Case report

Evaluation of recurrent and recalcitrant warts in a deaf adolescent male reveals GATA2 deficiency

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Prompt evaluation and genetic testing of patients who present with recurrent and recalcitrant warts, before onset of severe infection or myelodysplastic syndrome, leads to improved outcomes in patients with GATA2 deficiency. (J Allergy Clin Immunol Global 2024;3:100313.)

Key words: *Immunodeficiency, GATA2, GATA2 deficiency, inborn error of immunity, warts, cutaneous warts, bone marrow transplant*

Abbreviations used
BMT: Bone marrow transplantation
MDS: Myelodysplastic syndrome
SNHL: Sensorineural hearing loss

PATIENT PRESENTATION

An adopted 14-year-old deaf male was referred to the immunology clinic for a family history of autoimmune disease. His birth history, growth, and development were uncomplicated except for sensorineural hearing loss (SNHL), allergic rhinitis, and persistent warts. The warts developed when the patient was aged 2 years, and they were recalcitrant to treatment. His infectious history was remarkable for yearly sinusitis and otitis media.

The patient's family history was notable for multiple paternal uncles with SNHL and warts. The patient's biologic father had SNHL and recurrent warts, and he died of presumed pneumonia and an unknown underlying immunologic disease at age 34 years (Fig 1). Of the patient's 7 paternal uncles, 3 had SNHL (of these 7 uncles, 2 also had recurrent warts). One uncle died at age 32 years after developing cardiac complications during leukemia treatment. Another uncle died at age 46 years after developing an unknown condition that affected his gait. Another uncle with SNHL is still living; his medical history is unknown. Of the patient's 4 hearing paternal uncles, 1 has a daughter with a cochlear implant. Two of the hearing uncles died of myocardial infarction in their forties and fifties. The patient's 3 paternal aunts are healthy with healthy daughters. The patient's biologic mother is still living and has a history of myocardial infarction and stroke. The patient's full biologic sister has asthma.

The patient's vital signs were normal. He wore a hearing aid and communicated via American Sign Language. His notable physical findings included multiple flat and verrucous papules that ranged from 1 to 10 cm in diameter and were present on his scalp, face, hands, elbows, knees, and feet (Fig 2).

TESTING

Because of the patient's presentation of recalcitrant warts, recurrent sinusitis, SNHL, and concerning family history, there was suspicion for GATA2 deficiency. The patient's complete blood count showed marked monocytopenia (total white blood cell, 3.98 K/μL; absolute monocyte count, 50/μL). Mild microcytic anemia was present. Flow cytometry showed nearly absent B cells (8/μL), a low natural killer cell count (17/μL), and low T-cell count (CD3 cell count, 815/μL; CD4 cell count, 383/uL; and CD8 cell count, 366/μL). The patient's IgG, IgM, and IgE levels were within normal limits (IgG level, 588 mg/dL; IgM level, 183 mg/dL; and IgE level, 3.9 kU/L). The patient's IgA level was mildly low (34 mg/dL). Specific antibody testing found normal tetanus and diphtheria antibody (0.1 IU/mL) and nonprotective pneumococcal antibody levels (22% ≥1.3 μg/mL). The patient received routine childhood pneumococcal (Prevnar) and diphtheria, tetanus, and pertussis series. His postvaccination titers were not evaluated. His mitogen testing result was normal.

Genetic testing ordered at presentation found a pathogenic heterozygous variant (c1180C>T [p.Gln394*]) in *GATA2*.

Bone marrow biopsy showed hypocellularity for age (10%-40% cellularity) with trilineage maturation. There was no morphologic evidence of dyspoiesis. According to morphologic or flow cytometry analysis, there were no excess blasts. The result of fluorescence *in situ* hybridization was negative for myelodysplastic syndrome (MDS)-associated chromosomal alterations.

DIAGNOSIS

GATA2 is involved in hematopoiesis and cellular differentiation. GATA2 deficiency is a syndrome characterized by opportunistic infection and myelodysplasia. Its clinical picture is

