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Case Report

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Neutropenia and low ANC in a patient with Congenital Syphilis: A Case Report

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Abstract

Congenital Syphilis, is a condition that affects newborns who are either clinically diagnosed with active syphilis or born to mothers with untreated or inadequately treated syphilis. It is important to diagnose and treat both the mother and the baby to prevent further transmission and potential complications. Neutropenia is characterized by a reduction in the absolute count of circulating segmented neutrophils and band forms in the blood. This case report discusses a premature baby who was born at 29 weeks of gestation to a mother with untreated or inadequately treated syphilis. On the first day of life, the baby had a four-fold rise in RPR levels and skeletal evidence of syphilis. Based on these findings, the baby was diagnosed with congenital syphilis and treated with penicillin G for 10 days. Later, the baby developed profound neutropenia which resolved spontaneously at seven months of age. After investigation, it was attributed that a combination of congenital syphilis, prematurity, and the use of gentamycin prolonged the bone marrow suppression leading to persistent neutropenia. This case highlights the importance of early detection and treatment of syphilis in pregnant women to prevent congenital syphilis and its associated complications.

Keywords: Congenital syphilis; Neutropenia; Low ANC; Prematurity

Case Presentation

Our patient is a preterm male baby, delivered via emergency C-section at 29 weeks of gestation due to the new onset of Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome in a 27-year-old primigravida mom. The pregnancy was further complicated by diabetes, pre-eclampsia, and anxiety. Additionally, the mother had syphilis, which she reported was treated, although the records were not available. During the physical examination, the baby appeared non-dysmorphic overall, and the facial features were primarily familial. Initially, the baby was started on ampicillin (at a dose of 100 mg/kg) and gentamycin (at a dose of 3.5 mg/kg) for suspicion of clinical sepsis. The maternal RPR (Rapid Plasma Reagin) titer was 1:64, and initially, the baby's RPR was four-fold lower than the maternal RPR (1:16) on the day of birth. However, by day 1 of life, the baby's RPR had increased to match the maternal titer (1:64), despite the mother receiving treatment for syphilis. Additionally, baby's Syphilis IgM/IgG and TP-PA tests (Treponema Pallidum particle agglutination test) were reactive. Besides that, there were no symptoms/clinical characteristics of congenital syphilis at birth. Due to the unavailability of records regarding maternal treatment (the mother was unsure of the number and dates of injections), as well as there was rapid increase in the baby's RPR, the decision was made to switch from ampicillin to penicillin G for coverage of congenital syphilis. The baby was considered to be at significant risk for congenital syphilis. The pediatric infectious disease team recommended a 10-day course of penicillin G. An initial X-ray of the long bones revealed findings consistent with congenital syphilis, including a metaphyseal band of lucency without periostitis **(Figure 1)**. A lumbar puncture was performed to assess Cerebral Spinal Fluid (CSF) Venereal Disease Research Laboratory (VDRL) test, which ruled out neurosyphilis. Gentamycin was discontinued once the blood culture returned negative results at 48 hours.

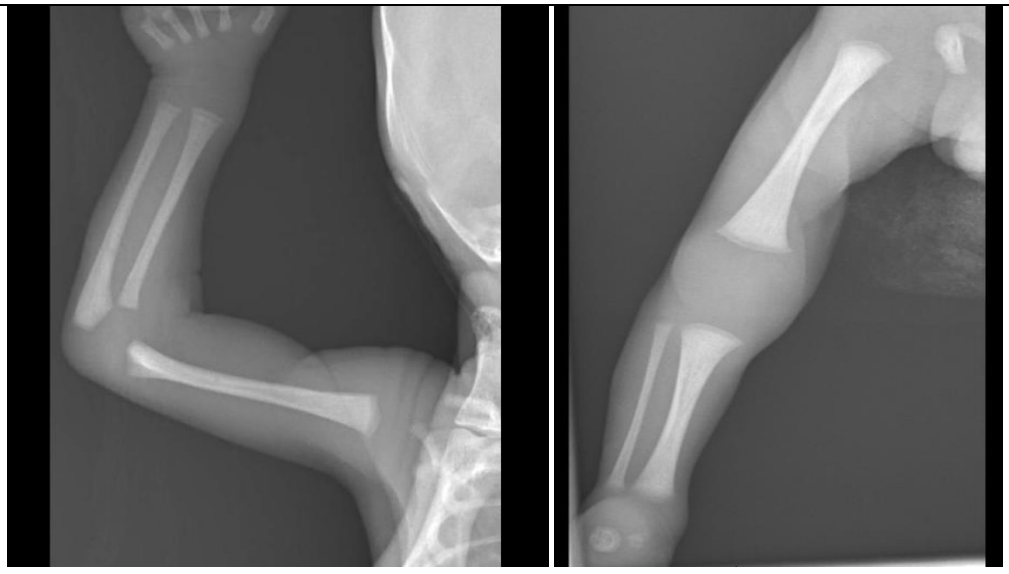

Figure 1: Skeletal survey showing metaphyseal band of radiolucency identified proximal and distal right humerus (left), proximal and distal right femur and right proximal tibia (right) without periostitis.

