

CASE REPORT

A fatal case of COVID-19 breakthrough infection due to the delta variant

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Abstract

COVID-19 infections that occur at least 2 weeks after complete vaccination are known as breakthrough infections. Herein, we report a clinical case resembling breakthrough infection that was correlated with a higher score of COVID-19 pneumonia on chest computed tomography (CT) in a patient who resulted positive for the delta variant and who died during the hospitalization.

KEYWORDS

COVID-19, COVID-19 breakthrough infections, immunodepressive state, SARS-CoV-2 variants, therapy

1 | INTRODUCTION

On February 11, 2020, the World Health Organization announced the official designation for the current coronavirus-associated disease to be COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The new coronavirus has infected millions and killed hundreds of thousands of citizens leading to worldwide social and economic disruption.

In the last year, different vaccines using RNA or DNA targets, including the Pfizer-BioNTech, Spikevax, Vaxzevria, and Janssen vaccines, have represented a hope for the future by inducing remarkable protection rates

of 95%, 94%, and 70%, respectively, leading to a reduced number of world deaths.¹

It is well known that the vaccines available for COVID-19, including mRNA vaccines, are not 100% effective; however, some concerns are related to the actual efficacy against the new ongoing COVID-19 variants as the current vaccines are "S-only" vaccines.²⁻⁴ The B.1.617.2 (delta) variant is currently causing concern because of the high transmissibility.⁵⁻⁸

Emerging variants have not only resulted in increased transmissibility or increase in disease severity, but they have also escaped the immune response, resulting in the risk of reinfections or breakthrough infections in vaccinated individuals.²⁻⁴ COVID-19 infections that occur at

least 2 weeks after complete vaccination are known as breakthrough infections.^{4–12}

However, some concerns are related to the actual efficacy of COVID-19 vaccines in patients with an immunodepressive state; in addition, their protection can decline over time, mainly for patients of advanced age.^{4–13}

Nevertheless, so far, severe cases of COVID-19 breakthrough infection with COVID-19 pneumonia have been rarely reported.

Herein, we described a case of a fully vaccinated patient with COVID-19 infection manifesting with severe extension of COVID-19 pneumonia on computed tomography (CT) scans.

2 | CASE PRESENTATION

A 61-year-old man with a history of arterial hypertension (PA 145/95 mmHg) and obesity with a body mass index (BMI) of 37.11 was vaccinated with a double dose of mRNA vaccine (first dose on 10th April and the second dose on 3rd May). At the beginning of September, he presented with dyspnea, cough, and fever (38°C). His nasopharyngeal/oropharyngeal (NP/OP) swabs resulted positive for SARS-CoV-2 on 4th September in an authorized laboratory. Four days later, he came to the emergency room of our hospital with a saturation oxygen level (SO₂) at 84%. He continued to test positive for SARS-CoV-2 on NP/OP swabs with detection of the delta variant. Upon laboratory examination, he showed a high white blood count value ($19.85 \times 10^3/\mu\text{l}$) (normal value range 4.5–11/ μl), elevated lactated dehydrogenase enzyme (LDH) (750 U/L), elevation of the C-reactive protein (CRP) (26.3 mg/dl), and a mild elevation of the liver aspartate aminotransferase (AST) (61 U/L) (normal value 0–34 U/L). The other laboratory values were in the normal range.

A chest CT scan showed a typical central and peripheral distribution of GGO COVID-19 pneumonia. The CT severity score (CT-SS score)¹⁴ showed a value of 16/20 (Figure 1).

Treatment with dexamethasone (8 mg once daily with intravenous administration for 10 days) along with conventional oxygen therapy was started together with LMWE 2000 IU (once daily with a subcutaneous administration for 10 days). The serology, performed with an immunoassay (Liaison XL), confirmed the presence of SARS-CoV-2 S1/S2 IgM associated with SARS-CoV-2 anti-spike IgG (2080 BAU/ml) related to the previous vaccination (<33.80 BAU/ml: absent) (>33.80 BAU/ml: presence).

