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ORIGINAL ARTICLE

Recurrent Infections in an Ethiopian Boy with Autosomal Recessive Major Histocompatibility Complex Type I Deficiency: a Case Report on a Very Rare Primary Immunodeficiency Disorder and a Review of Principles in Evaluation and Management

Tinsae Alemayehu[1,2] · **Netsanet Azene Gebeyehu**[3]

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Abstract
Little is known about major histocompatibility complex type I deficiency, a rare form of primary immunodeficiency. This report describes the presentation of a three-year-old Ethiopian boy with recurrent sinopulmonary infections and genetic analysis showing him having autosomal recessive major histocompatibility complex type I deficiency—the first such report in a child of black African descent—and follows it with a summary of existing literature on the epidemiology, presentation, and diagnosis as well as principles of management of this disorder.

Keywords MHC deficiency · Primary immunodeficiency · Child · Ethiopia

Background

Major histocompatibility complex (MHC) deficiency is a combined (T cell/B cell) primary immunodeficiency with less profound manifestations than severe combined immunodeficiency (SCID) (1). These disorders are divided into MHC class I and class II deficiencies according to the type of MHC affected (2). MHC deficiencies are very rare forms of primary immunodeficiency (PIDs) (3). A report on a young Ethiopian boy with recurrent infections due to MHC I deficiency is described below.

✉ Tinsae Alemayehu
tinsae.alemayehu@sphmmc.edu.et; tigisttinsae@gmail.com

Netsanet Azene Gebeyehu
netsanetazene@gmail.com

[1] Division of Infectious Diseases and Travel Medicine, American Medical Center, Addis Ababa, Ethiopia

[2] Division of Pediatric Infectious Diseases, Department of Pediatrics and Child Health, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

[3] Department of Dermatovenereology, St. Peter's Specialized Hospital, Addis Ababa, Ethiopia

Case Description

A 3-year-old boy was referred to our pediatric infectious diseases clinic for evaluation of recurrent infections. After an uneventful medical history (barring treatment during his first three days of life for respiratory distress due to meconium aspiration and hyperbilirubinemia due to Rh incompatibility), his medical history in the first 2 years was unremarkable. He presented with a three-day history of fever and diarrhea at age 2 years. This episode of acute gastroenteritis episode was notable for a marked neutrophil predominant (24,000/mm^3) leukocytosis of 29,500/mm^3 and elevated C-reactive protein (157 mg/dl). Parenteral ceftriaxone was required following the failure of oral therapy for bacterial enteritis. Throughout his third year of life, he was treated five times for commonly diagnosed infections: pneumonia, acute gastroenteritis (thrice), and acute tonsillopharyngitis. These episodes were similarly accompanied by prolonged symptoms, the need for parenteral antibiotics after failure of oral regimens, leukocytosis (up to 32,000/mm^3) with neutrophil predominance (80–90%), and lymphopenia for his age (< 2300/mm^3). He also had an episode of mild COVID-19 infection at age 2 years.

During his illnesses, his parents notice non-painful skin-colored and smooth, soft tissue small nodules without ulcerations at varying locations of his extensor parts of limbs,

which resolve along with his acute symptoms. He had no contact with pets and has no allergies. He was circumcised at ten days of age (uneventful). He shed his umbilicus at 1 week of age. He has received three doses each of pneumococcal (PCV10), *hemophilus influenzae* type b, oral polio, and hepatitis B vaccines; double doses of rotavirus (Rotarix) and measles vaccines; single doses of BCG and injectable polio vaccines during the first 2 years of life. He experienced a fever of less than 24 h during two rounds of vaccinations during infancy and none during other rounds. His maternal uncle had a "high predisposition for illnesses" during childhood and adolescence. He was born to non-consanguineous parents.

His physical examination upon first evaluation for recurrent infections was unremarkable. His complete blood count (including absolute neutrophil, lymphocyte, eosinophil, and platelet counts) in between episodes and at first evaluation was normal for his age. He had negative serologies for HIV. A blood smear was normal. His serum immunoglobulin levels were within normal limits, while his CD4 levels fell within normal limits for his age. His CD8 levels and post-vaccine titers could not be determined because of the unavailability of the tests (Table 1).

