Successful Anti-SARS-CoV-2 Spike Protein Antibody Response to Vaccination in MAGT1 Deficiency

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Abstract

Background: Novel messenger RNA vaccines against severe acute respiratory syndrome coronavirus (SARS-CoV-2) have been vital in resolving the coronavirus disease-2019 (COVID-19) pandemic. Detection of neutralizing antibodies (NAbs) against the SARS-CoV-2 spike protein (S) confirms immunogenicity with high sensitivity and specificity. Few recent studies with primary and secondary immunodeficient cohorts present adequate or reduced antibody response. We describe the first reported successful response to anti-SARS-CoV-2 S antibody post-vaccination in magnesium transporter 1 (MAGT1) gene deficiency, more commonly recognized as x-linked immunodeficiency with magnesium defect, Epstein-Barr Virus infection, and neoplasia (XMEN).

Case Presentation: We present a 30-year-old male with selective anti-polysaccharide antibody deficiency, peripheral blood CD5+ /CD19+ B-cell predominance (97%), MAGT1 mutation, and reduced CD16+ CD56+ natural killer- and/or CD8+ T-cell receptor, Group 2, Member D expression. His initial immunological evaluation revealed all seronegative post-vaccination antibody titers but clinically adequate response to protein antigens tetanus and diphtheria anti-toxoids. COVID-19 vaccination and associated serology antibody testing was recommended at this office visit. Anti-SARS-CoV-2 immunoglobulin (Ig)M and IgG antibodies before and after the first BNT162b2 mRNA COVID-19 vaccine doses, as well as nucleocapsid antibody, were negative. S protein total antibody was reactive after the second dose.

Discussion: Robust immunological sequelae post-COVID-19 vaccination in the general population are well-documented in the recent literature. Few studies have evaluated COVID-19 vaccination antibody response in immunodeficient patients. The majority positive anti-S antibody detection in most primary immunodeficient (PID) patients among the few studies in the literature, such as the present case, support the safety and efficacy of mRNA COVID-19 vaccination in immunodeficient patients, although larger scale studies are needed.

Conclusion: We demonstrate successful vaccination in the PID MAGT1 deficiency in this first reported case of reactive anti-S antibody post-COVID-19 vaccination.

Keywords

SARS-CoV-2, cOVID-19, bNT162b2, vaccine, immunization, spike protein, antibody response, primary immunodeficiency, cD5, XMEN

Background

Novel messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus (SARS-CoV-2) have been vital in resolving the coronavirus disease-2019 (COVID-19) pandemic.1-3 These lipid nanoparticle vaccines utilize host cells’ translational machinery to express viral antigens in situ, eliciting adaptive humoral and cellular immunity against the SARS-CoV-2 spike protein (S).3 Detection of these neutralizing antibodies (NAbs) confirms immunogenicity with high sensitivity and specificity.3

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Sufficient NAb production post-vaccination is standard practice for immunodeficient patients, who have higher susceptibility to SARS-CoV-2 among other infections. Few recent studies with primary and secondary immunodeficient cohorts present adequate or reduced antibody response. We describe the first reported successful response to anti-SARS-CoV-2 S antibody post-vaccination in magnesium transporter 1 (MAGT1) gene deficiency, more commonly recognized as x-linked immunodeficiency with magnesium defect, Epstein-Barr Virus (EBV) infection, and neoplasia (XMEN).\(^9\)\(^-\)\(^10\)

