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Case Report

Monoclonal Antibody Therapy in a Vaccine Breakthrough SARS-CoV-2 Hospitalized Delta (B.1.617.2) Variant Case

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ABSTRACT

We present two Delta (B.1.617.2) vaccine breakthrough individuals, a father and son living in separate households. The older, 63-year-old patient's symptoms were severe enough to require hospitalization. Despite having a high titer of anti-spike IgG in his serum, his symptoms resolved within 24 hours following monoclonal antibody (bamlanivimab/etesevimab) therapy.

INTRODUCTION

The SARS-CoV-2 Delta variant of concern (B.1.617.2, 20A/S:478K), originating in India and now emerging in the United States, has been shown to have increased transmissibility and a reduction in neutralization to some monoclonal antibody (mAb) treatments and post-vaccination sera (Centers for Disease Control and Prevention, 2021). To date, the vast majority of vaccine breakthrough cases have been mild or asymptomatic (Fischer et al., 2021).

We present Delta variant vaccine breakthrough cases in a father and son, with hospitalization of the father, which occurred despite a high level of IgG detected in the patient's serum, and resolution of symptoms within 24 hours following mAb therapy.

CASE REPORT

A 63-year-old man (Patient A) with a history of mild hypertension, benign prostatic hypertrophy, and a body mass index of 27, was found to be SARS-CoV-2 positive by reverse transcription polymerase chain reaction (RT-PCR) on June 3, 2021. His 25-year-old son (Patient B), whom he had seen the previous weekend, had developed upper respiratory symptoms and headaches 6 days earlier, and also had a SARS-CoV-2 positive PCR on June 3, 2021. Although Patient A was asymptomatic at the time of testing, he developed nasal congestion, headache, and a dry cough the following day. These symptoms became more pronounced over the next few days, and were associated with extreme fatigue and lassitude. His SPO2 was consistently above 98% by self-monitoring, except for a transient drop to 95%. Both patients had previously received two doses of COVID-19 vaccine BNT162b2 (Pfizer-BioNTech, LOT# EM9810, EN6207) 22 days apart in March and April of 2021.

After 4 days of symptoms following his diagnosis, Patient A presented to Mount Sinai Hospital in New York City. His vital signs were stable and he was afebrile. A SARS-CoV-2 IgG semi-quantitative anti-spike protein antibody was a "strong positive" at 178 AU/ml (negative <5AU/ml), suggesting a strong immune response to the vaccine. He received mAb infusion (bamlanivimab/etesevimab) and was discharged. He reported feeling a returned sense of well-being with complete resolution of symptoms by the next morning. The close contacts of both patients re-

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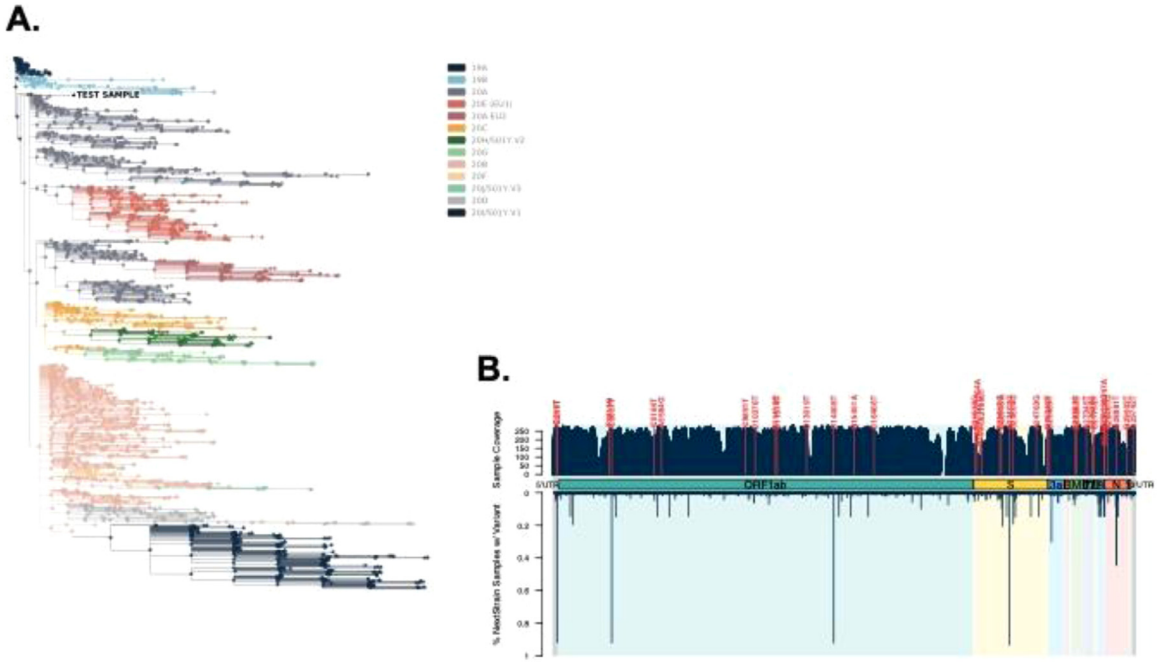

