Aerospace Medicine Clinic

This article was prepared by Maryrose D. Chuidian, D.O., M.P.H., and Kent-Andrew Boucher, M.D.

You are currently deployed as the flight surgeon at a location with only basic medical capabilities. One evening while manning the med bay, two airmen walk in assisting a third airman. This airman is a young female loadmaster you've flown with a few times during this deployment. As they get her to sit down, you observe she appears pale, disoriented, and extremely fatigued. Her friends inform you that they were all hanging out in their quarters when the loadmaster stood up, reached for a snack on the shelf, and passed out. One of her friends was able to catch her and assist her to the floor. The loadmaster appeared to be out for a "few minutes" prior to slowly regaining consciousness. She was able to sit up, although she required assistance to stand and walk to the med bay for further evaluation.

The loadmaster is a 24-yr-old woman with a past medical history significant for iron deficiency anemia (previously treated with oral iron supplements, but since discontinued), Hashimoto's thyroiditis (currently taking levothyroxine), and a gluten allergy with celiac disease ruled out. She reported worsening fatigue for approximately 1 mo, but in the past 3 d she developed increased dizziness and generalized weakness. She attributed her symptoms to being deployed, missing her family, and poor sleep hygiene, and thus did not seek medical attention. Additionally, she admitted to developing nausea, intermittent emesis, an episode of diarrhea, and decreased urine output over the last 48 h. She denies any dysuria, hematuria, or abdominal pain associated with the decreased urine output. She also denies any recent fevers, chills, myalgias, or contact with known COVID-19-positive individuals. Furthermore, she denies ever having lost consciousness before. Her initial vital signs were systolic blood pressure >100 mmHg, heart rate 140 bpm, and temperature 103°F. Her physical exam was positive for a pale and weak appearance, conjunctival pallor, tachycardia, and positive orthostatics. There were no concerns from medical personnel during her predeployment clearance regarding any of her medical history. Prior to deployment, thyroid-stimulating hormone (TSH) levels and complete blood counts (CBC) were within normal limits and were not a concern during medical out-processing.

1. What diagnoses are in your differential?
   A. Pernicious anemia.
   B. Undiagnosed alcohol use disorder.
   C. Hypothyroidism.
   D. Iron deficiency anemia.
   E. Infection.
   F. All of the above.

ANSWER/DISCUSSION

1. F. All of the choices above are potential etiology of this patient's symptoms. Pernicious anemia is a rare disorder that results in vitamin B12 deficiency, which is important to the functionality of hematologic and neurological systems. Your patient's history of present illness encompasses symptoms that can be associated with pernicious anemia: fatigue, nausea, diarrhea, and pale appearance.[12] Given her history of Hashimoto's thyroiditis, there is increased likelihood of anemia, since anemia and hypothyroidism are commonly found together. Thyroid hormone levels affect erythrocyte precursors, so inappropriate levels of TSH can negatively influence red blood cell (RBC) production. Thus, her history of Hashimoto's thyroiditis could be associated with a form of anemia and explain her presentation.[11] Additionally, a history of one autoimmune disorder increases the likelihood of another. Pernicious anemia, an autoimmune disorder, results in impaired absorption of cobalamin, i.e., vitamin B12.[12] The patient already reported a history of iron deficiency anemia; thus, it should remain on the differential. Both pernicious anemia and iron deficiency anemia can present together, so an iron panel and CBC with a peripheral smear could be of value to assist with differentiating origin. Usually, iron deficiency anemia is associated with microcytic anemia, while pernicious anemia can be normocytic or macrocytic, as seen with 30% of patients.[9] Chronic use of alcohol has harmful effects on RBCs, white blood cells, blood

DOI: https://doi.org/10.3357/AMHP.6264.2023

cell precursors, and platelets. Excessive use can lead to suppression of bone marrow and inhibit the growth of mature blood cell lines. Thus, undiagnosed alcohol use is also a potential etiology of the patient's underlying symptoms.[2]

