CASE IN POINT

Approach to Pancytopenia in a Deployed Service Member

Steven J. Gibson, MD[a]; Benjamin Swanson, MD[b]; Carl R. Tischbein, MD[c]; Kathleen E. Bathon[a]; Karen J. Shou[c]; and Karen G. Zeman[c]

Background: Pancytopenia is a result of increased destruction or decreased production of bone marrow cells and has a broad differential. Pernicious anemia commonly presents as a macrocytic anemia and is typically autoimmune in nature and the result of vitamin B_{12} deficiency. Pancytopenia is a rare presentation of this disorder especially in the setting of hemolysis. Testing in the deployed setting may be limited and/or challenging.
Case Presentation: A 24-year-old female patient with a history of Hashimoto thyroiditis presented during an overseas deployment with a witnessed syncopal episode and was found to be pancytopenic with a mild transaminitis and laboratory tests demonstrating hemolysis. Though initially she was hypotensive, tachycardic, and febrile, her vitals improved after multiple transfusions, but she had persistent cytopenia with transfusion dependence, concerning for aplastic anemia or acute leukemia.
Conclusions: Testing for B_{12} deficiency is crucial in symptomatic, patients with pancytopenic to either diagnose or exclude pernicious anemia and conserve resources by preventing costly workup and transfer/escalation of medical care, especially in the deployed setting. A predeployment screening in those with history of autoimmune disorders may be warranted.

Author affiliations can be found at the end of this article.
Correspondence: Steven J. Gibson (steven.j.gibson24.mil@mail.mil)

Fed Pract. 2022;39(7). Published online July 12. doi:10.12788/fp.0320

Pancytopenia is a condition in which all 3 hematologic cell lines are lower than expected in the blood, often representing either an increase in cellular destruction or decrease in bone marrow production. Destruction often occurs in the setting of autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis) or splenic sequestration, often affecting erythrocytes and platelets more than leukocytes. Decreased production represents central etiologies, which are often due to nutritional deficiencies, infections, drug toxicities, or malabsorption.[1] Pancytopenia secondary to vitamin B_{12} deficiency is rare, accounting for about 5% of the hematologic manifestations of symptomatic vitamin B_{12} deficient patients.[2]

Pernicious anemia, named for a once lethal disease, is a form of vitamin B_{12} (cobalamin) deficiency that results from an autoimmune (type II hypersensitivity) reaction to gastric parietal cells or intrinsic factor. Antibodies bind to gastric parietal cells and reduce gastric acid production, leading to atrophic gastritis, or they bind intrinsic factor and block the binding and absorption of vitamin B_{12} in the gastrointestinal tract. While first described in the 1820s, it was not until a century later when scientists were studying hematopoiesis in response to the heavy casualty burden from battlefield exsanguination in World War I that dogs fed raw liver were noted to have significantly better blood regeneration response than those fed cooked liver. This discovery led physicians Minot and Murphy to use raw liver to treat pernicious anemia and found that jaundice improved, reticulocyte counts increased, and hemoglobin (Hb) concentration improved, resulting in the duo becoming the first American recipients of the Nobel Prize in physiology or medicine.[3] It was ultimately determined in 1948 by chemists Folkers and Todd that the active ingredient in raw liver responsible for this phenomenon was vitamin B_{12}.[4]

Patients with pernicious anemia typically present with macrocytic anemia, low reticulocyte count, hypersegmented neutrophils, as well as mild leukopenia and/or thrombocytopenia, distinguishable from folate deficiency by an elevated serum methylmalonic acid level. World Health Organization cytopenia thresholds are listed in Table 1.[5] Treatment consists of lifelong vitamin B_{12} supplementation, and endoscopic screening is often recommended after diagnosis due to increased risk of gastrointestinal malignancy.[6] Pernicious anemia can be difficult to distinguish from thrombotic thrombocytopenia purpura (TTP), a microangiopathic hemolytic anemia that can cause rapid end-organ failure and death if treatment is delayed.[7] While pernicious anemia is not typically hemolytic, case reports of hemolysis in severe deficiency have been reported.[7] Adequate bone marrow response to hemolysis in TTP results in an elevated reticulocyte count, which can be useful in differentiating from pernicious anemia where there is typically an inadequate

bone marrow response and low reticulocyte count.[8,9]

The approach to working up pancytopenia begins with a detailed history inquiring about medications, exposures (benzenes, pesticides), alcohol use, and infection history. A thorough physical examination may help point the health care practitioner (HCP) toward a certain etiology, as the differential for pancytopenia is broad. In the deployed soldier downrange, resources are often limited, and the history/physical are crucial in preventing an expensive and unnecessary workup.

