SUNTEXT REVIEWS

SunText Review of Medical & Clinical Research
ISSN: 2766-4813

Open Access
Case Report
Volume 6:3

The Rare Case of ICF Syndrome Presenting in Adulthood with Successful Pregnancy Outcome

Rauf A, Arao-Arao M and Kumar P*

RACP, Respiratory Physician, Mackay Base Hospital, Australia

***Corresponding author:** Kumar P, FRACP, Respiratory Physician, Mackay Base Hospital; Australia; E-mail: Pranav.Kumar@health.qld.gov.au

Received date: 22 August 2025; **Accepted date:** 08 September 2025; **Published date:** 14 September 2025

Citation: Rauf A, Arao-Arao M, Kumar P (2025) The Rare Case of ICF Syndrome Presenting in Adulthood with Successful Pregnancy Outcome. SunText Rev Med Clin Res 6(3): 234.

DOI: https://doi.org/10.51737/2766-4813.2025.134

Abstract

Immunodeficiency, Centromeric instability, and Facial anomalies (ICF) syndrome is a rare autosomal recessive primary immunodeficiency. It is characterized by defective DNA methylation, chromosomal instability, and dysregulated immune function, often presenting in early childhood. Here, we describe a rare case of ICF syndrome diagnosed in a 20-year-old Australian female, initially misdiagnosed with common variable immunodeficiency (CVID), who presented with recurrent respiratory tract infections and bronchiectasis. Diagnosis was confirmed via cytogenetic karyotyping and DNMT3B mutation analysis. Remarkably, the patient had an uneventful pregnancy and delivered a healthy baby girl, expanding our understanding of the reproductive potential in ICF patients. This case underscores the importance of multidisciplinary evaluation in rare immunodeficiencies and highlights the potential for improved long-term outcomes with timely immunoglobulin therapy.

Keywords: Immunodeficiency; Centromeric instability: Facial anomalies

Introduction

ICF syndrome is a rare primary immunodeficiency disorder characterized by immunodeficiency, centromeric instability, and distinctive facial anomalies. Fewer than 100 cases have been reported worldwide. The most commonly implicated gene is DNMT3B, which encodes a DNA methyltransferase essential for de novo DNA methylation. The resultant hypomethylation affects pericentromeric regions, leading to chromosomal instability particularly involving chromosomes 1, 9, and 16. Clinical features typically include recurrent infections, hypogammaglobulinemia, and mild to moderate facial dysmorphism. Developmental delay is variably present. We report a unique adult case of ICF syndrome diagnosed following recurrent respiratory infections and pulmonary imaging indicative of bronchiectasis.

Case Presentation

A 20-year-old woman of Caucasian ethnicity was referred to a respiratory clinic for recurrent chest infections and chronic productive cough. She was born full-term to non-consanguineous parents, following an uneventful antenatal and postnatal course. At birth, she exhibited subtle dysmorphic features including hypertelorism and low-set ears (Figure 1). There was no history of developmental delay, cognitive impairment, or family history of genetic disorders. Two half-siblings were unaffected. From the age of two, she developed recurrent upper and lower respiratory tract infections, often requiring hospitalisation. Initial management was based on a presumed diagnosis of asthma, and she was treated with bronchodilators and intermittent corticosteroids without sustained benefit. At age 18, high-resolution computed tomography (HRCT) revealed moderate to severe bronchiectasis, particularly in the left lower lobe (Figure 2). Pulmonary function testing showed mild obstruction (FEV1 88.9% predicted, FVC 83.9% predicted). Immunological work-up demonstrated hypogammaglobulinemia with low IgG, IgA, and IgM levels, and a poor response to Pneumovax-23 vaccination. Lymphocyte subsets were normal. Work-up for cystic fibrosis, alpha-1-antitrypsin deficiency, and autoimmune diseases was negative, although heterozygosity for alpha-1-antitrypsin was noted without clinical significance. A provisional diagnosis of

CVID was made and monthly intravenous immunoglobulin (IVIG) therapy was initiated [1-12].

Figure 1*: Photograph of patient showing subtle facial dysmorphism including hypertelorism and low-set ears, features associated with ICF syndrome.*

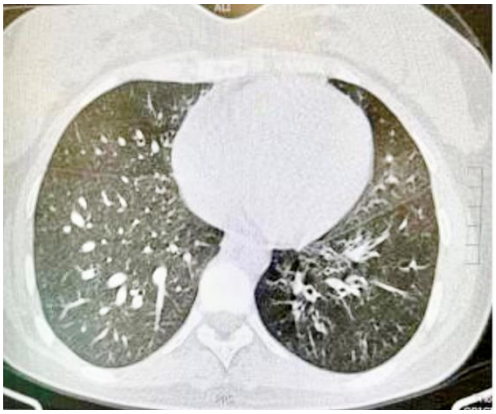

Figure 2*:High-resolution CT (HRCT) chest scan showing bronchiectatic changes and mucus plugging in the left lower lobe, consistent with chronic airway infection in immunodeficiency.*

