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LETTER TO EDITOR

The Many Faces of XMEN Disease, Report of Two Patients with Novel Mutations

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To the Editor,

X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia (XMEN) is a rare combined immunodeficiency caused by loss of function mutations in the magnesium transporter 1 (*MAGT1*) gene. This magnesium channel regulates basal free $Mg2^{+}$ and, during T cell activation, mediates a transient influx of Mg^{2+} that enhances lymphocyte activation. MAGT1 also plays a crucial role in the N-linked glycosylation (NLG) of a subset of proteins important for normal immune function [1]. Pathogenic mutations in *MAGT1* have been shown to decrease intracellular free Mg^{2+}, abolish the influx of Mg^{2+} during T cell activation, and to decrease the MAGT1-dependent NLG of specific proteins, decreasing their expression. XMEN patients are particularly susceptible to EBV infections as persistently low levels of intracellular Mg^{2+} and hypoglycosylation lead to defective expression of the activating receptor "natural killer (NK) group 2, member D" (NKG2D) in NK and CD8+ T cells and decreased cytotoxicity, resulting in impaired clearance of EBV-infected cells and susceptibility to EBV-driven lymphoproliferation [2].

Twenty-three cases of XMEN have been reported to date; clinically, it presents with recurrent ear and sinopulmonary infections, lymphadenopathy, autoimmune cytopenias, lymphoproliferation, and increased risk of EBV+ lymphoma in male patients. Common laboratory findings include increased B cells, CD4+ lymphopenia, inverted CD4+/CD8+ ratio, elevated αβ double negative T (DNT) cells, low IgG and IgA, thrombocytopenia, and chronic EBV viremia. All reported patients have loss of function mutations in *MAGT1* [1–5]. We present two unrelated patients with novel mutations in *MAGT1*.

Patient one is a 15-year-old male with history of herpes zoster at age 7 and 12 years. No consanguinity or family history of immunodeficiency. He presented with massive epistaxis and splenomegaly, his laboratory evaluation showed a platelet count of 3000 cells/μL, and was diagnosed with immune thrombocytopenic purpura (ITP). He was treated with five doses of IVIG, four pulses of methylprednisolone, rituximab, eltrombopag, mycophenolate, and vincristine without improvement in his platelets counts, and continued to have bleeding. After all medical treatments had failed, he underwent a splenectomy, which transiently increased his platelets to 110,000 cells/μL. Following splenectomy, he suffered retinal and epicortical hemorrhages in the context of thrombocytopenia. While treated for refractory ITP, he developed EBV, cytomegalovirus (CMV), and BK virus viremia and had pansinusitis with positive cultures for *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* in sinusoidal tissue. Immunological evaluation on IVIG and rituximab showed normal T cell and NK cell counts with absent B cells and normal immunoglobulins, 2% DNT cells, and normal vitamin B_{12} levels (Table 1). After his bleeding had stabilized and EBV and CMV viral loads became undetectable, he was discharged home and continued to be followed for chronic ITP. Seven months after his initial admission, he presented with persistent fever and a mediastinal mass; histological analysis was compatible with Hodgkin's lymphoma. Immune studies, before chemotherapy, showed low T cells, normal B and NK cells, and a low CD4+/CD8+ ratio. Due to the association of refractory ITP, EBV infection, and lymphoma, genetic studies

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Table 1 Immunological and genetic features of the patients

	Patient 1				Patient 2			
Months since presentation	0	3	7	Normal range for age	0	4	16	Normal range for age
Age	15 years				4 months	8 months	20 months	–
Hb (g/dL)	11	10.5	11	13–16	9.3	9.4	10.9	9.5–13.5
Platelets ($\times 10^3$ cells/uL)	3	8	373	140–400	322	425	339	140–400
WBC ($\times 10^3$ cells/μL)	5.9	9.6	3.4	4.5–13	7.7	9.7	18.3	6.4–13.0
ALC ($\times 10^3$ cells/μL)	29.6	29.3	33.8	25–40	5.0	5.5	10.5	3.4–9.0
CD3	1.8	1.0	0.6	0.8–3.5	1.1	1.7	4.6	1.9–5.9
CD4	1.0	0.5	0.2	0.4–2.1	1.0	0.5	1.4	1.4–4.3
CD8	0.6	0.4	0.4	0.2–1.2	0.8	1.0	2.7	0.5–1.7
CD19	0[§]	0.8	0.4	0.2–0.6	3.7	3.5	5.5	0.6–2.6
CD56	0.5	0.5	0.1	0.07–1.2	0.2	0.3	0.4	0.16–0.95
CD4/CD8	1.6	1.3	0.5	0.9–3.4	1.2	0.5	1.0	
$CD3^+TCR\alpha\beta^+CD4^+CD8^+$ (%)		2		< 2				
Proliferation to PHA (%)					100	95.7	29.9	≥ 50
IgG (mg/dL)	585[*]	1675[*]	481[*]	716–1711	811	871[*]	833[*]	240-440
IgM (mg/dL)	77	141	108	15–188	127	100	80	34–114
IgA (mg/dL)	24	40	33	47–249	17	15	30	27–86
Vitamin B_{12} (pg/mL)	473	204		197–1711				
MAGT1 mutation								
cDNA	c.737_738insGA				c.223C > T			
Protein	p.Phe246Leufs[*]18				p.Gln75[*]			
NKG2D (MFI)				HD				HD
$CD8^+$ T cells	204			1370	77			1370
NK cells	219			919	158			919