CASE PRESENTATION

A 24-year-old active-duty female patient presented in late December 2020 to a theater hospital in Djibouti after a witnessed syncopal episode. She had a history of Hashimoto thyroiditis and was taking levothyroxine sodium 75 mcg daily. The patient reported gluten intolerance, which was never formally evaluated. The syncopal episode lasted a few seconds and was not associated with any prodromal or postictal symptoms. No seizure activity was observed, and she had no history of syncopal episodes. She reported that she had been feeling ill 24 to 48 hours prior, with nausea, fatigue, decreased oral intake, decreased urine output, and 2 episodes of nonbilious, nonbloody emesis.

When the patient arrived, she was tachycardic with heart rate in the 130s beats per minute (baseline, 100-110 beats per minute), febrile (103 °F), and had systolic blood pressure (SBP) in the low 100s (baseline, SBP 120s-130s). An electrocardiogram and chest radiographs were unremarkable. Her complete blood count (CBC) could not be processed due to Hb and platelet levels too low to detect on assay (Table 2). Lactate dehydrogenase (LDH) was elevated at > 1000 U/L with mild elevation in liver enzymes (aspartate aminotransferase, 98 U/L; alanine aminotransferase, 51 U/L) and prolonged partial thromboplastin time 70 seconds. She did not report any increased bleeding or bruising. The peripheral blood smear demonstrated pancytopenia, without any schistocytes, and she was started on broad-spectrum antibiotics for presumed sepsis from urinary source and possible TTP.

TABLE 1 World Health Organization Cytopenia Thresholds

Blood component	Threshold value
Absolute neutrophil count, K/μL	< 1.8
Hemoglobin, g/dL	< 10
Platelets, K/μL	< 100

TABLE 2 Laboratory Results at Presentation

Tests	Value
White blood cells	Undetectable
Hemoglobin	Undetectable
Platelets	Undetectable
Aspartate aminotransferase, U/L	98
Alanine transaminase, U/L	51
Partial thromboplastin time, s	70
Total bilirubin, mg/dL	1.8
Peripheral smear	Pancytopenia, no schistocytes
Lactate dehydrogenase, U/L	> 1000

TABLE 3 Laboratory Results After Treatment/ Transfusions

Tests	Values
White blood cells, K/μL	1.7
Hemoglobin, g/dL	11.2
Platelets, K/μL	23
Vitamin B_{12}, pg/mL	< 50
Intrinsic factor antibody, AU/mL	34.5

The patient received 5 units of packed red blood cells, transfusion of platelets, and 2 doses of vitamin B_{12} in Djibouti with clinical improvement and resolution of orthostasis, hypotension, tachycardia, and fever. Her final posttransfusion CBC showed a Hb level of 11.2 g/dL, white blood cell (WBC) count of 1.7 K/μL, and platelet count of 23 K/μL (Table 3). Two days later her Hb level was 9.0 g/dL, WBC count 1.8 K/μL, and platelet count was 12 K/μL. She was evacuated via air to Landstuhl Regional Medical Center (LRMC) in Germany within 48 hours of presentation, given limited testing capabilities and persistent anemia and thrombocytopenia, refractory to transfusion, concerning for

aplastic anemia or acute leukemia.

On arrival at LRMC, she was transfused 1 unit of platelets and given 3 doses of intramuscular vitamin B_{12} for undetectable levels (< 50 pg/mL) at presentation. An extensive infectious workup was obtained, which did not reveal any viral, bacterial, or parasitic causes. The patient also had a bone marrow biopsy performed at a civilian site, which revealed hypocellular bone marrow. She was transferred to Walter Reed National Military Medical Center (WRNMMC) for further workup and evaluation, given the infectious workup, which was negative. Concern for hematologic malignancy remained. At the time of her arrival, the laboratory values had drastically improved with vitamin supplementation. The patient's absolute reticulocyte count indicated adequate bone marrow response and because of her improvement, a repeat bone marrow biopsy was not performed.

Intrinsic factor antibodies were elevated (34.5 AU/mL; reference range, 0.0-1.1), which confirmed that this patient's underlying etiology was secondary to pernicious anemia. The patient continued to improve and repeat vitamin B_{12} and folate levels revealed that she was responding to therapy. At discharge, intramuscular vitamin B_{12} injections were planned to continue monthly, indefinitely per guidelines. Oral supplementation is typically avoided due to poor absorption.

