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CASE REPORT

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Case report of congenital neutropenia type 4 with glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency

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Key Clinical Message

Congenital neutropenia syndromes encompass a group of genetic disorders characterized by persistent neutropenia and recurrent infections inherited in an autosomal recessive, dominant, or X-linked manner. These syndromes arise from mutations in various genes, and one of the significant genes involved is glucose-6-phosphatase catalytic subunit 3 (*G6PC3*), giving rise to a condition known as Dursun syndrome. As per existing knowledge, a total of 92 cases of Dursun syndrome have been reported globally, including eight cases from Saudi Arabia. Our study identified two additional cases exhibiting neutropenia since the early postnatal period and recurrent admissions due to infections. Additionally, these patients presented with oral ulcers, chronic diarrhea, and anomalies affecting the cardiac and genitourinary systems. The rising incidence of congenital neutropenia on a global scale necessitates heightened vigilance among clinicians to ensure thorough follow-up of patients with neutropenia. This proactive approach can lead to early detection and appropriate management of associated complications, ultimately improving patient outcomes.

KEYWORDS

abscess, congenital neutropenia, Dursun syndrome, immune deficiency, Jazan, Saudi Arabia

1 | INTRODUCTION

Congenital neutropenia syndromes encompass a group of genetic disorders resulting from autosomal recessive, autosomal dominant, or X-linked mutations in various genes. One notable gene implicated in these syndromes is glucose-6-phosphatase catalytic subunit 3 (*G6PC3*), which not only leads to neutropenia but also contributes to abnormalities in multiple organs, including dysmorphic facial features, cardiac anomalies, skin abnormalities, gastrointestinal tract malformations, and urogenital tract anomalies.[1–3] Patients may also exhibit prominent superficial veins (Figure 1). These distinctive clinical features collectively characterize the syndrome known as

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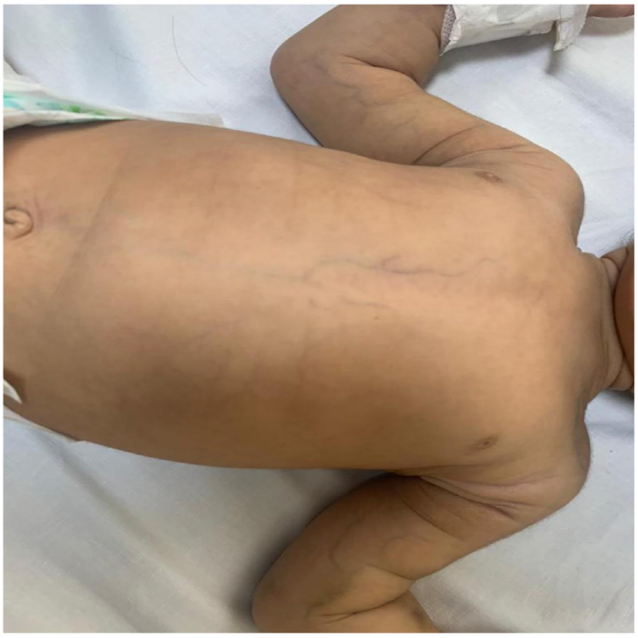

FIGURE 1 Case 1 with prominent superficial veins.

Dursun syndrome. In affected individuals, neutropenia is attributed to neutrophil apoptosis, leading to persistent depletion of neutrophil counts. This chronic neutropenia predisposes patients to recurrent infections, such as sepsis, chest infections, and abscesses, necessitating frequent hospital admissions.[1–3]

Globally, 92 cases of Dursun Syndrome have been reported in the literature, with eight of these cases originating from Saudi Arabia.[4,5] A specific genetic variant (c.479C>T; Ser160Leu) in the *G6PC3* gene has been identified as the causative mutation in these cases, leading to a substitution of serine to leucine at position 160. Interestingly, this novel mutation has been observed in only five patients, including the two cases presented in this study, all hailing from the southern region of Saudi Arabia. With the inclusion of our two cases, the published cases of Dursun syndrome in Saudi Arabia have now reached 10, contributing to the overall count of 94 cases reported worldwide.[4,5]

As our understanding of these syndromes deepens, it becomes crucial to recognize the increasing prevalence of congenital neutropenia globally. This growing incidence emphasizes the significance of closely monitoring patients with neutropenia, enabling early detection of potential complications and timely intervention. By highlighting these observations, we aim to draw attention to the importance of vigilant clinical management, especially in cases of neutropenia, to optimize patient outcomes and enhance our knowledge of these rare and complex disorders.