Figure 1. Phylogenetic analysis and SARS-CoV-2 viral genome coverage with genetic variants of Patient A. NGS using NEBNext® ARTIC SARS-CoV-2 FS Library Prep Kit and Illumina NextSeq 550 platform resulted in 3.4 million reads (with 99% coverage of the genome at 10X depth, 4880x mean target coverage). RT-PCR (N1) prior to NGS testing resulted in the following cycle threshold (Ct) values: 31.3 (Patient A) and 25.2 (Patient B). **(A)** The clinical sample was identified as B.1.617.2 lineage (clade 20A). The phylogenetic tree was generated using COVID-DX and Nextclade (version 4-22-2021). **(B)** The plot shows the depth of sequencing that was recovered across the genome. We detected 35 mutations, including 12 ORF1ab, 9 spike protein, and 3 nucleocapsid genes in reference to the Wuhan wild-type strain (NC_045512.2). The spike protein mutations include: C21618G (T19R), ATACATG21764A (H69_V70del), TTTA21990T (Y145del), T22917G (L452R), C22995A (T478K), A23403G (D614G), C23604G (P681R), A24783G (N1074S), G25352T (V1264L). The percent of the SARS-CoV-2 genome recovered from the sample and genetic variants identified compared to the reference genome (Wuhan wild-type strain) are indicated (top) with no coverage (pink), and higher callable coverage (blue) shown. The proportion of known genetic variants of SARS-CoV-2 strains as reported in NextStrain (version 03-07-2021) from across the world are shown (bottom).

mained asymptomatic and were negative by repeat SARS CoV-2 PCR testing.

The SARS-CoV-2 positive clinical specimens (nasopharyngeal swabs) were further tested by RT-PCR and next-generation sequencing (NGS). COVID-DX software (Biotia) was used to detect genetic variants, define PANGO lineage, and assess clade-level phylogenetic analysis.

NGS testing of Patient A identified the B.1.617.2 lineage with 35 mutations detected, including 9 in the spike protein (Figure 1). Patient B had a similar phylogenetic and variant profile to Patient A (B.1.617.2 lineage, with 7/12 shared S-gene mutations). Notably, we detected two spike protein deletions in Patient A that were not present in Patient B [H69_V70del (ATACATG21764A) and Y145del (TTTA21990T)].

The patients provided informed consent to provide specimen and clinical metadata, and the samples were processed under Protocol Number 00042824 (Advarra Institutional Review Board).

DISCUSSION

To our knowledge, this is the first known Delta variant vaccine breakthrough case with hospitalization in New York City. Interestingly, the two vaccine breakthroughs in the same family with similar variant profiles of the SARS-CoV-2 virus may be related to host genetics or the specific mutations of a shared virus.

At hospitalization, the patient described no fever, no loss of smell or taste, and no shortness of breath, presenting a clinical picture related to Delta variant cases. Despite his SARS CoV-2 IgG being strongly positive, he was treated with mAb (bamlanivimab/etesevimab) and his symptoms resolved quickly. The mAb therapy potentially influenced the patient's clinical course as within 12 hours of receiving this therapy the patient got better and within 24 hours he was completely free of all symptoms he had been suffering within the previous three days. Bamlanivimab and etesevimab combined therapy has been issued Emergency Use Authorization (EUA) with the U.S. Food and Drug Administration (FDA) for the treatment of people with mild and moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization (U.S. Food and Drug Administration, 2021). However, to date, there is no reported usage of mAb therapy for individuals with high anti-spike IgG serum level. Additionally, reduction of susceptibility to different variants such as E484K using mAb therapy has been reported but susceptibility to variants in B.1.617.2 has not been determined. A recent study suggests that there were only modest differences in vaccine effectiveness with the Delta variant compared to other variants after 2 doses of BNT162b2 (Bernal et al., 2021; Davis et al., 2021).

Genomic surveillance of novel variants in SARS-CoV-2 positive cases, especially vaccine breakthrough cases, as well as collection of related clinical metadata and therapeutic outcomes, will be necessary to fight the virus as it continues to evolve.

Conflicts of Interest

BAC, MCR, JEB, NBO, and DNS work with Biotia, a for-profit biotechnology company.

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Author Contributions

BAC, MCR, NBO, and DNS designed the case study and interpreted the data; BAC, MG, and MR provided the clinical sample and clinical metadata; MCR processed the clinical samples using NGS; JEB provided bioinformatic analysis. BAC, NBO, and DNS wrote the manuscript with input of all authors.

Ethical Approval

The patients provided informed consent to provide specimen and clinical metadata, and the samples were processed under Protocol Number 00042824 (Advarra Institutional Review Board).

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