Scurvy Masquerading as Leukocytoclastic Vasculitis: A Case Report and Review of the Literature

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GOAL

To understand scurvy to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the clinical symptoms of scurvy.
2. Discuss the laboratory findings in patients with scurvy.
3. Explain the role of vitamin C in the body's functioning.

CME Test on page 240.

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Scurvy, a disease rarely seen in modern times, results from dietary deficiency of vitamin C and is characterized in adults by hemorrhagic diathesis, hair follicle abnormalities, and osteopenia. We present a 59-year-old man with perifollicular petechiae of the extremities, a painful lower extremity hematoma, and sacral osteopenia, who was repeatedly misdiagnosed with leukocytoclastic vasculitis. The patient's dietary history revealed several months of virtually no vitamin C intake. The patient rapidly improved with vitamin C replacement. We review the biochemical basis and pathophysiology of scurvy, clinical scenarios in which it occurs, clinical signs and radiologic features of the condition, and recommendations for its diagnosis and treatment.

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Scurvy is prominent in world history. The disease was rampant among sailing crews from the Renaissance to the 18th century, when advances in shipbuilding and navigation facilitated sea voyages of long duration. From 1497 to 1499, half of the Vasco da Gama crew died from scurvy while sailing around the Cape of Good Hope to the east coast of Africa. In 1747, Scottish naval surgeon Sir James Lind was the first to conduct a clinical trial demonstrating improvement in scorbutic patients who ingested fresh lemons and oranges. It was not until the end of the 18th century, when Sir Gilbert Blane required British sailors to ingest lime juice routinely, that citrus fruits were used to prevent scurvy.[1] Outbreaks of scurvy have occurred throughout history, including during the 1845 potato famine in Ireland, the 1848 California Gold Rush, the US Civil War (1861–1865), and the 1915 Gallipoli campaign of World War I.[1,2]

Case Report

A 59-year-old white man with a medical history of chronic obstructive pulmonary disease presented to the emergency department with a petechial rash on his lower extremities. He denied having fever or arthralgias at that time. The rash was dismissed as leukocytoclastic vasculitis, and the patient was sent home. He failed to follow-up in the outpatient clinic for workup and returned to the emergency department 4 months later with severe right thigh pain. Results of a computed tomographic scan of the lower extremity revealed right thigh and right gluteal hematomas. Hemoglobin and hematocrit levels were 11.6 g/dL and 35.0%, respectively.

The dermatology department was consulted to evaluate the petechiae of the thighs and arms. On more careful examination, discrete perifollicular hemorrhages were noted (Figure 1), a large ecchymosis was found on the right leg and foot (Figure 2), and the patient was found to be emaciated. This combination of signs prompted a search for other stigmata of scurvy. Corkscrew hairs were noted (Figure 3), though no obvious gingivitis was present; however, the patient confirmed he had a history of bleeding gums, especially after brushing. An unprompted diet history revealed ingestion of canned tuna (which contains 0% vitamin C), pasta without tomato sauce, oatmeal, and water. The patient could not afford fruit, vegetables, or orange juice.

Although the patient's serum ascorbic acid level was not confirmed by testing, his symptoms promptly resolved within a week of oral administration of 1 g of vitamin C taken twice daily. Of note, the patient's platelet count; clotting factor level; international normalized ratio value; activated partial thromboplastin time; bleeding time; and concentrations of serum albumin (4.3 g/dL), total protein (7.3 g/dL), serum calcium (9.6 mg/dL), and serum phosphorus (3.7 mg/dL) were all within reference range. However, his erythrocyte

