LETTER TO THE EDITOR

Korean J Intern Med 2016;31:188-190
http://dx.doi.org/10.3904/kjim.2016.31.1.188

First Korean case of Emberger syndrome (primary lymphedema with myelodysplasia) with a novel *GATA2* gene mutation

Sang Kyung Seo[1], Kyu Yeun Kim[1], Seo Ae Han[1], Joon Seok Yoon[1], Sang-Yong Shin[2], Sang Kyun Sohn[1], and Joon Ho Moon[1]

[1]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu; [2]Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

To the Editor,

Emberger syndrome is characterized by congenital deafness and primary lymphedema of the lower limbs, and is associated with a predisposition to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Associated phenotypes are also known to present in various ways, including hypotelorism, epicanthic folds, long tapering fingers and/or neck webbing, recurrent cellulites in the affected limb, and generalized warts [1]. *GATA2* plays a critical role in the development of the lymphatics and hematopoietic systems, and haploinsufficiency of *GATA2* is known to predispose to MDS/AML in this syndrome [2]. Here, we report the first Korean patient with a novel *GATA2* gene mutation bearing the characteristic features of Emberger syndrome, along with profound peripheral monocytopenia and B/natural killer (NK)-cell lymphocytopenia.

A 20-year-old Korean female was referred to our hospital for persistent acute tonsillitis despite 2 weeks of treatment with systemic antibiotics. Her pregnancy and delivery were uneventful without any gestational problems. However, she developed hearing loss at the age of 4, lymphedema in both lower limbs at the age of 7, and periodically experienced multiple warts on both feet from the age of 18 years. On physical examination, her physical appearance included epicanthic folds, hypotelorism, and deep-set eyes. Additionally, her legs were edematous with multiple warts on her feet (Fig. 1A and 1B). From the initial laboratory tests, her blood counts were pancytopenic: a white blood cell count of 1.54×10^9/L with 73.3% neutrophils, 16.6% lymphocytes, and 2.8% monocytes, a hemoglobin level of 8.2 g/dL, and a platelet count of 32×10^9/L. Her lymphocyte subset showed B/NK-cell lymphopenia (T-cell, 91.3%; B-cell, 5.9%; T4, 30.3%; T8, 44.8%; NK, 0.4%; CD4/CD8 ratio, 0.68) and monocytopenia (2.8%, 0.07×10^9/L). A bone marrow (BM) examination revealed trilineage dysplasia and confirmed MDS with refractory cytopenia with multilineage dysplasia. BM cytogenetics of the patient showed a normal karyotype. The copy number of the Epstein-Barr virus (EBV), checked by polymerase chain reaction, was 2,536 copies. Her chest and abdominal computed tomography showed hepatosplenomegaly and scanty bilateral pleural effusion, while her audiometric test revealed high frequency sensorineural deafness, and lymphoscintigraphy demonstrated main lymphatic tract hypoplasia in both legs (Fig. 1C). The

Received: June 18, 2014
Revised : August 19, 2014
Accepted: October 15, 2014

Correspondence to
Joon Ho Moon, M.D.
Department of Hematology/Oncology, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-6314
Fax: +82-53-426-2046
E-mail: jhmoon@knu.ac.kr

