Case Report of an Adolescent Male With Unexplained Pancytopenia: GATA2-Associated Bone Marrow Failure and Genetic Testing

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Introduction

The approach to the patient with new-onset pancytopenia is complex and includes an extensive clinical and laboratory evaluation with bone marrow examination.1 Causes of pancytopenia include cytotoxic therapies, autoimmune disorders, infection, and congenital and acquired bone marrow failure syndromes.1 The congenital bone marrow failure syndromes include Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, and other genetic conditions.1-3 The accurate diagnosis of these congenital disorders is essential to inform clinical monitoring, family counseling, and hematopoietic stem cell transplantation planning, including donor selection and preparatory regimen choice.4 With the advent of multigene panels, pediatric and adolescent cases of bone marrow failure previously categorized as idiopathic are being reclassified. The use of targeted capture gene panels in the workup of these disorders has improved our diagnostic accuracy,5 and we report here one example of the clinical utility of this unbiased genetic screening in a community hospital setting.

Case Report

A 12-year-old, previously healthy, African American male with no significant past medical history presented to his primary care physician with a 2-week history of fever, cough, and 7-kg weight loss. Review of systems was negative for any warts or lymphedema. He was diagnosed with a right upper lobe pneumonia and treated with a 10-day course of azithromycin. He was subsequently admitted to the pediatric intensive care unit with bilateral pneumonia. Physical examination was notable for an acutely ill appearing adolescent in moderate respiratory distress; growth parameters at the time of admission were 49th percentile for height and 17th percentile for weight.

Laboratory studies at admission showed a normochromic, normocytic underproduction anemia with a hemoglobin of 9.7 g/dL (0.73%; mean normal 14 g/dL). White blood cell count/differential and platelet count were normal. Chemistries were notable for an alanine aminotransferase of 256 U/L (normal 10-40 U/L), aspartate aminotransferase of 186 U/L (normal 15-40 U/L), lactate dehydrogenase 544 U/L (normal 119-295 U/L), and C-reactive protein of 23.1 mg/dL (normal 0-0.5 mg/dL). Lymphocyte subset enumeration was performed and showed essentially normal count with the exception of a low CD4/CD8 ratio of 0.5. Blood cultures were all negative. Chest X-ray and computed tomography scan of the chest showed extensive bilateral multilobar pneumonia. He was treated with broad spectrum antibiotics and ultimately recovered and was discharged to home.

Of note, he remained anemic (8.4 g/dL) and was also noted to have monocytopenia at discharge. Over the next 6 months he developed progressive pancytopenia (hemoglobin 9.4 g/dL, white blood cell count 2.9 × 10⁹/L, absolute neutrophil count 0.4 × 10⁹/L, absolute lymphocyte count 2.4 × 10⁹/L, absolute monocyte count 0, and platelets 197 × 10⁹/L; Table 1).

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Bone marrow aspirate and biopsy showed a hypo-cellular marrow for age (60% to 70% cellular) with mildly elevated myeloid to erythroid ration with no morphologic or immunophenotypic dysplasia and no dysplastic megakaryocytes. Routine karyotype was normal. Additional testing to determine the etiology of his bone marrow failure was unrevealing (Table 2). Targeted gene capture and massively parallel sequencing were performed as previously described using a capture assay targeting mutations in known inherited and acquired bone marrow failure and MDS genes on DNA isolated from peripheral blood.

This revealed a novel, heterozygous, nonsense mutation in \textit{GATA2} at the +3 splice acceptor position of exon 3 (of 6 exons total): \textit{GATA2} p.S290X Chr3: 128204572 G>T (GRCh37/hg19 assembly). The result most likely represents a nonsense variant leading to nonsense-mediated decay and haploinsufficiency for \textit{GATA2}. However, as it disrupts a semiconserved splice acceptor site, it may also lead to an exon-skipping variant. Moreover, the serine at this position is phosphorylated, and if the latter could similarly disrupt transcriptional activity.\textsuperscript{6} The \textit{GATA2} mutation was also confirmed through a second laboratory test. This mutation is therefore consistent with \textit{GATA2} deficiency syndrome. Family studies indicated neither parents nor siblings have the \textit{GATA2} mutation, indicating this is a de novo mutation in our patient.

Additionally, the patient was heterozygous for a variant in \textit{ASXL1} (p.D741V; chr20: 31022373 A>T). This variant is predicted to be nondamaging by in silico modeling and is reported 48 times on the Exome Aggregation Consortium browser and therefore considered likely to be a benign change.

\section*{Discussion}

This case illustrates the utility of broad unbiased genetic screening in the workup of pediatric marrow failure in a community hospital setting. Our patient had remained without a diagnosis after marrow examination, telomere length testing, chromosome fragility, and paroxysmal nocturnal hemoglobinuria testing in addition to other extensive tests outlined. The elucidation of a novel \textit{GATA2} mutation and the diagnosis of \textit{GATA2} deficiency syndrome in our patient was a direct result of utilization of this panel.

Mutations in \textit{GATA2}, characterized first in 2011, have been implicated in several syndromes including familial myelodysplastic syndrome/acute myeloid leukemia, Emberger syndrome, monocytopenia and mycobacterial infection syndrome (monoMAC), and dendritic cell, monocyte B, and natural killer lymphoid deficiency.\textsuperscript{7,8} MonoMAC syndrome is characterized by nontuberculous mycobacterial infections with \textit{Mycobacterium avium} complex being the most common, but also may have \textit{M. kansasii}, \textit{M. scrofulaceum}, \textit{M. bovis}, and \textit{M. szulgai}. Patients may suffer viral infections such as human papillomavirus, herpesvirus infection, and also have fungal infections such as disseminated histoplasmosis, cryptococcal meningitis, and invasive aspergillosis.
infections, these patients can have complications including primary lymphedema and cytopenias.

Emberger syndrome was first described in 1979, by Emberger, who described a family with 3 individuals over 2 generations who had severe congenital deafness, and suffered limb lymphedema and hematologic abnormalities of pancytopenia in 2 individuals and acute myeloblastic leukemia in 1 individual. Patients with these conditions may present at any age and may present with a spectrum of features including leukemia to life threatening infections.

In addition to the GATA2 mutation, a benign variant was identified in the ASXL1 gene of our patient. Somatic ASXL1 mutations are found in 10% to 30% of patients with myeloid malignancies and associated with worse outcomes including myeloid transformation. Germline ASXL1 mutations occur in Bohring-Opitz syndrome, in which patients have severe intrauterine growth retardation, poor feeding, trigonocephaly, and nevus flammeus of the face. In addition, patients have been described to have flexion of the elbows and wrists with deviation of the wrists and metacarpophalangeal joints. The patient described in this report did not have these features, and given this the variant is likely an incidental finding.

Conclusion

In conclusion, the accurate diagnosis of GATA2 deficiency has guided our patient’s immediate and long-term care. The patient will be getting a human papillomavirus vaccination and has received evaluation for a bone marrow transplant at a local academic institution. This testing additionally allowed for appropriate screening of potentially affected family members: all were negative for this mutation. This is one of the first instances of previously diagnosed idiopathic pancytopenia being reclassified as a specific syndrome as a direct result of a genetic bone marrow failure screening panel performed through a community hospital in concert with a tertiary institution, thereby providing clinically important information to the patient, family, and care team.

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Author Contributions

LA: Contributed to conception; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AJ: Contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AL: Contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SK: Contributed to acquisition and analysis; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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MvH: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

HS: Contributed to conception and design; critically revised manuscript; critically revised manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Abraham is a consultant for Shire.

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