Two days later (on 10th September), his clinical condition worsened with SO₂ at 74%. The D-dimer level increased, reaching a value of 2,386 ng/ml (normal value <250 ng/ml) in the presence of persistent positive real-time reverse transcription–polymerase chain reaction (RT-PCR).

A chest CT scan accompanied by a pulmonary artery angiography (CTPA) study showed a mild worsening of the previous pneumonia with a CT-SS score of 18/20 (Figure 2). No major pulmonary embolism was visible on the CTPA. However, the patient died 9 days later.

3 | DISCUSSION

The approved COVID-19 vaccines represent a hope and a beneficial measure for control of the pandemic. COVID-19 vaccines have shown a great efficacy in inducing the immune response in clinical trials.^{15,16}

However, phase III trials are mainly focused on a healthy population, but this population does not represent elderly, frail, and other at-risk persons.^{4,5,7,9–13} Therefore, a small percentage of the fully immunized

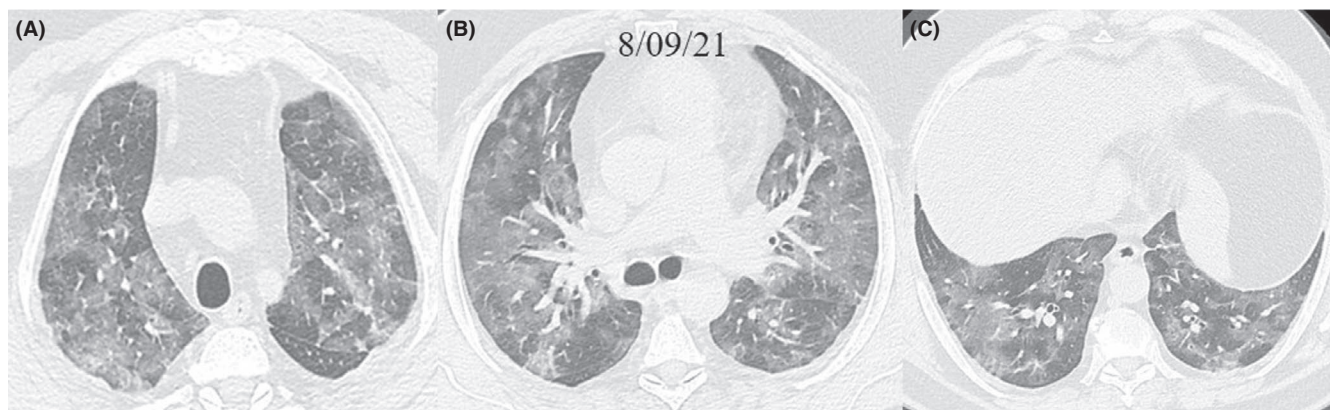
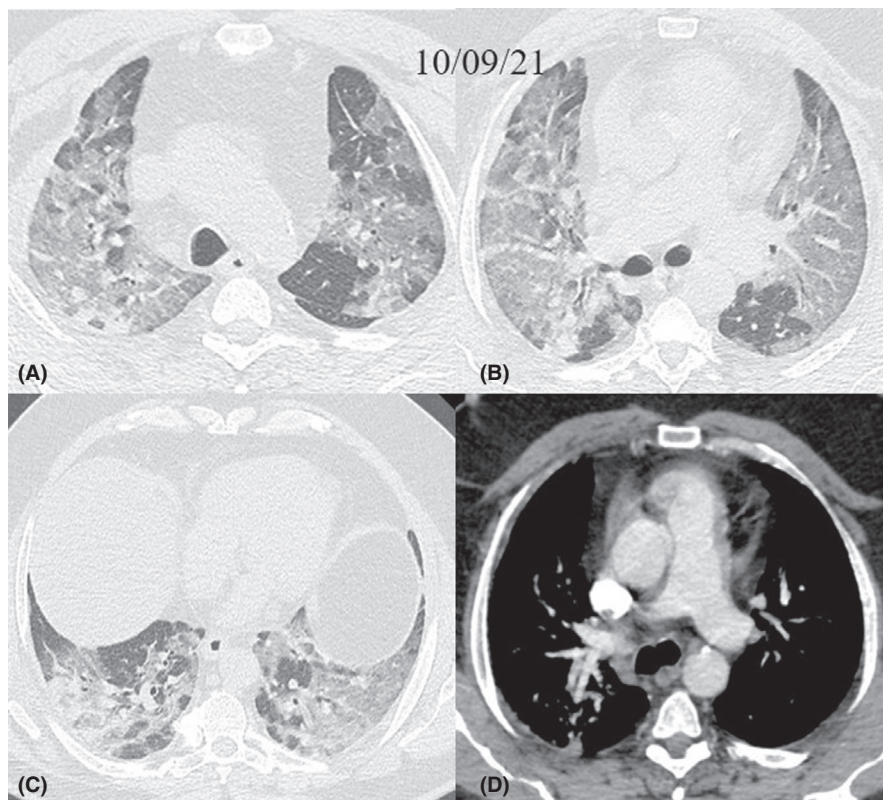


