1 Lost at Sea in Search of a Diagnosis: A Case of Explained Bleeding

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3 ABSTRACT

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| PT | prothrombin time |
| INR | international normalized ratio |
| aPTT | activated partial thromboplastin time |
| NOS | not otherwise specified |
| MRI | magnetic resonance imaging |
| US | ultrasound |
| ESR | erythrocyte sedimentation rate |
| CRP | C reactive protein |



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Scurvy results from a dietary deficiency of Vitamin C (ascorbic acid), and is rarely thought of in modern day medicine. It now almost always occurs in pediatric patients with behavioral diagnoses, nutritionally restricted diets, and food allergies. Symptoms of scurvy include ecchymoses, bleeding gums, and arthralgias. Here, we present a 17 year old male with autism spectrum disorder and a diet severely deficient in ascorbic acid due to textural aversion and food preferences. He presented with recurrent arthritis, hemarthrosis, bruising, and anemia. His vitamin C level was low, and his symptoms improved promptly after treatment with ascorbic acid.

BRIEF REPORT

A 17 year old male was admitted to the Hematology Service with fever, left knee arthritis, hemarthrosis, and anemia. His medical history was significant for autism spectrum disorder and constipation. Prior to this presentation, he had one episode of a right knee hemarthrosis and was diagnosed with von Willebrand Disease at an outside institution. He presented to our institution and a bleeding disorder evaluation was obtained which was largely inconclusive. Von Willebrand antigen, ristocetin cofactor, and von Willebrand factor multimer distribution were normal. Hemoglobin was 6.5 g/dL (normal range 13.5-17.5), white blood cell count was 3,890/µL (normal range 4,500-11,000), and platelet count was normal. Prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) were normal. Factor VIII was 245% (normal range 50-105). Factor II, V, VII, IX, X, XIII levels and platelet aggregation studies were normal. His hemarthrosis did not respond to desmopressin infusion, plasma derived factor FVIII/VWF concentrate, fresh frozen plasma, or ε-aminocaproic acid. The event resolved slowly on its own and he was discharged from the hospital with a diagnosis of bleeding disorder NOS. His evaluation was resumed two years later when his left knee hemarthrosis recurred. Orthopedics performed arthrocentesis which showed bloody fluid with

neutrophilic predominance. He had a normal muscle biopsy. He was then referred to Rheumatology and had a negative evaluation for rheumatologic causes of arthritis.

His hemarthrosis persisted and he then developed daily fevers and increased left knee pain. He was again admitted to the Hematology Service. Physical exam showed his weight and height between the 11$^{th}$ and 16$^{th}$ percentile for age. Musculoskeletal exam was significant for swelling of the left knee with overlying warmth and tenderness to palpation, but without erythema. Range of motion in flexion was limited to 60 degrees due to pain. Skin exam revealed pallor and mild jaundice, and there was ecchymosis present over the medial aspect of the left knee. Corkscrew hairs were present on bilateral lower extremities.

Due to concern for septic arthritis, blood cultures were obtained, and he was started on IV cefazolin. Complete blood count again showed leucopenia and anemia. Blood smear showed marked hypochromia and slight basophilic stippling. Erythrocyte sedimentation rate was 86 mm/hr (normal range 0-15) and C reactive protein was 5.8 mg/dL (normal range 0-1). Coagulation factors were abnormal with PT of 16.2 seconds (normal range 11.3-15.6), fibrinogen of 443 mg/dL (normal range 164-382), and D-dimer of 7.76 mcg/dL (≤0.49). Orthopedics was consulted and did not feel the patient's clinical exam was consistent with septic arthritis. MRI of left knee was obtained, and showed profound synovitis with the appearance of hemarthrosis of the knee, myositis, and patchy marrow signal changes in the distal femur and proximal tibia suggestive of osteopenia. US of the left knee showed a fluid collection which was drained and consistent with hemarthrosis. Blood culture remained negative, and aerobic, anaerobic, fungal and acid fast bacilli cultures from the fluid aspirate showed no growth. Antibiotics were discontinued as infection seemed unlikely.

