PennState Journal of Medicine

EBV-Induced Pancytopenia: An Unusual Presentation of EBV Causing Bone Marrow Suppression – A Case Report

Jessica Poulson[1], *Alice Cai[1], Jamal Benson[1], Monali Vasekar[2]

[1]Penn State College of Medicine, Hershey, PA [2]Department of Hematology/Oncology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA

KEYWORDS: EBV, pancytopenia, aplastic anemia, young adult, immunology, telomeres, infectious disease, hematology

Learning Objectives

1. Consider EBV and other viral pathogens as etiologies for pancytopenia in a young healthy adult

2. Recognize immune-mediated and genetic factors in the pathophysiology of aplastic anemia

3. Appreciate the discovery of EBV in this patient, which spared the patient from high treatment-related mortality of bone marrow transplant, the standard curative treatment for severe aplastic anemia in young adults

Case Description

A 22-year-old female with no significant past medical history presented after she was found to be pancytopenic through routine labs. One week prior, she developed a sore throat with fever, chills, headache, and cough productive of green sputum, which had not resolved at the time of evaluation. She also reported easy bruising without recollection of trauma.

Upon admission to the hospital, she was febrile with temperatures up to 39.6˚C, tachycardic at 120bpm, normotensive at 111/61 mmHg, and had a normal respiratory rate of 20/min. Physical exam was notable for tender bilateral anterior cervical lymphadenopathy, white patches on the posterior pharynx, hepatomegaly, significant bruising of her lower extremities, and petechiae on her right arm where a sphygmomanometer was placed. Repeat labs showed hemoglobin of 6.6g/dL, hematocrit of 18.3% with 8K/uL reticu-locytes, platelet count of 3K/uL, and white blood cell count of 0.49K/uL with undetectable neutrophils. She was treated empirically for neutropenic fever with broad spectrum antibiotics.

Respiratory viral panel and throat and blood cultures were negative. Computed tomography of her sinuses, chest, abdomen and pelvis showed no obvious infectious sources. Further work-up for possible etiologies of her pancytopenia, including human immunodeficiency virus, parvovirus, cytomegalovirus, hepatitides and antinuclear antibodies, were negative. Monospot test was positive and Epstein-Barr virus (EBV) viral load was notably elevated at 1908 units/mL. Blood smear showed severe pancytopenia and bone marrow biopsy revealed hypocellular marrow of 5-10% cells with panhypoplasia without dysplasia, consistent with severe aplastic anemia (AA). Over the course of her admission, she required multiple transfusions, a 3-day course of dexamethasone, and was discharged on oral acyclovir, ciprofloxacin, and posaconazole for prophylaxis due to neutropenia. Her blood counts recovered the following month. An Inherited Bone Marrow Failure Panel was conducted, which showed a heterozygous mis-sense mutation (c.400G>T, p.Ala134Ser) in telomeric repeat binding factor 2 (TERF2).

Discussion

EBV is a herpesvirus that infects B-lymphocytes and epithelial cells. EBV is often subclinical and persists as a latent infection but is known to cause infectious mononucleosis, which manifests as fever and malaise with acute pharyngitis, tonsillitis, lymphadenopathy, and splenomegaly lasting up to one month. Severe AA is a rare complication of EBV with only 24 cases reported in literature.[1]

The pathophysiology of AA is an immune-mediated process involving overactivation of cytotoxic T lymphocytes (CTLs) that target bone marrow and cause hematopoietic dysfunction.[2] EBV is thought to be implicated in this process as it induces proliferation of virus-specific CTLs and decreases the CD4+/CD8+ T-cell ratio.[2,3] Additionally, telomere shortening has been associated with both acquired and congenital AA due to a decreased leukocyte proliferative capacity.[4] Telomeres are long nucleotide repeats that flank the ends of chromosomes and protect them from erosion with each round of cell division due to incomplete replication of the lagging strand. Critical shortening of telomeres triggers a protective cascade that leads to replicative senescence and apoptosis.[4]

Acquired aplastic anemia is associated with mutations

DOI: 10.26209/psjm61974

in genes that regulate telomere length, which were detected through the inherited bone marrow failure panel; they include telomerase complex genes (TERC, TERT), Shwachman-Bodian-Diamond Syndrome (SBDS), and less commonly, TERF1 and TERF2.[4] TERF1 and TERF2 bind to telomeres to form a protein complex called shelterin to prevent degradation and fusion of chromosomal ends.[4,5]

In a study of 47 patients with acquired AA, a TERF1 variant was implicated in higher risk for acquired AA; a c.17476G>T (p.Ala273Ser) variant of TERF2 was not significantly implicated but was noted to be one of multiple possible genetic factors, highlighting that larger studies are necessary.[5] Due to the paucity of literature on TERF2 variants in humans, it is possible the heterozygous c.400G>T (p.Ala134Ser) missense variant in our case predisposed this patient to developing AA, but the clinical significance of this variant is unknown.

EBV-induced AA is a rare CTL-mediated manifestation of EBV and is associated with short telomeres. Viral causes of AA must be considered in young, previously healthy patients. While the mainstay of EBV treatment is supportive, corticosteroid treatment was likely helpful in the resolution of EBV-induced aplastic anemia in this case. Curative treatment for severe AA in a young adult is allogenic bone marrow trans-plant, which incurs a high treatment-related mortality; however, this patient was spared from such consequences through recognition of an underlying viral infection.

Author Information

Corresponding Author

* Alice Cai, BS
acai@pennstatehealth.psu.edu, (814)-308-2463

Author Contributions

All author(s) have given approval to the final version of the manuscript.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Disclosures

No author(s) have any disclosures or conflicts of interest at this time.

Acknowledgements

None.

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DOI: 10.26209/psjm61974