Clinical Immunology (2015) 159, 58–62

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

LETTER TO THE EDITOR

A case of XMEN syndrome presented with severe auto-immune disorders mimicking autoimmune lymphoproliferative disease

The magnesium transporter 1 (MAGT1) is a critical regulator of basal intracellular free magnesium (Mg^{2+}) concentrations. In 2011, Li et al. [1] reported a novel primary immunodeficiency associated with loss-of-function mutations in *MAGT1*, encoding the Mg^{2+}-channel MAGT1, and accordingly termed X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN syndrome). Lenardo and colleagues demonstrated that MAGT1-deficiency abrogates an Mg^{2+} flux required for T cell signaling and activation [1–3]. Here, we describe an adolescent with a novel hemizygous mutation in exon 4 of *MAGT1* (c.555dup) who presented with severe autoimmune disorders and Hodgkin lymphoma mimicking autoimmune lymphoproliferative syndrome (ALPS). Thus, our findings may expand the spectrum of diseases associated with XMEN syndrome.

The presented patient is a 17 year old boy who was born as the first child of unrelated parents. In his first decade of life, the patient had recurrent bronchitis and, frequent upper respiratory tract infections (8–10/year), including sinusitis. At the age of 15 years, patient sought medical attention for prolonged influenza-like symptoms and was referred to our university hospital due to elevated liver function tests. Abdominal ultrasound and computerized tomography (CT) showed multiple hypoechoic appearance in the liver and spleen, and generalized intra-abdominal lymphadenopathy. Thorax CT showed a large number of mediastinal lymph nodes. A portal lymph node biopsy revealed Hodgkin lymphoma. The patient was successfully treated using the COPP and ABVD protocols. One year later, the patient was again admitted to the pediatric emergency clinic with muscle weakness, ophthalmoplegia, and difficulty of walking. The patient was consulted by a pediatric neurologist. Electromyography of peripheral motor and sensory nerves in the lower limbs revealed an acquired demyelinating sensory and motor polyneuropathy. Spinal MRI was consistent with Guillain–Barré syndrome (GBS). Intravenous immunoglobulin (IVIG) was given to patient. With medical treatment and physiotherapy the patient recovered within two months. One month following recovery from GBS, the patient was diagnosed with immune thrombocytopenia (ITP). Platelets failed to increase with systemic steroids and IVIG and the patient was therefore subjected to splenectomy. Considering the elevated liver function tests, serology for hepatitis-A, hepatitis-B, hepatitis-C, rubella, herpes simplex virus (HSV) types 1 and 2, parvovirus B19, adenovirus, Epstein Barr virus (EBV), and human immunodeficiency virus (HIV) were negative. Biopsy of the liver was consistent with autoimmune hepatitis. Notably, anti-LKM, anti-SSA, and anti-SSB tests were positive without clinical manifestation of Sjögren's syndrome. Due to high CMV copy numbers, the patient was treated with gancyclovir. Almost 10 months later, CMV copy numbers remained high ($150–650 \times 10^6$ copies/mL), consistent with chronic CMV infection. The patient experienced severe autoimmune anemia, with 3 g/dL hemoglobin. Plasmapheresis was twice required. Two years later, EBV PCR was determined positive. The combined clinical manifestations of patient (lymphoma, GBS, chronic EBV, CMV infection) together with CD4 lymphopenia from the start of follow-up suggested combined immune deficiency (Table 1). The levels of IL-10, IL-18, and sFasL values were found normal which is inconsistent with a diagnosis of ALPS. Genetic studies did not show any mutations in Fas ligand related disorders. Genetic investigation with next generation sequence analysis indicated that there is hemizygous *MAGT1* c.555dup (p.Try186Ilefs*2) mutation, i.e. one base pair duplication in exon 4 of the gene. This result was confirmed by conventional Sanger sequence analysis. The *MAGT1* mutation is predicted to causes a frame shift mutation with premature termination of the MAGT1 protein. The mutation is therefore likely to be the disease-causing mutation. This mutation has not previously been reported. Sequence analysis demonstrated that the mother of the patient is heterozygous for the *MAGT1* c.555dup mutation. Allogeneic hematopoietic stem cell transplantation is planned for the patient. Meanwhile, the patient is on oral magnesium supplementation treatment. Corroborating findings in 9 previously described patients with *MAGT1* mutations (Table 2) [2–4], immunological analyses of our patient revealed selective CD4 lymphopenia, resulting in a CD4:CD8 T cell ratio of <1 in the patient, as well as low numbers of granulocytes (Table 1). Normal neutrophil and CD4 T lymphocyte numbers were observed in the patients' two healthy siblings (data not shown). Of note, in the B cell compartment, a low frequency of $IgD^{-}CD27^{+}CD38^{low}$ class-switched B cells was observed in the patient (1.9% of the B cell compartment, compared to 15.6% and 17.2% in the siblings, data not shown). Consistent with a previous report

http://dx.doi.org/10.1016/j.clim.2015.04.015

Table 1 Immunological and clinical features of the patient.

