Fellow's Column: Co-Occurrence of Hyperleukocytosis and Candidemia in a Neonate: A Case Report

Violet Quann, OMS3; Anh-Tram Bui, OMS3; Mitchell Goldstein, MD, MBA, CML

"Normal white blood cell (WBC) count in neonates ranges from 9,000 - 30,000 cells/mcL. Leukocytosis, in which white blood cells increase up to 30,000 cells/mcL, is a well-documented and often physiological finding in neonates. Cases of hyperleukocytosis, however, are exceedingly rare, especially in extremely preterm infants."

Introduction:

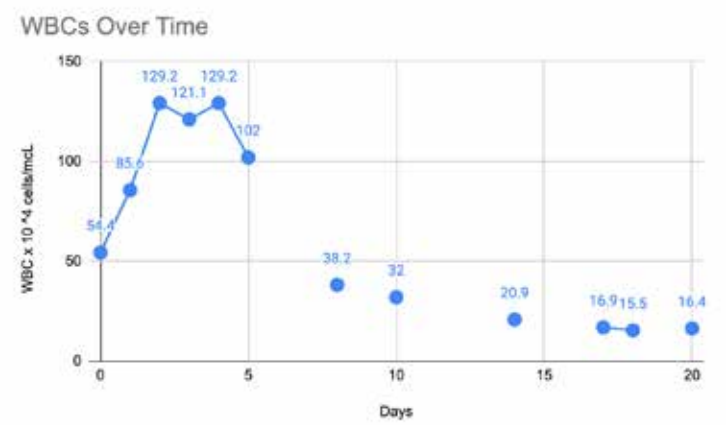
Normal white blood cell (WBC) count in neonates ranges from 9,000 - 30,000 cells/mcL. Leukocytosis, in which white blood cells increase up to 30,000 cells/mcL, is a well-documented and often physiological finding in neonates. Cases of hyperleukocytosis, however, are exceedingly rare, especially in extremely preterm infants. A WBC count of 100,000 cells/mcL or greater is cause for concern, as only a few differentials could be the cause. One must rule out congenital leukemia, transient abnormal myelopoiesis, leukocyte adhesion deficiency, and sepsis-induced leukemoid reaction (1). Only after they have been excluded can the diagnosis of neonatal leukemoid reaction be established. Complications of hyperleukocytosis are related to increased blood viscosity, including intracranial hemorrhage and renal and respiratory failure.

Candida is one of the most common organisms in the United States to cause a bloodstream infection (2). This infection is acquired from the environment, with risk factors including intubation, catheter placement, and those receiving total parenteral nutrition (TPN). In the neonatal population, additional risk factors include prematurity and low birth weight (<1000g). Some of the most severe complications of candidemia are meningitis, endophthalmitis, osteomyelitis, and endocarditis (3).

We present a co-occurring hyperleukocytosis and candidemia case in a preterm infant with favorable outcomes.

Case Presentation:

A 25-week-old baby girl was born at 740g to a G7P5 mother that received prenatal care and antenatal steroid therapy. APGAR scores were 5 at one minute and 9 at five minutes. However, the baby required respiratory support soon after birth and was intubated. The baby was admitted to the NICU for apnea of prematurity. On day zero, a routine sepsis workup showed her WBCs to be 54.4 cells/mcL, but her blood culture had no growth. On day two, her WBCs were 85.6 cells/mcL. On day four, the WBCs had risen to 129.9 cells/mcL, and the blood culture grew *Candida albicans*. The next day, her WBCs were down to 102 cells/mcL, which started a steep downward slope until the WBC count was within normal range by day fourteen, at 20.9 cells/mcL.



Management and Outcome:

In light of the high WBC count and risk for sepsis, given her prematurity and low birth weight, the baby was started on ampicillin, gentamicin, and azithromycin in the first few days of life. On day four, Vancomycin and Cefepime were started. Soon after, when the culture grew Candida, Fluconazole was added. Sensitivity came back on the culture on day fifteen, showing *Candida* resistant to Fluconazole, and the infant was switched to Micafungin, at which point the WBC was already within normal range.

"Soon after, when the culture grew Candida, Fluconazole was added. Sensitivity came back on the culture on day fifteen, showing Candida resistant to Fluconazole, and the infant was switched to Micafungin, at which point the WBC was already within normal range."

On day two, a head ultrasound revealed a grade two germinal matrix hemorrhage with mild ventriculomegaly, resolved by day nineteen. Serial chest x-rays were consistent with neonatal respiratory distress syndrome with the potential to develop into bronchopulmonary dysplasia. Both of these complications were consistent with hyperleukocytosis. Detection of possible complications from the candidemia included an eye exam and an echocardiogram, which revealed no intraocular fungal infection or endocarditis, respectively. The baby had a suspected seizure on day seventeen, received one dose of phenobarbital, and the EEG returned normal

shortly thereafter.

"The baby had no physical exam findings of congenital leukemia, including hepatomegaly, splenomegaly, papilledema, or skin lesions (5). The baby also did not present with delayed umbilical cord separation, bacterial infections, or absent pus formation, making leukocyte adhesion deficiency less likely (6)."

