CLINICAL VIGNETTE

Graves' Disease with Leukopenia and Microcytosis

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Case Presentation

A 25-year-old female presented to primary care clinic with complaints of shortness of breath for 2 months. The patient stated she also had intermittent dizziness and a 10 lb. weight loss over the preceding 2 months. No changes in appetite, heat intolerance, increased perspiration, emotional liability, or palpitations were reported. She otherwise denied any additional symptoms. Her family history was significant for hyperthyroidism in her maternal grandmother who had hyperthyroidism. The patient was originally from Egypt and migrated to the U.S. in 2011.

On the initial physical exam, patient was a thin female in no acute distress. Her vitals were blood pressure 118/54, heart rate 120, temperature 98.1^{o}F, and a BMI of 19.02. Her head and neck exam was significant for right-sided, non-tender goiter. No exophthalmos lid retraction or lid lag on eye exam. She was mildly tachycardic, but otherwise no murmurs or extra heart sounds were appreciated. Her lungs were clear to auscultation; abdominal exam was within normal limits. She was noted to have fine tremor bilaterally; her skin was warm to touch, no hair loss, and reflexes 2+ and symmetric.

Initial labs were notable for a WBC count of 3.47 x 10E3/uL (which was below range of normal on our laboratory parameters), hemoglobin of 12.7 g/dL, red blood cell count of 4.81 x10E6/uL (which was elevated on our laboratory parameters), MCV of 78.4 fL (microcytosis) and RDW 12.8%, platelets 180x10E3/uL, Neutrophil percentage of 59.6, ANC 2.4x10E3/uL, lymphocyte percentage of 32.6, and ALC 1.3x10E3/uL. Her thyroid studies were consistent with Graves' Disease, TSH <0.02 mcIU/mL, Free T3 813, Free T4 2.7 ng/dL, TSH stimulating Ig 445 %, TSH receptor ab 5.7 U/L, Thyroglobulin antibody <0.9 IU/mL, and TPO Ab 5.9 IU/mL. Iron studies were within normal limits with an Iron level of 125 mcg/dL, TIBC 277 mcg/dL, percent sat 45, and Ferritin 74 ng/mL. Chemistry panel was significant for creatinine of 0.4 mg/dL, hemoglobin A1C of 4.7, calcium of 10.4 mg/dL, bilirubin of 1.5 mg/dL, alkaline phosphatase of 62 U/L, and AST / ALT of 29/34 U/L. Albumin was 4.1 g/dL, total protein 6.5 g/dL. Her folate was found to be normal at 17.1 ng/mL. Peripheral blood smear showed microcytosis with hypochromic red blood cells and no other abnormalities.

A diagnosis of Graves' disease hyperthyroidism was made at this time. The patient was initially started on methimazole 20 mg by mouth daily and propranolol 10 mg by mouth three times per day, as well as referred to endocrinology. She was seen by endocrinology two weeks after her initial primary care clinic appointment, and her methimazole was increased to 30 mg PO daily. Two weeks after the increased dose of methimazole, her labs were as follows: WBC 6.22 x10E3/uL, hemoglobin 13.8 g/dL, RBC count of 5.22 x10E3/uL, MCV 81.2 fL, RDW 16%, platelets 187 x10E3/uL, neutrophils 67.4%, ANC 4.2 x10E3/uL, lymphocyte 23.8%, and ALC 1.5 x10E3/uL. Thyroid studies indicated TSH <0.02 U/L, FT3 289 pg/dL, and FT4 0.9 ng/dL. Her chemistry panel was within normal limits, and her total bilirubin returned to 0.8 mg/dL.

Discussion

Graves' disease is a common cause of hyperthyroidism, accounting for about 50-80% of the cases of hyperthyroidism with a prevalence of 2.5% among women and 0.23% among men.[1-3] The peak incidence is between 40-60 years of age, although the disease can occur at any age. Symptoms of hyperthyroidism include weight loss, heat intolerance, difficulty sleeping, tremors, increased defecation, proximal muscle weakness, irritability, and irregular menses. Signs may include tachycardia, lid lag, proptosis, goiter, resting tremor, hyperreflexia, and warm/moist skin.[1] Laboratory findings include elevated serum T4 and T3 (with T3 usually higher than T4), elevated thyrotropin receptor antibodies or thyroid stimulating immunoglobulin.[4] Interestingly, hematologic abnormalities are frequently identified in the setting of thyrotoxicosis. Patients with thyrotoxicosis may have increase RBC mass, with a microcytosis, leukopenia, anemia, and rarely pancytopenia.[5,6] Exact mechanisms involved are poorly understood with many potential explanations including influence hematopoiesis, increased erythropoietin, impaired iron utilization, and ineffective erythropoiesis.