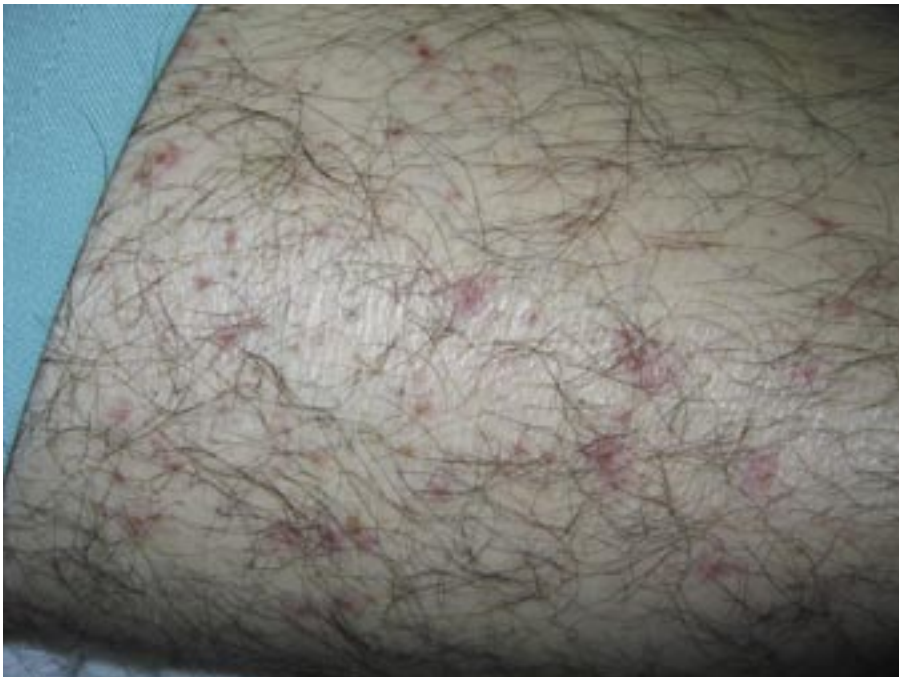

Figure 1. Perifollicular hemorrhages.

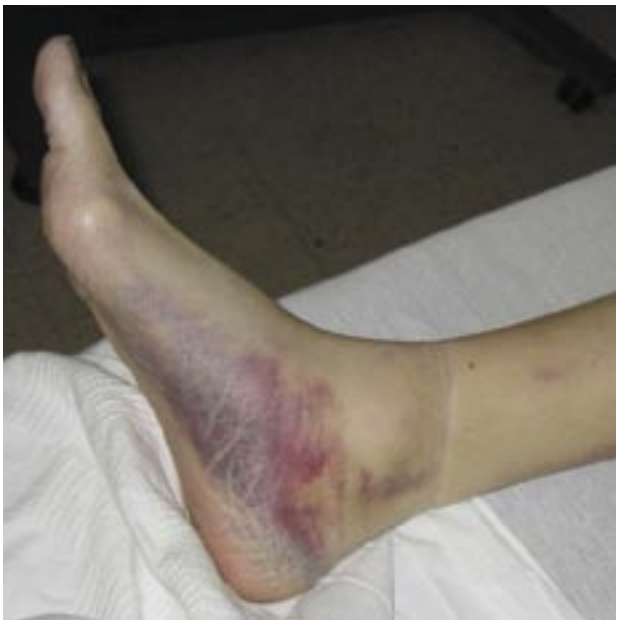

Figure 2. Ecchymosis on the lower extremity.

sedimentation rate was elevated at 60 mm/h. Results of a skin biopsy revealed only interstitial perivascular hemorrhage without significant infiltrate. Results of a bone scan revealed 4 small foci of uptake—2 in the sacrum and 1 in each sacroiliac joint. Results of a computed tomographic scan revealed diffuse sacral osteopenia, which is a characteristic finding in adult scurvy.

Comment

Scurvy is a clinical condition resulting from inadequate intake of vitamin C. Although scurvy is well documented historically, it is relatively uncommon in industrialized countries and, therefore, may be underdiagnosed.[3] Most animals are able to synthesize ascorbic acid from glucose[4]; however, humans harbor only a nonfunctional partial copy of the L-gulono-γ-lactone oxidase (GULO) gene, the product of which catalyzes the last step in ascorbic acid synthesis—specifically, the conversion of glucuronic acid to glucuronolactone and ascorbate.[5] Therefore, vitamin C, a water-soluble vitamin, is essential for humans and must be acquired from diet.

Scurvy most commonly is seen in individuals with a diet lacking in vitamin C. Citrus fruits, green vegetables, tomatoes, and potatoes are especially rich sources of vitamin C; additionally, the vitamin can be found in milk, liver, fish, multivitamins, and artificially fortified foods.[6-7] The people most at risk for scurvy due to poor diet are the elderly,[8] especially those who are institutionalized[9]; men who live alone[8]; alcoholics[8,10]; people following fad diets[8]; and the mentally ill.[11,12] Scurvy also has been reported in patients with cancer. In this setting, the condition is thought to be a consequence of increased vitamin C requirements (as is true of smokers and diabetic patients) and poor dietary intake secondary to depression, impaired taste, dysphagia, and abdominal pain, as well as the mucositis, nausea, vomiting, and diarrhea that can accompany chemotherapy.[8,13] In addition, scurvy has been reported as a complication of total parenteral nutrition,[8] enteral feeds,[14] and malabsorption secondary to either radiotherapy[8] or intestinal processes such as Whipple disease.[15] Peritoneal dialysis and hemodialysis also have been implicated in cases where water-soluble vitamin C is removed from the body during the dialysis process.[16]