**Case Presentation**

We present a 30-year-old male with selective antipolysaccharide antibody deficiency (SPAD) and peripheral blood CD5\(^+\)/CD19\(^-\) B-cell predominance (97%, control 52.5 ± 17.3%) diagnosed at 5 years old.\(^9\) His past medical history was significant for persistent childhood sinopulmonary infections, severe hemorrhagic varicella at 2 years old, ulcerative colitis in early adolescence, and ongoing autoimmune hepatitis. His initial immunological evaluation revealed seronegativity of 12 Streptococcus pneumoniae subtypes, Neisseria meningitidis A and C, Haemophilus influenza b, human parainfluenza viruses 1 to 3, influenza A and B, poliovirus 1 to 3, and respiratory syncytial virus.\(^3\) Post-vaccination antibody titers demonstrated negative pneumococcal valent conjugate serology but clinically adequate (≥0.1 IU/mL) response to protein antigens tetanus and diphtheria anti-toxoids. Other immune laboratory assessments included persistently stable hypogammaglobulinemia. Blood leukocytes and mitogen- and antigen-induced lymphocyte proliferation panel were within normal limits. Serologic evidence of human immunodeficiency virus, EBV, and cytomegalovirus was absent. Immunological re-evaluation at 28 years old confirmed CD5 \+ B-cell predominance and revealed a MAGT1 mutation (c.923-1_934del) and reduced CD16 + CD56 + natural killer- and/or CD8 + T-cell receptor, Group 2, Member D (NKG2D) expression consistent with the XMEN genotype and phenotype.

The patient presented for a routine office visit with no acute symptoms. He denied recent history of COVID-19. COVID-19 vaccination and associated serology antibody testing was recommended. Anti-SARS-CoV-2 immunoglobulin (Ig)M and IgG antibodies before and after the first BNT162b2 (Pfizer/BioNTech) mRNA COVID-19 vaccine doses, as well as nucleocapsid antibody, were negative (Table 1). S protein total antibody was reactive after the second dose.

**Discussion**

Robust immunological sequelae post-COVID-19 vaccination are well-documented in the recent literature.\(^1\)\(^-\)\(^3\) The US FDA-authorized mRNA vaccines, including BNT162b2 and mRNA-1273 (Moderna/NIAID), have demonstrated high efficacy against severe SARS-CoV-2 into Phase III clinical trials and consistent data across different demographics.\(^2\) Röltgen et al identified that BNT162b2 mRNA vaccination induces a dominant sustained anti-SARS-CoV-2 IgG response consistent with its reported 95% efficacy in clinical trials, compared to more robust but short-term IgM and IgA elevations in infected individuals.\(^3\) Side effects experienced after the prime or boost vaccination have not been associated with reduced serological IgG antibody responses.\(^2\)

SARS-CoV2 immunogenicity is determined by quantifying neutralizing antibody (NAbs) against the viral S protein, which prevents binding of its receptor-binding domain (RBD) to the host angiotensin-converting enzyme 2 (ACE2) receptor.\(^2\)\(^-\)\(^3\) A surrogate virus neutralization test established by Tan et al demonstrated 95 to 100% sensitivity and 99.39% specificity of anti-S1-RBD antibody in 2 convalescent COVID-19 patient cohorts with recent infection.\(^3\) This high sensitivity and specificity may exclude cell-mediated mechanisms but this assay provides a rapid, safe, and accessible assessment of COVID-19 vaccine efficacy in immunized individuals, such as the present patient.\(^3\) Abnormalities among this NAb generation, effector T cell populations, and other immune interactions prevent coordinated recognition and defense mechanisms.\(^7\)

Antibody response to antigenic challenge from vaccination reveals the immunological status of patients with suspected PID, which typically involves quantitative and/or qualitative antibody deficiencies.\(^4\) These patients present with history of recurrent respiratory tract infections, infectious susceptibilities, and/or subsequent comorbidities.\(^4\) Direct genetic diagnosis of single-gene disorders, flow cytometric analysis of lymphocytic subpopulations, and serum IgG evaluation offer other laboratory-based tools to assess PID.\(^4\) Our present patient had been diagnosed with SPAD, considering his recurrent infections, stable Ig levels, and seronegativity to multiple immunizations but response to protein antigens, including anti-S antibody reactivity.\(^4\)\(^,\)\(^9\)