2 | CASE PRESENTATION

2.1 | Case 1

The first case involved a newborn female baby born to consanguineous healthy parents at 35 weeks of gestation. Notably, this family had a history of two previous babies with cardiac anomalies who unfortunately passed away during the neonatal period. The newborn exhibited several clinical features: a broad forehead, high anterior hairlines, high-arched eyebrows, deep-seated eyes with relatively long palpebral fissures, a depressed nasal bridge, and a prominent superficial venous pattern over the trunk and limbs—additionally, the patient presented with a large clitoris and labia minora, and no palpable gonads.

Initially, the complete blood count (CBC) during the first few days after birth appeared normal; however, subsequent assessments revealed persistent severe neutropenia. Notably, renal and liver panels and electrolytes, adrenocorticotropic hormone (ACTH), cortisol and glucose levels were within normal ranges. Radiological studies of the internal female genitalia exhibited normal findings, and echocardiography revealed the presence of patent foramen, oval mitral valve regurgitation, and tricuspid regurgitation. Further, postnatal metabolic screening results were unremarkable. An endocrinologist excluded any associated endocrinological diseases underlying the abnormal genitalia.

At the age of 3 months, the patient was readmitted to the hospital due to chest infection, skin rash, and chronic diarrhea. Frequent CBC with differential blood cell counts demonstrated persistent neutropenia. Lymphocyte subset interpretation using flow cytometry and immunoglobulin level assessments yielded normal results. Bone marrow aspiration did not reveal any abnormalities. Given the recurrent and puzzling nature of the patient's symptoms, whole exome sequencing was conducted, confirming the diagnosis of Dursun syndrome.

2.2 | Case 2

This case involves a 9-year-old boy with a history of recurrent admissions due to frequent infections since early neonatal days. The most commonly reported complaints included abdominal pain, joint pain, chronic diarrhea, and oral ulcers. At the age of 3 years, the patient underwent surgery for undescended testes. Family history revealed important information, with a sister diagnosed

with inflammatory bowel disease and experiencing persistent neutropenia until her unfortunate passing at the age of 7 years. Additionally, an infant boy died at the age of 8 months, although the parents were unable to provide a specific cause of death.

Clinical examination of the patient revealed a failure to thrive and dysmorphic features, including a triangular face, long eyelashes, abnormal ear shape, thick lips, and skeletal deformities affecting the knees and feet. Further, he was diagnosed with tricuspid, mitral regurgitation, and a patent ductus arteriosus. Abdominal examination revealed splenomegaly, and the patient was at Tanner stage 2 with anal tags. CBC results showed hypochromic microcytic anemia with neutropenia, while erythrocyte sedimentation rate was mildly elevated.

To investigate the possibility of inflammatory bowel disease, the gastroenterology team conducted a comprehensive blood workup and scope, ultimately excluding this condition. Subsequently, whole exome sequencing was performed, definitively confirming this patient's diagnosis of Dursun syndrome.