Upon further discussion with the patient, she admits that since arriving at your deployed location a few months ago, she has transitioned to a full vegan diet. She denies a history of ever using drugs or drinking alcohol. Initial laboratory workup was limited to CBC, prothrombin time/partial thromboplastin time, aspartate aminotransferase/alanine aminotransferase, lactate dehydrogenase, and urinalysis. Pertinent positives included hemoglobin (Hb)/hematocrit (Hct), white blood cell, and RBC values reported as "undetectable." Partial thromboplastin time was within normal limits, and lactate dehydrogenase was elevated at $1000\,U \cdot L^{-1}$.

2. Aside from adding an iron panel and TSH/free T4, what other labs would you consider ordering to assist in narrowing the differential diagnosis?
   A. Serum B12.
   B. Peripheral blood smear.
   C. Intrinsic factor antibody.
   D. Parietal cell antibody.
   E. Phosphatidylethanol (PEth).
   F. All of the above.

ANSWER/DISCUSSION

2. F. All of the labs above can help narrow the differential diagnosis. Given the discovery that the patient has been a vegan for several months, there is a potential for vitamin B12 deficiency. Vitamin B12 is a critical component for producing blood cells and myelination of the nerves. Pernicious anemia results in impaired absorption of vitamin B12, leading to its deficiency, and can therefore result in profound anemia. There are no specific or "gold standard" tests for pernicious anemia. However, intrinsic factor antibody and parietal cell antibody are potential markers for pernicious anemia, although results are varied. Intrinsic factor antibody is highly specific (95–100%); however, it has a low sensitivity at 50–60%. As such, a positive test helps rule it in, although a negative test doesn't rule it out. Additionally, parietal cell antibody testing can be positive, but also has a mixed specificity between 50–100%.[7,12] The diagnosis is usually established after considering a combination of patient presentation, clinical evidence, laboratory testing of biomarkers, peripheral blood smear, and CBC.[7,12]

PEth is a lab test that is used to detect the presence of abnormal phospholipid formation secondary to the presence of alcohol. It has a half-life between 4–7 d and thus can be detectable in the blood of someone who has abstained from alcohol up to the 28th day.[10] Although the member has been in theater for a few months, the potential for alcohol use is still plausible. Thus, it would be useful to obtain this test if other diagnostic results are negative and the etiology is still in question.

In a deployed setting, you aren't likely to have the laboratory capabilities to obtain specialized tests such as PEth, parietal cell, or intrinsic factor antibodies. Potentially, you could do a peripheral blood smear yourself if you have a microscope in your small clinic. You should have the capability of ordering a CBC or Hb/Hct via an i-STAT device to check for anemia. That said, you likely will not be able to differentiate between pernicious or iron deficiency anemia, but you may be able to narrow your differential. A glucose check should be performed to evaluate for symptomatic hypoglycemia as a potential etiology for her loss of consciousness, dizziness, and fatigue. Lastly, you should perform a pregnancy test. An unknown pregnancy in a healthy young woman with a history of anemia, previously on iron supplements, could cause recurrence of anemia.

3. What is the pathophysiology of pernicious anemia?
   A. Poor dietary intake of vitamin B12.
   B. Poor dietary intake of folate.
   C. Infection of RBCs by a parasite leading to RBC lysis.
   D. Impaired absorption of dietary vitamin B12.
   E. Toxic accumulation of iron due to genetic disorder.