Neutropenia has been an ongoing concern for this baby during NICU stay. At birth, the white blood cell count (WBC) was 3.62 x 10^3/µL, and the Absolute Neutrophil Count (ANC) was 0.9 x 10^3/µL. Over time, the counts gradually increased, reaching a peak ANC of 2.08 x 10^3/µL around 2 weeks of age. Unfortunately, the counts then declined once more. The baby also required a packed red blood cell (RBC) transfusion due to anemia. Briefly, the WBC normalized to 5.93 x 10^3/µL and 5.33 x 10^3/µL around 1 month of age, but subsequently dropped again. At 2 months of age, the WBC and ANC were 3.29 x 10^3/µL and 0.33 x 10^3/µL, respectively **(Figure 2 and 3)**.

Days of Life	WBC (10^3/uL)	ANC (10^3/uL)
0	3.62	0.9
1	3.74	1.87
2	3.66	1.13
3	4	1.2
7	4.9	1.32
14	5.99	1.8
21	4.84	1.06
25	3.24	0.68
28	5.28	0.9
32	5.93	1.72
45	4.29	0.6
60 (2 months)	3.84	0.72
74	4.71	1.22
210 (7 months)	6.25	1.23

Figure 2: WBC and ANC within 1st few months of life.

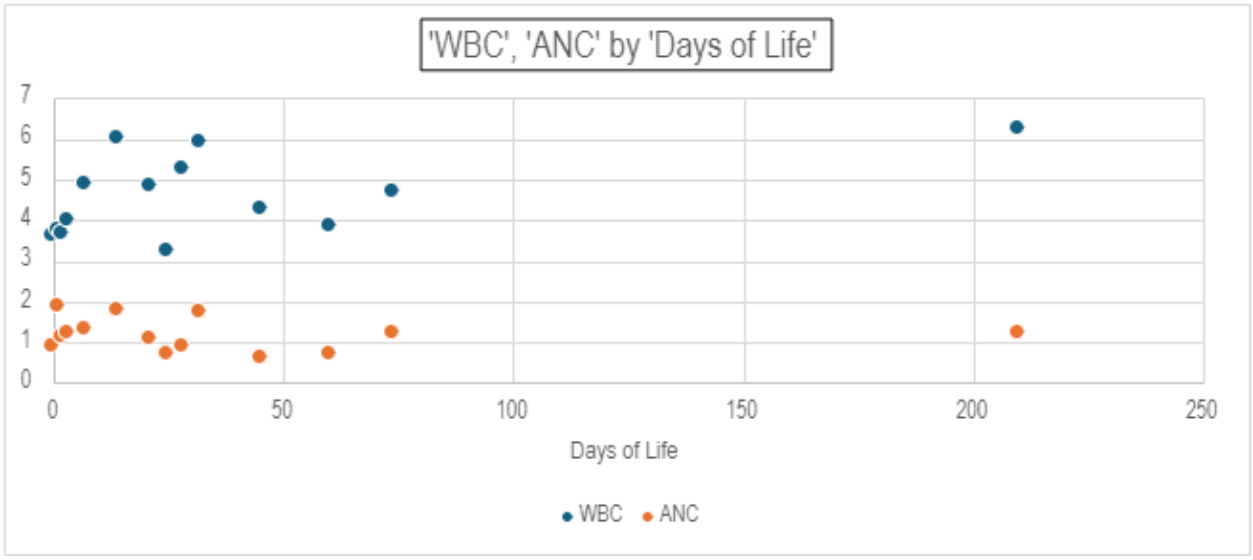

Figure 3: Graphical representation of WBC and ANC within 1st few months of life.

