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A coronavirus disease 2019–vaccinated patient with phosphoinositide 3-kinase disease with mild illness after severe acute respiratory syndrome coronavirus 2 infection

Phosphoinositide 3-kinase (PI3K) disease is a rare disorder that causes severe impairment of the immune system and the ability to fight both bacterial and viral infections. PI3K disease can be caused by a mutation in the PIK3R1 gene. The PIK3R1 gene encodes the regulatory subunit of PI3K holoenzyme, activating the pathway involved in modulation of cell proliferation and growth. The PI3K disease is characterized by recurrent ear, nose, throat, and respiratory tract infections that can lead to progressive airway damage. Patients have also been found to experience recurrent infections of Staphylococcus aureus, Epstein-Barr virus, and cytomegalovirus. PIK3R1 mutations have been found to lead to impaired and dysregulated immunity. Clinical phenotypes can also include chronic lymphoproliferation, growth restriction, mild neurodevelopmental delay, and malignant disease (mostly B-cell lymphomas). Patients, at the time of diagnosis, can present with decreased serum immunoglobulin (Ig)A and IgG levels and increased IgM level. Most patients require treatment with immunoglobulin replacement. We describe a case of a patient with heterozygous pathogenic variant of PIK3R1 splice site mutation presenting with coronavirus disease 2019 (COVID-19) infection after vaccination with 2 doses of BNT162b2 messenger ribonucleic acid (mRNA) COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine). Our case reveals both safety and efficacy of the BNT162b2 mRNA COVID-19 vaccination, along with the need for vaccination in this subset of the patient population. Our patient is a 30-year-old White woman born at term without complications with genetic testing remarkable for heterozygous pathogenic variant of PIK3R1, c.1425+1G>A splice donor, and SHORT syndrome (Table 1). Before her diagnosis, she had presented with a history of recurrent ear, sinus, throat, and bronchopulmonary infections. The infections resolved while being maintained on intravenous immunoglobulin at 900 mg/kg every 3 weeks. She received the initial dose of the BNT162b2 mRNA COVID-19 vaccine on March 8, 2021, and the second dose subsequently on March 28, 2021, at the age of 30 years old. After the initial dose of the vaccination, the patient had 1 day of generalized headache and no significant symptoms with the second dose of the vaccination. On September 11, 2021, the patient’s mother, and close contact, developed sinus pressure and fatigue. On the following day, the patient also developed symptoms consisting of sinus pressure, runny nose, sneezing, subjective fever, nausea, ageusia, anosmia, and dry cough. The symptoms persisted for 48 hours and were associated with progressive fatigue. A rapid COVID-19 antigen test done on September 12, 2021, resulted as positive for both the patient and mother. Results of COVID-19 polymerase chain reaction test 5 days after were also positive for both the mother and the patient. The patient experienced resolution of all symptoms within 1.5 weeks, except for her dry cough which lingered for more than 3 weeks from initial infection. After the infection, result of severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody IgG was found to be positive, and severe acute respiratory syndrome coronavirus 2 spike total antibody was reactive 10 days after the initial positive test. Ultimately, our patient did not require hospitalization after acute infection with COVID-19 after receiving the BNT162b2 mRNA COVID-19 vaccine.

Patients with inborn errors of immunity represent a subset of the high-risk population at risk for viral and bacterial illnesses. Although PIK3R1 mutation disease is rare, it is of importance to note the need to vaccinate in this and other immunodeficient populations. Though COVID-19 vaccines were found to have efficacy in the general population, it is not well known how efficacious these vaccines are in the immunocompromised patients. Furthermore, although small-scale studies have revealed evidence of both cellular and humoral responses in cases of patients with inborn errors of immunity, this has not been found in patients with PIK3R1 mutation disease. There are currently no other known cases or case reports of patients with PIK3R1 mutation disease and efficacy of the COVID-19 vaccinations in patients with an acute COVID-19 infection. Our case reveals both the safety and efficacy of the BNT162b2 mRNA COVID-19 vaccination in patients with PIK3R1 mutation disease with acute COVID-19 infection and the ability to prevent severe disease or need for hospitalization.

Table 1

| Physical examination findings | Cervical LAD bilaterally |
|-------------------------------|--------------------------|
| LAD Cervical LAD bilaterally  | Short stature, deep-set eyes, micrognathia, prominent forehead and ears, downturned corners of the mouth |

Abbreviations: LAD, lymphadenopathy; PI3K, phosphoinositide 3-kinase.

