.

vitamin C excretion,[8,9] and this is one of the reasons why alcoholism is a risk factor for the development of scurvy.

Case Report

An 18-year-old man was admitted to the emergency department of our university hospital for acute onset of spontaneous large ecchymosis of the thighs (Figure 1). In the preceding month, he noticed progressive muscle pain of the lower limbs with the appearance of diffuse petechiae into the 4 limbs (Figure 2), edema and pain of the right knee, and bilateral pretibial subcutaneous nodules. At the same time, he presented with acute periodontitis, gingival hypertrophy, and bleeding (Figure 3). He presented with a mixed anxiety-depressive disorder since adolescence and has an unspecified, self-diagnosed, and never-investigated allergy to inhalants and foods. Consequently, he developed an anxious attitude toward food and started a particularly restrictive diet. He did not take any medications.

On clinical examination, he appeared weak and pale, his blood pressure was 120/70 mm Hg, his heart rate was 90 beats per minute, his respiratory rate was 15 breaths per minute, and his peripheral oxygen saturation was 98% in air. Nocturnal fever (37.6 °C) occurred during the first 3 days of hospitalization. The electrocardiogram (ECG) showed nonspecific changes of the T waves. Echocardiogram findings were normal. Laboratory tests revealed that the patient had microcytic anemia with a reduction of hemoglobin levels from 11.6 to 7.7 g/dL (normal values, 13.0–17.0 g/dL) in just 5 days; hypoalbuminemia; deficiency of zinc, folate, and vitamin D; and an increase in the inflammation parameters (Table 1). Laboratory tests excluded recent infections (hepatitis B and C viruses, influenza A and B viruses, parainfluenza virus, cytomegalovirus, Epstein-Barr virus, echovirus, parvovirus B19, *Coxiella brunetii*, *Toxoplasma gondii*, and *Streptococcus agalactiae* type B); autoimmune diseases and vasculitis were unlikely (Table 1). Upon careful clinical examination, the skin lesions appeared to be hyperkeratotic papules with perifollicular hemorrhages. The trichoscopic examination of the hair highlighted the presence of twisted hairs and pseudomoniletrix, with pilar nodosities and coiled hairs in correspondence of the petechiae.

Table 1. Laboratory Tests at Admission.

Tests	Results	Normal values	Units of measure
Hematologic tests			
Hemoglobin	7.7[a]	13.0–17.0	g/dL
Mean corpuscular volume	82[a]	83.0–101.0	fL
Haptoglobin	185	45–320	mg/dL
Ferritin	151	21–275	ng/mL
Transferrin	289	200–360	mg/dL
Serum iron	25[a]	60–160	μg/dL
Lactate dehydrogenase	167	<250	UI/L
Systemic inflammatory tests			
Fibrinogen	684[a]	200–400	mg/dL
Erythrocyte sedimentation rate	75[a]	0–15	mm/hr
C-reactive protein	100.3[a]	<5.0	mg/L
Serum albumin level	28[a]	34–48	g/L
Hepatic and renal function tests			
Creatinine	0.7	0.67–1.17	mg/dL
Alanine aminotransferase	5[a]	7–45	UI/L
Total bilirubin	1.1	0.3–1.2	mg/dL
Micronutrients tests			
Zinc	50[a]	68–107	μg/dL
Folic acid	1.7[a]	>4.0	ng/mL
Vitamin D	12.5[a]	31–100	ng/mL
Vitamin B_{12}	0.570	0.187–0.883	ng/mL
Vitamin C	8[a]	28.4–85.2	μmol/L
Autoimmune tests			
ANA	negative	negative	
Anti-ENA	<10	<10	AU/mL
ANCA	<10	<10.0	AU/mL
Rheumatoid factor	<10.00	<15	UI/mL
C3	151	90.0–180.0	mg/dL
C4	49.9[a]	8.0–32.0	mg/dL
Antitransglutaminase (IgA)	98[a]	<10.0	AU/mL

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AU, arbitrary units; ENA, extractable nuclear antigen; IgA, immunoglobulin A.
[a] Values out of range.

