A woman with warts, leg swelling, and deafness

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CASE SUMMARY

History

A 45-year-old white woman was referred to the National Institutes of Health (NIH) for the evaluation of warts, lower extremity swelling, and immunodeficiency of 35 years' duration. The patient was born after an uneventful pregnancy and was in a normal state of health until 9 years of age when she developed right lower extremity lymphedema that progressed to bilateral lymphedema over the next 2 years. During this time, she also developed verrucae on her hands that were recalcitrant to therapy.

Subsequently, the patient was hospitalized multiple times for recurrent episodes of cellulitis of the lower legs that required treatment with intravenous antibiotics. These incidents were further complicated by central line infections and recurrent sepsis, including a history of fungemia with *Exophiala dermatitidis*. At 30 years of age, she was found to have bilateral sensorineural hearing loss that was initially attributed to multiple courses of antibiotics. Autoimmune thyroiditis was diagnosed at 31 years of age.

Several squamous cell carcinomas in situ developed on the face and upper aspect of the chest and were excised from the patient when she was in her mid-30s. One year before presenting to the NIH, she developed chronic osteomyelitis of the left femur and was found to have pancytopenia with a hypoplastic marrow.

Physical examination

The physical examination revealed multiple periungual hyperkeratotic and subungual verrucous papules and plaques involving most of her fingers (Fig 1). The right forearm and right elbow had several pink verrucous plaques. Several well-healed surgical scars were present on the forehead and chest. The bilateral lower legs had significant pitting edema extending to the midthigh (Fig 2).

Abbreviations used:

DCML:	dendritic cell, monocyte, B lymphocyte, and natural killer lymphocyte deficiency
MAC:	*Mycobacterium avium* complex
MonoMAC:	monocytopenia and mycobacterial infection syndrome
NIH:	National Institutes of Health

Significant diagnostic studies

Laboratory investigations were significant for a white blood cell count of 5.63 $\times$ $10^3/\mu$L (normal, 3.98-10.04) with 4.91 $\times$ $10^3/\mu$L neutrophils (normal, 1.56-6.13 $\times$ $10^3/\mu$L), 0.61 $\times$ $10^3/\mu$L lymphocytes (normal, 1.18-3.74 $\times$ $10^3/\mu$L), and 0.02 $\times$ $10^3/\mu$L monocytes (normal, 0.24-0.86 $\times$ $10^3/\mu$L); a hemoglobin level of 11.7 g/dL (normal, 11.2-15.7 g/dL); and a platelet count of 751 $\times$ $10^3/\mu$L (normal, 173-369 $\times$ $10^3/\mu$L). Flow cytometric analysis of peripheral blood revealed a deficiency in dendritic cells, B cells, and natural killer (NK) cells with significant monocytopenia. Immunologic analyses revealed immunoglobulin G (IgG) levels of 824 mg/dL (normal, 700-1600 mg/dL), IgA levels of 65 mg/dL (normal, 70-400 mg/dL), IgM levels of 64 mg/dL (normal, 40-230 mg/dL), and IgE levels of 14.1 IU/mL (normal, 0.0-90.0 mg/dL).

DNA mutation analysis from a previous hospitalization identified a heterozygous null mutation in *GATA2* (exon 5 c.1009 C$\rightarrow$T), resulting in the substitution of a stop codon for arginine at amino acid 337.

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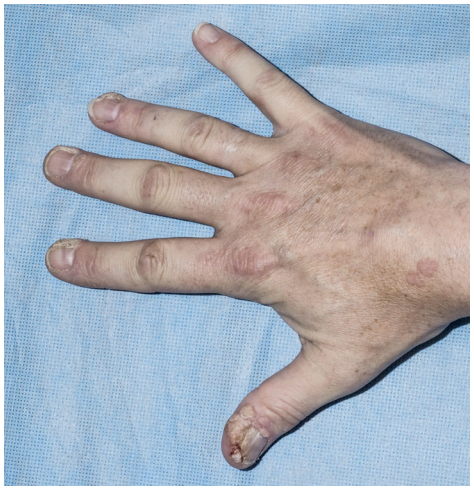

Fig 1. Recalcitrant verruca. Periungual hyperkeratotic and subungual verrucous papules.

