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Article begins on next page
Behind the Skin: A Rare Case of Scurvy-Associated Megaloblastic Anemia

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ABSTRACT: Scurvy, caused by vitamin C deficiency, is very rare nowadays in the developed world. Scattered cases are found in people with unusual eating habits, alcoholism, intestinal malabsorption, mental disorders, or elderly living alone. Because of its rarity, clinical presentations of scurvy, especially anemia and bleeding, are no longer well appreciated, and consequently extensive evaluation is commonly launched to pursue scurvy mimics, such as deep vein thrombosis, vasculitis, systemic coagulation disorders, and myelodysplasia. Herein, we describe the clinical manifestations and lab findings in a scurvy patient to raise awareness of this uncommon disease.

KEYWORDS: scurvy, vitamin C deficiency, megaloblastic anemia, follicular hyperkeratosis, perifollicular hemorrhage

Introducing

Scurvy, resulted from vitamin C deficiency, is a very rare disease in the United States nowadays. It is mostly found in people whose age, disability, or apathy lead to an inadequate dietary intake.1 Other risk factors include intestinal malabsorption and dialysis3; infants whose intake includes only cow’s milk for the first year of life; development disorders including autism; eating disorders; certain individuals who have higher requirements of vitamin C including smokers; patients with type I diabetes, AIDS, iron overload disorders, renal failure requiring hemodialysis, or with diseases affecting the small intestine; diabetes, AIDS, iron overload disorders, renal failure requiring hemodialysis, or patients with type I diabetes, AIDS, iron overload disorders, renal failure requiring hemodialysis, or with diseases affecting the small intestine; elderly living alone. Because of its rarity, clinical presentations of scurvy, especially anemia and bleeding, are no longer well appreciated, and consequently extensive evaluation is commonly launched to pursue scurvy mimics, such as deep vein thrombosis, vasculitis, systemic coagulation disorders, and myelodysplasia. Herein, we describe the clinical manifestations and lab findings in a scurvy patient to raise awareness of this uncommon disease.

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Case Presentation

A 56-year-old white man was sent to the emergency room with shortness of breath, ankle swelling, and bruising on both legs. He described onset of skin rash about 1 year ago, and leg bruising 2 weeks ago. He felt fatigue recently and developed shortness of breath several days ago. He denied any trauma, frank bleeding from any source, previous or current medication usage. Regarding patient history, he admitted having used alcohol daily for the last 40 years and smokes 1 to 2 packs per day. He had poor gum with bad dentition requiring extraction, and poor diet habits for a long time. He denied anorexia, involuntary weight change, fever, or night sweats. Physical examination revealed extensive follicular hyperkeratosis, multiple ecchymoses on the inner thighs and multiple perifollicular petechiae on both legs. His heart rate, blood pressure, and body temperature all were within normal limits. His lab values were as follows: white blood cell (WBC) = 3.4 K/µL (low), red blood cell (RBC) = 1.9 millions/µL (low), hemoglobin (HGB) = 7.6 g/dL (low), hematocrit = 22.2% (low), mean cell volume = 116.8 fL (high), mean cell hemoglobin = 40 pg (high), red blood cell distribution width = 17.7% (high), platelets (PLT) = 133 K/µL (normal). Patient’s prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen were within normal limits. Peripheral blood smear showed macrocytes (Figure 1A), mild anisocytosis, and rare nucleated RBCs. WBCs showed normal maturation, with few metamyelocytes present. Few giant PLT were identified. Level of serum vitamin C was 0 mg/dL, Ferritin = 720 ng/mL (normal), vitamin B12 = 317 pg/mL (normal), and folate = 4.3 ng/mL (normal).

