WHEN BONE PAIN AND BLEEDING MEAN MORE THAN LEUKEMIA: THE CASE OF NUTRITIONAL DEFICIENCIES

Karen Fernandez¹, Anahita Emamian¹, Isra Abugroun¹, and Fred Laningham¹

¹Valley Children's Healthcare

February 2, 2023

WHEN BONE PAIN AND BLEEDING MEAN MORE THAN LEUKEMIA: THE CASE OF NUTRITIONAL DEFICIENCIES

AUTHORS:

Anahita Emamian, M.D. Valley Children's Pediatric Residency Program Stanford Medicine 9300 Valley Children's Place, Madera, CA 93736 Tel: (559) 353-5141. Fax: (559) 353-5318 AEmmamian2@valleychildrens.org Isra Abugroun, MBBS Division of Pediatric Endocrinology Valley Children's Healthcare 9300 Valley Children's Place, Madera, CA. 93636 IA bugroun@valleychildrens.orgFred Laningham, M.D. Department of Radiology Valley Children's Healthcare 9300 Valley Children's Place, Madera, CA. 93636 FLaningham@valleychildrens.org Karen S. Fernández, M.D. Division of Hematology/Oncology, Cancer and Blood Disorders Center Stanford Medicine Valley Children's Healthcare 9300 Valley Children's Place, Madera, CA. 93636 KFernandez@valleychildrens.org

Word count: 498

Figure: 1

Running Title: Nutritional deficiencies

Key Words: Scurvy, vitamin D deficiency, bone pain, bleeding, nutritional deficiencies

Conflict of Interest: The authors have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

WHEN BONE PAIN AND BLEEDING MEAN MORE THAN LEUKEMIA:

THE CASE OF NUTRITIONAL DEFICIENCIES

Anahita Emamian MD^{1,6}, Isra Abugroun MD^{1,2,6}, Fred Laningham^{3,6}, Karen S. Fernández MD^{1,4,5,6}

¹Department of Pediatrics,²Division of Endocrinology,³Department of Radiology,⁴Division of Hematology/Oncology, Cancer and Blood Disorders Center, ⁵Stanford Medicine

⁶ Valley Children's Healthcare. Madera, CA.

To the Editor

Bone pain and bleeding are among the most common symptoms of leukemia. Vitamin deficiencies are more commonly seen in developing countries where the access to healthy food is difficult. In resource-rich countries severe vitamin deficiencies are rarely seen and not always considered in the differential diagnosis¹. In developed countries, severe vitamin deficiencies are associated with restricted diets secondary to developmental or psychiatric problems¹. Both deficiencies can cause significant bone pain, which may mimic other diseases, including leukemia.^{1,2,3} Here we report two cases that presented with bone pain and/or bleeding and were found to have severe vitamin deficiencies.

CASE 1: 3-year-old Caucasian female with a history of autistic spectrum disorder (ASD) and developmental delay presented with a four-week history of worsening bilateral lower extremity pain and refusal to bear weight. X-rays of the pelvis and lower extremities showed lumbosacral spinal dysraphism and no other abnormalities. MRI of the spine was suggestive of an infiltrating marrow process. A dietary history uncovered a very restrictive diet consisting of almond milk and mashed potatoes. Complete blood cell count and bone marrow biopsy and aspirate were normal. 1-25-dihydroxy vitamin D and vitamin C levels were low. A follow up bone survey showed changes consistent with scurvy but not rickets.

CASE 2: A 4-year-old African-American female with history of ASD and severe developmental delay presented with an eight-week history of worsening bilateral lower extremity pain and decreased mobility with mild edema and bruising on her left ankle. On examination the patient was smaller for her age and her weight was < 1%ile. She was in severe pain and barely tolerated palpation. She had gum bleeding and bruises in her legs. CBC informed hypochromic microcytic anemia. Inflammatory markers, ESR and CRP were elevated. Bone marrow biopsy was normal. 1-25-hydroxy vitamin D level was low at 18 ng/dL. A bone survey showed metaphyseal radiolucencies to varying degrees, concerning for scurvy. Dietary history informed of a restrictive diet of mashed potatoes.