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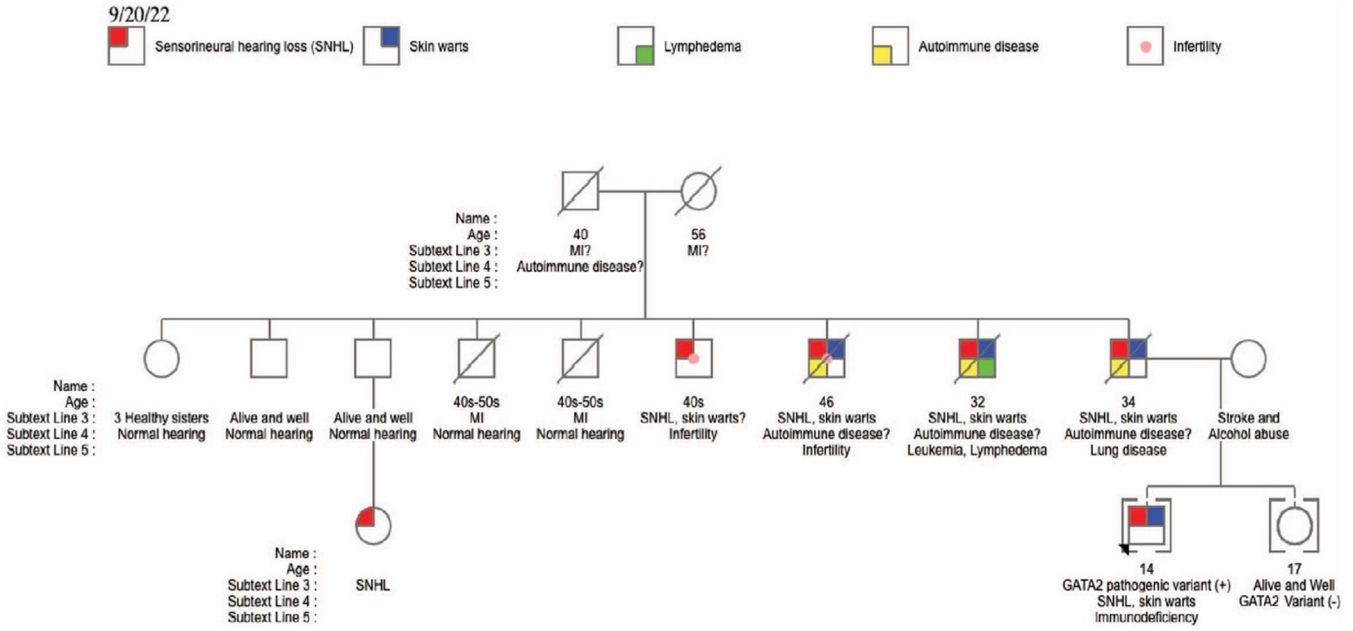

FIG 1. This pedigree illustrates the presence of characteristics, including skin warts, sensorineural hearing loss, leukemia, lymphedema, and autoimmune disease associated with GATA2 deficiency in the index patient and his paternal aunts and uncles.