FIGURE 1 The chest CT scan performed at baseline. It shows a multifocal pneumonia with GGO in the superior (A), in the middle and superior lobes (B), and in the inferior lobes (C)

FIGURE 2 The chest CT scan performed 2 days later. It shows a mild worsening of the previous multifocal pneumonia (A,B,C) and with absence of clear defect in the major branches of the pulmonary artery on the CTPA (D)



population may remain infected to varying degrees with COVID-19 disease^{4–13} and may have a vaccine breakthrough infection. A vaccine breakthrough infection is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥ 14 days after full vaccination, usually reported in immunocompromised patients or in patients with older age and comorbidities as hypertension and diabetes. Recent studies reported that the COVID-19 vaccine efficacy may also decline during the time, and low titers of neutralizing antibody and the S-specific IgG antibody may be markers for the breakthrough infection.^{7,10} In fact, on the base data from Israel, the vaccine effectiveness declines after 2 months and effectively vanishes after about 6 months.¹¹ There are different studies in the recent literature that confirmed the presence of breakthrough infections in several vaccinated people.

Brown et al.⁵ found that the RT-PCR cycle threshold (Ct) values in specimens from 127 vaccinated persons with breakthrough cases were similar to those from 84 persons who were unvaccinated or not fully vaccinated. Among persons with breakthrough infections, 79% reported signs or symptoms such as a cough, headache, sore throat, myalgia, and fever.

Berwerk et al.¹⁰ analyzed 39 cases of COVID-19 breakthrough infections among 1497 fully vaccinated healthcare workers during the 4-month period after the second vaccine dose and presenting with mild symptoms. However,

the authors also reported long COVID-19 symptoms in 19% of the cases.

Brosh-Nissimov et al.⁹ reported a cohort of 152 patients with COVID-19 characterized by a high rate of comorbidities with older age and also a high rate of immunosuppression: Half of hospitalized patients were fully vaccinated, and poor outcomes were observed in 38 cases.

Deng et al.⁴ described 14 cases of COVID-19 breakthrough infection in fully vaccinated patients, and half of them were in an immunodepressive state.

In the study of Butt et al.,¹³ increasing age was strongly associated with a higher risk of severe disease in patients with COVID-19 breakthrough infections.

On the other hand, breakthrough infections correlated to mild symptoms have been reported in vaccinated patients. It has been reported that vaccinated people with breakthrough infections, including infection with the delta variant, are less likely to develop symptoms.¹⁷

In the study of Van Vinh Chau et al.,⁸ breakthrough delta variant infections caused asymptomatic and mild disease with high viral loads and prolonged PCR positivity.