Few studies have evaluated COVID-19 vaccination antibody response in immunodeficient patients. Ou et al identified significantly lower or absent anti-S antibody production in renal transplant recipients on versus off the immunosuppressant belatacept, which selectively inhibits CD28-CD80/86

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### Table 1. SARS-CoV-2 antibody immunoassays.

| Timeframe relate to vaccination | SARS-CoV-2 serology antibody | Result |
|--------------------------------|-----------------------------|--------|
| Post-Dose 2                    | Spike glycoprotein total    | +      |
| Post-Dose 2                    | Nucleocapsid IgG            | -      |
| Post-Dose 1                    | IgG, IgM                    | -      |
| Baseline/Pre-Dose 1            | IgG, IgM                    | -      |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ig, immunoglobulin
pathway T-cell co-stimulation. This poor antibody response on immunomodulatory therapy was consistent in cancer patients receiving the immune checkpoint inhibitor programed cell death receptor (ligand) 1 [anti-PD(L)1].

Two small PID cohorts demonstrated COVID-19 mRNA-vaccination antibody response in most patients. A retrospective chart review of 11 PID patients by Squire and Joshi revealed undetectable anti-S antibodies in only x-linked agammaglobulinemia (XLA). Hagin et al also reported lack of anti-S antibodies in 4 XLA patients. Cellular response to an S-peptide mix by IL-2/IFN-γ secretion was absent in 7 PID patients, with diagnoses of common variable immunodeficiency (CVID), nuclear factor-kappa-β p105 subunit (NFκB1) haploinsufficiency, and autoimmune lymphoproliferative syndrome (ALPS)-like disease.

This is the first report of SARS-CoV-2 S antibody response post-vaccination in MAGT1 deficiency, more commonly known as X-MEN, which has been under recent proposal by Ravell et al to revise its nomenclature to “X-linked MAGT1 deficiency with increased susceptibility to EBV-infection and N-linked glycosylation defect.” This update acknowledges the key role of MAGT1 deficiency in asparagine (N)-linked glycosylation impairment, resulting in decreased NKG2D expression, increasing EBV susceptibility. This defective CD8+ T cell response is consistent with the patient’s prior seronegative post-vaccination antibody titers, unlike the majority of vaccinated individuals with mounted cell-mediated immune response. The majority positive anti-S antibody detection in most PID patients among the few studies in the literature, such as the present patient, support the safety and efficacy of mRNA COVID-19 vaccination in immunodeficient patients, although larger scale studies are needed.

**Conclusion**

SARS-CoV-2 BNT162b2 and mRNA-1273 vaccination induces potent NAbS and T cell responses. Detectable anti-S antibodies post-COVID-19 vaccination demonstrate vaccination efficacy. Immune response may be reduced or abrogated in immunodeficient patients, as demonstrated in several primary and secondary immunodeficient cohorts. We demonstrate successful vaccination in the PID MAGT1 deficiency in this first reported case of reactive anti-S antibody post-COVID-19 vaccination.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Author Contributions**

Jalil and Hostoffer: Conception of the work; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the version to be published. Rowane and Rajan: Design of the work; analysis and interpretation of data; drafting and revision of the manuscript critically for important intellectual content; approval of the version to be published.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

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**Statement of Human and Animal Rights**

This article does not contain any studies with human or animal subjects.

**Statement of Informed Consent**

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

**Trial Registration**

Not applicable, because this article does not contain any clinical trials.

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**Abbreviations/Acronyms**

mRNA messenger RNA
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2
COVID-19 coronavirus disease-2019
S spike
NAb neutralizing antibodies
RBD receptor binding domain
PID primary immunodeficiency
XMEN X-linked immunodeficiency with magnesium defect, Epstein-Barr Virus infection, and neoplasia
SPAD selective anti-polysaccharide antibody deficiency
MAGT1 magnesium transporter 1
Ig immunoglobulin
CDCD16+CD56+ natural killer/T-cell receptor, Group 2, Member D glycoprotein
CD8+ T-cell receptor
NKG2D