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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 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 progressing to bilateral lymphedema over the next two years. During this time, she also developed verruca on her hands that were recalcitrant to therapy.

Subsequently, the patient was hospitalized multiple times for recurrent episodes of cellulitis of the lower legs requiring IV 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, 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 chest and were excised from the patient in her mid – thirties. One year prior to presenting to the NIH, she developed chronic osteomyelitis of the left femur and was found to have pancytopenia with a hypoplastic marrow.

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Physical examination

On examination, the patient had multiple periungual hyperkeratotic and subungual verrucous papules and plaques involving most 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 mid-thigh (Fig 2).

Significant diagnostic studies

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

DNA mutation analysis from previous hospitalization identified a heterozygous null mutation in *GATA2*; exon 5 c.1009 C-> T resulting in the substitution of a stop codon for arginine at amino acid 337.

Diagnosis

GATA2 deficiency*

DISCUSSION

The clinical manifestations of GATA2 deficiency are quite 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's 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 at initial presentation (age range 5 months to 78 years).¹ Thus, informed dermatologists may be the first physicians to identify patients with this syndrome.

GATA2 is a zinc finger transcription factor that regulates vascular and lymphatic development, as well as hematopoietic differentiation.³ Recent investigations have determined that mutations in *GATA2* are responsible for several different syndromes including monocytopenia and mycobacterial infection (MonoMAC) syndrome or Dendritic cell, monocyte, B lymphocyte and natural killer lymphocyte deficiency (DCML) (OMIM 614172); primary lymphedema with myelodysplasia or Emberger syndrome (OMIM

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

614038); susceptibility to myelodysplastic syndrome (MDS, OMIM 614286) and susceptibility to acute myeloid leukemia (AML, OMIM 614286); and congenital neutropenia.^{2,4-6} Previously, these syndromes were 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 development of persistent and profound peripheral monocytopenia, severe B- 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 (MDS), and some go on to frank leukemia.⁸ Cuellar-Rodriguez et al.⁹ recently demonstrated 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 *Mycobacterium avium* complex (MAC) organisms. The most common fungal infection is disseminated histoplasmosis; however, cryptococcal meningitis and invasive aspergillosis have also been reported. Absence of NK cells in GATA2 deficient patients may account for widespread viral infections that are characteristic of this condition.⁴ Over 50% of patients will have severe or persistent human papilloma virus infections, and these are often a presenting sign of GATA2 deficiency.¹ Patients may develop skin malignancies related to HPV dysplasia in the head and neck or genital region that may progress to invasive SCC.¹ Clinicians should biopsy rapidly changing or painful lesions, particularly in these body locations.

Noninfectious conditions such as pulmonary alveolar proteinosis or erythema nodosum can occur in up to one-third of patients and may be the presenting feature. The increased incidence of pulmonary alveolar proteinosis in GATA2 deficiency is likely related to impairment of GATA2-mediated surfactant metabolism by pulmonary alveolar macrophages leading to accumulation of surfactant in alveoli and decreased gas exchange.⁶ These patients often develop cough and dyspnea, and are at increased risk for opportunistic infections as mentioned above.^{1,2,7}

In a cohort of 52 patients, 6 patients (11%) developed lymphedema in one or both legs early in childhood. Interestingly, only patients with null mutations (mutations predicted to result in no protein product) or regulatory mutations (mutations demonstrating reduced expression of wild-type protein) developed lymphedema; those with missense mutations (mutations predicted to result in mutated protein) did not display this phenotype.¹ A high index of suspicion is needed to recognize GATA2 deficiency-associated lymphedema because lymphedema may otherwise be attributed to an unrelated traumatic event or previous soft tissue infection. Recently, Kazenwadel et al. demonstrated that GATA2 expression is high in

lymphatic valves. Complete loss of function of GATA2 has been implicated in defective lymphoendothelial valve development, possibly promoting the mechanism for lymphedema development.³ Other conditions associated with primary hereditary lymphedema include Milroy disease (mutation in VEGFR-3), hypotrichosis-lymphedema-telangiectasia (mutation in SOX18) and Hennekam syndrome (mutation in CCBE1).³

Although our patient's sensorineural hearing loss was attributed to toxicity from antibiotics, it may have been caused by GATA2 deficiency. Murine studies have identified GATA2 as essential for vestibular morphogenesis and development of semicircular canals.¹⁰

GATA2 deficiency has variable clinical expressivity with differing presentations including infection, hematopoietic abnormalities, immunodeficiency, lymphedema and cancer. Since these patients may have HPV-related dysplasia that can progress to squamous cell carcinomas, dermatologists play an important role in managing these patients as members of a multidisciplinary team. Extensive and recalcitrant verruca, history of multiple infections, and lymphedema should prompt clinicians to inquire about other manifestations of GATA2 deficiency, especially given the potential risk of developing AML.

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ABBREVIATION LIST

AML	Acute myeloid leukemia
DCML	Dendritic cell, monocyte, B lymphocyte and natural killer lymphocyte deficiency
HPV	Human papillomavirus
MAC	<i>Mycobacterium avium</i> complex
MDS	myelodysplastic syndrome
MonoMAC	Monocytopenia and mycobacterial infection syndrome
NIH	National Institutes of Health
SCC	squamous cell carcinoma

References

1. Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics and immunity. *Blood*. Nov 13.2013
2. Mutsaers PG, van de Loosdrecht AA, Tawana K, Bodor C, Fitzgibbon J, Menko FH. Highly variable clinical manifestations in a large family with a novel GATA2 mutation. *Leukemia*. Nov; 2013 27(11):2247–2248. [PubMed: 23563236]
3. 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*. Feb 2; 2012 119(5):1283–1291. [PubMed: 22147895]

4. Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nature genetics*. Oct; 2011 43(10):929–931. [PubMed: 21892158]
5. Pasquet M, Bellanne-Chantelot C, Tavitian S, et al. High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. *Blood*. Jan 31; 2013 121(5):822–829. [PubMed: 23223431]
6. 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*. Sep 8; 2011 118(10):2653–2655. [PubMed: 21670465]
7. Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Sep; 2013 57(5): 697–699. [PubMed: 23728141]
8. Ishida H, Imai K, Honma K, et al. GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia. *European journal of pediatrics*. Aug; 2012 171(8):1273–1276. [PubMed: 22430350]
9. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, et al. Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. *Blood*. Sep 29; 2011 118(13):3715–3720. [PubMed: 21816832]
10. Haugas M, Lillevali K, Hakanen J, Salminen M. Gata2 is required for the development of inner ear semicircular ducts and the surrounding perilymphatic space. *Developmental dynamics : an official publication of the American Association of Anatomists*. Sep; 2010 239(9):2452–2469. [PubMed: 20652952]

KEY TEACHING POINTS

- We describe a 45 year old female with GATA2 deficiency associated with verruca, lymphedema, immunodeficiency, and history of infections and skin cancer.
- GATA2 deficiency has variable clinical expressivity with differing presentations including infection, hematopoietic abnormalities, immunodeficiency, lymphedema, and cancer.
- Cutaneous manifestations include verruca vulgaris, soft tissue infections, lymphedema, and panniculitis.
- Patients may have verruca that can progress to squamous cell carcinomas; thus dermatologists play an important role in managing these patients as members of a multidisciplinary team.

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

Figure 2.
Lymphedema. Extensive bilateral leg edema with pronounced edema of bilateral dorsal feet.