Discussion:

In cases of hyperleukocytosis, it is crucial to conduct a thorough investigation to rule out troubling diagnoses. The baby did not have Down Syndrome, which removes transient abnormal myelopoiesis from the differentials (4). The baby had no physical exam findings of congenital leukemia, including hepatomegaly, splenomegaly, papilledema, or skin lesions (5). The baby also did not present with delayed umbilical cord separation, bacterial infections, or absent pus formation, making leukocyte adhesion deficiency less likely (6). Considering the WBC count was within range before the *Candida* was known to be resistant and an effective antifungal administered, we can safely rule out sepsis as the cause of the hyperleukocytosis. Neonatal hyperleukocytosis is an extremely high WBC count that resolves spontaneously without an identifiable cause (7). The rate at which this patient's WBCs increased from birth to day four of life and re-normalized by day fourteen indicated neonatal hyperleukocytosis. The timeline of the blood culture growing *Candida* was consistent with late-onset sepsis. Late onset is defined as occurring >3 days after birth (8), and it affects 10-20% of extremely low birth weight babies (9). This baby had multiple risk factors for developing candidemia.

With the separation of these two disease processes, it is clear that this was a rare case of co-occurring candidemia and neonatal hyperleukocytosis.

References:

1. Parvez Y, Mathew AG. Hyperleukocytosis in Newborn: A Diagnosis of Concern. Indian Journal of Hematology & Blood Transfusion [Internet]. 2014 Sep [cited 2023 Apr 22];30(Suppl 1):131. Available from: https://doi.org/10.1007/s12288-013-0305-5
2. Greenberg RG, Benjamin DK Jr. Neonatal candidiasis: diagnosis, prevention, and treatment. J Infect. 2014 Nov;69 Suppl 1:S19-22. doi: 10.1016/j.jinf.2014.07.012. PMID: 25448311.
3. Kauffman CA. Complications of candidemia in ICU patients: endophthalmitis, osteomyelitis, endocarditis. Semin Respir Crit Care Med. 2015 Oct;36(5):641-9. doi: 10.1055/s-0035-1562891. Epub 2015 Oct 5. PMID: 26437407.
4. Bhatnagar N, Nizery L, Tunstall O, Vyas P, Roberts I. Transient abnormal myelopoiesis and AML in Down syndrome: An update. Curr Hematol Malig Rep. 2016 Oct;11(5):333-341. doi: 10.1007/s11899-016-0338-x. PMID: 27435308.
5. Calvo C, Fenneteau O, Leverger G, Petit A, Baruchel A, Méchinaud F. Infant acute myeloid leukemia: A unique clinical and biological entity. Cancers (Basel). 2021 Apr 8;13(4):777. doi: 10.3390/cancers13040777. PMID: 33917962; PMCID: PMC8066802.
6. Justiz Vaillant AA, Ahmad F. Leukocyte Adhesion Deficiency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470537/
7. Duran R. The relationship between leukemoid reaction and perinatal morbidity, mortality, and chorioamnionitis in low birth weight infants. Int J Infect Dis. 2010 Nov;14(11):998-1001. doi: 10.1016/j.ijid.2010.06.012. Epub 2010 Sep 8. PMID: 20825929.
8. Flannery DD, Edwards EM, Coggins SA, Horbar JD, Puopolo KM. Late-onset sepsis among very preterm infants. Pediatrics. 2022 Dec;150(6):e2022058813. doi: 10.1542/peds.2022-058813. Epub 2022 Nov 16. PMID: 34786767.
9. Fu J, Ding Y, Jiang Y, Mo S, Xu S, Qin P. Persistent candidemia in very low birth weight neonates: Risk factors and clinical significance. BMC Infect Dis. 2018 Sep 3;18(1):439. doi: 10.1186/s12879-018-3487-9. PMID: 30176802; PMCID: PMC6121286.

Disclosures: *Authors have no competing interests to declare.*

NT

Corresponding Author

Violet Quann, OMS III
3rd Year Medical Student
College of Osteopathic edicine of the Pacific
Western University of Health Sciences
Pomona, CA
Email: violet.quann@westernu.edu

Anh-Tram Bui OMS III
3rd Year Medical Student
College of Osteopathic edicine of the Pacific
Western University of Health Sciences
Pomona, CA

Mitchell Goldstein, MD, MBA, CML
Professor of Pediatrics
Loma Linda University School of Medicine
Division of Neonatology
Department of Pediatrics
Email: mgoldstein@llu.edu

Fellow's Column is published monthly.

- Submission guidelines for "Fellow's Column":
- 2000 word limit not including references or title page. Exceptions will be made on a case by case basis
- QI/QA work, case studies, or a poster from a scientific meeting may be submitted..
- Submission should be from a medical student, resident, fellow, or NNP in training.
- Topics may include Perinatology, Neonatology, and Younger Pediatric patients.
- No more than 20 references.
- Please send your submissions to:

Elba Fayard, MD, Interim Fellowship Column Editor
or Saba Saleem, OMS IV Fellowship Column Assistant Editor
LomaLindaPublishingCompany@gmail.com