Recurrence of Neonatal Lupus Post-Cord Blood Transplant for Severe Congenital Neutropenia

Neonatal lupus erythematosus (NLE) is a rare autoimmune disorder associated with transplacental migration of maternal autoantibodies against SS-A (Ro) or SS-B (La) antigens that results in cardiac, hepatic, cutaneous, and hematologic manifestations. Although NLE-associated neutropenia is considered transient and benign, neutropenia caused by severe congenital neutropenia (SCN) is life-threatening. Diagnosing a complicated picture of neonatal neutropenia can be challenging because there are many overlapping features between the acquired and inherited etiologies. This article highlights this diagnostic challenge with a case of delayed diagnosis of SCN due to an initial diagnosis of concurrent NLE. Secondary to SCN refractory to granulocyte colony-stimulating factor, our patient underwent a matched sibling cord blood transplant. Posttransplant, the patient developed recurrence of NLE symptoms, representing the first case of maternally transferred autoantibodies causing symptoms in a cord blood recipient. This novel finding prompted a review of the standards for collecting, processing, and storing of cord blood donations. This article also discusses the importance of physician familiarity with the differences and similarities between publicly and privately banked cord blood donations to adequately counsel expectant parents.

Neonatal lupus erythematosus (NLE) is a rare autoimmune disorder caused by the passive transplacental passage of maternal autoantibodies against SS-A (Ro) or SS-B (La) antigens that results in cardiac, hepatic, cutaneous, and/or hematologic abnormalities.1,2 The most common finding of NLE is dermatologic involvement of the face, scalp, or trunk, with erythematous annular plaques with central atrophy. Other less common rashes include a malar-like rash and persistent telangiectasias. Another complication of NLE is transient cytopenias.1 Although thrombocytopenia has historically been considered the most prevalent cytopenia, neutropenia has been reported more recently.3 Neutropenia is defined as an absolute neutrophil count (ANC) <1.0  × 10^9/L in an infant and <1.5  × 10^9/L thereafter and can be caused by a variety of disorders.4 Overlapping features between acquired forms (eg, NLE) and inherited forms (eg, severe congenital neutropenia [SCN]) of neutropenia contribute to the diagnostic uncertainty. There is limited information regarding the clinical course of neutropenia in NLE; however, it generally resolves as maternal autoantibodies clear, with minimal risk of infection.5 In contrast, with SCN, neutropenia persists and is associated with life-threatening infection and risk for malignant transformation without definitive therapy4.

We present a unique case illustrating the difficulty of differentiating SCN from immune-mediated neutropenia in an infant with NLE and concurrent...
SCN. This case is also the first, to our knowledge, of transfer of maternal lupus autoantibodies in a cord stem cell product resulting in symptoms. This case draws attention to the utility and safety of private cord blood banking, a common question brought to physicians by expectant parents.

CASE PRESENTATION

An infant male was born at 41 weeks with type I heart block, severe neutropenia (ANC: \(0 \times 10^9/L\)), and an erythematos annular rash (Fig 1A) to nonconsanguineous parents. Notably, his mother carried a diagnosis of systemic lupus erythematosus (SLE). Results of laboratory tests revealed positive anti-Ro and anti-La antibodies consistent with NLE. Although antineutrophil antibodies were not measured, the neutropenia was presumed autoimmune given his diagnosis of NLE.

The patient continued to be severely neutropenic at 3 months of age, prompting a bone marrow evaluation at an outside hospital that demonstrated 100% cellularity with rare neutrophil precursors arrested at the promyelocyte stage with no evidence of dysplasia. Although maturation arrest is more consistent with a genetic cause of neutropenia, his neutropenia continued to be ascribed to NLE. At 6 months of age, he was diagnosed with mastoiditis, and a genetic evaluation revealed a sporadic Gly185Arg mutation in the ELANE gene, confirming a diagnosis of SCN. Granulocyte colony-stimulating factor was initiated, with inadequate response despite high doses (>30 \(\mu g/kg\) per day); treatment therefore proceeded to hematopoietic stem cell transplantation.

The patient’s 4-year-old brother was a 10/10 human leukocyte antigen match and ELANE mutation negative, but he had developed cutaneous neonatal lupus erythematosus (CNLE) without neutropenia at 3 weeks of age (Fig 1B). Our patient underwent a successful sibling transplant at age 13 months with confusion of his brother’s cryopreserved umbilical cord from a private bank and bone marrow. Additional bone marrow was collected secondary to low total cell dose in the cord blood unit (CBU). His conditioning regimen included fludarabine, busulfan, and thymoglobulin. On day 9 posttransplant, the patient developed a malar-like facial rash (Fig 2) that was unresponsive to antihistamines as well as to topical and oral steroids. Given the appearance of his rash and history of NLE in the sibling donor, maternal autoantibodies were tested in the patient. He was anti-Ro and anti-La positive, suggesting a recurrence of CNLE from autoantibodies transferred from the cord product. Attempts to test the original cord product were not possible secondary to insufficient cryopreserved sample postinfusion. His rash resolved in 1 month, likely from clearance of the maternal autoantibodies. Antineutrophil antibodies were not assessed, but neutrophil engraftment occurred on day 15, suggesting an absence or minimal effect of maternally derived antineutrophil antibodies. The child is doing well, >1 year out from transplant, without reappearance of the facial rash or neutropenia.