Patients with scurvy can present with fatigue and malaise early on and with myalgia as the vitamin C deficiency progresses. The clinical signs of scurvy include hair follicle abnormalities, complications from bleeding diathesis, and osteopenia. Cachexia may be an associated finding. Follicle findings include perifollicular palpable purpura, follicular hyperkeratosis, and bent or coiled body hairs, which are often termed *entrapped corkscrew hairs*.[4] Other findings can include xerosis, leg edema, and poor wound healing. Bleeding diathesis often results in hemarthroses and soft tissue hematomas that are produced by mild or inapparent trauma and tend to involve the legs.[4,17] Interestingly, gingival findings occur only in patients with teeth and include gingival swelling, petechial lesions, purplish discoloration, bleeding with little provocation, and secondary bacterial periodontal infections.[4,7,18] Bleeding complications in children can be more dramatic than in adults and include possible subperiosteal hematomas and retrobulbar, subarachnoid, and intracerebral hemorrhages.[18] In rare extreme cases, the bleeding complications of scurvy can involve the peritoneum, pericardium, and adrenal glands.[6] Anemia frequently accompanies scurvy secondary both to bleeding and to a decrease in iron absorption that is precipitated by ascorbic acid deficiency.[4,7]

Scurvy that is left untreated is fatal as a result of either sudden death or infection. The late stages of scurvy are characterized by neuropathy, edema, oliguria, syncope, leukopenia, and intracerebral hemorrhage.[4,19,20] Severe hypertension was reported in one case.[11] Because vitamin C is intimately involved in collagen synthesis, the pathophysiology of bleeding in scurvy originates in the decreased tensile strength of the connective tissue collagen that supports blood vessels and that is found within vessel walls. Biochemically,

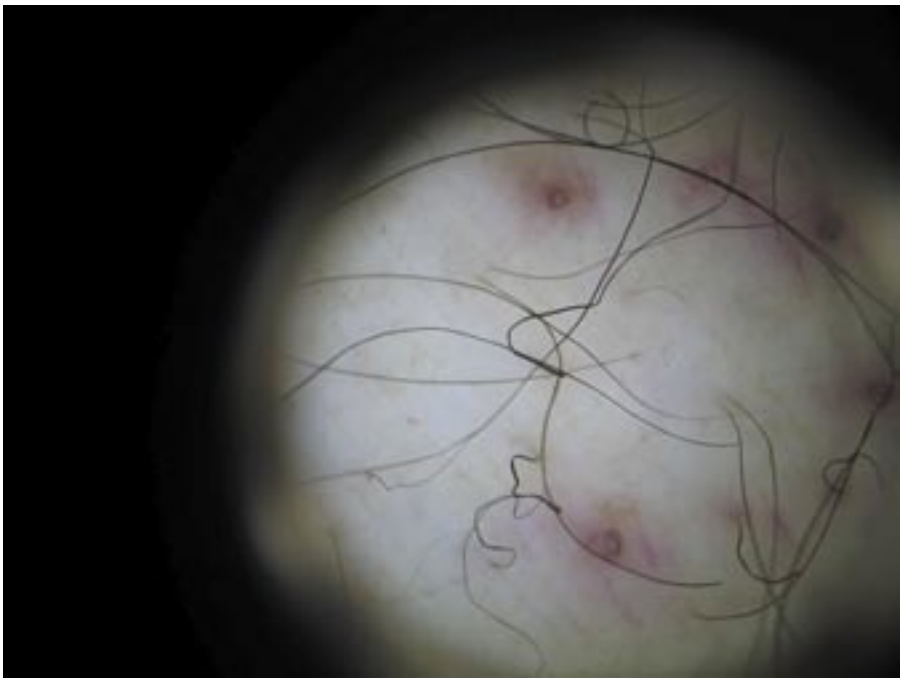

Figure 3. Corkscrew hairs seen through a dermatoscope at ×10 magnification.

vitamin C regenerates the prosthetic metal ions in prolyl and lysyl hydroxylase.[21] This enzyme hydroxylates proline and lysine residues in the procollagen polypeptide chain. The hydroxylated residues serve to crosslink and stabilize the ensuing collagen triple helix. Impaired cross-linking destabilizes collagen fibrils, decreases collagen secretion from fibroblasts, and increases collagen solubility, which makes the protein more vulnerable to enzymatic degradation.[7] Scurvy-related bleeding tendencies revolve around the collagen content of dermal structures: the dermis and blood vessel tunica adventitia primarily contain type I collagen, blood vessel tunica media contains type III collagen, and the blood vessel basement membrane contains type IV collagen.[22]

Vitamin C deficiency also has been shown to suppress the rate of synthesis of procollagen peptides independent of proline and lysine hydroxylation,[23] with additional evidence demonstrating lower expression of type IV collagen and elastin messenger RNA in scorbutic states.[24]