Additional investigations were scheduled to explore other potential causes of neutropenia. Pediatric Hematology evaluation included testing for anti-neutrophil antibodies and Periodic Fever syndromes panel including ELANE gene testing all yielded normal results. Allergy/Immunology evaluated the patient to rule out immunodeficiencies and checked Dihydrorhodamine (DHR) flow cytometry, Immunoglobulins levels, and Flow cytometry which were within normal limits. Despite these reassuring findings, the underlying cause of neutropenia remained elusive. Around 2 months of age, a follow-up X-ray revealed that the previously observed area of lucency had largely resolved. Repeat RPR at 2 months of age was non-reactive. Regarding congenital syphilis, the patient remained clinically stable without any new signs or symptoms of syphilis. The Pediatric Infectious Disease team was consulted due to the concern about persistent neutropenia. They recommended that since the specific cause of the neutropenia has not been identified, antimicrobial prophylaxis was not indicated. However, they advised considering a bone marrow biopsy to pinpoint the source of the neutropenia. Pediatric Hematology advised ongoing monitoring, with repeated WBC and ANC assessments every 2-3 days. Furthermore, the Pediatric Medical Genetics team was consulted, but they did not recommend additional genetic testing at that time. The patient was placed in reverse isolation due to severe neutropenia at 2 months of age. His vital signs remained stable, he was afebrile, and he has been successfully weaned off oxygen support, which was initially provided due to Respiratory Distress Syndrome (RDS). As there were no signs or symptoms of infection, the reverse isolation precautions were discontinued based on the recommendation from the Pediatric Hematology team. Upon discharge, the patient received instructions to avoid crowded areas, including close contact with sick individuals, practice good hygiene when caring for the baby and follow strict return-to-Emergency Room precautions. During outpatient follow-up with Genetics, a Phagocytic Disorders Including Neutropenia Panel was sent, and the results returned as normal. The baby continued to thrive, meeting age-appropriate milestones, with improvement in WBC count and ANC over time. At the Hematology follow-up when the baby was 7 months old (corrected age of 5 months), both the WBC count and the ANC were

within the normal limits. An informed consent was obtained before writing this case report. Figure 1 and data for figures &3 were taken from the patient's chart after parental consent.

Discussion

Congenital Syphilis, is a condition that affects newborns who are either clinically diagnosed with active syphilis or born to mothers with untreated or inadequately treated syphilis. It is important to diagnose and treat both the mother and the baby to prevent further transmission and potential complications. Mucocutaneous manifestation is present in 70% of cases. Classical finding includes vesiculobullous/maculopapular rash on palms and soles. Additionally, lymphadenopathy, hepatosplenomegaly, fever, jaundice, failure to thrive, non-immune hydrops, pneumonitis, rhinitis, and osteochondritis with pseudoparalysis of extremities, Coombs negative hemolytic anemia, leukocytosis, thrombocytopenia, hypoproteinemia, hypoalbuminemia, elevated liver enzyme levels and hyperbilirubinemia [1]. These symptoms were not present in our patient however we treated him for syphilis due to reactive RPR and skeletal evidence of congenital syphilis. Neutropenia is characterized by a reduction in the absolute count of circulating segmented neutrophils and band forms in the blood [2]. Persistent leukopenia and neutropenia can have various underlying causes, including prematurity, poor marrow reserves for neutrophil production, infections including syphilis and congenital neutropenic syndromes. This patient had neutropenia since birth. Interestingly, the band forms (immature neutrophils) remain normal, despite the overall neutropenia. This suggests a potential issue with neutrophil production. Notably, tests for the ELANE gene and antineutrophil antibodies have returned normal results. Considering the circumstances, it is plausible that the neutropenia may be linked to either the syphilis infection itself or gentamicin administration. In our patient, white blood cell counts have exhibited fluctuations since birth. Initially, they trended downward, then normalized, and subsequently decreased again. This pattern raises the possibility of cyclical neutropenia. However, the absence of a positive ELANE gene mutation effectively rules out cyclic neutropenia as the cause [3]. Despite appropriate treatment with a full 10-day course of penicillin, the repeat RPR test yielded a non-reactive result. Additionally, there was improvement in skeletal findings observed on the X-ray. Consequently, it becomes less likely that the neutropenia is directly attributable to congenital syphilis. However, we cannot entirely rule out the possibility that the neutropenia may have developed in response to the treatment of syphilis or as part of the underlying disease process itself. This was supported by a study conducted by PubMed data base search where they found that beta lactams can cause antibiotic induced neutropenia and use of filgastrim reduces the duration of neutropenia [4]. Another line of reasoning emerged when the patient exhibited neutropenia following the administration of gentamicin. This raised concerns about potential bone marrow suppression. However, it is important to note that the patient received gentamicin for only 48 hours, and the medication was subsequently discontinued. Based on this timeline, we do not believe that the neutropenia was a direct side effect of gentamicin. This was supported by a study where use of gentamycin in a geriatric patient resulted in agranulocytosis [5]. Differential for congenital neutropenic syndromes includes Severe Congenital Neutropenia (SCN), Kostmann's Syndrome, Shwachman-Diamond-Oski Syndrome, and cyclical neutropenia. Other syndromes are less likely as our patient did not have any dysmorphic features. SCN can be transmitted via recessive, dominant, or X-linked inheritance. The mechanism of neutropenia in SCN is due to increased apoptosis of myeloid cells. SCN usually