Regarding dietary habits, the patient reported that he started a restrictive diet ~10 years earlier, when he suffered from an episode of severe throat ache and dyspnea after ingestion of rice with shellfish. Since then, he made the decision to eliminate shellfish from his diet, without consulting a physician. Later, he suffered from oropharyngeal itching after eating fruits and vegetables; therefore, he decided to stop eating them. In summary, over the last 2 years, his diet had literally consisted of only pasta, bread, eggs, fish, and meat. In addition, in the last 4 months, he had also excluded fish because of the fear of accidentally swallowing a bone.

The skin lesions, gingival hypertrophy with gingival bleeding, severe food restriction, anemia, and ECG alterations led us to hypothesize a vitamin C deficiency. Serum levels of ascorbic acid, measured by high-performance liquid chromatography, were found to be decreased (Table 1). So an intravenous vitamin C supplementation (500 mg once a day) was started. Folate and vitamin D supplementation were also administrated.

We also performed a complete allergy evaluation, with skin-prick tests to plant-derived food extracts and to panallergens (profilin, non–lipid-specific transfer protein [nLTP], and PR-10 proteins; Alk-Abellò, Milan, Italy) to investigate a possible cross-reactivity between pollens and food. The patient displayed positive skin-prick tests to garlic, onion, sunflower, corn, barley, celery, soy, spinach, strawberry, peach, hazelnuts, tomato, and 2 panallergens (profilin and nLTP). These results were confirmed by specific immunoglobulin E assays (UniCAP; Phadia, Uppsala, Sweden).

In consideration of the allergic diathesis and vitamin deficiencies, we also investigated whether the patient had a malabsorption syndrome. We found a positivity for antitransglutaminase antibodies (IgA), and an esophagogastroduodenoscopy showed celiac disease stage 3b, according to Marsh-Oberhuber Classification. So a gluten-free diet was started.

One week after the beginning of vitamin C supplementation, weakness and fatigue decreased and there was a significant improvement of the skin lesions and the gingival hypertrophy. Hemoglobin increased from 7.7 g/dL to 9.9 g/dL, with an elevated percentage of reticulocytes (10.9%; normal values, 0.5%–2.0%). C-reactive protein decreased dramatically from 100.3 mg/L to 10.9 mg/L (normal, <5.0 mg/L). At discharge, he was prescribed 500 mg of vitamin C once a day, 25,000 units of vitamin D (cholecalciferol) once a week, and 5 mg of folate once a day by oral route. One month later, he showed a complete resolution of the mucocutaneous manifestations and normalization of hemoglobin levels. The patient was recommended consultation with a nutritionist for diet education regarding his celiac disease and polyallergies.

Discussion

Although rare, scurvy does still occur. This is surprising, considering the current availability of fresh products and multiple nutritional supplements. People living in social isolation and affected by psychiatric disorders (such as autism and anorexia nervosa), alcohol abuse disorders, or malabsorption (especially caused by digestive surgery)[6,10] are at increased risk of scurvy.[3,4,6,11–14] Our patient has had a mixed anxiety-depressive disorder since adolescence that, combined with his belief of suffering from food allergies, led him to start a particularly restrictive diet.

Signs and symptoms of scurvy appear generally from 1 to 3 months after the beginning of vitamin C deprivation, when storage levels fall to 300 mg[3]. Plasma or leukocyte

ascorbic acid levels are usually performed to confirm the diagnosis of scurvy. Although plasma levels are influenced by recent intake, leukocyte levels are more stable and better reflect storage amount.[3] Plasma ascorbic acid levels <0.2 mg/dL (<10 μmol/L) suggest scurvy.[6] Alternatively, disappearance of the clinical abnormalities after vitamin C replacement establishes diagnosis of scurvy without laboratory studies.[3] In our patient, the onset of the clinical manifestations of the disease occurred 4 months after he stopped eating fish. Because the patients used to season his fish with lemon juice, it is likely that his decision to stop eating fish resulted in the elimination of the only source of vitamin C present in his diet.