[§] On rituximab

[*] On intravenous immunoglobulin

HD healthy donor

were done and showed a novel hemizygous pathogenic variant in *MAGT1* (c.737_738 insGA); this mutation is predicted to cause a frameshift with premature termination of the protein. Familial studies revealed the mother to be a carrier of the disease, while his two male siblings were unaffected. Pathogenicity was confirmed by a decreased expression of NKG2D in NK and CD8 cells (Table 1). On follow-up, platelet count significantly increased after chemotherapy and completely normalized since the beginning of his second chemotherapy cycle, he has been free of infections and has undetectable EBV viral load.

Patient two is now a 2-year-old male, sole child of non-consanguineous parents without a family history of lymphoma, EBV disease, or opportunistic infections. At age of 4 months, he was admitted to the intensive care unit because of pneumonia requiring mechanical ventilation. Infectious studies from bronchoalveolar lavage were positive for *Pneumocystis jirovecii* and CMV. Initial immune evaluation showed T cell lymphopenia with normal B and NK cells, normal CD4+/CD8+ ratio, lymphocyte proliferation to phytohemagglutinin (PHA), and immunoglobulins (Table 1). After completing treatment for his pneumonia, he was started on prophylactic trimethoprim-sulfamethoxazole. On follow-up, he had persistent T cell lymphopenia, affecting mostly CD4+ T cells and was found to have a low CD4+/CD8+ ratio. At the age of 7 months, he presented an upper respiratory tract infection with negative infectious workup, due to persistent T cell lymphopenia, and suspecting a combined immunodeficiency (CID), treatment with intravenous immunoglobulin (IVIG) was started. Genetic studies were done and reported a novel hemizygous pathogenic variant in *MAGT1* (c.223C>T), this mutation is predicted to create a premature stop codon at position 75 of the MAGT1 protein. Familial studies revealed the mother to be a carrier of the disease. Pathogenicity was confirmed by a decreased expression of NKG2D in NK and CD8 cells (Table 1). The patient has remained healthy on trimethoprim-sulfamethoxazole and IVIG prophylaxis; EBV viral loads are measured by PCR regularly and have been persistently low.

No genotype-phenotype correlation has been described for XMEN disease to date, and there is a wide range of age of presentation. Recurrent ear and sinus infections are the most common infectious complications of XMEN (70%), followed by molluscum contagiosum (39%), skin warts (30%), and HSV infection (13%) [1]. Although the pattern of infections seen in patient one is as previously reported for XMEN, he did not have a significant infectious history until requiring aggressive immunosuppression to try to manage his ITP. On the other hand, the second case presented with pneumonia due to *Pneumocystis jirovecii*, a pathogen not previously reported to affect XMEN patients. Up to 35% of the reported XMEN, patients presented with autoimmune cytopenias which, as seen in patient one, can precede the development of immune abnormalities that might point to an underlying immunodeficiency. When managing autoimmune manifestations of XMEN disease, caution is recommended as aggressive immunosuppression might unmask the patient's susceptibility to infections, as seen in patient 1.

Oral magnesium supplementation has been proposed as a targeted therapy for XMEN disease based on in vitro studies that showed an increase in free intracellular magnesium and NKG2D expression in patient cells after magnesium supplementation of culture media and in vivo studies, in a limited number of XMEN patients, showing restoration of NKG2D expression and a reduction in the number of EBV (+) cells with oral magnesium supplementation [2]; however, no prospective trials have been published to confirm these findings. Two groups have reported the use of hematopoietic stem cell transplantation (HSCT) to treat XMEN disease in a total of 5 patients, all of them had significant bleeding after transplantation and three of them patients died because of transplant related complications [2, 5]. Although the molecular basis for the hemorrhagic risk of XMEN patients has not been clarified, a qualitative platelet dysfunction has been suggested. The risk of bleeding in these patients is not limited to the post-transplant period, as significant bleeding events, like those seen in patient one, have been described before transplantation [5]. Reports of further cases of XMEN are needed to better delineate the phenotypic spectrum of the disease and establishing optimal therapies.

Compliance with Ethical Standards

Approval for the study was obtained from the Scientific Ethics Committee, School of Medicine, Pontificia Universidad Católica de Chile and Hospital Luis Calvo Mackenna. Informed consent was provided according to the Declaration of Helsinki.

Conflict of Interest The authors declare that they have no conflict of interest.

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