Both patients were started on vitamin C and D supplementation with resolution of bone pain, bleeding and recovery of motor function and overall wellbeing.

In children, vitamin D deficiency can lead to muscle pain, skeletal defects, and osteopenia.⁴ Scurvy or vitamin C deficiency is a rare and mostly a forgotten disorder in modern times.^{1,2}Classical signs of scurvy include gingival lesions with inflammation, hypertrophy and bleeding resulting in loosened teeth. The deficiency worsens in stages. Mucocutaneous manifestations appear in the second stage including dry skin, folliculitis, vascular purpura and painful hematomas. Third stage symptoms are of musculoskeletal nature, involving

osteoporosis, bone growth abnormality, and subperiosteal or intraosseous hemorrhagic lesions. In the final fourth stage the general physical condition worsens with asthenia which perpetuates food selectivity.

Radiographic findings suggestive of scurvy have been previously described and were seen in both cases (Figure 1).^{5,6}

These cases of advanced scurvy and vitamin D deficiency highlight the importance of recognizing the clinical manifestations and radiographic findings of the disorder to avoid extensive hospitalization and expensive work-up, and provide prompt supplementation.

References:

- Trapani S, Rubino C, Indolfi G, Lionetti P. A Narrative Review on Pediatric Scurvy: The Last Twenty Years. Nutrients. 2022 Feb 6;14(3):684. doi: 10.3390/nu14030684. PMID: 35277043; PMCID: PMC8840722.
- Chalouhi C, Nicolas N, Vegas N, Matczak S, El Jurdi H, Boddaert N and Abadie V (2020) Scurvy: A New Old Cause of Skeletal Pain in Young Children. Front. Pediatr. 8:8. doi: 10.3389/fped.2020.00008
- Algahtani HA, Abdu AP, Khojah IM, Al-Khathaami AM. Inability to walk due to scurvy: A forgotten disease. Ann Saudi Med. 2010 Jul-Aug;30(4):325-8. doi: 10.4103/0256-4947.65266. PMID: 20622353; PMCID: PMC2931787.
- Wacker, Matthias, and Michael F Holick. "Vitamin D effects on skeletal and extraskeletal health and the need for supplementation." Nutrients vol. 5,1 111-48. 10 Jan. 2013, doi:10.3390/nu5010111
- Snoddy AME, Buckley HR, Elliott GE, Standen VG, Arriaza BT, Halcrow SE. Macroscopic features of scurvy in human skeletal remains: A literature synthesis and diagnostic guide. Am J Phys Anthropol. 2018 Dec;167(4):876-895. doi: 10.1002/ajpa.23699. Epub 2018 Oct 9. PMID: 30298514; PMCID: PMC6282809.
- Niwa T, Aida N, Tanaka Y, Tanaka M, Shiomi M, Machida J. Scurvy in a child with autism: magnetic resonance imaging and pathological findings. J Pediatr Hematol Oncol. (2012) 34:484–7. 10.1097/MPH.0b013e318236c519
- 7. Wacker, Matthias, and Michael F Holick. "Vitamin D effects on skeletal and extraskeletal health and the need for supplementation." *Nutrients* vol. 5,1 111-48. 10 Jan. 2013, doi:10.3390/nu5010111



FIGURE 1. Patient exhibited radiographic signs of scurvy on X-ray of the left knee and on a CT of the left hip, and showed similar findings in other long bones on a skeletal scurvy. Demineralization of the cortex of metaphyses results in a characteristic radiographic "ground glass" appearance, alternating radiolucent (Trümmerfeld zone) and radiopaque (White line of Frankel) bands, which represent defective bone matrix formation and poor resorption respectively. Wimberger Ring Sign was more subtle in our cases.



FIGURE 1. Patient exhibited radiographic signs of scurvey on X-ray of the left knee and on a CT of the left hip, and showed similar findings in other long bones on a skeletal survey: Demineralization of the cortex of metaphyses results in a characteristic radiographic "ground glass" appearance, alternating radiolucent (Trümmerfeld zone) and radiopaque (White line of Frankel) bands, which represent defective bone matrix formation and poor resorption respectively. Wimberger Ring Sign was more subtle in our cases.