ANSWER/DISCUSSION

3. D. Pernicious anemia is an autoimmune disorder that encompasses antigastric parietal cell antibodies and anti-intrinsic factor antibodies.[4,7,12] This leads to destruction of gastric parietal cells, resulting in an autoimmune gastritis.[4] Autoimmune gastritis and anti-intrinsic factor antibodies cause decreased intrinsic factor, which is critical for dietary vitamin B12 absorption.[4,7] Autoimmune gastritis also causes decreased gastric hydrochloric acid release, which decreases the amount of vitamin B12 released from dietary sources for absorption in the ileum.[1] The decreased release and decrease in absorption combined lead to worsening vitamin B12 deficiency.[4,7,12] Vitamin B12 deficiency causes impaired DNA synthesis and delayed cell division, resulting in the megaloblastic anemia that is associated with pernicious anemia.[7]

Autoimmune gastritis is a condition that can be present alongside pernicious anemia. Autoimmune gastritis results in a decrease of gastric hydrochloric acid release, leading to reduced iron absorption and iron deficiency anemia in addition to pernicious anemia.[4,7]

Poor dietary intake of vitamin B12 can lead to megaloblastic anemia, which can occur with a vegetarian or vegan diet. It can take up to 3 yr to fully deplete vitamin B12 and may take time to develop clinical symptoms.[1] However, coupled with the patient's other medical conditions, a mild deficiency may be an exacerbating factor of her presentation. Poor dietary intake of folate can also cause megaloblastic anemia, but this is not related to the pathophysiology of pernicious anemia. Malaria infects RBCs, causing lysis due to the parasite reproductive pattern, but this is associated with a microcytic anemia, unlike the megaloblastic anemia of pernicious anemia.[15]

Hereditary hemochromatosis is the genetic disorder that causes toxic accumulation of iron, which can cause anemia secondary to multiple organ damage caused by the toxic accumulation of iron.[6]

After you stabilize the patient, she is transferred to a higher level of care for additional treatment. Further workup reveals she is severely vitamin B12 deficient and thus diagnosed with pernicious anemia. She responds well to treatment with intramuscular (IM) vitamin B12. However, despite treatment, she continues to have intermittent episodes of fatigue and lightheadedness. Given her continued IM treatment and symptoms, she still requires routine appointments with a hematologist.

4. Which of the following would be most concerning regarding this aviator's ability to return to flying duties?
   A. Aviator requires continued vitamin B12 treatment.
   B. Aviator still being followed by a hematologist.
   C. Aviator continues to maintain a vegan lifestyle.
   D. Aviator continues to have intermittent episodes of fatigue and lightheadedness despite treatment of weekly IM vitamin B12.

ANSWER/DISCUSSION

4. D. The aviator is still undergoing evaluation by hematology and immunology regarding the underlying cause of her pernicious anemia. The fact that she's still seeing specialists isn't in and of itself a grounding condition, unlike whether or not her condition is adequately being treated. Despite continued therapy with IM vitamin B12, the member remains symptomatic.

Each of the three military services has specific criteria regarding aeromedical waivers and the ability to return to flying duties with a history of anemia. The Air Force requires evaluation for a flying waiver if symptoms persist despite an appropriate treatment course and if the aviator requires more than an annual follow-up with a hematologist.[13] Additionally, the Air Force specifically requires a waiver for anemia if Hb measures below the lower limit of normal based on ethnicity and gender.[5] The Navy waiver guide requires a normal physical exam and normal Hct levels using an average of three levels drawn on different days.[8] Similar to the Air Force, the Army will grant a waiver for a flyer with a history of acquired anemia if it has been resolved without residual symptoms and need for continued specialty care.[14] In civil aviation, any case with a history of anemia must be deferred by an aviation medical examiner to the Federal Aviation Administration for any aeromedical disposition.[3] As the flight surgeon considering this patient for a waiver, it would be difficult to consider even recommending one at this time. Using the Air Force medical standards, your loadmaster meets the requirement for maintaining Hb levels above the specified lower limit of normal for a Caucasian female, $12.2\,g \cdot dL^{-1}$.[5] However, she continues to have symptoms despite continued care and appropriate treatment by a hematologist. As a flight surgeon, you have to evaluate the aviator's overall condition and determine if there would be an increased safety risk in allowing the aviator to return to flying duties. Your loadmaster continues to have intermittent episodes of lightheadedness and fatigue, which would impair any aviator from performing his or her duties, thus placing the entire crew and mission at risk.