However, Shastri et al.⁶ reported on the case of a patient who had three RT-PCR-confirmed SARS-CoV-2 infections. Two breakthrough infections occurred 3 weeks after the complete vaccination. The first breakthrough infection was due to the alpha variant and the second due to the delta variant that resulted in hypoxia and hospitalization.

However, not always an immunocompromised system could be associated with a breakthrough infection.

In our case, the patient who was fully vaccinated and had comorbidities such as obesity and arterial hypertension, without an immunocompromised system resulted to be positive for the delta variant showing severe disease with a poor outcome.

Therefore, these results suggested that, as the Centers for Disease Control (CDC) recommends, all persons, including those who are fully vaccinated, should wear masks in indoor public settings where COVID-19 transmission is high.⁵

Furthermore, the Food and Drug Administration (FDA) approved in August the use of an additional booster dose of the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccines in immunocompromised individuals, specifically solid organ transplant recipients or those diagnosed with conditions that leave them equally immunocompromised.¹⁸

On September 22, 2021, the FDA authorized an additional dose of the Pfizer-BioNTech vaccine after completion of the primary series for persons aged ≥ 65 years or for individuals at high risk for severe COVID-19.¹⁹

However, improvement of the therapeutical approach should be not overlooked for COVID-19, especially in patients at high risk of progression.

The pathogenic mechanism of COVID-19 is mainly induced by two processes. In the early stage, the disease is driven by the replication of SARS-CoV-2 and later by excessive inflammatory response.^{20,21} Therefore, current treatments are based on an antiviral drug to block the virus entry and replication and on therapeutic strategies that have the potential to inhibit the cytokine storm; these include the early use of anti-inflammatory drugs followed by specific and nonspecific immunomodulatory approaches in advanced stages.^{20,21}

Nonspecific immunomodulatory approaches include immunoglobulin, corticosteroids, and interferons.²¹ However, all of these therapeutical approaches showed different limitations.²¹

Promising data are coming from clinical trials on Mulpinavir, a newer oral antiviral drug that has been recently tested in COVID-19. It has demonstrated a significant benefit in reducing hospitalization or death mainly in mild and moderate forms of COVID-19. However, Mulpinavir should be used in the first 5 days from symptom onset.²²

The FDA has given the Emergency Use Authorization (EUA) for two neutralizing therapeutic monoclonal antibody “cocktails,” casirivimab/imdevimab (REGEN-COV) and bamlanivimab/etesevimab, and one monotherapy, bamlanivimab, for prophylactic postexposure therapy in individuals at high risk of progressing to severe COVID-19.²³

However, the monoclonal antibody therapy has limitations, such as the use of antibodies being confined to and authorized for the early phase of the illness.²³

Finally, many other therapeutic targets are being investigated.²⁰ Recent emerging research studies are exploring the possible role of the gut microbiome in COVID-19 severity as a target for future therapy.²⁴

4 | CONCLUSIONS

Although current approved vaccines have shown a great efficacy in reducing COVID-19 severity and newer ones are also under development, concerns have emerged with new virus variants.

However, we should also consider the decline in the immune response over time, especially in older people presenting with comorbidities. Therefore, so far, COVID-19 vaccines represent an optimal medical solution; however, the improvement of therapeutical strategies should not be overlooked, especially for patients with comorbidities and with an immunosuppressive state that may not show sufficient immune response after vaccination. More studies are needed to explore this field of research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization E.B., B.B., C.C., C.B.; methodology E.B.; B.B. and C.B.; software, B.B., E.B.; validation, E.B., B.B., C.B., C.C.; formal analysis, E.B.; B.B., C.B., C.C.; writing—review and editing, E.B., C.C.; C.B and B.B.; visualization, project administration, E.B. and B.B. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The authors comply with international and national ethical standards. The study was conducted in accordance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient's next kin to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The

data are not publicly available due to privacy or ethical restriction.

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