Recurrence of 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

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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.

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 was notable for a marked neutrophil predominant (24,000/mm3) leukocytosis of 29,500/mm3 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/mm3) with neutrophil predominance (80–90%), and lymphopenia for his age (<2300/mm3). 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), *Haemophilus 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/mm³ | 4000–12,000               | 10,780      |
| Absolute neutrophil count/mm³    | 2500–4120                 | 4610        |
| Absolute lymphocyte count/mm³    | 2700–3940                 | 4780        |
| Absolute eosinophil count/mm³    | 100–290                   | 210         |
| Absolute monocyte count/mm³      | 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/mm³                   | 900–2100                  | 1400        |
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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