Chuidian MD, Boucher K-A. ***Aerospace medicine clinic: pernicious anemia*****. Aerosp Med Hum Perform. 2023; 94(10):796–799.**

ACKNOWLEDGMENTS

The authors thank Cody L. Hedrick, M.D., Pharm.D., Capt, USAF, MC, FS, Aeromedical Consultation Service, U.S. Air Force School of Aerospace Medicine, for his professional review of this article. The views expressed are those of the authors and do not reflect the official guidance or position of the U.S. Government, the Department of Defense (DoD), or the U.S. Air Force. The appearance of external hyperlinks does not constitute endorsement by the DoD of the linked websites, or the information, products, or services contained therein. The DoD does not exercise any editorial, security, or other control over the information you may find at these locations.

REFERENCES

1. Ankar A, Anil K. Vitamin B12 deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. [Accessed November 10, 2022]. Available from https://www.statpearls.com/point-of-care/31217.
2. Ballard HS. Hematological complications of alcoholism. Alcohol Clin Exp Res. 1989; 13(5):706–720.
3. Federal Aviation Administration. III. Aerospace medical disposition. Blood and blood-forming tissue disease: anemia. In: Guide for aviation medical examiners. Washington (DC): Federal Aviation Administration; 2023. [Accessed February 3, 2023]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/.
4. Hall SN, Appelman HD. Autoimmune gastritis. Arch Pathol Lab Med. 2019; 143(11):1327–1331.
5. Keirns C, Menner L, Bridge L. Anemia, blood loss, and bone marrow donation (Nov. 2020). In: Aerospace medicine waiver guide. Wright-Patterson AFB (OH): U.S. Air Force School of Aerospace Medicine; 2023. [Accessed February 25, 2023]. Available from https://www.afrl.af.mil/711HPW/USAFSAM/.
6. Khan AA, Hadi Y, Hassan A, Kupec J. Polycythemia and anemia in hereditary hemochromatosis. Cureus. 2020; 12(4):e7607.
7. Mohamed M, Thio J, Thomas RS, Phillips J. Pernicious anaemia. BMJ. 2020; 369:m1319.
8. Naval Aerospace Medical Institute. 8.1. Anemia. In: U.S. Navy aeromedical reference and waiver guide. Pensacola (FL): Naval Aerospace Medical Institute; 2023. [Accessed February 23, 2023]. Available from https://www.med.navy.mil/Navy-Medicine-Operational-Training-Command/Naval-Aerospace-Medical-Institute/Aeromedical-Reference-and-Waiver-Guide/.
9. Ohio State University. Iron deficiency anemia. Pathophysiology. [Accessed November 4, 2022]. Available from https://u.osu.edu/irondeficiency anemia/pathophysiology/.
10. ScienceDirect. Phosphatidylethanol. [Accessed November 18, 2022]. Available from https://www.sciencedirect.com/topics/neuroscience/phosphatidylethanol.
11. Szczepanek-Parulska E, Hernik A, Ruchała M. Anemia in thyroid diseases. Pol Arch Intern Med. 2017; 127(5):352–360.

12. Tun AM, Thein KZ, Myint ZW, Oo TH. Pernicious anemia: fundamental and practical aspects in diagnosis. Cardiovasc Hematol Agents Med Chem. 2017; 15(1):17–22.
13. U.S. Air Force. Section N: blood, blood forming and tissue USAF medical serial profile annotation, N1, N2. In: Medical standards directory; 2021:52. [Accessed March 16, 2023]. Available from https://afspecialwarfare.com/files/MSD%2019%20Mar%202021.pdf.
14. U.S. Army Aeromedical Activity. Anemia/acquired (including iron deficiency anemia). In: Flight surgeon's aeromedical checklists. Aeromedical policy letters. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2014. [Accessed January 30, 2022]. Available from https://docplayer.net/5184761-Aeromedical-checklist.html.
15. White NJ. Anaemia and malaria. Malar J. 2018; 17(1):371.