Apart from its role in structural integrity, vitamin C is essential for the conversion of histamine to aspartic acid. Exponential increases in blood histamine with corresponding decreases in aspartic acid as a consequence of vitamin C deficiency causes vascular endothelial cells to separate, which also may contribute to the bleeding tendency in scurvy.[25] Of note, vitamin C has not been reported to affect bleeding time or clotting factor production or function. Examples of decreased structural integrity of the microcirculation and supporting tissue other than scurvy include senile purpura, in which long-term sun damage and decreased structural components secondary to aging results in purpuric patches; potent topical corticosteroid excess, in which cutaneous atrophy can lead to purpura; Ehlers-Danlos syndromes, which have various collagen defects; and amyloid infiltration of blood vessel walls in a primary systemic amyloidosis that is associated with, for example, multiple myeloma.[18]

The impairment of connective tissue components that occurs in patients with scurvy also can manifest in bone and produce radiographic findings such as osteopenia, as in the case presented here. Epidemiologic studies have reported a positive association between vitamin C intake and bone density,[26] and guinea pig models of scurvy have demonstrated lower bone density in scorbutic animals.[27] Impaired collagen leads to a primary disturbance in the formation of the osteoid matrix, with no effect on mineralization. Decreased osteoblast function with unimpaired osteoclast function also contributes to the osteopenia. Osteoporosis related to vitamin C deficiency is seen primarily in the axial skeleton.[28]

Other radiographic findings in patients with scurvy are typically related to growing children[7] and include metaphyseal spurs and marginal fractures known as Pelkan sign; a ring of increased density surrounding the epiphysis, or Wimberger sign; widening of the zone of provisional calcification,

or the white line of Frankl; and a transverse band of radiolucency in the metaphysis, known as the *scurvy line* or *Trummerfeld zone*.[28] Other bony deformities may be observed, such as a bowing of the long bones, an abnormally depressed sternum, and an outward projection of the ends of the ribs.[7] Infantile scurvy, also known as *Barlow disease*, is characterized by ecchymoses, bone fractures, and nonhealing ulcers[29] and can be mistaken for child abuse.

A vitamin C dose of 60 to 100 mg/d is sufficient to prevent scurvy; the consumption of 5 daily servings of fruits or vegetables provides more than 60 mg of vitamin C.[6,8] Good dietary sources of vitamin C include citrus fruits, broccoli, tomatoes, and potatoes[6] (eg, a 100-g orange contains 50 mg of vitamin C).[8] Despite the inconclusive role of the antioxidant function of ascorbic acid in preventing disease, the higher US recommended daily allowance of vitamin C established in 2002 (75 mg for women, 90 mg for men) is based on the vitamin's antioxidant function and not just on the amount required to protect against deficiency[30]; the requirement for smokers may be up to 140 mg/d. The rationale for a higher recommended daily allowance of vitamin C may be due to the fact that higher daily intakes of the vitamin (150–200 mg) possibly may augment the role of ascorbic acid in immune response, pulmonary function, and iron absorption.[31] Weeks to months of deficient vitamin C intake, defined as consuming as little as 10 mg/d,[6] is usually necessary to drop the body's normal vitamin C reserves (1500 mg) down to 300 mg; below this level, symptoms may appear.[8]

Diagnosis of scurvy is based on clinical findings and results of laboratory tests to assess vitamin C levels. Low serum vitamin C, typically defined as less than 0.1 mg/dL,[20] reflects inadequate recent dietary intake. The level of ascorbate in leukocytes more accurately reflects the body's stores, though is not a routinely available test.[8] Fortunately, however, all cases of scurvy, even those with advanced involvement, respond to administration of vitamin C. Recommended and reported treatment regimens vary from 200 mg/d, with symptoms improving over several days, to 1 g/d for 2 weeks, with symptom resolution within 2 weeks.[6,9,12] Complete absorption of vitamin C occurs if less than 100 mg is administered in a single dose, whereas only 50% or less is absorbed at doses greater than 1 g. Side effects of oxalate-related nephrolithiasis, abdominal pain, nausea, and diarrhea may be observed with greater than 2 g/d; increased alanine aminotransferase, lactate dehydrogenase, and serum uric acid levels may occur with greater than 3 g/d.[6] High-dose vitamin C can induce hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, and doses of more than 1 g/d can cause false-negative guaiac reactions.[6]

Conclusion

Given its rarity in the modern day, scurvy might easily be mistaken for child abuse[29] or misdiagnosed as a connective tissue disease, systemic vasculitis,[32] or malignancy. Despite its rarity and because of its simple treatment, scurvy must not be overlooked as a possible diagnosis in a patient presenting with suggestive findings in the appropriate context.

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