LETTER TO THE EDITOR
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XMEN Disease Associated with Recurrent Autoimmune Cytopenias and EBV-Positive Hodgkin Lymphoma: A Case Report

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To the editor,

X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia (XMEN) is a rare primary immunodeficiency caused by mutations in the magnesium transporter 1 (MAGT1) gene [1,2]. Due to its rarity and variable clinical course, each case offers valuable insight into this complex condition.

A 29-year-old male presented with fever, jaundice, and fatigue. He had a childhood history of idiopathic thrombocytopenic purpura (ITP) and surgery for patent ductus arteriosus. Laboratory tests showed severe anemia (Hb: 4.6 g/dL), mild thrombocytopenia, indirect hyperbilirubinemia, elevated lactate dehydrogenase, C-reactive protein (CRP), and undetectable haptoglobin. The direct Coombs test was negative, and schistocytes were noted on peripheral smear. Thrombotic microangiopathy (TMA) was suspected, but paroxysmal nocturnal hemoglobinuria (PNH) and ADAMTS13 tests were normal. He received plasmapheresis and corticosteroids without benefit. Eculizumab was initiated for suspected atypical hemolytic uremic syndrome (aHUS), leading to hematologic improvement.

Bone marrow biopsy showed erythroid hyperplasia with dyserythropoiesis. Computed tomography (CT) examination revealed pathologic axillary lymphadenopathy. Biopsy confirmed EBV-positive nodular lymphocyte predominant Hodgkin lymphoma (Stage 3A), treated with six cycles of R-CHOP, achieving remission.

About 2.5 years after the initial presentation, he developed Coombs-positive autoimmune hemolytic anemia (AIHA) with thrombocytopenia. Steroids were ineffective; eltrombopag and rituximab were given. Cytomegalovirus (CMV) reactivation was treated with ganciclovir. Rituximab resolved cytopenias.

Approximately 2 years later, severe hemolysis recurred after cefprozil. Rituximab was resumed but paused due to CMV reactivation, which was managed with valacyclovir.

About 7 months later, hemolytic anemia relapsed. Azathioprine was started. Thrombocytopenia recurred with infections but responded to intravenous immunoglobulin (IVIG). Due to persistent EBV DNA positivity, as determined by PCR, and thrombocytopenia, eltrombopag was reinitiated. The summary of the treatment course is presented in Figure 1 .

Recurrent cytopenias and frequent infections prompted an evaluation for underlying immunodeficiency. Serum immunoglobulin levels and subclasses were decreased (IgG1: 3.4 g/L; IgG2: 1.46 g/L). Family history revealed that the patient's brother had developed gait disturbance, ataxia, and dysarthria following a COVID-19 infection at the age of 26. Genetic analysis of the brother identified a hemizygous X-linked MAGT1 mutation and a heterozygous autosomal dominant COL4A1 mutation. The asymptomatic mother was heterozygous for the same MAGT1 variant. Genetic testing of the patient confirmed a hemizygous MAGT1 mutation (Figure 1). Flow cytometry revealed a CD4/CD8 ratio of 1.1. Serum magnesium concentrations in our case were consistently within normal limits. Hemoglobin and platelet counts returned to normal without further eltrombopag therapy. No evidence of lymphoma recurrence was observed. The patient was initiated on IVIG therapy every 21 days and placed under regular follow-up.

Although the diagnostic criteria for XMEN disease have not yet been fully standardized, they can be summarized based on reported cases in the literature and current clinical guidelines. The diagnosis of XMEN disease is based on the identification of a loss-of-function mutation in the MAGT1 gene, which is located on the X chromosome. Hemizygous mutations are typically seen in males, while heterozygous female carriers are usually asymptomatic. Immunological findings often include CD4+ T-cell lymphopenia, impaired T-cell activation, decreased intracellular magnesium levels, and reduced surface expression of the NKG2D receptor on $CD8^+$ T cells and NK cells [1]. Clinically, affected individuals may present with persistent or chronic EBV viremia, EBV-related lymphoproliferative disorders , recurrent infections and autoimmune cytopenias[3]. Additional features may include dysgammaglobulinemia, lymphadenopathy, and splenomegaly. A decreased CD4/CD8 ratio and