Of note, during her inpatient admission at WRNMMC, further evaluation of reported gluten intolerance was performed, which revealed a negative celiac disease panel (IgG/IgA tissue transglutaminase antibodies). On discharge, she was to establish care with gastroenterology for further evaluation, likely including endoscopic evaluation, at her next duty station. She was able to resume full travel and duty functions on discharge from WRNMMC.

DISCUSSION

We highlight a complex case of pancytopenia secondary to pernicious anemia in a deployed service member. With limited resources downrange, the workup of pancytopenia can be resource intensive, expensive, and time sensitive, which can have detrimental impacts on medical readiness. Additionally, undiagnosed coagulopathies can have lethal consequences in a deployed service member where bleeding risk may be elevated depending on the mission. The differential for pancytopenia is vast, and given its relative rarity in pernicious anemia, the HCP must use key components of the history and laboratory results to narrow the differential (eAppendix available at doi:10.12788/fp.0294).[10]

Pernicious anemia commonly presents as an isolated anemia. In a study looking at the hematologic manifestations of 201 cohort patients with well-documented vitamin B_{12} deficiency, 5% had symptomatic pancytopenia and 1.5% had a hemolytic anemia.[2] The majority (> 67%) of hematologic abnormalities were correctable with cobalamin replacement.[2] In our case, the solider presented with symptomatic anemia, manifesting as syncope, and was found to have transfusion-resistant pancytopenia. She had a hemolytic anemia with an LDH > 1000 U/L, haptoglobin < 3 mg/dL, and mild transaminitis with hyperbilirubinemia (1.8 mg/dL). No schistocytes were observed on peripheral smear, suggesting intramedullary hemolysis, which is believed to be due to the destruction of megaloblastic cells by macrophages in bone marrow.[11] A French study found high LDH levels and low reticulocyte counts to be strongly suggestive of vitamin B_{12} deficiency and helpful in differentiating pernicious anemia from TTP, given that bone marrow response to anemia in TTP is preserved.[8]

While vitamin B_{12} deficiency is not often associated with hemolytic anemia, multiple cases have been reported in the literature.[6] Screening for vitamin B_{12} deficiency may have shortened this patient's clinical course and limited the need for air evacuation to a stateside quaternary medical center. However, testing for cobalamin levels in overseas deployed environments is difficult, timely, and costly. New technologies, such as optical sensors, can detect vitamin B_{12} levels in the blood in < 1 minute and offer portable, low-cost options that may be useful in the deployed military setting.[12]

Diet plays a key role in this case, since the patient had a reported history of gluten intolerance, although it was never documented or evaluated prior to this presentation. Prior to deployment, the patient ate mostly rice, potatoes, and vegetables. While deployed in

an austere environment, food options were limited. These conditions forced her to intermittently consume gluten products, which led to gastrointestinal issues, exacerbating her nutritional deficiencies. In the 2 months before her first syncopal episode, she reported worsening fatigue that impacted her ability to exercise. Vitamin B_{12} stores often take years to deplete, suggesting that she had a chronic nutritional deficiency before deployment. Another possibility was that she developed an autoimmune gastritis that acutely worsened in the setting of poor nutritional intake. Her history of Hashimoto thyroiditis is also important, as up to one-third of patients with autoimmune thyroid disease have been associated with pernicious anemia (range, 3%-32%) with certain shared human leukocyte antigen alleles implicated in autoimmune gastritis.[13,14]

CONCLUSIONS

This rare case of pernicious anemia presenting as pancytopenia illustrates the challenge in working up pancytopenia, especially in austere military environments with limited testing capabilities. Screening for chronic dietary and nutritional deficiency is important in a service member, raising the question of what role predeployment screening may have and what dietary accommodations may be available during overseas deployments, which can potentially dampen inflammation of the gastrointestinal tract, especially for those with preexisting autoimmune gastrointestinal conditions. Also, newer technology allows portable, low-cost testing of cobalamin and may aid in its diagnosis. In patients who are anemic with low vitamin B_{12}, HCPs can begin vitamin B_{12} supplementation while continuing the workup (eg, antibody testing, endoscopy). If the patient responds appropriately, further workup becomes less urgent, therefore, decreasing resource use and increasing military readiness. When hemolysis is present, a low reticulocyte count can be beneficial to help differentiate this condition from TTP, a life-threatening condition that must also be ruled out or treated. Pernicious anemia should be on the differential in any patients with autoimmune conditions presenting with cytopenias, especially in those with a history of autoimmune thyroid disorders.

