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LETTER TO EDITOR

Familial Emberger Syndrome With Autoimmunity, Hyper-Immunoglobulin E and Lymphatic Impairment Caused by a Novel GATA2 Mutation

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To the Editor

Emberger syndrome is an autosomal dominantly inherited multisystemic disorder characterized by primary lower limb lymphedema associated with predisposition to myelodysplasia and acute myeloid leukemia [1]. It was first described in 1979 by Emberger et al. [2] who reported a two generational family with four individuals affected with severe postlingual congenital deafness, lymphedema, and hematological malignancies.

In 2011, Ostergaard et al. [1] identified heterozygous (haploinsufficiency) *GATA2* germline mutations in patients with Emberger syndrome [3]. GATA2 deficiency is now recognized as a protean disorder of hematopoiesis, lymphatics, skin, and immunity [4]. *GATA2*, which encodes three transcripts, is one of six 'WGATAR' DNA motif binding transcription factors that regulate gene expression and also interact with other transcription factors via two zinc finger domains where most described mutations cluster. In primitive hematopoietic cells, GATA2 complexes with six other factors (TAL1, LYL1, LMO2, ERG, FLI1, and RUNXI) as a core heptad regulatory unit within a much larger complex [5].

Here, we report a family of three siblings who presented with various features of GATA2 deficiency syndrome despite the lack of symptoms in their consanguineous 67-year-old father and 54-year-old mother. This study was approved by the King Faisal Specialist Hospital and Research Center Institutional Review Board (RAC #2060021). The proband (Patient 1) was a 20-year-old female who presented with biopsy-proven bilateral lower limb panniculitis, which was partially responsive to oral prednisone. She had marked bilateral lower limb lymphedema. Also, she complained of diffuse joint pain without other signs of inflammation. Laboratory studies showed persistent normocytic normochromic anemia with anisopoikilocytosis (hemoglobin 92 g/L), monocytopenia (0.07×10^9/L), T cell (0.69×10^9/L) and B cell lymphopenia (0.007×10^9/L), and transient hypereosinophilia (2.2×10^9/L). She also had hyperimmunoglobulin E (hyper-IgE) (6,620 KU/L) and normal IgA, IgG, and IgM levels. Extensive autoimmune studies showed only elevated antinuclear antibody (1:160, speckled), anticardiolipin IgG (18.1 GPL U/ml), antiphosphatidylserine IgG and IgM antibodies (17.8 GPS and 32.8 MPS U/mL, respectively), and raised soluble CD25 level (2415 pg/mL). Major histocompatibility class (MHC) II genotyping

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revealed *HLA-DRB1*07:01*07:01, DQB1*02:02;*02:03* alleles. Blood chromosome breakage analysis with diepoxybutane was normal, while bone marrow examination was not done. Total body positron emission tomography-computed tomography scan showed widening of the auditory canals, otosclerosis, and massive lower limb edema with fat stranding and fascial circumferential soft tissue density localized in both calves and feet. Full *GATA2* gene mutation analysis of peripheral blood genomic DNA using next generation sequencing revealed a novel and likely pathogenic heterozygous missense mutation (NM_001145661.1:c.1121G > A; p.Gly374Asp), located on chr3(GRCh37):g128200684. The mutation resides in exon 5 within the second zinc-finger domain of GATA2. This novel mutation is absent from the public gnomAD (www.gnomad.broadinstitute.org) as well as our internal Saudi Genome Program (www.saudigenomeprogram.org/) databases. The proband's 32-year-old sister (Patient 2) had hypocellular myelodysplastic bone marrow with subsequent transformation to acute myeloblastic leukemia. Lung biopsy showed lymphocytic interstitial pneumonia which appeared as cystic lung disease on chest computed tomography. Pulmonary function testing showed obstructive and restrictive features. She also had monocytopenia, B and T cell lymphopenia, with intermittently positive rheumatoid factor, SS-B (La), anticardiolipin IgG/IgM, anti-β_2-glycoprotein I IgM, and lupus anticoagulant. MHCII genotyping showed *HLA-DRB1*03:01;03:01*, *DQA1*05:01;05:10*, and *DQB1*02:01;02:01*. Bone marrow karyotype showed monosomy 7 and trisomy 8. She died shortly after receiving induction chemotherapy. Work up of the 20-year-old asymptomatic brother (Patient 3) who was a potential bone marrow donor showed leukopenia (lymphopenia, monocytopenia), thrombocytopenia, and moderately hypocellular nondysplastic bone marrow with some megaloblastoid changes. MHC genotyping showed *HLA-A*03:01, B*50:01*, *C*06:02:04*, *DRB1*03:01;03:01, DQB1*02:01;02:01*. Two other siblings (25-year-old sister and 27-year-old brother) appeared to be healthy. The parents of these five siblings denied any significant health problems. However, they have not had direct analysis of this novel *GATA2* mutation.

In this new family with the GATA2 deficiency syndrome, we observed the full spectrum of the clinical features of this syndrome which involved hematopoiesis, skin, vasculature/lymphatics, and immunity. We are particularly intrigued by the autoimmunity, hyper-IgE level as well as the lack of symptoms (non-penetrance so far) in either parent, although one of them is an obligate carrier. Autoimmune conditions like autoimmune hepatitis, autoimmune cytopenias, and arthritis have been reported in patients with GATA 2 deficiency [6,7]. One possible mechanism is the expansion of a small subset of $CD38^-$ $CD21^-$ B cells associated with autoimmunity [8].

While a few large series of patients with GATA2 deficiency have been published, to our knowledge, hyper-IgE has not been recognized as a component of this syndrome. GATA2 induced by STAT5 is also critical for mast cell and basophil differentiation which in addition to monocytes and dendritic cells constitutively express the high-affinity IgE receptor FcϵR1A. Endocytosis of this receptor contributes to normal serum IgE clearance [9,10]. Consequently, the monocytopenia and dendritic cell deficiency found in GATA2 deficiency may impair the kinetics of serum IgE clearance. Although the proband had several drug allergies, she lacked the clinical features of the autosomal dominant (Job syndrome, STAT3) or autosomal recessive (DOCK8/PGM3/IL6ST/ZNF341) hyper-IgE syndrome. The mechanism which underlies high IgE levels in these disorders remains poorly understood, but may involve an increase in Th2 cells. In some patients, T cells displayed defects in both nuclear factor-kappa B and mammalian target of rapamycin complex 1 activation, which might underlie their abnormal IgE production [11,12].

Despite their lymphopenia, the three affected siblings have not had any significant history of severe viral, fungal, or nontuberculous mycobacterial infections. The presence of low levels of likely nonpathogenic antinuclear and antiphospholipid antibodies could relate to the HLA-*DQB1*02:02* and *02:03* alleles, which in conjunction with *DRB1*03:01*, are associated with several autoimmune disorders, like in their sister with triple-positive antiphospholipid antibody syndrome who carried both risk alleles *DRB1*03:01* and *DQB1*02:01* [13,14].

Finally, due to the complexity of GATA2 deficiency, affected patients and their families need comprehensive multidisciplinary clinical care. Also, additional multi-omics investigations may help unravel its complex pathogenesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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