Thyroid hormones are thought to influence hematopoiesis through a variety of mechanisms, including direct stimulation of erythroid progenitor cells.[2,7-11] Golde found an increase in the CFUs in those cells exposed to thyroid hormone compared

to controls using in vitro assays with murine and human bone marrow.[9] The data suggest a direct stimulatory effect on the cell populations. Maglor investigated thyroid hormone effects in vivo using mouse models and found that thyroid hormones were capable of directly stimulating the bone marrow.[10] Finally, Axelrod collected bone marrow aspirates from patients in a hyperthyroid state were found to have a greater relative cell content compared to those who were euthyroid.[11] These studies support the idea of thyroid hormone's positive influence on hematopoiesis.

Other potential mechanisms for changes in the peripheral blood of hyperthyroid patients may be due to the increase in the metabolic rate and oxygen consumption. This can lead to tissue hypoxia and increased secretion of Erythopoeitin, leading to increase in red blood cells. In a study by Ma et al,[12] cell cultures were exposed to T3 and T4, and the EPO mRNA levels measured after the cultures were exposed to thyroid hormones. They found a statistically significant increase in the amount of EPO mRNA compared to controls. This may explain the increase in RBC mass in patients with hyperthyroidism. Interestingly, hemoglobin concentrations are generally normal because of a concomitant increase in plasma volume.[13] In our patient, we found an increase in the total RBCs with normal hemoglobin and hematocrit concentrations, which would support the previous findings.

If thyroid hormone stimulates hematopoiesis, then how can one explain anemia seen in thyrotoxicosis? A microcytic, normocytic, or macrocytic anemia has been found in 12-34% of patients with the disease.[2,5] Pernicious anemia may occur in 1-3% of cases, and 15-20% may have high concentration of anti-parietal cell antibodies.[6,14] Other explanations for the anemia seen include impaired iron utilization, ineffective erythropoiesis and, in long standing severe hyperthyroidism, malnutrition.[2,15,16] With treatment, the anemia can be reversed.[2,3,5,17] Our patient did not have an anemia but was found to have a microcytosis. Microcytosis can be seen in hyperthyroidism, in contrast to the macrocytosis seen in hypothyroidism. Etiologies to explain the microcytosis include iron deficiency or ineffective erythropoiesis. A study conducted by Nightingale looked at the hematologic profile of 239 patients pre- and post-treatment for hyperthyroidism. About 28% of the patients were anemic at the time of diagnosis. Complete pre- and post-treatment data were available for 111 patients who were not anemic at the time of diagnosis. In reviewing the data of the 111 non-anemic patients, the authors found a statistically significant increase in their MCV after treatment by 6 fl (SD +/-3.5 $p<0.01$).[17] Similar to the 111 patients studied in this project, our patient had a normal iron panel with a microcytosis. With treatment of her hyperthyroidism, her microcytosis improved.

In addition to microcytosis and anemia, leukopenia and neutropenia are well-known manifestations of thyrotoxicosis. Leukopenia and neutropenia have been reported in as many as 15-30% of patients with untreated thyrotoxicosis; however, the exact etiologies are poorly understood.[5] Per Irvine, in 1908 Emil Theodore Kocher described a characteristic blood picture of leukopenia, relative and absolute lymphocytosis with relative and absolute neutropenia in 106 patients with "Basedow's disease," also known as Graves' disease.[18] Since Kocher's description, there have been many papers confirming the finding. In 1977, Irvine et al[18] looked at 104 thyrotoxic patients compared to 107 controls and found a statistically significant difference in their blood count. Specifically, they found a statistically significant reduction in the total leukocyte count, which was attributed to a fall in the absolute neutrophil count.[18] After reviewing our patient's blood profile, there is a reduction in the total leukocyte count consistent with Kocher's originally observation, as well as the 1977 study by Irving et al.[18] Unfortunately, we did not have a baseline leukocyte count. However, her leukocyte count recovered once her thyrotoxic state was adequately treated. Furthermore, her initial absolute neutrophil count was 2.4, lower limit of normal. Upon improvement of her thyrotoxic state, her neutrophils rebounded, increasing to 4.2. The exact pathophysiology behind the changes in white blood cells is poorly understood and is an area for further research.

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