Bone Marrow Biopsy

A bone marrow biopsy was performed. The biopsy showed hypercellular marrow for age (90%) with trilineage hematopoiesis (Figure 1B). There was absolute erythroid hyperplasia and megaloblastic change (Figure 1B and C). The number and morphology of megakaryocytes were within normal limits. The iron stain revealed abundant amount of iron storage (Figure 1D), and retic stain revealed no increase in reticulin fibers. The aspirate smear revealed that the erythroid lineage had marked hyperplasia, left shift, and megaloblastic change. Flow cytometry analysis showed no immunophenotypic evidence for abnormal myeloid maturation, an increase in blasts or lymphoproliferative disorder. Cytogenetics and fluoro-
Clinical Medicine Insights: Case Reports

The patient was diagnosed as scurvy-associated anemia and was put on vitamin C therapy (500 mg, orally, twice a day), supplemented with multivitamin pills. Two weeks later, he reported back that his dyspnea was gone, skin discoloration disappeared, and his lab results showed HGB increased to 11.8 g/dL. The patient was continuing with oral vitamin C and multivitamin pills.

Discussion

Vitamin C (ascorbic acid) is an essential part of the well-being of HGB synthesis. Food that are high in vitamin C, include broccoli, brussels sprouts, and cauliflower, green and red peppers, spinach, cabbage, turnip greens, and other leafy greens, sweet and white potatoes, tomatoes and tomato juice, and winter squash. Vitamin C regulates iron metabolism and connective tissue remodeling via co-enzymatic activity of hydroxylation. A healthy adult maintains about 1500 mg Vitamin C in the body pool. When this pool drops below 350 mg, clinical symptoms, including follicular hyperkeratosis, perifollicular petechia, gum bleeding, and anemia start to appear. Scurvy-associated anemia can be microcytic, normocytic, or macrocytic. Diagnostically and therapeutically, the importance is self-evident to differentiate it from anemia of other etiologies. Table 1 summarizes the most important features of vitamin C, iron, folate, and vitamin B12 deficiency. All anemias present clinically with fatigue, shortness of breath, and muscle weakness. However, vitamin C deficiency has some unique changes such as follicular hyperkeratosis, coiled/corkscrew hairs, gingivitis, and perifollicular hemorrhage. Complete blood count and bone marrow biopsy are not that helpful to differentiate vitamin C deficiency from vitamin B12 or folate deficiency, in which all share similar features such as megaloblastic changes, but it is very helpful to differentiate it from other hematologic abnormalities such as myelodysplasia, anaplastic anemia, infectious or metastatic disorders. Due to bleeding tendency (petechia, ecchymosis, etc) for vitamin C deficiency, coagulation study for PT and activated PTT is also necessary to rule out coagulation-related disorders. Ultimately, serum level of vitamin C is the gold standard for making the diagnosis. Treatment-wise, patient should gradually recover within 1 week after the initiation of vitamin C intake.

The mechanism of the hematologic changes seen in vitamin C deficiency has been targeted in previous reports (Figure 2). It was long proposed that vitamin C is essential to folate and vitamin B12 metabolism. In a cross-sectional study, plasma folate concentration was 25% higher in vitamin C supplement users comparing to the control group. In another study, taking vitamin C alone was associated with a significant increase in red-cell folate, serum folate concentrations, and homocysteine concentrations. In another cross-sectional study, it is found that some folate metabolism-associated gene expression was influenced by the combination of vitamin C and natural folate intakes. In-vitro experiments have demonstrated that vitamin C assisted the converting of 5-Methyltetrahydrofolate.

