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Case Report

ELANE gene mutation related cyclic neutropenia with childhood systemic lupus erythematosus: a case report

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ABSTRACT

ELANE related neutropenia includes congenital and cyclic neutropenia which are primary haematological disorders characterised by recurrent fever, skin and oropharyngeal inflammation (i.e., mouth ulcers, gingivitis, sinusitis, and pharyngitis). A congenital cyclic neutropenia syndrome is a rare genetic disorder characterised by a cyclic reduction in the granulocyte proliferation pool in the bone marrow followed by the onset of neutropenia. Patients suffering from this disorder are susceptible to infections and clinically presents at early age. Patients having ELANE mutation combined with autoimmune diseases may have recurrent infections. This was a case report of a 3-year and 6-month-old female child presenting with recurrent pneumonia and oral ulcer. She had ELANE gene mutation associated cyclic neutropenia and was later diagnosed with childhood-onset systemic lupus erythematosus. Hence, it is important to identify rare causes of immunosuppressive conditions in children presenting with recurrent infections to prevent several long-term complications.

Keywords: Cyclic neutropenia, Juvenile systemic lupus erythematosus, ELANE gene mutation, Recurrent infection

INTRODUCTION

The neutrophils play an important role of first-line defense. If these cells are deficient, the organisms present on the body surfaces, predispose an individual to many infections during the acute inflammatory reaction and in the host's defense against bacterial infections.[1-3] Neutropenia is considered an inherent immune deficiency and systemic lupus erythematosus (SLE) is considered a classical autoimmune diseases.[2] These two types of immune disorders can be manifested in the same disease, so neutrophils may affect T and B lymphocyte differentiation, and different mutation sites of the elastase, neutrophil expressed (ELANE) gene have different effects on neutrophil elastase (NE), which may be the reason for different clinical phenotypes.[4] Severe congenital neutropenia (SCN) and cyclic neutropenia are rare haematologic disorder characterized by a significant decline in the number of neutrophils in the peripheral blood occurring at a regular interval or sometimes the symptoms are cyclical with the intervals varying between 14-36 days.[1,5] Heterozygous mutations of gene encoding neutrophil elastase 2 (ELANE) have been associated with cyclic neutropenia and severe congenital neutropenia.[6,7] This article described the history, clinical, radiographic, and haematologic findings of a young female child having ELANE gene-associated cyclic neutropenia with childhood SLE.

CASE REPORT

A 3-year and 6-month-old female, second born child with normal birth and normal development history from non-consanguineous parent of Indian origin with no family history of hereditary disease presented with high grade fever, skin and soft tissue infections and cough for 5 days. She was fully vaccinated for her age as per National Immunization Schedule. She was well till 1 year of age

when she started having recurrent pneumonia and oral ulcer for which she was repeatedly hospitalized.

Table 1: Laboratory reports showing absolute neutrophils count (ANC), haemoglobin (Hb), and platelet count.

Date	ANC (per cumm)	Hb (g%)	Platelet (lakh/cumm)
30/10/23	2342	6.8	2.32
03/11/23	1426	7.1	0.70
04/11/23	286	6.7	1.34
11/11/23	677	7.6	1.32
14/11/23	1082	7.4	0.70
19/11/23	1120	7.7	0.72
22/11/23	435	7.8	0.78
23/11/23	394	7.4	1.02
24/11/23	416	9.2	1.00
25/11/23	395	9.5	0.70
27/11/23	791	9.5	-
28/11/23	439	9.6	0.27
29/11/23	365	9.3	0.36
02/12/23	702	9.2	0.68
06/12/23	686	8.0	0.91
11/12/23	784	6.7	1.37
14/12/23	492	8.8	0.86
22/12/23	529	9.5	0.79

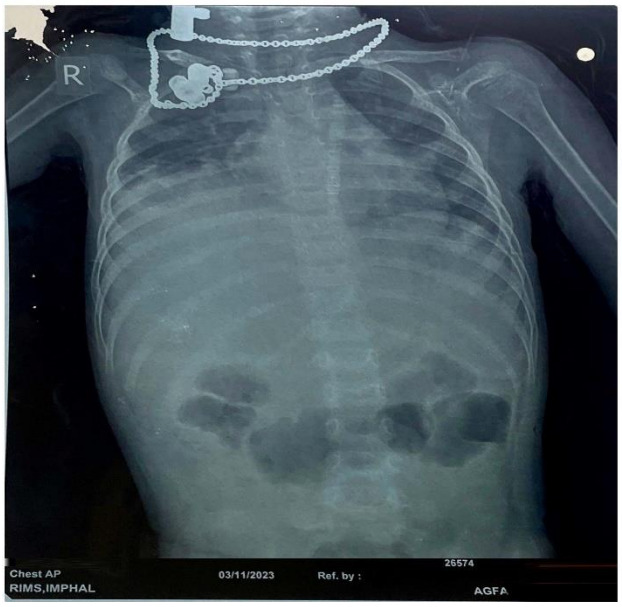

Figure 1: Chest X-ray P-A view of the patient showing homogeneous opacity of bilateral lower zone and infiltrations.