His chest X-ray was normal (including a normal thymic shadow). Due to limitations in immunology diagnostics in Ethiopia, assessing antibody responses to vaccines, determining serum complement levels, and performing respiratory burst assays could not be done. Sequence analysis and deletion/duplication genetic test done at Invitae Molecular Genetics Diagnostic Center, USA revealed a pathogenic variant, c.373del (p.Gln125Argfs*8), identified on the transporter 2, ATP binding cassette protein (TAP2) gene associated with autosomal recessive hereditary major histocompatibility complex class I deficiency. MHC class I expression was not tested in this patient. The parents were counseled on the course of the illness, and he is on follow-up without prophylactic antimicrobials. Further genetic testing of family members could not be conducted due to a constraint in resources.

Table 1 Accessible and performed immunologic evaluation for the patient

Test	Normal values for his age	Test results
Total white blood cell count/mm^3	4000–12,000	10,780
Absolute neutrophil count/mm^3	2500–4120	4610
Absolute lymphocyte count/mm^3	2700–3940	4780
Absolute eosinophil count/mm^3	100–290	210
Absolute monocyte count/mm^3	310–500	610
Serum immunoglobulin A (g/l)	0.2–1.3	0.64
Serum immunoglobulin E (ku/l)	0–113	15.8
Serum immunoglobulin M (g/l)	0.3–2.6	1.2
Serum immunoglobulin G (g/dl)	3.7–15.0	9.38
CD4 counts/mm^3	900–2100	1400

Discussion

MHCs are molecules normally found on the surface of lymphocytes and which present antigens to T cells (2). MHC deficiency or bare lymphocyte syndrome is a very rare form of PID—with no more than 30 cases of MHC-I and 150 cases of MHC-II deficiencies (most of them from North African countries) reported worldwide. Both exhibit an autosomal recessive inheritance (2, 4).

MHC class I deficiency can occur due to mutations in the TAP1, TAP2, TAPBP, or B2M genes. It is notable for absent MHC I expression on lymphocytes due to defective peptide transport or surface presentation as well as low CD8 counts (5). Mutations in the first three genes cause vasculitis and pyoderma gangrenosum (6). The syndrome is associated with low CD8, normal CD4, and absent MHC-I on lymphocytes, normal immunoglobulin levels, and B-cell counts (7). The severity of manifestations depends on the level of MHC-I expression, with people having at least 10% or more of normal expression being asymptomatic, 1–10% having mild symptoms during the first few years of life, and developing recurrent chest infections and granulomatous skin lesions starting from 4 to 7 years of age, and those with less than 1% expression presenting with severe recurrent infections in the first year of life. Long-term complications include chronic lung disease and bronchiectasis, and ulcerating granulomas, especially in the extremities (5). Some children have been treated with intravenous immunoglobulin (IVIG) and prophylactic antibiotics, while there are emerging reports of the use of hematopoietic stem cell transplantation (HSCT) for MHC-I deficiency, where previously treatment was deferred as MHC class I expression is not restricted to hematopoietic cells (8, 9). HSCT may cure the immune defect and its clinical manifestations (some of which may not improve with interferon-γ therapy alone, like granulomas) (9).

Our patient presented with recurrent sinopulmonary infections, normal serum immunoglobulin and CD4 levels, and with a genetic analysis confirming autosomal recessive MHC class I deficiency. Though we could not confirm by biopsy, we attributed the transient nodules to episodes of panniculitis associated with this syndrome. Ultrasound studies of nodules were unremarkable and biopsies could not be taken because of the transient nature of nodules. Our patient's pathogenic genetic mutation [c.373del (p.Gln125Argfs*8)] identified on the TAP2 gene creates a premature translational stop signal and is expected to result in absent or disrupted protein associated with hereditary

major histocompatibility complex class I deficiency (10). Biologic relatives of an affected individual may also be carriers for the trait and screening should be done when clinically appropriate (5). Our case report was backed by genetic confirmation but was limited by the constraints in immunologic diagnostics in Ethiopia, namely our inability to perform post-vaccine titers, CD8 determination, and levels of MHC-I expression.

Conclusion

We report on a young Ethiopian boy with recurrent infections due to autosomal recessive MHC I deficiency. To the best of our knowledge, this is the first report of this syndrome in a child of black African descent. Health professionals should consider a primary immunodeficiency when a child presents with recurrent and atypical infections in the context of negative work-up for acquired immunodeficiency and also consider MHC I deficiency in the presence of normal serum immunoglobulins and B cells, normal CD4 counts, and low CD8 cells while striving for molecular diagnostic confirmation.

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Author Contribution TA: Conception and design of the study, data collection, data analysis, and manuscript preparation and revision. NAG: Data collection, data analysis, and manuscript revision.

Data Availability All data pertaining to the report are included within the manuscript.

Materials Availability All data pertaining to the report are included within the manuscript.

Declarations

Ethics Approval Approval was not required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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