Figure 1. Histopathology of vitamin C deficiency-associated megaloblastic anemia. (A) Macrocytic red blood cells on peripheral blood smear (×1000). (B) Bone marrow biopsy shows hyperplastic marrow with megaloblastic erythroid and myeloid precursors (×400). (C) Megaloblastic erythroid and myeloid precursors on marrow aspirate smear (×1000). (D) Moderate amount of iron storage in spicules, iron staining (×400).
Table 1. Comparison between patients with deficiency of vitamin C, iron, folate, or vitamin B12.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>VITAMIN C</th>
<th>IRON</th>
<th>FOLATE</th>
<th>VITAMIN B12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Dizziness</td>
<td>Headache, dizziness, or lightheadedness</td>
<td>Mouth and tongue sores</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Mental confusion or forgetfulness</td>
<td>Infarction or soreness of tongue</td>
<td>Shortness of breath</td>
<td>Decreased appetite</td>
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<tr>
<td></td>
<td>Shortness of breath</td>
<td>Unusual cravings for nonnutritive substances, such as ice, dirt, or starch.</td>
<td>Failure to thrive in infants</td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>Fatigue</td>
<td>Chest pain</td>
<td>Fatigue</td>
<td>Diarrhea</td>
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<tr>
<td></td>
<td>Weight loss</td>
<td>Extreme fatigue</td>
<td>Weakness</td>
<td>Tachycardia</td>
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<td>Numbness or tingling in extremities</td>
<td>Pale skin</td>
<td>Lethargy</td>
<td>Failure to thrive in infants</td>
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<tr>
<td></td>
<td>Muscle weakness</td>
<td>Brittle nails</td>
<td>Pale skin</td>
<td>Muscles weakness</td>
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<td></td>
<td>Unsteady movements</td>
<td></td>
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<td>Follicular hyperkeratosis</td>
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<td>Walking difficulty</td>
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<td>Perifollicular hemorrhages</td>
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<td></td>
<td>Wounds heal poorly</td>
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</table>

| CBC | Microcytic, normocytic, or macrocytic anemia. | Microcytic/hypochromic erythrocyte indices in conjunction with ovalocytes. Reticulocyte count is not appropriately elevated for the degree of anemia. The RBC distribution width is elevated. Mild thrombocytosis. | Macrocytic/normochromic anemia with oval macrocytes and disrupted erythrocytes. Pancytopenia and hypersegmented neutrophils. The RBC distribution width is elevated. Normal serum cobalamin and serum methylmalonic acid and increased homocysteine. | Macrocytic/normochromic anemia with oval macrocytes and disrupted erythrocytes. Pancytopenia and hypersegmented neutrophils. The RBC distribution width is elevated. Decreased serum cobalamin and increased serum methylmalonic acid and homocysteine. |
| Differential diagnosis | Hematologic abnormalities | Thalassemia Hemoglobin E | Drug treatments Reticulocytosis Alcohol abuse Liver disease Myelodysplasia HIV-1 | Drug treatments Reticulocytosis Alcohol abuse Liver disease Myelodysplasia HIV-1 |
| | Medication side effects | Lead poisoning Anemia of chronic disease Congenital sideroblastic anemia Copper deficiency-associated anemia Congenital ataxia/frenkinemia | | |
| | Infections Ulcerative gingivitis Collagen vascular disorder Deep venous thrombosis Vitamin deficiencies Trauma to the legs and joints | | |

Abbreviations: CBC, complete blood count; GI, gastrointestinal; RBC, red blood cell.

Vitamin C is controversial, varying from 75 to 200 mg/d for healthy adults to ensure tissue saturation between 60% to 100%.4,15-19 However, some authors argue that this amount is not enough to protect the fully reduced folates and suggest 500 mg/d vitamin C intake instead.20

Conclusions
Due to its rarity in modern society, scurvy is usually not in the first line of differential diagnoses for anemia/bleeding patients. Skin manifestations, such as follicular hyperkeratosis and perifollicular hemorrhage, are relatively unique for scurvy-associated anemia/bleeding and should trigger the clinician to look into vitamin C deficiency. Morphologic examination of peripheral blood and bone marrow is largely not very useful to differentiate among...
nutrition-related anemia (except iron deficiency anemia), but these examinations have pivotal value to rule out nondeficiency-related anemia, such as myelodysplasia, and aplastic anemia. Serum level of vitamin C is the gold standard for definite diagnosis, and supplement of vitamin C provides cure for the disease.

Author Contributions
Conception or design of the work (DC). Data collection (AA, DC). Data analysis and interpretation (AA, DC). Drafting the article (AA). Critical revision of the article (DC). Final approval of the version to be published (AA, DC).

References