At 2 years of age, the cyclic trend of neutropenia was noted after every 20-25 days interval for more than 3 months and the genetic test showed ELANE gene mutation. Then, she was started on granulocyte-colony stimulating factor (G-CSF).

Later, she was brought at 3-year and 6-month for cough, fever, and oral ulcer for 5 days. She was conscious, thin built, and dull looking. On examination, she had pallor, mouth ulcers and external hordeolum. On systemic examination, tachypnoea with mild subcostal retractions were present with desaturation (SpO_2-88%) under room air. On auscultation, crepitations were present in the bilateral chest. On anthropometry, stunting and wasting were present. On repeated investigations, cyclic neutropenia was noted. However, thrombocytopenia with normocytic normochromic anemia were also present as shown in Table 1. She was transfused PRBC but did not require platelets or FFP transfusion. Viral markers (HIV, hepatitis B and C) Dengue serology, scrub typhus, Widal test, kidney function test (KFT), serum electrolytes, complement levels (C3, C4), direct combs test, PTINR and aPTT were normal. Treatment was started with injectable antibiotics (piperacillin+tazobactum), anti-fungal, oxygen therapy and intravenous fluid. Filgastrim was continued with regular complete blood count (CBC) monitoring. Chest X-ray showed right sided lower lobe consolidation with bilateral lungs infiltrates, urine C/S (culture and sensitivity) test had *Escherichia coli* growth within 24 hours incubation, blood culture was sterile, CBNAAT (Cartridge Based Nucleic Acid Amplification Test) for tuberculosis was negative. In view of persisting fever for 4 days of hospital stay, antibiotics were changed (injection meropenem+amikacin) as per the culture and sensitivity reports. Repeat urine C/S and blood C/S were sterile, Procalcitonin level showed sepsis unlikely, and bone marrow aspiration examination showed ELANE gene mutation. Symptoms were persisting till 14 days of hospital stay for which she was further evaluated. CBC showed severe thrombocytopenia and neutropenia for which platelets transfusion was given and increased the dose of filgrastim after consultation with clinical haematologist. Throat swab C/S showed *Acinetobacter baummanii* sensitive to cefoperazone and sulbactum and antibiotic was changed accordingly but fever was persisting. Antinuclear antibodies and anti-double stranded deoxyribonucleic acid (anti-ds DNA) were positive, and she was diagnosed with childhood SLE according to EULAR (European League against Rheumatism) criteria and started on oral prednisolone. Patient showed a good response to treatment, improved symptomatically, and was discharged.

DISCUSSION

Cyclic neutropenia is a rare hematological disorder considered an inherent immune deficiency associated with a mutation of gene encoding neutrophil elastase 2 (ELANE) while SLE is a rare classical autoimmune/inflammatory disease in paediatric age group.[4,6,7] The incidence of juvenile systemic lupus erythematosus (jSLE) ranges between 0.36 and 2.5 per 1,00,000 children reported by Charras et al.[8] And the incidence ELANE gene-related mutation of severe congenital neutropenia and cyclic neutropenia are extremely rare in children.[3]

Cyclic neutropenia is an autosomal dominant disease characterised by the regular fluctuation of peripheral neutrophils from near normal to severe low levels, generally with a cycle of 21 days, but also can be 2-4 weeks. Clinical manifestations include fever, lymphadenitis, oral ulcers, and infections such as sinusitis, pharyngitis, cellulitis, pneumonia, and acute peritonitis.[4,9-12]

Unlike adult onset SLE, SLE in children are more aggressive with disease activity and medication burden which can increase the morbidity and mortality due to both the diseases and the treatment itself.[8]

Though there was no clear pathogenesis of ELANE mutation combined with autoimmune disease, it has been shown that dysregulation of innate immune pathways related to the host defense has profound effects on various aspects of SLE pathogenesis.[4]

The present case was brought to us at 3-year 6-month with a history of recurrent pneumonia and oral ulcers. After further evaluation, she was found to have ELANE gene mutation associated with cyclic neutropenia. She was treated with subcutaneous injection G-CSF and other symptomatic treatments. In view of persisting fever associated with thrombocytopenia, she was further evaluated for autoimmune disease and was diagnosed with childhood SLE according to EULAR criteria 2019.8 Patient showed good response to oral prednisolone and other symptomatic treatment and improved clinically. Autoimmune symptoms associated with ELANE mutation is rare and if autoimmune disease is associated with ELANE mutation-associated cyclic neutropenia, steroids and immunosuppressive therapy are effective.[4]

CONCLUSION

In conclusion, when treating children with recurrent fever and infections, clinicians should carefully evaluate proper history, thorough clinical examinations, complete haemogram with periodic patterns, radiographic evaluations, and even bone marrow examination as this might indicate rare cases like cyclic neutropenia or severe congenital neutropenia. Even though ELANE gene mutation associated with autoimmune disease like childhood SLE is extremely rare but when present together can aggressive the disease activity which can cause multi-system damages such as cytopenia, kidney, respiratory system and even central nervous system involvement. Hence, it is important to timely diagnose rare immunosuppressive conditions in children so that effective therapies like glucocorticoids and immunosuppressive agents can be administered at the earliest which will prevent several life threatening and long-term complications.

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