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

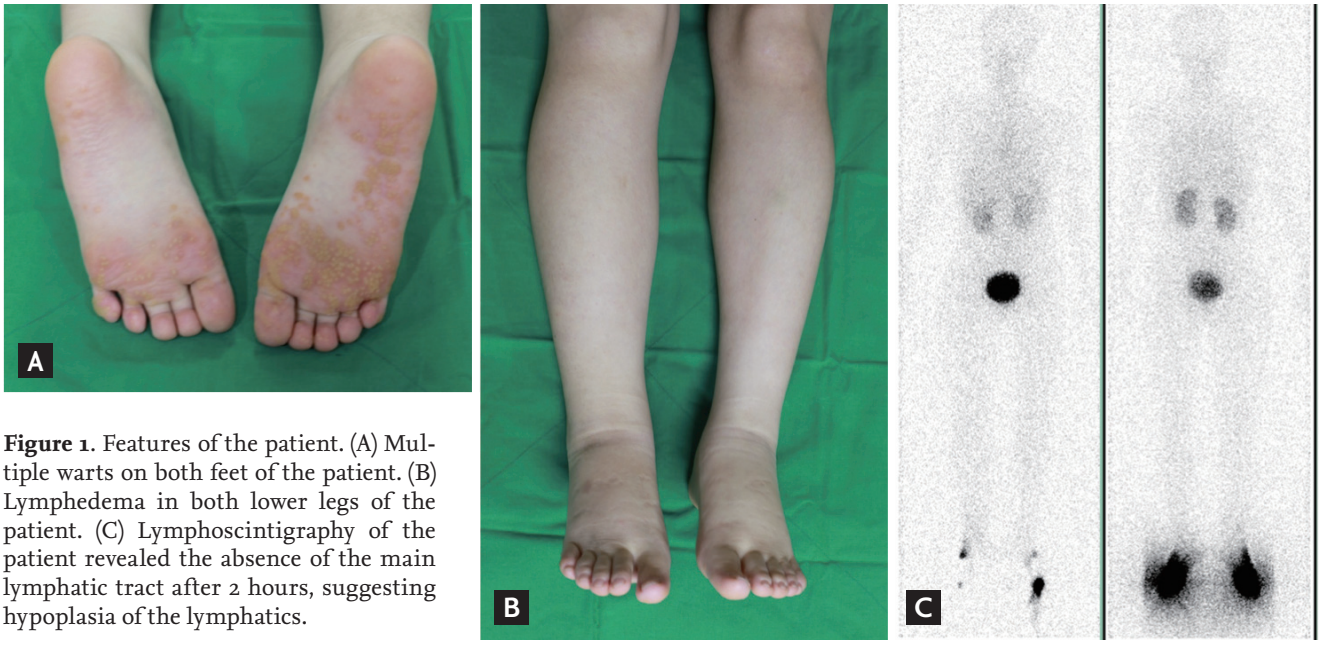

Figure 1. Features of the patient. (A) Multiple warts on both feet of the patient. (B) Lymphedema in both lower legs of the patient. (C) Lymphoscintigraphy of the patient revealed the absence of the main lymphatic tract after 2 hours, suggesting hypoplasia of the lymphatics.

patient did not show any intellectual disability. From her appearance and the results of laboratory tests, Emberger syndrome was suspected. Direct DNA sequencing analysis of the *GATA2* gene of the patient demonstrated a deletion of the 1,054th base (T) in exon 7, resulting in a frame-shift mutation (p.Cys352Valfs*35) in the zinc finger (ZF)-2 domain that was a novel variation with respect to previous cases of Emberger syndrome (Fig. 2). Her family members, parents, and one brother did not show any physical sign or laboratory abnormality related with Emberger syndrome.

This patient presented with the characteristic features of Emberger syndrome, such as sensorineural deafness and lymphedema in both legs, prior to the diagnosis of MDS. Her appearance also suggested Emberger syndrome, including epicanthic folds, hypotelorism, deep-set eyes, and multiple warts on both feet. Furthermore, laboratory tests revealed profound peripheral monocytopenia, B/NK-cell lymphocytopenia, and her *GATA2* gene analysis revealed a novel frame-shift mutation (p.Cys352Valfs*35) in the ZF-2 domain.

GATA2 is a transcription factor that plays an essential role in gene regulation during vascular development and hematopoietic differentiation. Recently, *GATA2* mutations have been identified in heterogeneous diseases, such as familial MDS/AML, monocytopenia and mycobacterial infection (MonoMAC) syndrome, and in Em-

