Radiology: Cardiothoracic Imaging COMMENTARY

Breakthrough COVID-19 Infections: What Are They and What Do They Look Like?

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The COVID-19 pandemic has been ongoing for nearly 2 years and has progressed through different stages. The first phase was composed of the initial outbreak in China that subsequently rapidly spread throughout the world. This phase was primarily characterized by attempts to slow the spread of infection via various techniques, including mask wearing, reduction in local transmission via closing of businesses and stay-at-home orders, and reductions in travel. After vaccine development and deployment, the nature of the pandemic has changed. This next phase has been characterized by symptomatic infections that primarily affect unvaccinated individuals, the emergence of more transmissible variants, and eventually the realization that vaccine effectiveness wanes over time. While the cost of this pandemic has been devastating, it has highlighted the ability of our health care system to rapidly disseminate information and develop new treatments and vaccines in a time frame that has been unprecedented compared with prior infectious outbreaks. Additionally, it has provided an opportunity to study the widespread use of a new class of vaccines based on messenger RNA (mRNA), the characteristics of which are poorly defined.

Breakthrough infections occur when previously vaccinated individuals develop active COVID-19 infection. The rate of breakthrough infections in previously vaccinated individuals and their nature is just now being investigated. In a study of 11 453 fully vaccinated health care workers in Israel (1), a total of 39 cases of breakthrough infection were identified (rate of 0.34%) with a median time between vaccination and a positive polymerase chain reaction (PCR) test of 39 days. Most individuals with breakthrough infection in this study were asymptomatic or had mild symptoms. A subsequent letter from the same group identifies an additional 127 individuals with late breakthrough infection (rate of 1.1%) with a median time between vaccination and a positive PCR test of approximately 195 days.

In the December 2021 issue of *Radiology: Cardiothoracic Imaging*, Hossain et al (2) investigate the imaging findings of breakthrough COVID-19 infection. They identify a total of eight previously vaccinated patients admitted to the University of Maryland Medical Center with a positive COVID-19 PCR test. Seventy-five percent of these patients had received the Pfizer-BioNTech vaccine, whereas 12.5% had received the Moderna vaccine and 12.5% had received Johnson & Johnson vaccine. Respiratory symptoms were present in 75% of patients and 63% of patients were immunocompromised. Two patients required intensive care unit admission. Six of eight patients had been discharged at the time of article submission with an average hospital stay of 13.5 days, while the other two were still admitted at the time of article submission. No patients died of their disease.

With regard to the imaging, seven of eight patients had chest radiographs and five of eight patients had CT scans. Chest radiographs were normal in 57% of cases, while the remainder showed consolidation and hazy opacities. Ground-glass opacity and/or consolidation were the predominant CT findings, with a distribution that was peripheral in 60% and mid to lower lung in 60%. Centrilobular nodules were seen in one patient, and the reversed halo sign was present in one patient. Only two of five patients underwent serial CT imaging, one of whom demonstrated near complete resolution of the abnormalities, and the other of which showed a decrease in the lung opacities with interval development of reticulation and traction bronchiectasis.

Breakthrough respiratory viral infections can occur for a variety of reasons. An inadequate antibody response may result from an immunocompromised state or for other reasons. In a study of 1212 patients receiving mRNA vaccines for COVID-19, vaccine effectiveness was 91.3% in nonimmunocompromised patients and 62.9% in immunocompromised patients (3). Alternatively, an individual's immunity can wane over time. In one study, the effectiveness of mRNA vaccines against COVID-19 infection was 88% during the 1st month but declined to 47% after 5 months (4). Last, new strains of the virus may show resistance to previous immunizations. The effectiveness of vaccines against the alpha versus the delta variants of COVID-19 were shown to be 74.5% versus 67%, respectively, for the AstraZeneca vaccine and 93.7% versus 88.0%, respectively, for the Pfizer-BioNTech vaccine (5). While breakthrough infections are uncommon, they will likely increase in significance as vaccine immunity lessens over

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Conflicts of interest are listed at the end of this article.

time, emphasizing the potential importance of booster vaccine doses. While breakthrough infections tend to be mild in severity, it is possible that more severe manifestations may increase in frequency as the length of time between immunization and infection increases. The study by Hossain et al (2) demonstrates that the imaging findings of breakthrough infections seem to be similar to those in unvaccinated patients, albeit generally less severe.

The pulmonary manifestations of viral infection represent a combination of direct injury by the viral organisms and the immune response to their presence, although arguably the latter is a more important driver in the moderate to severe forms of lung injury. The most common imaging findings of nonbreakthrough COVID-19 described previously include bilateral consolidation and ground-glass opacity that may be peripheral or diffuse in distribution. It appears that organizing pneumonia is a relatively common pattern of injury in these patients as evidenced by the presence of perilobular opacities and/or the reversed halo sign in many patients. More severe manifestations of COVID-19 infection include diffuse alveolar damage, which on imaging manifests as generalized ground-glass opacity and consolidation. It is known that both diffuse alveolar damage and organizing pneumonia may, over time, result in lung fibrosis. This was seen on serial CT scans in one patient in the study by Hossain et al who developed signs of fibrosis at serial CT imaging.

The study by Hossain et al (2) had several limitations that need to be considered in the interpretation of its results. It is a small cohort that only included hospitalized patients, which biases the results toward the most severe manifestations of breakthrough infection. Also, as a retrospective study that describes a small cohort of patients with breakthrough infection, it is challenging to put some of the results in an overall context. For instance, the fact that 75% of patients received the Pfizer-BioNTech vaccine, while interesting, doesn't necessarily reflect that this specific vaccine is more susceptible to breakthrough infections compared with others given that overall vaccination patterns in the region are not known. Similarly, 63% of patients were immunocompromised, however, in theory, that could reflect referral patterns to this specific medical center.

In summary, breakthrough infections after COVID-19 vaccination are uncommon and typically present with mild symptoms and radiologic abnormalities that resemble primary COVID-19 infection, albeit less severe. As the pandemic continues and the length between vaccine administration lengthens, it is likely that the severity of breakthrough infections will increase and thus radiologists should be aware of the possibility of breakthrough infections and their typical imaging findings.

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