Middle Eastern Adolescent With Macrocytic Anemia

Sneha Butala, BS¹ and Brian Berman, MD²

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Case Presentation

A 14-year-old previously healthy adolescent female was referred to the emergency department for complaints of fatigue and weakness. She had been seen 1 day prior at her primary care physician’s office and was found to have a hemoglobin level of 6.7 g/dL. Over the past month, she had been feeling “weak” and “looking more pale.” She was born and raised in Iraq, of Chaldean ethnicity, and recently moved to the United States with her family. When she was 2½ years old she was diagnosed with anemia. A blood transfusion was attempted but discontinued because of a rash. Her mother was told that her stomach “couldn’t suck out the iron,” and the patient was placed on folic acid and vitamin B₁₂ for treatment of her anemia. However, she only took the medication when she felt fatigued, and since moving to the United States, she had not taken any medication. Her last menstrual period was 4 days prior to presentation. Her menstrual cycles occurred regularly every 4 weeks and generally lasted 2 days in length.

In the emergency department, she was afebrile, with a heart rate of 115 bpm and blood pressure of 119/74 mm Hg. She was alert and interactive. Physical examination was remarkable for pallor, but otherwise normal without jaundice, adenopathy, or hepatosplenomegaly. Initial laboratory analysis as depicted in Table 1 revealed pancytopenia with macrocytic anemia and reticulocytosis.

Blood smear showed polychromasia with target cells, teardrop cells, schistocytes, and spherocytes. Her lactate dehydrogenase was elevated at 1870 U/L (100-275), and iron studies showed a decreased iron level at 20 µg/dL (30-160), normal total iron binding capacity of 294 µg/dL (228-417), and decreased % saturation of 7% (15% to 55%). A vitamin B₁₂ level of 106 pg/mL (271-870) and a folate level of 17.3 ng/mL (>5.4) were obtained. Her comprehensive metabolic panel was within normal limits.

On further evaluation in the hematology clinic, serum homocysteine and serum methylmalonic acid (MMA) levels were both elevated at 35 µmol/L (4-14) and 25 nmol/mL (<0.40), respectively, and a red blood cell folate level was normal at 582 ng/mL (>280), supporting the diagnosis of vitamin B₁₂ deficiency. Anti-parietal cell antibody test for pernicious anemia was negative, and she was diagnosed with a presumed genetic defect causing intrinsic factor deficiency.

She was placed on weekly vitamin B₁₂ 1000 µg intramuscularly as well as a course of iron polysaccharide 300 mg daily. Over subsequent visits, she became more energetic. She became fully active without limitations and exhibited no neurologic symptoms including paresthesias or weakness. Her complete blood count, reticulocyte count, and vitamin B₁₂ levels normalized (see Table 2).

Table 1. Initial Evaluation.

| Component | Reference Range | Result  |
|-----------|-----------------|--------|
| WBC       | 4.5-13.0 bil/L  | 2.8 bil/L |
| RBC       | 3.83-5.30 tri/L | 1.91 tri/L |
| Hemoglobin| 11.7-15.6 g/dL  | 6.7 g/dL |
| Hematocrit| 34.6% to 45.5%  | 20.9%   |
| MCV       | 80-96 fl        | 109 fl   |
| MCH       | 27-33 pg        | 36 pg    |
| MCHC      | 33-35 g/dL      | 33 g/dL  |
| RDW       | 11% to 14%      | 23%     |
| Platelets | 150-450 bil/L   | 119 bil/L|
| Neutrophils| 1.8-8.0 bil/L  | 0.8 bil/L|
| Lymphocytes| 1.2-5.2 bil/L  | 1.6 bil/L|
| Monocytes | 0.2-0.7 bil/L   | 0.2 bil/L|
| Eosinophils| 0.1-0.4 bil/L  | 0.1 bil/L|
| Reticulocytes| 19-80 bil/L    | 408 bil/L|

Abbreviations: WBC, white blood cell; RBC, red blood cell; bil, billion; tri, trillion; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

¹William Beaumont School of Medicine, Oakland University Rochester, MI, USA
²Beaumont Children’s Hospital, Royal Oak, MI, USA