Author affiliations

[a]National Capital Consortium, Bethesda, Maryland
[b]Uniformed Services University of the Health Sciences, Bethesda
[c]Walter Reed National Military Medical Center, Bethesda

Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

Ethics and consent

The authors obtained written informed consent from the patient.

References

1. Takeshima M, Ishikawa H, Kitadate A, et al. Anorexia nervosa-associated pancytopenia mimicking idiopathic aplastic anemia: a case report. *BMC Psychiatry*. 2018;18(1):150. doi:10.1186/s12888-018-1743-6
2. Andrès E, Affenberger S, Zimmer J, et al. Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. *Clin Lab Haematol.* 2006;28(1):50-56. doi:10.1111/j.1365-2257.2006.00755.x
3. Sinclair L. Recognizing, treating and understanding pernicious anaemia. *J R Soc Med.* 2008;101(5):262-264. doi:10.1258/jrsm.2008.081006
4. Shampo MA, Kyle RA, Steensma DP. William Murphy—Nobel Prize for the treatment of pernicious anemia. *Mayo Clin Proc.* 2006;81(6):726. doi:10.4065/81.6.726
5. Hong M, He G. The 2016 revision to the World Health Organization classification of myelodysplastic syndromes. *J Transl Int Med.* 2017;5(3):139-143. doi:10.1515/jtim-2017-0002
6. Tunio NA, Sheriff MZ, Cooper G. Prevalence of gastric cancer in patients with pernicious anemia: a population-based study. *Am J Gastroenterol.* 2020;115:S665. doi:10.14309/01.ajg.0000707332.16739.72
7. Bailey M, Maestas T, Betancourt R, Mikhael D, Babiker HM. A rare cause of thrombotic thrombocytopenic purpura- (TTP-) like syndrome, vitamin B12 deficiency: interpretation of significant pathological findings. *Case Rep Hematol.* 2019;2019:1529306. doi:10.1155/2019/1529306
8. Stanley M, Michalski JM. *Thrombotic Thrombocytopenic Purpura.* StatPearls Publishing LLC; 2021.
9. Noël N, Maigné G, Tertian G, et al. Hemolysis and schistocytosis in the emergency department: consider pseudothrombotic microangiopathy related to vitamin B12 deficiency. *QJM*. 2013;106(11):1017-1022. doi:10.1093/qjmed/hct142
10. Chiravuri S, De Jesus O. *Pancytopenia.* StatPearls Publishing LLC; 2021.
11. Gladstone E. Pernicious anemia presenting with pancytopenia and hemolysis: a case report. February 8, 2019. Accessed June 9, 2022. https://www.journalmc.org/index.php/JMC/article/view/3269/2563
12. ScienceDaily. Developing a sensor for vitamin B12 deficiency. October 17, 2016. Accessed June 9, 2022. https://www.sciencedaily.com/releases/2016/10/161017103221.htm
13. Rodriguez NM, Shackelford K. *Pernicious Anemia.* StatPearls Publishing LLC; 2021.
14. Fernando MM, Stevens CR, Walsh EC, et al. Defining the role of the MHC in autoimmunity: a review and pooled analysis. *PLoS Genet.* 2008;4(4):e1000024. doi:10.1371/journal.pgen.1000024

eAPPENDIX Pancytopenia Differential Diagnosis

Etiologies	Examples
Autoimmune	Systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis
Medications, classes	NSAIDs, thiazides, chemotherapy agents, antiepileptics, antimicrobials
Environmental exposures/toxins	Alcohol, arsenic, heavy metals, radiation, benzenes
Nutritional deficiencies	B_{12}, copper, folate, malnutrition
Malignancies	Multiple myeloma, leukemia, lymphoma, myeloproliferative neoplasms
Fibrotic	Myelofibrosis
Infectious	Fungal, tuberculosis, HIV, hepatitis, Epstein-Barr virus
Consumptive/destructive	Disseminated intravascular coagulation, cirrhosis, aplastic anemia, paroxysmal nocturnal hemoglobinuria, hemophagocytic lymphohistiocytosis
Storage/congenital	Gaucher disease, Fanconi anemia, Wiskott-Aldrich syndrome

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.