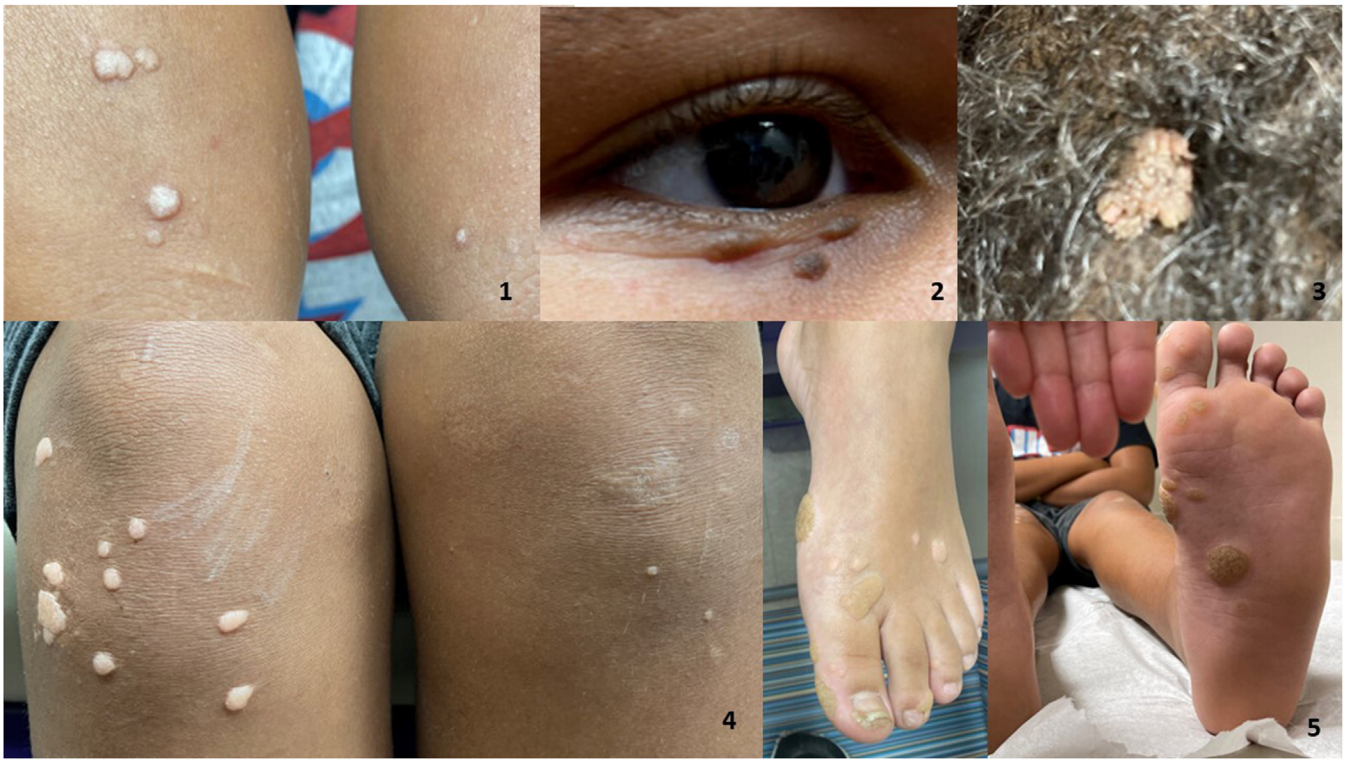

FIG 2. Recurrent and recalcitrant warts on (1) bilateral elbows, (2) eyelid, (3) scalp, (4) bilateral knees, and (5) feet.

broad and variable, with different phenotypes even within the same family.[1] Other differential diagnoses included warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome but was likely not due to lack of hypercellularity on bone marrow biopsy.[2]

Our patient displayed 2 significant signs of GATA2 deficiency: SNHL and recurrent/recalcitrant warts. Of patients with GATA2 deficiency, 76% have SNHL.[1] Warts are often the earliest indicator of GATA2 deficiency (occurring in 53% of patients). The patient's laboratory findings also support a diagnosis of GATA2

deficiency: marked monocytopenia; B-cell, natural killer cell, and CD4 cell lymphopenia; and normal immunoglobulin levels.[1-3]

Genetic testing confirmed a heterozygous pathogenic variant in *GATA2*, which supports haploinsufficiency associated with GATA2 deficiency (a single working copy is insufficient for normal function).[4,5] The patient's family history demonstrates the autosomal dominant inheritance pattern observed in GATA2 deficiency. Each generation of the patient's family is affected by SNHL and/or warts; those affected include 4 of his 10 paternal uncles, a female cousin, and the patient himself (Fig 1).

Other attributes of GATA2 deficiency are characterized by variable expressivity. The cause of death of the patient's father is suspicious for pulmonary alveolar proteinosis. One of his paternal uncles was diagnosed with leukemia, which occurs in 14% of patients with GATA2 deficiency.[1] The diagnosis of another of the patient's paternal uncles is unclear, but chronic arthralgia, lymphedema, and deep vein thrombosis are findings associated with GATA2 deficiency.[1] Although 1 study showed that 84% of patients with GATA2 deficiency will develop MDS,[1] our patient had no evidence of MDS, likely owing to early detection.

TREATMENT AND PATIENT OUTCOMES

Because of the increased risk for mycobacterial and viral infection, the patient began prophylaxis with oral azithromycin and valacyclovir. Although bone marrow biopsy did not show MDS, the hematology and oncology department was consulted for bone marrow transplantation (BMT), as outcomes are best if the transplant procedure is done before development of MDS.[6] Because of the patient's B-cell lymphopenia, low-normal IgG level, and nonprotective pneumococcal titers, he began receiving monthly intravenous immunoglobulin before BMT.

An unrelated donor search did not show any potential 8 of 8 HLA-allele match donors or cord blood units in the registry. The patient's full biologic sister was negative for a pathogenic variant in *GATA2*. HLA typing revealed that she was a haplotype match.

The patient underwent uncomplicated haploidentical BMT following busulfan-based a nonmyeloablative preparative regimen.[6] He was engrafted for neutrophils on day 17 after BMT and for platelets on day 28 after. His post-BMT complications included acute renal injury and adenovirus hemorrhagic cystitis at day 88 after the transplant. His adenoviremia was successfully treated with cidofovir and intravenous hydration.

The patient is now at day 368 after haplo-BMT, with 100% donor DNA chimerism in CD3- and CD33-enriched peripheral blood cells. He is continuing *Pneumocystis* prophylaxis with trimethoprim/sulfamethoxazole and viral prophylaxis with acyclovir. He has been able to discontinue antifungal prophylaxis, antiviral prophylaxis, intravenous immunoglobulin, and tacrolimus. The results of surveillance pulmonary function testing to assess risk for pulmonary alveolar proteinosis have remained normal. Surveillance echocardiograms have continued to show normal function, and he continues to show no signs of graft-versus-host disease. The patient has remained clinically well, and his warts have resolved.

LESSONS LEARNED

Recurrent and recalcitrant warts should always raise suspicion for an inborn error of immunity. Early genetic testing, even at initial presentation, is invaluable to immunologists for obtaining an appropriate diagnosis.[7] Early treatment with BMT improves survival in GATA2 deficiency even when fully matched donors are not available.[1,6] If the results of genetic testing are positive, then prompt family screening can be initiated.

CONSENT

Written consent was obtained by the caregiver to publish this case report along with all accompanying visual elements.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: J. E. Farrar reports research funding from Novartis. A.J. Modi is involved in editorial services for Sanofi Genzyme. A.A. Jefferson reports funding from the National Center for Advancing Translational Sciences of the National Institutes of Health. The rest of the authors declare that they have no relevant conflicts of interest.

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