3 | DISCUSSION

There has been a notable increase in the number of reported cases of Dursun syndrome globally, each exhibiting different mutation sites within the same *G6PC3* gene. Our report adds to the growing body of evidence, as these two cases represent the fourth and fifth reported instances of Dursun syndrome in Saudi Arabia, characterized by the variant (c.479C>T; Ser160Leu) in the *G6PC3* gene.[5] Consistent with previous cases, both of our patients experienced failure to thrive, chronic diarrhea, skin rash, and recurrent admissions due to frequent infections. Moreover, abnormalities in the genitalia were observed, with the first case presenting a large clitoris and labia majora, while the second case had an undescended testis. Both patients displayed dysmorphic features, and the first case exhibited a prominent superficial venous pattern. Cardiac anomalies were also a common feature, including persistent patent foramen ovale, mitral regurgitation, and tricuspid regurgitation in both cases. In the first case, the results of whole exome sequencing (WES), coupled with the abnormal genitalia, may suggest the possibility of associated congenital adrenal hyperplasia. Even though there was a slight increase in the ACTH level, the cortisol level remained normal during the neonatal period. Furthermore, there were no episodes of adrenal crisis or electrolyte disturbances in subsequent admissions. However, this does not rule out congenital adrenal hyperplasia. Repeating the investigations as the patient ages might reveal abnormal results. If no abnormalities are found, the abnormal genitalia might be considered a secondary condition. Future reported cases may help clarify this question. It is too early to label this variant as a founder effect in southern Saudi Arabia. Hopefully, this case report will encourage the documentation of similar cases in the region, and the carrier frequency of this variant could then be better understood.

Remarkably, our two cases, along with only five others, share a novel homozygous missense variant in exon number 4 of the *G6PC3* gene (c.479C>T; Ser160Leu), all of which are from the southern region of Saudi Arabia.[5] However, it is crucial to recognize that the actual number of cases may be higher than those published, as many instances of Dursun syndrome may go undiagnosed. Given the increasing prevalence of congenital neutropenia worldwide, greater attention is warranted toward neutropenia as a common medical issue in daily clinical practice. While neutropenia can be transient following viral infections or linked to certain medications or illnesses, it may indicate an underlying severe or life-threatening condition. Consequently, we emphasize the importance of closely monitoring any pediatric patient with neutropenia to ascertain its persistence. Further investigations are essential to uncover potentially severe and rare etiological factors if they persist.

Management strategies for patients with congenital neutropenia primarily focus on preventing or minimizing recurrent infections. This can involve regular granulocyte colony-stimulating factors infusions to maintain absolute neutrophil counts above 0.5×10^9/L.[6,7] In mildly affected patients, prophylactic antibiotics alone have proven to be effective.[8]

Additionally, such patients require regular dental care, and dentists should consider administering prophylactic antibiotics for those undergoing dental procedures, particularly in the presence of cardiac defects, to mitigate the risk of infective endocarditis. Prompt administration of antibiotics and necessary workup is crucial for infected patients.[8] Overall, a comprehensive and proactive approach to managing congenital neutropenia is vital to improve patient outcomes and enhance their quality of life.

4 | CONCLUSION

Congenital neutropenia disorders, while rare, can easily go unnoticed in patients with neutropenia, especially those of younger age. Persistent neutropenia should always be taken seriously. A diligent and regular follow-up of neutrophil counts is crucial until there is evident improvement. If persistence is observed, it is important to conduct further investigations to determine the root cause, including potential congenital factors. Our cases underscore the importance of early detection and thorough evaluation. They serve as a poignant reminder that

even rare disorders can have profound implications and that medical vigilance can significantly impact patient outcomes. These cases offer valuable insights into the subtle nuances of diagnosis and emphasize the necessity of continuous learning in medical practice.

AUTHOR CONTRIBUTIONS

Nabil S. Dhayhi: Conceptualization; data curation; supervision; writing – original draft. **Mohammed A. Mahnashi:** Conceptualization; writing – original draft. **Alanoud I. Mokhasha:** Writing – review and editing. **Lana F. Ahmed:** Writing – review and editing. **Ahmed E. Shamakhi:** Writing – review and editing. **Adeeb A. Ageel:** Writing – review and editing. **Mohammed A. Tohary:** Writing – review and editing. **Abdulaziz H. Alhazmi:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

Available upon request from the authors.

ETHICS STATEMENT

Ethical approval was obtained from the Health Ethics Committee in Jazan, Saudi Arabia, Approval No. 2277.

CONSENT

Written informed consent was obtained from the patient's guardian to publish this report in accordance with the journal's patient consent policy.

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