Sepsis-induced Hyperleukocytosis in a Preterm

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Abstract
Hyperleukocytosis is defined as a white blood cell (WBC) count of ≥ 100,000/µL. Leukostasis refers to symptomatic hyperleukocytosis and is considered a medical emergency. In pediatric practice, hyperleukocytosis is most commonly described in leukemia and other myeloproliferative disorder, but other etiologies, such as infection, are less commonly mentioned.

In this case report, a one-day-old, preterm, male baby (26 weeks of gestation) was referred for preterm care. A sepsis-induced leukemoid reaction hyperleukocytosis diagnosis was presumed, and he was successfully treated with an empirical antibiotic with a gradual improvement in WBC counts.

Categories: Pediatrics, Allergy/Immunology, Infectious Disease
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Introduction
Leukocytosis is commonly seen as a physiological or infectious response in neonates, but the white blood cell (WBC) count rarely exceeds 30,000/µL. Hyperleukocytosis is when the WBC count is over 100,000/µL, with one-week mortality that could reach 40% especially when WBCs exceed 300,000/µL [1]. Hyperviscosity syndrome can manifest as leukostasis by causing thrombosis, bleeding, or disseminated intravascular coagulation (DIC), particularly affecting intracerebral and pulmonary circulations [2].

By identifying and treating the primary cause, lowering the WBC count, preventing hyperviscosity and tumor lysis syndrome, all under close monitoring, we can possibly prevent or reduce complications.

We report here a case of sepsis-induced hyperleukocytosis in a preterm neonate and discuss the differential diagnoses with a brief literature review.

Case Presentation
A preterm male (26 weeks of gestation), born to a 31-year-old middle eastern multigravida mother by normal vaginal delivery, was referred for preterm care on Day 1. The mother had poor antenatal care and had not received antenatal steroids. There was no ABO or Rh incompatibility. On examination, the baby weighed 900 gm and had no obvious dysmorphic feature. He was lethargic, tachypneic, with intercostal retractions.

Investigations revealed Hb 10.5 g/dl and WBC count 159,000/µL (64% neutrophils). His platelet count was 258,000/µL while C-reactive protein (CRP) was negative. The complete metabolic panel, coagulation studies, and chest X-ray were within normal limits.

The baby was started on supportive care, fluid, and IV antibiotics (ampicillin+gentamycin). WBC counts were repeated on Day 4 and showed an increasing WBC count (185,500/µL) with predominant neutrophils. Blood and cerebrospinal fluid (CSF) cultures were taken, and antibiotics were changed empirically to vancomycin and meropenem. The result of blood and CSF cultures came back negative. Peripheral blood smear and bone marrow aspiration were requested; the results were not suggestive of leukemia. Sepsis was presumed clinically to be the promoter of hyperleukocytosis. No source of infection could be identified.

The patient was closely monitored for intracranial hemorrhage, respiratory failure, hyperuricemia, renal failure, and other known complications of hyperleukocytosis. The WBC counts were closely monitored and repeated every other day; they showed a dramatic reduction within five days of starting vancomycin and meropenem and were eventually 14,700/µL on the 15th day of life. The patient responded well to supportive care and was discharged after 62 days of hospital stay.

Discussion
The normal leukocyte count in neonates is physiologically higher than in adults with a range from 9000-30,000/µL [3]. Leukemoid reactions are known to be caused by infections, malignancies, hemolysis,
hemorrhage, medications, and others.

Although a few conditions can present with elevated WBCs at such an early age, the major causes are congenital leukemia and leukocyte adhesion disorder. Another known cause of leukocytosis is a transient myeloproliferative disorder, which is reported in about 10% of Down syndrome cases [4-6].

Hyperleukocytosis caused by a severe leukemoid reaction can be presumed when leukemia has been ruled out. The exact etiology and mechanism are unknown, and a differential diagnosis is usually challenging. However, this can occur as a result of infections (Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Clostridioides difficile, and others), carcinomas, severe hemorrhage, following exposure to certain drugs, such as corticosteroids, and it also has been reported in preterm infants without any identifiable cause [7-9]. A negative CRP does not rule out the possibility of bacterial infection in children [10].

The diagnostic workup consists of the exclusion of leukemias and the detection of an underlying cause. It should include a complete blood count, peripheral blood smear, bone marrow biopsy, blood culture, CSF fluid analysis and culture, complete metabolic panel, coagulation studies, and chest X-ray.

Hyperleukocytosis might cause severe, life-threatening complications, including leukostasis, thrombosis, DIC, intracranial hemorrhage, pulmonary hypertension, intrapulmonary hemorrhage, heart failure and hypoxemia, tumor lysis syndrome, and acute renal failure [11-12]. The main goal of hyperleukocytosis management is cytoreduction and decreasing blood viscosity to prevent complications. Management includes close monitoring with aggressive hydration, maintaining good diuresis, prevention of tumor lysis syndrome and DIC, and correction of any metabolic abnormalities.

In literature differentiating hyperleukocytosis from leukemia, cytoreduction can be achieved by either leukapheresis or exchange transfusion. Leukapheresis is the treatment of choice in symptomatic hyperleukocytosis but poses a higher risk and complications. An exchange transfusion is often a more practical option, easier and much safer than leukapheresis, especially when hyperleukocytosis is complicated by severe anemia [13-14]. Leukapheresis often is recommended for hyperleukocytosis because of its quick cytoreductive effect [15]. However, a recent study of an adult cohort failed to demonstrate that leukapheresis is associated with an improved early mortality rate and a similar study on the pediatric population concluded the same [16-18].

In our case, hyperleukocytosis was probably caused by sepsis. This is supported by the dramatic response to the antibiotic, despite having no pathogen isolated, as a negative culture does not exclude sepsis in neonates [19].

Conclusions
The hyperleukocytosis and leukostasis mechanisms are poorly understood, and making a diagnosis is challenging. A negative culture and a negative CRP does not exclude infection or sepsis in a neonate. Management starts with close monitoring, followed by supportive care and directions to identify and treat the underlying cause and to prevent complications by good hydration and a proper empirical antibiotic selected based on the suspected pathogen. Leukapheresis should only be considered in symptomatic patients.

Additional Information
Disclosures
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