CLINICAL VIGNETTE

43-Year-Old Female Presenting with Yellowing of the Skin and Severe Anemia

Ana Rivera, MD

A 43-year-old female with a past medical history of type 2 diabetes mellitus, hyperlipidemia and hypertension presented with yellowing of the skin for the past few weeks. She denied any physical symptoms but was concerned about jaundice. She also shared that she had been eating about 20 oranges per day.

Review of systems was negative for headaches, fevers, chills, scleral icterus, rashes other than the jaundiced skin tone, abdominal pain, nausea, vomiting, diarrhea, arthralgias, or myalgias. She was taking metformin and rosuvastatin. She was no longer on anti-hypertensive medications, and she denied taking any supplements or vitamins. There were no recent medication changes nor recent travel. She denied any smoking or alcohol use and did not have any occupational exposures. Family history negative for liver disease or blood disorders.

On physical exam her vital signs were stable, and exam was only noticeable for jaundiced skin.

Laboratory evaluation revealed an abnormal complete blood count with hemoglobin of 6.4 g/dL decreased from 13.0 g/dL 8 months prior. The mean corpuscular volume was 63.9 g/dL from 82.9 g/dL. Platelets and white blood cell count were within normal limit. Given the acuity of the drop in hemoglobin, the patient was referred to the emergency department to rule out acute hemolytic anemia with jaundice and possible need for blood transfusion. Oher labs included normal comprehensive metabolic panel including total bilirubin (0.2 g/dL.) and conjugated bilirubin (<0.2 g/dL). On further history, patient revealed recent heavier menstrual bleeding. Patient was discharged from the emergency department with iron supplementation and outpatient follow up.

After taking the iron sulfate 325mg daily for 3 weeks, hemoglobin increased to 10.2 g/dL and normalized to 14.3 g/dL after 4 more weeks of treatment. The yellow skin tone resolved as well.

Definition and Epidemiology

This case demonstrates the potential of iron deficiency anemia to cause carotenemia if it induces pica. Carotenemia is defined as yellow-orange skin pigmentation due to high levels of carotene in blood.[1] The main foods that cause carotenemia are fruits and vegetables high in carotene such as carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, cantaloupe, and squash. It is important to consider this diagnosis in the differential as it can be indistinguishable from jaundice due to liver or hemolytic diseases leading to unnecessary investigations.[1]

Differential Diagnosis

The differential diagnosis of carotenemia includes liver diseases such as hepatitis from all causes: infectious, autoimmune, gallbladder-related, drug-induced. Also, hemolytic anemia can present similar and would include infections (malaria, babesiosis), autoimmune, drug-induced, alloimmune, enzymopathies (G6PD-deficiency, hemoglobinopathies, membranopathies (hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria), microangiopathic hemolytic anemia and thrombotic microangiopathy as the underlying causes.

Testing should include complete blood count, comprehensive metabolic panel with direct hemoglobin, iron studies and peripheral blood smear. If no other abnormalities are noted except iron deficiency anemia, further testing is not required.

Pathogenesis

The pathogenesis of how iron deficiency anemia can cause carotenemia was outlined in a case report by Nakagami et al. They reported a similar case of a woman with menorrhagia, gradual onset yellowing of the skin without scleral icterus and iron deficiency anemia to 6.9 ug/dL. She also reported changes to her diet that included increased number of uncooked carrots and 20 mint candies per day for 3 months. Similarly, the administration of iron supplementation resolved all cravings as well as the anemia and skin tone changes.[2] Pica has been reported in about half of patients with iron deficiency anemia and can take different forms.[3] If a patient's particular manifestation of iron deficiency-induced pica does not involve carotene-containing foods, the patient would not be expected to present with yellowing of the skin. It is also interesting to note that it is the iron deficiency and not the anemia that induces the pica behavior because within days of iron administration, pica resolves while it takes weeks for the anemia to fully resolve.[3]

Clinical Manifestations and Diagnosis

As in this case, the patient presented with yellow skin tone but no true jaundice or scleral icterus. The lack of scleral icterus in addition to a lack of other lab abnormalities except for the iron studies support the diagnosis of carotenemia as opposed to liver or hemolytic disease.

Treatment and Prognosis

The patient was treated with iron supplementation which was sufficient to overcome the heavy menstrual cycles and her hemoglobin normalized. Her pica resolved and she was also counseled to decrease consumption of oranges. All symptoms and lab abnormalities resolved.

Summary

This case illustrates the need to consider carotenemia when patients present with skin yellowing without scleral icterus. Of course, one should also consider new onset liver disease and hemolytic anemia. However, in the absence of scleral icterus, carotenemia should be high on the differential diagnosis and may also prompt physicians to inquire about dietary changes and guide the diagnostic evaluation. It is also important to consider anemia may be due to iron deficiency then as the underlying cause.

REFERENCES

1. **Al Nasser Y, Jamal Z, Albugeaey M**. Carotenemia. [Updated 2022 Jan 24]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534878/
2. **Nakagami F, Nozato Y, Yamamoto K, Rakugi H**. Carotenemia induced by iron deficiency. *BMJ Case Rep*. 2021 Jan 28;14(1):e236597. doi: 10.1136/bcr-2020-236597. PMID: 33509860; PMCID: PMC7845686.
3. **Crosby WH**. Pica. *JAMA*. 1976 Jun 21;235(25):2765. PMID: 946894.