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Hereditary alpha-tryptasemia despite normal tryptase-encoding gene copy number owing to copy number loss in trans

The human tryptase locus is a gene-dense region within the subtelomeric portion of the short (p) arm of chromosome 16 at position 13.3 (16p13.3). Because the 2 genes that encode secreted a- and b-tryptases TPSAB1 and TPSB2 are in such close proximity to one another, they do not randomly assort and are in near-complete linkage disequilibrium. Moreover, individuals inherit tryptase genes as haplotypes from their parents that contain both of these genes. Whereas TPSB2 encodes b-tryptases, TPSAB1 may encode a- or b-tryptases. Thus, the canonical TPSAB1/TPSB2 haplotypes are a/b or b/b, leading to the canonical tryptase genotypes of b/b:b/b, a/b:b/b, or a:b:a:b. Structural homology among tryptase-encoding genes and other features of the tryptase locus (eg, GC-rich, repetitive sequences) render conventional next-generation sequencing incapable of resolving tryptase genotypes. However, a droplet digital polymerase chain reaction assay is available for clinical genotyping of patients.

Although the 3 common genotypes b/b:b/b, a/b:b/b, and a:b:a:b account for an estimated greater than 90% of individuals, copy number variation at TPSAB1 and potentially TPSB2 has been reported and may complicate interpretation of tryptase genotype. In many of these cases, examination of family pedigrees assists in the clinical interpretation of genotypic findings and Mendelian inheritance of tryptase haplotypes can often clarify seemingly discordant genotype or phenotype observations.

Hereditary alpha-tryptasemia (HxT) is an autosomal dominant genetic trait characterized by elevated basal serum tryptase (BST) resulting from increased copy number of the TPSAB1 gene encoding a-tryptase. Several studies in the United States and Europe have found that this is present in 4% to 6% of the general population in which it has been studied, affecting an estimated 16 million people in the United States. Increased TPSAB1 gene copy number and elevated BST can be associated with multisystem complaints, including cutaneous flushing and pruritus, anaphylaxis, and gastrointestinal symptoms. Here, we report 2 symptomatic individuals who presented with elevated BST and were ultimately found to have HxT despite having normal total tryptase gene copy number.

The first patient presented with flushing, itching, hives, joint pain and swelling, and diarrhea. She also had a history of anaphylaxis requiring intramuscular epinephrine administered in an emergency department. Her BST was 18 ng/mL but tryptase genotyping revealed only 2 copies of TPSAB1 encoding a-tryptase and 2 copies of TPSB2 encoding b-tryptase (presumed a/b:a/b genotype). Her son was subsequently diagnosed with HxT (b/b:aa/b genotype) after presenting with gastrointestinal food sensitivities, abdominal pain, diarrhea, joint pain, and muscle pain. However, his father did not have HxT (b/b:b/b genotype). The symptoms of the index patient’s parents revealed that her father also had HxT (a/b:aa/b genotype) but her mother had germline loss of a tryptase-encoding sequence at either TPSAB1 or TPSB2 (−/b/a/b genotype). The symptoms of the index patient’s father included flushing, joint pain, headaches, food sensitivities, abdominal pain, and diarrhea.

The second patient came to attention because both of her sons had been diagnosed with HxT. She reported a history of migraine headaches, asthma, intermittent hives, and joint pain. Her older son (b/b:aa/b genotype) presented with mild pruritus, intermittent hives, joint pain, and a BST of 13.5 ng/mL. Her younger son (also b/b:aa/b genotype) presented with BST of 12.5 ng/mL, multiple food sensitivities, bloody diarrhea, hives, rash, and failure to thrive. When she was tested, her BST was 10 ng/mL, but her genotype did not initially seem to be consistent with HxT (presumed a/b:aa/b genotype). However, when her sons’ father was tested, his BST was only 5 ng/mL, and he had only 1 copy of TPSAB1 encoding a-tryptase (b/b:aa/b genotype). Genotyping of the children’s maternal grandfather found that he did not have any a-tryptase-encoding sequences, and had only 3 b-tryptase—encoding sequences (−/b/b genotype), requiring the maternal grandmother (who was deceased and unavailable for testing) to be an obligate carrier of an extra-allelic copy of TPSAB1 encoding a-tryptase for her daughter to have 2 germline copies, and thus HxT. Her genotype could be fully deduced as b/b:aa/b genotype because her son—the initial patients’ maternal uncle—also had no a-tryptase—encoding copies (b/b:aa/b genotype), thus, requiring he received a b/b haplotype from both grandparents.

This report reiterates the importance of evaluating family pedigrees when considering tryptase genotypes, in particular when BST seems to be discordant with genotypic findings. We have described 2 individuals with HxT associated with the previously unreported −/b: aa/b genotype that would not have been identified without genotyping family members and evaluating inheritance patterns. This analysis prevented the erroneous conclusion that HxT was occurring denovo in the children of these 2 families, or that elevated BST in the 2 individuals with HxT and tryptase-encoding gene copy loss was associated with a clonal mast cell disorder inappropriately prompting unnecessary testing. More importantly, whereas these individuals did not have other indications for bone marrow biopsy, diagnosing HxT should not preclude an evaluation for concomitant clonal mast cell disease in which there is clinical suspicion, given that there is an

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