presents in infancy with an ANC of <200 and there are usually no characteristic dysmorphic features. The ELANE gene mutation is for neutrophil elastase and is an autosomal dominant condition responsible for 50-60% of cases of SCN. Although in about 40% of cases, the genetic basis of SCN is unknown [6,7]. One of the subtype of SCN is Kostmann Syndrome, where a mutation in the HAX1 gene, which has autosomal recessive inheritance [8]. X-linked inheritance of SCN is due to mutation in the Wiskott-Aldrich Syndrome (WAS) gene [9]. Other causes include hypersplenism, neonatal alloimmune neutropenia, marrow infiltrative process, chronic secondary neutropenia, chronic benign neutropenia, and benign ethnic neutropenia which are best evaluated by a bone marrow biopsy. The Pediatric Infectious Disease team advised performing a bone marrow biopsy to definitively investigate the cause of neutropenia in our patient. Despite its invasiveness, this procedure is endorsed by the Pediatric Hematology Oncology Association as part of the workup for neutropenia when other tests yield normal results. The goal is to identify any underlying conditions that may be contributing to the neutropenia [10]. Reverse isolation, also referred to as immunosuppressed isolation, is a precautionary measure to safeguard individuals who are particularly vulnerable to infections. By implementing reverse isolation, healthcare providers aim to shield patients with compromised immune systems from exposure to harmful pathogens. This practice is crucial for ensuring the well-being of vulnerable patients in healthcare settings [11]. Despite low WBC and ANC, our patient had no signs of ongoing infections, hence Filgrastim (Granulocyte-Colony Stimulating Factor) was not indicated. Its use is reserved for severe leukopenia with sepsis and inability to increase WBC count [12].

Conclusion

In conclusion, we believe that the neutropenia present in our patient was a manifestation of congenital syphilis. We also attribute the persistent neutropenia to a combination of congenital syphilis, prematurity, and the use of gentamycin which prolonged the bone marrow suppression. While the exact mechanism remains unclear, the neutropenia resolved spontaneously by the time the patient reached seven months of age. This case highlights the importance of early detection and treatment of syphilis in pregnant women to prevent congenital syphilis and its associated complications.

References

1. Basu S, Kumar A. Varied presentations of early congenital syphilis. J Trop Pediatr. 2013;59(3):250-4.
2. Walkovich K, Boxer LA. How to approach neutropenia in childhood. Pediatr Rev. 2013;34(4):173-84.
3. Dale DC, Bolyard AA, Aprikyan A. Cyclic neutropenia. Semin Hematol. 2002;39(2):89-94.
4. Holz JM, Chevtchenko AV, Aitullina A. Acute antibiotically induced neutropenia: a systematic review of case reports. Br J Clin Pharmacol. 2022;88(5):1978-84.
5. Chang JC, Reyes B. Agranulocytosis associated with gentamicin. JAMA. 1975;232(11):1154-5.
6. Welte K, Zeidler C, Dale DC. Severe congenital neutropenia. Semin Hematol. 2006;43(3):189-95.
7. Welte K, Zeidler C. Severe congenital neutropenia. Hematol Oncol Clin North Am. 2009;23(2):307-20.

8. Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schäffer AA, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet. 2007;39(1):86-92.
9. Ochs HD. The Wiskott-Aldrich syndrome. Semin Hematol. 1998;35(4):332-45.
10. Fioredda F, Onofrillo D, Farruggia P, Barone A, Veltroni M, Notarangelo LD, et al. Diagnosis and management of neutropenia in children: The approach of the Study Group on Neutropenia and Marrow Failure Syndromes of the Pediatric Italian Hemato-Oncology Association (Associazione Italiana Emato-Oncologia Pediatrica-AIEOP). Pediatr Blood Cancer. 2022;69(6):e29599.
11. Luciano JR. Reverse Isolation Systems. InAir Contamination Control Hospitals. 1977;313-48.
12. Awad M, Singh P, Hilas O. Zarxio (Filgrastim-sndz): the first biosimilar approved by the FDA. P T. 2017;42(1):19-23.

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