Recalcitrant warts and lymphopenia in a young male

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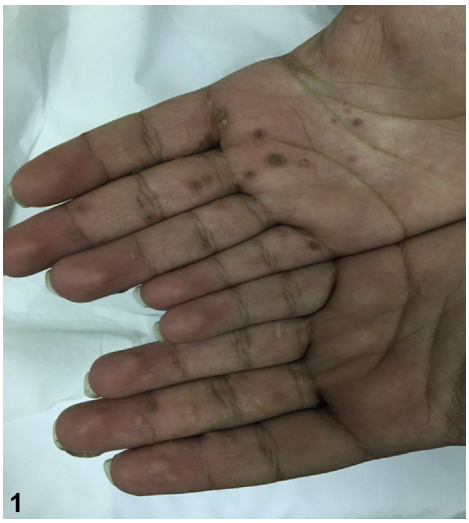

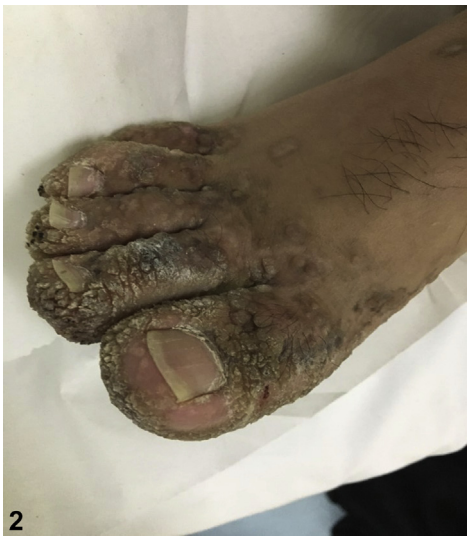

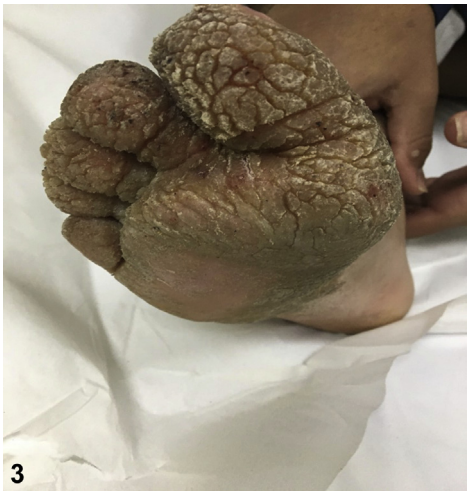

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INRODUCTION

A 21-year-old male presented to the dermatology outpatient clinic with progressive warty lesions for 14 years. The patient was born after an uncomplicated pregnancy and was in a normal state of health until 7 years of age, when he started to develop multiple verrucous papules on the hands, bilaterally (Fig 1). This was followed 1 year later by extensive verrucous plaques on both his feet (Figs 2 and 3). Different treatment modalities were found to be unsuccessful in improving the skin lesions. Skin punch biopsy showed viral cytopathic changes with no evidence of malignancy. His peripheral blood count showed persistent lymphopenia that prompted a referral to hematology service and a flow cytometry analysis (Table I). The immunoglobulin levels were found to be normal. Based on the low peripheral blood B and natural killer (NK) cells, bone marrow biopsy was performed, which revealed a hypocellular marrow.

Table I. Peripheral blood count and flow cytometry analysis results of our patient

Complete blood counts	Patient results	Reference range
White blood cells	3.3 × $10^3/\mu$L	4-11 × $10^3/\mu$L
Neutrophils	1.8 × $10^3/\mu$L	1.6-8.1 × $10^3/\mu$L
Lymphocytes	0.7 × $10^3/\mu$L	1.5-4 × $10^3/\mu$L
Monocytes	0.1 × $10^3/\mu$L	0.1-0.8 × $10^3/\mu$L
Eosinophils	0.7 × $10^3/\mu$L	0-0.8 × $10^3/\mu$L
Basophils	0 × $10^3/\mu$L	0-0.2 × $10^3/\mu$L
Platelet	93 × $10^3/\mu$L	150-450 × $10^3/\mu$L
Hemoglobin	13 g/dl	12.5-18 g/dl
Flow cytometry analysis		
Total B cells	1%	7-23%
Total T cells	91%	60-85%
Suppressor T cells	45%	19-48%
Helper T cells	41%	29-59%
Activated T cells	19%	4%-17%
Natural killer cells	4%	6%-29%

Question 1: What is the most likely diagnosis?

A. Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome

B. Epidermodysplasia verruciformis

C. GATA2 deficiency

D. Netherton syndrome

E. Severe combined immunodeficiency

Answers:

A. Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome — Incorrect. Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome is characterized by the presence of cutaneous and genital warts, recurrent bacterial infections in infancy and early childhood, hypogammaglobulinemia, and neutropenia. The bone marrow shows hypercellularity due to a defect in the release of mature neutrophils.[1]

B. Epidermodysplasia verruciformis — Incorrect. Epidermodysplasia verruciformis is characterized by an increased susceptibility to beta genus of human papillomavirus, which usually causes asymptomatic infections in immunocompetent individuals. Clinically, the lesions are composed of flat-topped papules resembling flat warts, scaly patches, and plaques resembling pityriasis versicolor.[1] The immunophenotype in these patients maybe normal or it may show a decrease in T- cell lymphocytes.

C. GATA2 deficiency — Correct. GATA2 deficiency is a recently described immunodeficiency disorder that presents with heterogenous hematological, immunological, and dermatological manifestations.[2] GATA2 is a zinc finger transcription factor that is essential for effective hematopoiesis.[3] Both sporadic cases and inheritance in an autosomal dominant manner with high penetrance have been described.[4] It typically presents in childhood or adolescence with peripheral blood monocytopenia and NK, B cell, and dendritic cell lymphocytopenia.[1] Extensive warts are the presenting manifestation in 20% of the patients, their overall prevalence is up to 70%.[2] Nontuberculous mycobacterial infections, lymphedema, and sensorineural deafness are among the other common systemic features.[4] The combination of peripheral blood lymphopenia and recalcitrant warts in a young patient is highly suggestive of GATA2 deficiency.[4] Our patient has a heterozygous missense mutation in the GATA2 gene, c.1123C>T p.(Leu375Phe).

D. Netherton syndrome — Incorrect. Although patients with Netherton syndrome have increased susceptibility to cutaneous viral infections including human papillomavirus (HPV), it is also characterized by a high IgE level, congenital

icthyosiform erythroderma, and hair shaft abnormalities.[1]

E. Severe combined immunodeficiency — Incorrect. Severe combined immunodeficiency classically presents in infancy with chronic diarrhea, failure to thrive, and severe viral, bacterial, and fungal infections. Typical laboratory abnormalities include severe T cell lymphopenia and hypogammaglobulinemia.[1]

Question 2: What is the leading cause of death in patients affected with this disease?

A. Hematological malignancy

B. Severe bacterial and/or viral complications

C. Solid organ malignancy

D. Vascular thrombosis

E. Pulmonary alveolar proteinosis

Answers:

A. Hematological malignancy — Correct. By age 40, more than 80% of the patients present with a hematologic malignancy. Myelodysplastic syndrome and acute myeloid leukemia are the leading causes of death in patients with GATA2 deficiency.[2]

B. Severe bacterial and/or viral complications — Incorrect. Severe viral and nontuberculous mycobacterial infections are the most common presenting symptoms, affecting 60% of the patients at presentation. The complications from these infections are the second most common cause of death in the affected patients.[5]

C. Solid organ malignancy — Incorrect. Solid organ malignancies, especially HPV-related, affects 20%-35% of the patients with GATA2 deficiency. Their high frequency is hypothesized to be due to delayed viral clearance and impaired immunosurveillance mechanisms.[4] However, they result in lower mortality rates than the hematological malignancies and infectious complications.

D. Vascular thrombosis — Incorrect. GATA2 is highly expressed in endothelial cells, megakaryocytes, and platelets. Although thromboembolic phenomena are reported in up to 25% of the patients,[4] they are not the leading cause of death.

E. Pulmonary alveolar proteinosis — Incorrect. Pulmonary alveolar proteinosis affects 18% of the patients. Their increased incidence is possibly due to an impaired GATA2-mediated surfactant metabolism and excretion by lung macrophages.[3] However, it is not the leading cause of death in patients with GATA2 deficiency.[4]

Question 3: What is the most effective treatment modality for this condition?

A. Systemic steroids

B. Hematopoietic stem cell transplantation (HSCT)

C. HPV vaccine

D. Antimicrobials

E. Chemotherapy

Answers:

A. Systemic steroids — Incorrect. Pulmonary complications and inflammatory lesions may respond promptly to systemic steroids. However, the routine use of systemic steroids is not recommended due to its profound effect on the immune system.[4]

B. HSCT — Correct. HSCT has an overall good outcome and usually results in the correction of hematological, infectious, and pulmonary complications.[5] Early intervention with HSCT improves the survival in the affected patients.[6]

C. HPV vaccine — Incorrect. Although early vaccination of children with GATA2 deficiency is recommended, the exact role of HPV vaccine in the affected patients is not yet clearly defined.

D. Antimicrobials — Incorrect. Antibiotics and antivirals are used to treat secondary bacterial and viral infections in the affected patients, while Azithromycin is used as a prophylactic treatment in high-risk cases. However, the mainstay of treatment of this condition is HSCT.

E. Chemotherapy — Incorrect. Chemotherapy is of limited efficacy and is used to treat the malignant complications of this disease until HSCT becomes available.

Abbreviations used:

HPV: human papillomavirus
HSCT: hematopoietic stem cell transplantation

Conflicts of interest

None disclosed.

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