Progressive weakness, fatigue, myalgias, and low-grade fever often occur as nonspecific symptoms of scurvy, and they were all present in our patient. He also presented with many mucocutaneous features of scurvy, such as gingival hypertrophy and bleeding, petechiae of legs and arms, bilateral pretibial subcutaneous nodules, hyperkeratotic papules, perifollicular hemorrhages, and coiled hairs.[3,4,6,10–16] Moreover, hemorrhagic events can occur in muscles (hematomas), joints (overt hemarthrosis or joint swelling), bone (subperiosteal bleeding),[17] the peripheral nervous system, eyes, and lungs.[3,11,13,14,18,19] Furthermore, scurvy can lead to osteopenia with subsequent fractures[20] and loss of teeth.[14] Cardiac manifestations include hemopericardium, ST-segment elevations, and atrioventricular blocks.[3,16] In our patient, an ECG showed only unspecific alterations of repolarization. Vasomotor instability can also be present, leading to severe hypotension, syncope, and shock.[21] The reason of vasomotor instability stands in impaired catecholamine synthesis and attenuated vasomotor response to α-adrenergic stimulation (ascorbic acid binds to the α-adrenergic receptor, improving its activation by adrenaline).[21]

The most common laboratory finding of scurvy is normochromic normocytic anemia.[22] Anemia may be ascribed to hemorrhages, but in some cases, an increased serum level of indirect bilirubin suggests an underlying hemolytic cause.[3] Instead, our patient presented a microcytic anemia and folate deficiency. This, in addition to vitamin D and zinc deficiency, led us to investigate the possible presence of a malabsorption condition, such as celiac disease. To our knowledge, this is the first case of an association between scurvy and celiac disease reported in the literature. However, we believe that, in our patient, vitamin C deficiency can be ascribed only to a lack of intake because vitamin C levels are not usually altered in patients affected by celiac disease.[23] No zinc supplementation was started because of the absence of clinical changes related to zinc deficiency.

Scurvy's differential diagnosis includes other causes of purpura (vasculitis, infectious disease, idiopathic thrombocytopenic purpura), hemorrhages (coagulation disorders), and joint effusion (rheumatoid arthritis, septic arthritis). These manifestations, together with subcutaneous nodules and increased inflammatory markers, can easily mimic rheumatologic diseases. Our diagnostic process allowed us to exclude all these conditions.

Regarding treatment, an initial dose from 300 mg to 1 g daily is usually administered for the first 3 or 5 days, followed by a lower maintenance dose.[3,4,6,16] As treatment is started, scurvy symptoms recede in a few days, and signs recede in a few weeks. Our patient responded quickly to supplementation therapy. Weakness and fatigue decreased in 2 or 3 days, cutaneous lesions receded in 2 weeks, and anemia gradually improved until normalization in 1 month.

Conclusion

Although rare, scurvy should be considered in the differential diagnosis of patients with petechiae and ecchymosis, especially when food restriction, malabsorption, psychiatric disorders, or social isolation are present. People with food allergies need specialized dietary and nutrition education, and possible nutrition supplementation, to meet all nutrient requirements.

Statement of Authorship

M. Montalto, E. Porceddu, and E. Pero equally contributed to the conception and design of the research; E. Nucera and A. Aruanno contributed to the design of the research; M. Montalto, E. Porceddu, E. Pero, E. Nucera, A. Aruanno, and C. De Simone contributed to the acquisition and analysis of the data; A. Gallo, A. Lupascu, I. Giarretta, R. Pola, and R. Landolfi contributed to the interpretation of the data; and M. Montalto, E. Porceddu, E. Pero, E. Nucera, and A. Aruanno drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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