Corresponding Author:
Sneha Butala, Oakland University William Beaumont School of Medicine, O’Dowd Hall Rm 428, 586 Pioneer Drive, Rochester, MI 48309-4402, USA.
Email: srbutala@oakland.edu
Table 2. Evaluation Posttreatment.

| Component   | Reference Range | Result   |
|-------------|-----------------|----------|
| WBC         | 4.5-13.0 bil/L  | 5.3 bil/L|
| RBC         | 3.83-5.30 tri/L | 4.63 tri/L|
| Hemoglobin  | 11.7-15.6 g/dL  | 13.4 g/dL|
| Hematocrit  | 34.6% to 45.5%  | 39.0%    |
| MCV         | 80-96 fl        | 84 fl    |
| MCH         | 27-33 pg        | 29 pg    |
| MCHC        | 33-35 g/dL      | 34 g/dL  |
| RDW         | 11% to 14%      | 14%      |
| Platelets   | 150-450 bil/L   | 235 bil/L|
| Reticulocytes| 19-80 bil/L    | 70 bil/L |
| Vitamin B<sub>12</sub> level | 271-870 pg/mL | 303 pg/mL |

Abbreviations: WBC, white blood cell; RBC, red blood cell; bil, billion; tri, trillion; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

After normalization of hematologic parameters, she was placed on lifelong monthly vitamin B<sub>12</sub> injections (1 mg).

**Final Diagnosis**

Vitamin B<sub>12</sub> deficiency secondary to an autosomal recessive founder mutation in the intrinsic factor gene, GIF, limited to the Chaldean Middle Eastern population.

**Discussion**

Vitamin B<sub>12</sub> deficiency results in defective DNA synthesis, presenting with hematological, gastrointestinal, and neurologic manifestations.<sup>1</sup> The major hematologic findings are a result of ineffective erythropoiesis.<sup>2</sup> A delay in blood cell maturation causes macrocytic anemia (mean corpuscular volume >100), decrease in white blood cell counts and platelets.<sup>3</sup> Characteristic megaloblastic changes include hypersegmented neutrophils on peripheral blood smear. Intramedullary hemolysis due to death of erythroid precursors eventually result in elevated serum levels of lactic dehydrogenase and bilirubin.<sup>1,4</sup> In distinguishing folate deficiency from vitamin B<sub>12</sub> deficiency (cobalamin [Cbl]) deficiency, it is important to obtain a homocysteine level and MMA level. While folate deficiency will cause an elevation in homocysteine levels, only a deficiency in Cbl will cause an elevation of both homocysteine and MMA.<sup>5</sup> These above-mentioned findings were present in our patient. Cbl is required for myelin synthesis and a deficiency can lead to peripheral neuropathy including paresthesias, myelopathy, and optic nerve atrophy.<sup>7</sup> A serious demyelinating complication is subacute combined degeneration of the spinal cord in which the dorsal and lateral tracts of the spinal cord degenerate producing progressive paresthesias, weakness, decreased vibration sense, sensory ataxia, spasticity, paraplegia, and bowel and/or bladder incontinence.<sup>1</sup> All of the above-mentioned clinical findings can occur in both adults and children; however, children can also present with failure to thrive, irritability, developmental delay regression, and poor school performance.

Half of the body’s vitamin B<sub>12</sub> reserve is stored; it takes years of malabsorption to develop a deficiency.<sup>4</sup> Dietary sources of vitamin B<sub>12</sub> are primarily found in animal products including meat and dairy.<sup>6</sup> On ingestion, Cbl is liberated from food binding proteins by gastric acid and peptic and binds R-proteins found within saliva and gastric secretion. Gastric parietal cells release intrinsic factor (IF), which enter the duodenum along with newly formed Cbl-R-protein complexes. Here, pancreatic proteases act to free R-proteins from Cbl and allow it to bind to IF. The Cbl-IF complex then binds specific Cb-IF receptors in the terminal ileum, and Cbl is absorbed.<sup>2</sup>

