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Case Report

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Development of common variable immunodeficiency in a patient with severe aplastic anemia: a case report

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ABSTRACT

Severe aplastic anemia (AA) and common variable immunodeficiency (CVID) are distinct clinical entities that may rarely coexist due to shared molecular mechanisms. This report describes a 43-year-old male patient diagnosed with severe AA who subsequently developed CVID associated with an IKZF1 gene variant. Bone marrow examination confirmed severe hypocellularity. Although initial immunosuppressive therapy failed to achieve transfusion independence, hematologic recovery was obtained with eltrombopag. Approximately one year later, immunologic evaluation demonstrated hypogammaglobulinemia (IgA 0,7 g/L, IgM 0,63 g/L, IgG 4,78 g/L) and marked B-cell lymphopenia (total lymphocytes 1,990/mm³; B cells 100/mm³) with preserved T-cell counts. Genetic analysis revealed a heterozygous IKZF1 (c.115A>G, p.Thr39Ala) variant, supporting the diagnosis of CVID. This case highlights the importance of integrating genetic evaluation into the diagnostic work-up of patients presenting with combined hematologic and immunologic abnormalities, enabling accurate classification, appropriate management, and long-term follow-up.

Keywords: Aplastic anemia, common variable immunodeficiency, IKZF1 gene

INTRODUCTION

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by marked hypocellularity of the bone marrow and peripheral pancytopenia.[1] Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder resulting from defective B-cell differentiation and impaired immunoglobulin production.[2]

Although these conditions are traditionally considered distinct, recent genetic studies suggest that shared molecular pathways, particularly involving transcription factors regulating hematopoiesis and lymphopoiesis, may link bone marrow failure and immune deficiency. Herein, we report a rare case of severe AA followed by CVID associated with an IKZF1 gene variant, highlighting the importance of genetic evaluation in patients presenting with combined hematologic and immunologic features.

CASE

A 43-year-old male with no significant past medical history presented with gingival bleeding, ecchymosis, and purpura. Initial laboratory evaluation revealed hemoglobin 8.7 g/dl, mean corpuscular volume 62.4 fL, leukocytes 1,370/mm³, neutrophils 350/mm³, lymphocytes 880/mm³, platelets 2,000/mm³, lactate dehydrogenase 238 U/L (reference range: 125–243 U/L), and a reticulocyte count of 12,500/mm³.

Viral and autoimmune markers, including hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus, Epstein–Barr virus viral capsid antigen IgM, cytomegalovirus polymerase chain reaction, and antinuclear antibody, were negative. Paroxysmal nocturnal hemoglobinuria and Fanconi anemia were excluded using flow cytometric fluorescent aerolysin (FLAER) analysis and diepoxybutane testing, respectively.

Bone marrow aspiration and biopsy demonstrated approximately 15% cellularity with mild reticulin fibrosis (+1), consistent with severe AA. The patient received cyclosporine combined with horse anti-thymocyte globulin as first-line immunosuppressive therapy; however, he remained transfusion-dependent and lacked a human leukocyte antigen–matched donor. Eltrombopag (150 mg/day) was subsequently initiated, leading to progressive hematologic recovery and transfusion independence within three months.

Approximately one year later, the patient developed a carbuncle on the anterior thoracic wall. Immunologic evaluation revealed hypogammaglobulinemia, with immunoglobulin A 0.7 g/L (0.5–4 g/L), immunoglobulin M 0.63 g/L (0.5–2.5 g/L), and immunoglobulin G 4.78 g/L (6–15 g/L). Lymphocyte subset analysis showed 1,990 lymphocytes/mm³, including only 100 B cells/mm³, while

T-cell counts were preserved. These findings could not be fully explained by prior immunosuppressive therapy. Molecular genetic testing identified a heterozygous IKZF1 (c.115A>G, p.Thr39Ala) variant, supporting the diagnosis of CVID. Notably, the patient had no prior history of recurrent infections and demonstrated a normal serologic response to hepatitis B vaccination (anti-HBs seroconversion) before this presentation.

Given the absence of recurrent or severe infections at the time of evaluation, the patient was not started on regular intravenous immunoglobulin replacement therapy. Preventive counseling regarding infection control was provided, and close clinical and laboratory follow-up was recommended.

DISCUSSION

The IKZF1 gene encodes Ikaros, a zinc-finger transcription factor essential for lymphoid lineage commitment and immune homeostasis. Pathogenic variants in IKZF1 have been associated with a spectrum of immune dysregulation disorders, including CVID, combined immunodeficiency, and bone marrow failure syndromes such as AA.[2-6]

In this patient, CVID was considered more likely to represent a shared immune dysregulation spectrum related to the IKZF1 variant rather than a treatment-related complication or a coincidental association, since there is no established evidence that equine anti-thymocyte globulin (ATG) or eltrombopag induces CVID.

This case illustrates a rare but clinically relevant overlap between severe AA and CVID, suggesting a shared genetic background. While IKZF1-associated disorders have been reported to present with CVID/dysgammaglobulinemia and various cytopenias, a distinctive aspect of our case is the clinical predominance of severe AA at onset, followed by the delayed emergence of hypogammaglobulinemia and profound B-cell lymphopenia approximately one year after the initial presentation, with preserved T-cell counts after hematologic recovery with eltrombopag. This temporal dissociation supports a shared IKZF1-related immune dysregulation that may evolve along hematologic and immunologic axes over time. Recognition of such associations is crucial, as immune deficiency may evolve after apparent hematologic recovery. Comprehensive genetic analysis should therefore be considered in patients with bone marrow failure who later develop immunologic abnormalities, enabling timely diagnosis, appropriate surveillance, and individualized management strategies.

CONCLUSION

Clinicians should remain vigilant for the development of immune deficiency in patients with AA, particularly when pathogenic variants such as IKZF1 are identified. Early molecular diagnosis facilitates accurate disease classification, guides follow-up strategies, and improves long-term patient care.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Concept: İ.Ö., İ.Y; Design: İ.Ö.; Control: İ.Ö., İ.Y.; Resources: İ.Ö., İ.Y.; Materials: İ.Ö., İ.Y.; Data Collection and/or Processing: İ.Ö.; Analysis and/or Interpretation: İ.Ö., İ.Y.; Literature Review: İ.Ö.; Writing the Article: İ.Ö.; Critical Review: İ.Y.

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