Due to his recurrent hemarthrosis, arthritis, and anemia, we searched for a unifying diagnosis. Rheumatology was consulted and conducted a thorough dietary history. It was found that the patient's diet was extremely limited due to texture aversion and food preferences. His diet

consisted primarily of grilled cheese sandwiches, cottage cheese, chocolate milk or soda. He ate no citrus fruits or vegetables. This raised clinical suspicion for scurvy, as his diet contained no Vitamin C. Vitamin C level was obtained and was extremely low at less than 0.1 mg/dL (normal range 0.6-2.0 mg/dL). He was started on IV ascorbic acid 250 mg daily, which was then transitioned to 250 mg orally twice daily. His left knee showed decreased swelling, warmth, and tenderness to palpation. He was able to be discharged home.

The patient was seen as an outpatient in Rheumatology Clinic 8 months later, and reported no joint pain or swelling. His pallor, jaundice, and ecchymoses had resolved. He remained on Vitamin C and multivitamin supplementation. Laboratory values including white blood cell count, hemoglobin, vitamin C level, ESR, CRP, and bilirubin normalized.

## DISCUSSION

Scurvy was first widely described by James Lind in his study of sailors at sea in 1753. Since that time, the disease has largely been eradicated due to advances in dietary content. [1] It is a clinical syndrome seen due to ascorbic acid deficiency. Ascorbic acid is needed as a cofactor for collagen synthesis. Many of the clinical symptoms of scurvy relate to its role in collagen synthesis. Humans, due to their inability to convert glucose to ascorbic acid, must ingest ascorbic acid, or Vitamin C, orally. Today, scurvy is largely thought of as a disease of the past. Scurvy still occurs in the adult population, most commonly in alcoholics, elderly, and patients with eating disorders. It is far rarer in the pediatric population, but can be seen in children with psychiatric or behavioral syndromes, such as our patient. [2]

Scurvy can present with petechiae, ecchymosis, and perifollicular hemorrhages. [3] Other early findings include corkscrew hairs, gingival bleeding, and hyperkeratosis. Symptoms can progress to arthritis, bone and joint pain, fatigue, depression, poor wound healing and jaundice. [4] Bone pain is a common symptom in children, and is due to subperiosteal

hemorrhages and disordered bone formation. Anemia is also well-documented. [2] Case reports have also reported elevated inflammatory markers and defects in platelet aggregation. [5] Hemarthrosis can also occur, and is attributed to damage to synovial blood vessels. [6]

Our patient initially presented with recurrent hemarthrosis and arthritis. Bleeding disorder work-up was negative. In retrospect, he had many other clinical findings consistent with scurvy including persistent anemia, recurrent ecchymosis, and corkscrew hairs. He progressed to develop elevated inflammatory markers and jaundice. His MRI showed typical changes including patchy marrow suggestive of osteopenia, muscular signal abnormalities, and hemarthrosis. After a thorough dietary history, he was found to consume no essential Vitamin C. His Vitamin C level was very low, and his symptoms resolved with adequate Vitamin C supplementation. This case illustrates that scurvy should be considered in a patient with recurrent hemarthrosis or other significant bleeding manifestations with negative bleeding disorder evaluation and lack of clinical response to factor containing infusions. In addition, it is important to remember other etiologies for bleeding in the setting of a negative bleeding disorder work-up such as collagen vascular disorders like Ehlers-Danlos Syndrome. As hematologists, we should strive to expand our differential diagnosis when faced with significant or recurrent bleeding and normal hematologic evaluation.

CONFLICT OF INTEREST STATEMENT:

The authors have no conflicts of interest to report.

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Legend:

Figure 1: Corkscrew hairs, perifollicular hemorrhages, and petechiae on our patient which are a typical physical exam finding in scurvy.

Figure 2: Axial T2-weighted image with fat suppression reveals a moderate-sized joint effusion with layering blood products consistent with hemarthrosis.