There are 5 main factors required for proper Cbl absorption: adequate dietary intake, presence of gastric acid and peptic, functional pancreatic enzymes, intrinsic factor, and an intact ileum with Cbl-IF receptors. In adults, the most common cause of Cbl deficiency is due to lack of intrinsic factor secondary to pernicious anemia or gastric disease.<sup>2</sup> In pernicious anemia, auto-antibodies destroy gastric parietal cells, inhibiting the secretion of intrinsic factor, although auto-antibodies directly against intrinsic factor itself are seen in a minority.<sup>2</sup> Gastrectomy, especially during bariatric surgery, and gastritis cause an absence of gastric acid and peptic. Other etiologies include a vegan diet, *Helicobacter pylori* infection, chronic alcoholism, long-term use of antacids such as proton pump inhibitors or H2 antagonists, and severe pancreatic disease. Conditions such as inflammatory bowel disease (especially Crohn’s disease), celiac disease, tropical sprue, and prior pelvic radiation can affect the terminal ileum, impeding Cbl absorption.<sup>5</sup>

In children specifically, deficiency is attributed to inadequate diet, infection, or hereditary disorders.<sup>7</sup> Over the past 50 years, there has been a dramatic decrease in the incidence of nutritional or infectious Cbl deficiency, and inherited defects have become a leading cause of Cbl deficiency in children.<sup>8</sup> Reports of dietary insufficiencies are mainly seen in breastfed infants of vegan mothers who have untreated vitamin B<sub>12</sub> deficiency and low vitamin B<sub>12</sub> storage, children with unrecognized pernicious anemia, previous gastric bypass surgery, or short gut syndrome.<sup>5</sup> Long-term use of medications that affect gastric acid secretion such as antacids and pancreatic insufficiency also cause Cbl deficiency in children, but these are relatively rare etiologies compared to the adult population. In developing countries, parasitic infections, especially *Diphyllobothrium latum* (tape-worm) cause low serum vitamin B<sub>12</sub> levels.<sup>5,8</sup>
There are 2 known hereditary conditions of Cbl deficiency: Imersland-Gräsbeck syndrome (IGS) and inherited intrinsic factor deficiency (IFD). In IGS there are various biallelic mutations in either the cubulin (CUBN) or amnionless (AMN) gene, both of which are required for formation of the Cbl-IF receptor located in the terminal ileum of the small intestine. IFD involves various mutations of the gastric intrinsic factor gene, GIF, and leads to a complete absence of intrinsic factor. Both IGS and IFD are inherited as autosomal recessive mutations and present with symptoms of Cbl deficiency. However, they differ in that IGS usually presents with proteinuria and is not corrected by administration of intrinsic factor. Moreover, IGS is specifically described in patients from a northern European or Scandinavian descent. IFD is linked to patients of Mediterranean descent, and cases in literature have identified 2 different novel mutations in GIF responsible specifically in the Chaldean population.

Our patient’s final diagnosis was vitamin B₁₂ deficiency secondary to an autosomal recessive founder mutation in the intrinsic factor gene, GIF, limited to Chaldeans. Her symptoms of fatigue and pallor, in association with macrocytic anemia and mild pancytopenia, led to a diagnosis of B₁₂ deficiency. Given the absence of gastrointestinal symptoms, no medication use, and negative studies for pernicious anemia, coupled with her Chaldean ethnicity, the diagnosis of IFD became readily apparent. Although the historical and gold standard confirmation for IFD is the Schilling test, it is largely unavailable and rarely used in the clinical setting in the current era. Despite the ability to sequence all 3 genes involved in IGS and IFD, the task is complicated due to genetic heterogeneity and extremely limited availability. Beyond hematologic manifestations, it is critically important that vitamin B₁₂ deficiency is diagnosed to avoid potential irreversible neurologic consequences. Treatment is straightforward and lifelong—essentially monthly vitamin B₁₂ injections. Our patient responded well to treatment with full resolution of clinical and laboratory findings.

Conclusion

Macrocytic anemia in a child of Middle Eastern origin, particularly Chaldean ethnicity, should immediately raise the consideration of constitutional intrinsic factor deficiency, leading to appropriate evaluation and intervention.

Author Contributions

SB: Contributed to conception and design; contributed to analysis; drafted the manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

BB: Contributed to conception and design; contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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