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LETTER TO THE EDITOR

Onset of autoimmune hemolytic anemia after dimethyl fumarate treatment in a patient with multiple sclerosis

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Drug-induced autoimmune hemolytic anemia (DIAIHA) is a rare but potentially life-threatening condition in which medications trigger immune-mediated red blood cell (RBC) destruction. Diagnosis may be challenging because serological findings may overlap with idiopathic autoimmune hemolytic anemia (AIHA), particularly in patients receiving multiple therapies. More than 130 drugs have been implicated in DIAIHA, and drug withdrawal remains the cornerstone of management.[1] Among disease-modifying therapies used in multiple sclerosis (MS), alemtuzumab has the strongest association with paradoxically secondary autoimmune disorders,[2] while isolated cases have been described with fingolimod and interferon beta.[3] To date, only one case of dimethyl fumarate (DMF)-induced hemolytic anemia has been reported.[4] We present what is, to our knowledge, the second reported case.

A 46-year-old female with relapsing-remitting MS diagnosed in 2014 was initially admitted with left optic neuritis and recovered completely after high-dose intravenous methylprednisolone. Interferon beta-1a was initiated as first-line therapy. In January 2024, the patient experienced a second sensory relapse, again treated successfully with intravenous methylprednisolone, and therapy was switched to DMF. A written informed consent was obtained from the patient.

Nine months after initiating DMF, the patient presented with progressive weakness of the hands and feet, ecchymoses on the arms, and tea-colored urine. She had no history of transfusion, trauma, or exposure to other new medications. Two months before admission, laboratory tests showed a normal RBC count (4.21 M/µL [reference range, 3.93-5.22 M/µL]) and hemoglobin level (13.6 g/dL [reference range, 11.2-15.7 g/dL]). Routine monitoring performed every six months over the preceding two years had consistently demonstrated hemoglobin values within the normal range.

At presentation, laboratory evaluation revealed severe anemia: RBC, 0.10 M/µL; hematocrit, 14.3% (reference range, 34.1-44.9%); hemoglobin, 7.3 g/dL; reticulocytes, 5.23% (reference range, 0.5-1.7%); white blood cell count, 19 K/µL (reference range, 3-10 K/µL); mean corpuscular volume, 110 fL (reference range, 79.4-94.8 fL); and platelet count, 183,000 (reference range, 135,000-350,000). Biochemical tests showed elevated lactate dehydrogenase (1754 U/L [reference range, 135-214 U/L]), C-reactive protein (25 mg/L [reference range, 0-5 mg/L]), and indirect bilirubin (2 mg/dL [reference range, 0.2-1.1 mg/dL]) levels. Liver enzymes were also elevated. Physical examination revealed icteric sclerae and right upper quadrant tenderness.

Peripheral blood smear demonstrated macrocytosis, anisocytosis, and polychromasia without schistocytes. Direct antiglobulin testing (DAT) was positive and showed strong reactivity for both anti-immunoglobuline (Ig)G and anti-C3d on

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four repeated measurements. Indirect antiglobulin testing was positive. Viral serology for hepatitis viruses, HIV, EBV, and CMV was negative. Iron parameters and vitamin B12 levels were within normal limits. Quantitative IgA, IgM, and IgG levels were normal. Bone marrow biopsy, serum protein electrophoresis, and immunoelectrophoresis excluded lymphoproliferative disease. Hepatobiliary ultrasonography was unremarkable.

Given the suspicion of DIAIHA, DMF was discontinued, and oral prednisolone (1 mg/kg/day) was initiated. Hematologic parameters improved progressively: hematocrit levels increased to 27.2%, hemoglobin levels to 9.2 g/dL, RBC to 2.72 M/µL, and reticulocytes to 6.56%, while white blood cell count decreased to 13 K/µL. Hemolysis parameters normalized during follow-up. Corticosteroids were gradually tapered and discontinued. In January 2025, glatiramer acetate was initiated for MS, and no recurrence of hemolysis was observed.

Drug-induced autoimmune hemolytic anemia is serologically similar to warm AIHA and typically presents with IgG or C3d positivity on DAT.[1,5] Distinction from idiopathic AIHA relies primarily on temporal association and resolution after drug withdrawal. In the previously reported DMF-related case, initial DAT and indirect antiglobulin testing were negative,[4] whereas our patient demonstrated persistent DAT positivity for both IgG and C3d. In a large series of 73 patients with DIAIHA, DAT positivity was observed in nearly all patients, and mortality reached 23%, underscoring the potential severity of this entity.[1]

Although DMF is not commonly associated with autoimmune hematologic complications, our case supports a probable causal relationship based on temporal association, exclusion of alternative etiologies, and complete recovery following drug discontinuation.

In conclusion, DMF may rarely induce AIHA. Early recognition and immediate withdrawal of the suspected drug are crucial to prevent life-threatening outcomes.

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