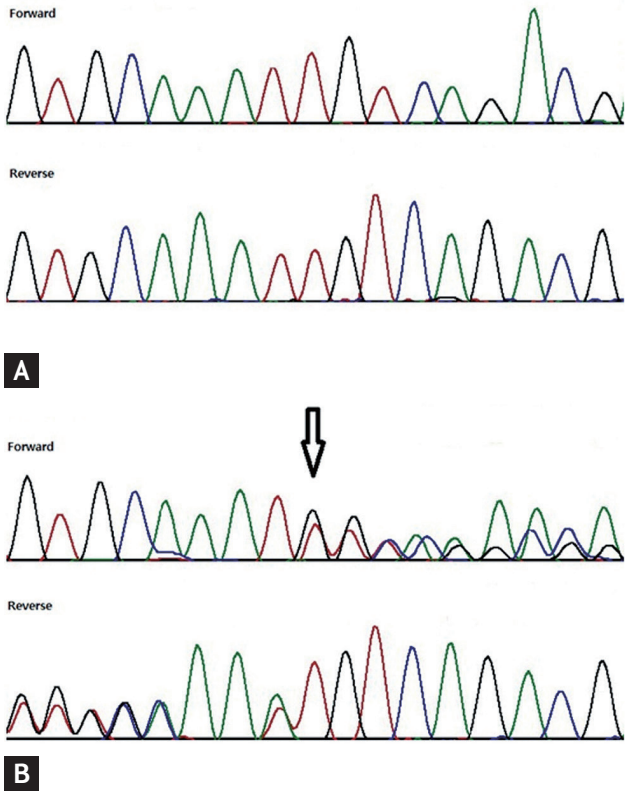

Figure 2. Sequence analysis of the patient and the patient's brother. *GATA2* gene sequence analysis of the patient's brother (A) and patient (B). Deletion of the 1,054th base (T) in exon 7 resulted in a frame-shift mutation (p.Cys352Valfs*35) in the patient. The arrow indicates the 1,054th base (T). The patient's only brother did not harbor the *GATA2* gene mutation.

berger syndrome [2-4]. Mutations leading to frame-shifts and premature termination of gene function and haploinsufficiency have been frequently found in Emberger syndrome and MonoMAC syndrome, whereas missense mutations of the *GATA2* gene have been most frequently found in cases of familial MDS/AML [2-4]. Ostergaard et al. [2] identified eight mutations in *GATA2* from eight ancestries of the Emberger syndrome, where each variant had a substantial impact on the function of *GATA2* and inherited predisposition to MDS/AML. Hsu et al. [3] described 12 *GATA2* mutations affecting 20 patients and relatives with MonoMAC syndrome.

It remains unclear why the same *GATA2* gene mutations are related to three different diseases. Hahn et al. [4] postulated that *GATA2* mutations with different phenotypes were merely described according to how the patient data were ascertained. However, the effect of *GATA2* mutations as a transcription factor seem to vary according to the position and type of mutation, thereby explaining the different phenotypes among the three disease categories. Kazenwadel et al. [5] demonstrated high levels of the *GATA2* protein in lymphatic vessel valves, and also that *GATA2* controls the expression of genes important for programming lymphatic valve development. Three patients with lymphedema and MDS/AML showed either complete or partial gene deletions or a frameshift mutation, rather than missense mutations, where all of these mutations were predicted to result in the complete loss of function of one *GATA2* allele and hence haploinsufficiency [5].

According to previous reports, most patients with *GATA2* mutations have opportunistic infections many years before the development of overt MDS/AML [1-4]. Similar to other Emberger syndrome patients, the current patient had previously experienced a human papillomavirus (HPV) infection and had a high copy number of EBV-DNA. MonoMAC syndrome also presents with impaired control of opportunistic infections (nontuberculous mycobacteria, dimorphic molds, and HPV), suggesting that the function of tissue macrophages is impaired before the development of myelodysplasia [3]. In addition, significant HPV infection and other viral infections with *GATA2*-related diseases probably reflect the profound absence of NK cells. However, the relatively narrow spectrum of infectious organisms is distinct from the common clinical features of neutropenia in MDS. Therefore, such evidence has drawn speculation over the connection between a predisposition to myeloid malignancy and opportunistic infections, possibly providing a second hit in the development of MDS/AML.

In conclusion, this report is the first Korean case of Emberger syndrome with a novel *GATA2* gene mutation. The present findings indicate that *GATA2* gene mutation screening is needed for patients with primary lymphedema and myelodysplasia, particularly when associated with monocytopenia, due to variable clinical presentations at onset and frequent MDS/AML transformation.

Keywords: Myelodysplastic syndromes; GATA2 gene mutation; Emberger syndrome

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

The authors would like to thank the patient and her family for their participation in the present study.

REFERENCES

1. Mansour S, Connell F, Steward C, et al. Emberger syndrome-primary lymphedema with myelodysplasia: report of seven new cases. Am J Med Genet A 2010;152A:2287-2296.
2. Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). Nat Genet 2011;43:929-931.
3. Hsu AP, Sampaio EP, Khan J, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood 2011;118:2653-2655.
4. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet 2011;43:1012-1017.
5. Kazenwadel J, Secker GA, Liu YJ, et al. Loss-of-function germline GATA2 mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature. Blood 2012;119:1283-1291.

http://dx.doi.org/10.3904/kjim.2016.31.1.188