persistent elevation of EBV DNA levels support the diagnosis. MAGT1 is a magnesium transporter located in the endoplasmic reticulum and plays a key role in maintaining intracellular magnesium homeostasis [2]. Although early studies demonstrated that the loss of MAGT1 leads to a decrease in intracellular free Mg^{2+} levels, more recent research has revealed that MAGT1 is a non-catalytic accessory protein required for the function of the oligosaccharyltransferase (OST) complex, which is responsible for asparagine (N)-linked glycosylation [1,4]. While mutations in MAGT1 functionally result in defective glycosylation, the clinical presentation manifests as an immunological disorder.As a result of this glycosylation defect, the expression of the NK cell receptor NKG2D is lost in both NK cells and T cells, playing a critical role in anti-EBV and antitumor immune responses. Although EBV-specific cytotoxic T lymphocytes (CTLs) can be generated in vivo, these CTLs are unable to effectively eliminate autologous EBV-immortalized lymphoblastoid B-cell lines and other tumor cell targets.. Definitive diagnosis is confirmed through molecular genetic testing, typically via whole-exome sequencing. Most cases present during the second or third decade of life [5]. Unfortunately, magnesium supplementation is currently not considered effective for treatment [6]. IVIG replacement and antiviral agents have shown limited efficacy in preventing EBV infections. Gene therapy is not yet available. Although allogeneic hematopoietic stem cell transplantation has been successful in a limited number of cases, it still carries a high mortality risk [7]. Compared to previously reported cases our patient exhibited several distinguishing clinical features. While most documented cases present in childhood or early adolescence, often with mild immunodeficiency or isolated EBV positivity, our case involved an adult male with recurrent, steroid-refractory autoimmune cytopenias, persistent EBV viremia, and EBV-positive Hodgkin lymphoma. In our case, serum magnesium levels were normal, which is a rare finding in the literature.Furthermore, the patient's disease course was complicated by multiple episodes of viral reactivation and immune dysregulation, requiring a broad spectrum of immunosuppressive and antiviral therapies. These findings suggest that phenotypic variability in XMEN disease may be broader than previously appreciated and underscore the importance of considering this diagnosis even in atypical adult-onset presentations.

Ethics

Informed Consent: Informed consent was obtained from the patient reported in this study.

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Time (years/months)	Event/Relapse	Treatment	Outcome
At presentation	AIHA, TMA suspicion	Plasmapheresis + steroids → eculizumab	Partial response
2.5 years later	AIHA + thrombocytopenia	Steroids → Eltrombopag + Rituximab	Resolved cytopenias
~2 years later	Severe hemolysis (post-cefprozil)	IVIG → Rituximab → Valacyclovir	Controlled
~7 months later	AIHA relapse	Azathioprine → IVIG → Eltrombopag	Improved

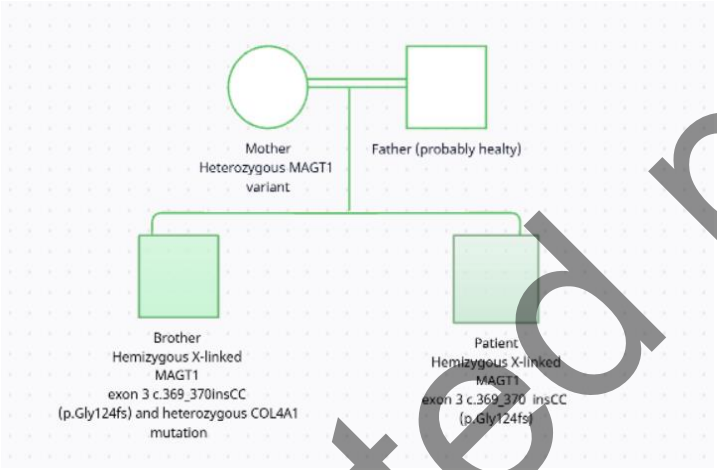

Figure 1: Summary of the therapies administered during follow-up, the family pedigree, and the mutation distribution.