Given the presence of dysmorphic features, genetic testing was pursued. Karyotyping demonstrated multibranched chromosomes 1, 9, and 16, consistent with centromeric instability. Further genetic testing revealed three variants of uncertain significance in the DNMT3B gene, confirming the diagnosis of ICF syndrome. Subsequently, she was transitioned to weekly subcutaneous immunoglobulin (SCIG; Hizentra 7g), which was better tolerated and associated with reduced infections and improved quality of life. Two years later, she became pregnant and had an uneventful gestation. She delivered a healthy baby girl without dysmorphic features or signs of immunodeficiency. No genetic testing was deemed necessary at the time, given the autosomal recessive inheritance pattern and absence of parental consanguinity. The patient remains clinically stable on SCIG, with normal lung function (FEV1 90.1%) and no recurrent infections.

Diagnostic Evaluation

ICF syndrome diagnosis was confirmed via cytogenetic analysis, demonstrating the classical chromosomal multibranching pattern involving chromosomes 1q, 9q, and 16q. This was supplemented by next-generation sequencing that identified VOUS in the DNMT3B gene. Diagnosis was supported by clinical presentation, immunological findings, and radiological evidence of bronchiectasis.

Management and Outcome

The patient was initially treated with monthly IVIG but was later transitioned to SCIG due to venous access difficulties. Since initiation of SCIG, she has had no further lower respiratory tract infections. Lung function has remained stable, and she continues to be monitored by a multidisciplinary team including immunology, respiratory, and genetic specialists. Her successful pregnancy and delivery further expand the known phenotype and long-term prognosis for individuals with ICF syndrome.

Discussion

ICF syndrome is a clinically heterogeneous disorder. The hallmark features are chromosomal instability, dysmorphic facies, and a variable degree of immunodeficiency. Most patients present in early childhood, and diagnosis in adulthood is rare. Misdiagnosis with CVID is common due to overlapping features of hypogammaglobulinemia and recurrent infections. The presence of facial anomalies and failure to respond to standard immunisation should prompt further genetic evaluation. Karyotyping remains a useful and accessible diagnostic tool in such settings. The long-term prognosis in ICF syndrome is dependent on early diagnosis and the timely initiation of immunoglobulin replacement. Our case illustrates that with effective management, patients can achieve near-normal quality of life and even undergo successful pregnancy. This case is one of the first reported instances of pregnancy in a genetically confirmed ICF patient in Australia.

Conclusion

This case highlights the importance of considering ICF syndrome in patients with recurrent infections and subtle dysmorphism. Timely diagnosis through karyotyping and genetic testing, followed by appropriate immunoglobulin therapy, can significantly alter the disease trajectory. Multidisciplinary care and long-term follow-up are essential to manage complications and support quality of life. This case also contributes to the limited literature on reproductive outcomes in ICF patients.

References

1. Maraschio P, Zuffardi O. Immunodeficiency, centromeric region instability, and facial anomalies syndrome: ICF syndrome. Hum Genet. 1988; 80: 257-260.
2. Ehrlich M. The ICF syndrome, a DNA methyltransferase deficiency and chromatin disease. Prog Mol Biol Transl Sci. 2003; 109: 117-130.
3. Wijmenga C. Genetic mutations in DNMT3B and their role in ICF syndrome. Nat Genet. 2000; 24: 50-52.
4. Tuck-Muller CM. Chromosomal instability in ICF syndrome. Am J Med Genet. 2000; 91: 61-68.
5. Weemaes CM. Clinical and immunological features of ICF syndrome. Eur J Pediatr. 2013; 172: 171-181.
6. Notarangelo LD. Primary immunodeficiencies: The ICF syndrome spectrum. J Clin Immunol. 2014; 34: 9-19.
7. Picard C. Management and outcome of ICF syndrome patients. J Allergy Clin Immunol. 2015; 136: 626-635.
8. Xu GL, Bestor TH, Bourchis D, Hsieh CL, Tommerup N, Bugge M, et al. Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene. Nature. 1999; 402: 187-191.
9. Hansen RS, Wijmenga C, Luo P, Stanek AM, Canfield TK, Weemaes CMR, et al. The DNMT3B DNA methyltransferase gene is mutated in the ICF immunodeficiency syndrome. Proc Natl Acad Sci USA. 1999; 96: 14412-14417.
10. Van der Burg M. ICF syndrome: a curious blend of immunodeficiency and chromosomal instability. Immunol Rev. 2003; 203: 216-231.
11. Mahlaoui N. Bronchiectasis and lung disease in primary immunodeficiencies. Clin Immunol. 2007; 122: 151-158.
12. Jolles S. Long-term efficacy and safety of subcutaneous immunoglobulin therapy in primary antibody deficiency. Clin Exp Immunol. 2005; 141: 365-369.