DISCUSSION

This case illustrates the difficulty in diagnosing a newborn with neutropenia due to the overlapping characteristics between acquired and inherited etiologies. Our patient presented at birth with classic findings of NLE: congenital heart block, maternally derived anti-Ro/La autoantibodies, neutropenia, and a distinctive annular rash. This presentation, combined with his family history of a SLE-positive mother and an older sibling born with NLE, seemed to confirm the diagnosis. Unfortunately, this misdiagnosis delayed the detection of the patient’s more critical underlying cause of neutropenia (ie, SCN).

SCN is a genetically heterogeneous group of rare disorders characterized by an ANC <0.2 \(\times 10^9/L\) on at least 3 separate occasions over a 1-month period, maturation arrest of myeloid precursor cells at the promyelocyte stage, high risk of myeloid malignancies, and near 50% mortality within the first year of life from infection if not treated appropriately.7,8 Modes of inheritance include autosomal dominant, autosomal recessive, X-linked, and sporadic.9 Most cases of SCN are either autosomal dominant or sporadic in nature, with 50% to 60% of cases ascribed to mutations in ELANE.9 The neutropenia caused by SCN is treated with granulocyte colony-stimulating factor; however, if
the patient is refractory to treatment or malignant transformation occurs, curative treatment with hematopoietic stem cell transplantation is recommended. The present case emphasizes the need to remain watchful of alternative diagnoses in the setting of presumed immune-mediated neutropenia.

In most instances, NLE-associated neutropenia is asymptomatic and transient, typically resolving with the disappearance of circulating maternal autoantibodies at 6 to 8 months of age. However, much of the current knowledge of NLE-associated cytopenias is based on small, outdated retrospective studies or case reports. Some case reports have described more critical manifestations such as aplastic anemia, hemorrhagic stroke, gastrointestinal bleeding, and persistent severe neutropenia.

Assessment for the presence of antineutrophil antibodies may assist in guiding the need for further evaluation if the antibodies are not detected. However, caution should be used with patients who have documented positive antineutrophil antibodies, which have a more concerning clinical course. Long-term follow-up on a large cohort of patients with NLE is necessary to thoroughly illustrate the risks and long-term outcomes of NLE-associated cytopenias.

After the cord blood transplant, our patient developed a malar-like rash. Many diagnoses were entertained, including graft-versus-host disease, engraftment syndrome, allergy, infection, and recurrence of CNLE. Initially, recurrence of CNLE was low on the differential diagnosis because all cryopreserved cord blood products undergo required testing and processing to prevent transfusion-related reactions. All accredited banks, whether private or public, provide testing for bacterial contamination, presence of highly transmissible diseases such as HIV and hepatitis C and B viruses, and are plasma- and red blood cell-reduced before cryopreservation to eliminate concerns of ABO or Rh incompatibility between donor and recipient.

Our patient’s CBU was retrieved from a nationally accredited private bank, similar to public banks. Despite the standardized processing performed on this CBU, it may have contained small amounts of plasma constituents, including maternal anti-Ro or anti-La antibodies, which could account for the symptoms observed. Although coinfusion of cord blood with bone marrow from the same donor has demonstrated excellent efficacy for low cellular content CBUs, we would advise caution when using cord blood from families with known autoimmune disorders given the recurrence of CNLE in this case.

Although this case is the first report of passive transference of autoantibodies through a privately banked cord blood transplant, we expect that a similar phenomenon could also occur in publicly banked CBUs. Knowledge of cord blood banking is essential for pediatricians because they are frequently asked questions by expectant parents about storing their child’s cord blood. Currently, 2 distinct methods of banking exist: private banking (used by families to provide a source for autologous transplants or for future sibling use) and public banking (which serves as the national source of allogeneic stem cells). The appeal of theoretically preserving “biological insurance” for future children has resulted in an inventory of privately stored CBUs estimated to be >3 times that of publicly banked specimens (currently, >600 000 publicly banked CBUs worldwide). Unfortunately, at present, privately banking CBUs does not seem practical. The probability of releasing an autologous CBU for transplant is estimated between 0.005% and 0.04%, whereas the chance is >4% for the use of an allogeneic CBU during the first 10 years of banking. In addition, although many private banks are accredited and abide to similar standardization practices as public banks, many still do not.

Interest in the fields of regenerative medicine and genetic therapy may lead to future uses for privately banked cords for a variety of illnesses; however, it is currently difficult to ethically and financially justify private banking. The high cost of private banking, the few uses for autologous cord blood transplants, and the possible lack of standardized processing in private banks has many physician organizations, including the American Academy of Pediatrics, the
American College of Obstetrics and Gynecology, and the American Society for Bone Marrow Transplantation, encouraging public donation unless private banking is clinically indicated for family use of a known disorder.17

CONCLUSIONS
This case highlighted the importance of considering alternative diagnoses when presented with a complicated picture of neonatal neutropenia. It also emphasized the significant gaps in the literature describing the clinical variability of NLE, especially concerning NLE-associated cytopenias. Finally, the novel finding of passively transferred autoantibodies in the cord blood product resulting in clinical disease elucidated the need for further investigation into the storage, processing, and application of cord blood products in public and private banks.

ABBREVIATIONS
ANC: absolute neutrophil count  
CBU: cord blood unit  
CNLE: cutaneous neonatal lupus erythematosus  
NLE: neonatal lupus erythematosus  
SCN: severe congenital neutropenia  
SLE: systemic lupus erythematosus

REFERENCES
Recurrence of Neonatal Lupus Post-Cord Blood Transplant for Severe Congenital Neutropenia

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