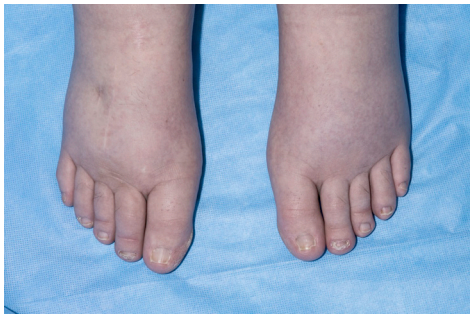

Fig 2. Lymphedema. Extensive bilateral leg edema with pronounced edema of bilateral dorsal surfaces of the feet.

Diagnosis

This patient was diagnosed with GATA2 deficiency and was included in a cohort of patients with GATA2 deficiency previously described by Spinner et al.[1]

DISCUSSION

The clinical manifestations of GATA2 deficiency are variable, but can include immunodeficiency, multiple infections, lymphedema, and sensorineural hearing loss.[1,2] The cutaneous manifestations include recurrent soft tissue infections, recalcitrant verruca vulgaris, squamous cell carcinoma, panniculitis, erythema nodosum, Sweet syndrome, and lower limb lymphedema, but they vary among patients. A recently published analysis of 57 patients noted that cutaneous manifestations of GATA2 deficiency often suggest an underlying infection or malignancy.[1] Unlike most other genetic disorders with profound immunodeficiency, this syndrome typically presents later in life with a median age of 20 years at initial presentation (age range, 5 months-78 years).[1] Informed dermatologists may therefore be the first physicians to identify patients with this syndrome.

GATA2 is a zinc finger transcription factor that regulates vascular development, lymphatic development, and hematopoietic differentiation.[3] Recent investigations have determined that mutations in *GATA2* are responsible for several different syndromes, including monocytopenia and mycobacterial infection complex (MonoMAC) syndrome or dendritic cell, monocyte, B lymphocyte, and NK lymphocyte deficiency (DCML; Online Mendelian Inheritance in Man [OMIM] 614172); primary lymphedema with myelodysplasia or Emberger syndrome (OMIM 614038); susceptibility to myelodysplastic syndrome (OMIM 614286) and susceptibility to acute myeloid leukemia (OMIM 614286); and congenital neutropenia.[2,4-6] These syndromes were previously thought to have distinct etiologies; however, these syndromes are now understood to be phenotypic variants of GATA2 deficiency. Genetic testing for GATA2 deficiency is available from several commercial laboratories and academic institutions.

The underlying immunodeficiency is characterized by the development of persistent and profound peripheral monocytopenia, severe B cell and NK cell lymphocytopenia, and variable T cell lymphocytopenia.[1,2,5,7] Patients may have neutropenia and associated monocytopenia for many years before they develop additional signs and symptoms of this condition; therefore, screening of *GATA2* mutations in this population is recommended.[2,5] Unfortunately, most patients with GATA2 deficiency develop hypoplastic myelodysplastic syndrome, and some go on to frank leukemia.[8] Cuellar-Rodriguez et al[9] recently found that allogeneic hematopoietic stem cell transplantation can successfully reverse the hematologic, immunologic, and clinical manifestations of GATA2 deficiency.

Patients with GATA2 deficiency are at risk for multiple infections, including disseminated and pulmonary nontuberculous mycobacterial infections, fungal infections, and severe viral infections. The most common nontuberculous mycobacterial infections are caused by *M avium* complex (MAC) organisms. The most common fungal infection is disseminated histoplasmosis; however, cryptococcal meningitis and invasive aspergillosis have also been reported. The absence of NK cells in GATA2-deficient patients may account for widespread viral infections that are characteristic of this condition.[4] More than 50% of patients will have severe or persistent human papillomavirus infections, and these are often a presenting sign of