	At 15 years	At 16 years	At 17 years	Normal values
White blood cell count (/mm^3)	8580	8900	8890	4300–11,400
Absolute neutrophil count (/mm^3)	4810	6540	2540	1500–8500
Absolute lymphocyte count (/mm^3)	2470	1950	4180	1700–5710
CD3: (/mm3)	1235	897	2000	1100–4100
CD4: (/mm^3)	395	351	543	600–2400
CD8: (/mm^3)	765	490	1380	400–1500
NK: (/mm^3)	210	140	240	200–1000
CD19: (/mm^3)	960	890	1776	200–1400
IgG (mg/dL)	1100	1650	880	579–1610
IgA (mg/dL)	53	75	50	27–198
IgM (mg/dL)	145	94	52	30–187
IgE (iu/mL)	22	18	16	0–200
Clinical features	Hodgkin lymphoma	CMV infection, GBS, AH	CMV infection, AHA	

GBS, Guillain–Barré syndrome; AH, autoimmune hepatitis; AHA, autoimmune hemolytic anemia

[4], NKG2D expression on patient CD3$^-$CD56^{dim} NK cells and CD3$^+$CD8$^+$CD57$^+$ T cells was very low, whereas expression of additional co-activating receptors 2B4 and DNAM-1 was normal (Figs. 1a and b). In terms of cytotoxic lymphocyte function, patient NK cells displayed normal cytotoxic granule protein content relative to controls (Fig. 1c). While NK cell degranulation towards K562 cells was abnormally low in the patient, NK cell degranulation in response to engagement of the Fc receptor CD16 or co-engagement of 2B4 and DNAM-1 was normal (Fig. 1d). Lysis of K562 cells was somewhat low in the patient (Fig. 1e), which could partly be explained by the low frequency of NK cells among PBMC at the time of analysis (3.0% in the patient vs. 17.7% and 14.6% in the siblings). With respect to CTL, cytotoxic CD8$^+$CD57$^+$ T lymphocytes also displayed normal cytotoxic granule protein content relative to controls (Fig. 1f). Moreover, cytotoxic CD8$^+$CD57$^+$ T lymphocytes in the patient displayed strong degranulation in response to TCR engagement (Fig. 1g). Notably, patient cytotoxic CD8$^+$CD57$^+$ T lymphocytes also displayed strong production of cytokines IFN-γ and TNF in response to TCR engagement (Figs. 1h and i). In summary, cytotoxic lymphocyte function was not generally impaired in the MAGT1-deficient patient.

Idiopathic CD4 lymphopenia (ICL) is defined as the repeated presence of a CD4$^+$ T-lymphocyte count of less than 300 cells/μL or frequency of total T cells of less than 20% with no evidence of human immunodeficiency virus (HIV) infection and no other known condition that might cause depressed CD4 counts [5]. Besides HIV infection, differential diagnoses of ICL include other infections (mycobacteria, EBV, CMV), malignancies/hematologic conditions (lymphoma, aplastic anemia, myelodysplastic syndrome), autoimmune diseases [systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), Kikuchi disease], medications (chemotherapy, immunosuppressants, corticosteroids), sarcoidosis, common variable immunodeficiency and genetic syndromes (XMEN, WHIM, or *UNC119* mutation). Thus representing a diagnosis of exclusion, ICL requires an extensive immunologic, hematologic, rheumatologic, and infectious disease work up as well as follow-up testing to confirm persistent CD4 lymphopenia [6]. CD4 lymphopenia was noted at initial presentation of our patient. In addition, during clinical follow-up, the patient manifested Hodgkin lymphoma, chronic viral infection (EBV, CMV infection), and GBS, suggesting a primary immunodeficiency deficiency (PID). In our patient, we excluded PID commonly associated with autoimmune manifestations, such as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED), autoimmune lymphoproliferative syndrome (ALPS) and immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX). Moreover, our patient did not carry mutations in genes associated with PID commonly presenting with lymphoma, including ataxia–telangiectasia (AT), common variable immunodeficiency (CVID), Wiskott–Aldrich syndrome (WAS) and severe combined immunodeficiency (SCID). Rather, whole exome sequencing revealed a hemizygous one base pair duplication in exon 4 of *MAGT1* (c.555dup). Loss-of-function mutations in *MAGT1* cause XMEN syndrome which is characterized by chronic EBV infection often leading to B cell malignancies. MAGT1 mediates TCR-induced Mg^{2+} flux and also regulates the basal free Mg^{2+}. In XMEN patients, cells contain normal bound Mg^{2+}, but low free Mg^{2+}. Decreased intracellular free Mg^{2+} causes defective expression of the NKG2D receptor on lymphocytes, impairing cytotoxic responses against EBV-infected target cells. NKG2D mediates antiviral and antitumor cytotoxic responses by NK cells, CTL, and $\gamma\delta$ T cells [2, 4]. In addition, NKG2D has been implicated in promoting autoimmune diseases such type I diabetes mellitus, rheumatoid arthritis, and multiple sclerosis [7]. All these mechanisms may be predisposed, severe autoimmunity, chronic EBV, CMV infection and Hodgkin lymphoma in presented patient. Furthermore, this presentation of XMEN is unlike any of the published cases in the literature (Table 2). To our knowledge this report is the 10th patient for XMEN syndrome which presented with features of autoimmune disorders that is differently from the previously published cases.

Conflicts of interest

The authors declare that they have no conflict of interest.