CLINICAL VIGNETTE

Iron Deficiency Neutropenia

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A 23-year-old female presented with an abnormal complete blood count (CBC). She was otherwise healthy with no significant past medical history. The patient had a white blood cell count of 2.8 ($x10^3$/microL), hemoglobin of 8.7 g/dL, mean corpuscular volume of 64 fL and platelets elevated at 407 ($x10^3$/microL). She also had mild neutropenia with absolute neutrophil count of 1200 ($x10^3$/microL). Given the microcytic anemia, the patient confirmed heavy menses which were being evaluated by gynecology. She had no other sources of bleeding. She noted fatigue but no chest pain or shortness of breath and no recent infections. She had no personal or family history of hemoglobinopathies. Examination was unremarkable without hepatosplenomegaly or lymphadenopathy. Laboratory testing included: ferritin of 3 ng/mL, iron of 21 mcg/dL, iron binding capacity of 543 mcg/dL with 4% saturation. Folate and vitamin B12 levels were normal. She had been previously told to start oral iron but did not tolerate high doses due to worsening constipation and nausea. She received two weekly infusions of ferumoxytol with subsequent normalization of her labs by six weeks. Repeat white blood cell count was 4.3 ($x10^3$/microL), absolute neutrophil count of 2260($x10^3$/microL), hemoglobin of 13.2 g/dL, mean corpuscular volume of 86 fL and platelets of 245 ($x10^3$/microL). Iron values also improved to ferritin of 36 ng/mL, iron of 84 mcg/dL, TIBC of 310 mcg/dL, and % Sat of 27. She was monitored closely and when iron values fell, she developed recurrent anemia, leukopenia/neutropenia, and thrombocytosis. Repeat iron infusions would readily resolve all her blood count abnormalities. She continued with periodic iron infusions following drops in her blood counts and/or iron values.

Iron deficiency anemia is the most common nutrient deficiency in the world and develops when the limited presence of iron interferes with erythropoiesis.[1] Iron absorption needs to compensate for blood losses.[1] In addition to low hemoglobin, hematocrit, and red blood cell values, there can be microcytosis, ferritin levels<30ng/mL, and reactive thrombocytosis.[1] Leukopenia due to neutropenia (defined as ANC<1500cells/microL) is related to low total white blood cell numbers and is not a common consequence of iron deficiency.[1,2] However, published case reports have indicated an association between neutropenia and iron deficiency anemia.[1] While iron supplementation is expected to correct iron deficiency anemia, the mechanism by which it helps the rare cases of concurrent neutropenia is unclear.[1] Interestingly, in most of the published case reports, correction of the leukopenia was incidentally noted after resolution of the known iron deficiency anemia.[2] Iron deficits have known effects on other parts of the body including thyroid metabolism, cognitive development, sleep disorders, fertility, and even diabetes management.[1] However, the consequences of low iron with regards to the immune system and white blood cells are not well-characterized.[1] Some proposed theories report iron is necessary in the bone marrow microenvironment to stimulate myeloid production or that it has effects on progenitor cells.[2,3] Animal models report high erythropoietin (the hormone that instigates red blood cell production in the bone marrow) levels in iron deficiency anemia, but with the same hormone decreasing neutrophil development.[3] Some report the incidence of leukopenia with iron deficiency anemia is more common than recognized and low white blood cell counts correlate with the degree of anemia.[4] Another retrospective study found neutropenia in 4% of patients with iron deficiency anemia and all cases of neutropenia corrected with iron repletion.[3]

In our premenopausal patient, iron deficiency anemia is not uncommon given heavy monthly menstrual iron losses that could not be maintained with gastrointestinal absorption of oral iron alone. Although gynecology worked to control the bleeding, there was no quick improvement of her menorrhagia. Thus, monitoring and treatment of her iron deficiency became a chronic issue. She was followed for many years off and on oral iron with inconsistent compliance. Her white blood cell counts could be as low as 2.0 ($x10^3$/microL) with neutrophil counts below 800 ($x10^3$/microL) when her iron deficiency was severe. When she received periodic iron infusions when iron values started to decline before any cytopenias, she avoided neutropenia and anemia. While not conventional to check iron levels when patients present with neutropenia, several case reports suggest that iron repletion may be an easy solution in some patients and may minimize unnecessary and expensive evaluation.

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