

Possible COVID-19 reinfection in a patient with X-linked agammaglobulinaemia

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SUMMARY

This report highlights the case of a patient with X-linked agammaglobulinaemia (XLA) and resultant bronchiectasis who was discharged from hospital after recovering from real-time reverse transcriptase-PCR positive COVID-19 infection having had a subsequent negative swab and resolution of symptoms, but was readmitted 3 weeks later with recrudescing symptoms and a further positive swab. Although there are reports of COVID-19 infection in XLA, for the first time we report a case of possible reinfection. Lessons learnt from this case include the potential for reinfection of COVID-19 in a patient with a weakened immune system and the importance of repeating COVID-19 swabs in inpatients. Extra caution needs to be taken when providing care in groups of patients who have a weakened or absent immune system.

BACKGROUND

The global COVID-19 pandemic has had an unparalleled impact on the health, social and economic well-being of the human population worldwide, spreading rapidly between cities since it began to breakout in Wuhan city, China in December 2019 via person-to-person transmission.¹ Given the immense scale of this pandemic, understanding how individuals gain immunity from this virus has been critical in efforts to develop a vaccine and to reduce transmission. The current understanding is that once infected, the majority of individuals develop antibodies, at least for a period of time, the mechanism of which is not well understood.

Real-time reverse transcriptase-PCR (rRT-PCR)-based assays performed on respiratory samples are the gold standard for diagnosing COVID-19.² Despite this, questions still remain in screening asymptomatic people who are in the incubation phase of the virus, as well as in the accurate determination of live viral shedding during convalescence to decide when isolation ends.² rRT-PCR is valuable at the early stage of infection, when the viral load is lowest and can differentiate it from other similar viruses, due to its sensitivity and specificity, respectively.² The advantages of rRT-PCR are that it detects RNA prior to infectivity and antibody formation, however the test has low sensitivity, low stability and a long processing time. In addition, there are reports of false negative in subjects for up to 2 weeks.²⁻⁵

Here we report on the case of a patient with X-linked agammaglobulinaemia (XLA) who was discharged from hospital after recovering from COVID-19 and having a negative rRT-PCR result

following a positive rRT-PCR when he was symptomatic. He was then readmitted with symptoms of COVID-19 and a positive swab result 3 weeks later. There are previous reports of patients with agammaglobulinaemia contracting COVID-19 and recovering, however to our knowledge there are no case reports of patients with XLA being potentially reinfected.

CASE PRESENTATION

The patient was a 55-year-old man with a background of X-linked primary immunodeficiency with resultant bronchiectasis and type 2 respiratory failure. He required home oxygen and had a 20 year-pack smoking history. He had previously declined lung transplantation. In April 2020, he presented with increasingly purulent sputum, fever and breathlessness, and a COVID-19 rRT-PCR swab taken on admission was negative. Despite treatment with intravenous antibiotics, prednisolone, physiotherapy and bronchodilator therapy, his condition worsened with persistent fever, headache, myalgia and chest tightness. Chest X-rays taken 1 week apart showed progressive middle zone changes (see figure 1). A further COVID-19 swab at 10 days was positive. Intravenous antibiotics were changed and oral azithromycin added. He continued to have swinging fevers and a CT pulmonary angiogram showed ground glass changes typical of COVID-19, but no pulmonary embolism. His clinical condition improved and at 29 days a repeat COVID-19 rRT-PCR swab was negative. He was given standard immunoglobulin replacement therapy at a lower dose, his intravenous antibiotics were stopped, but he continued on oral azithromycin and a reducing course of prednisolone. He was discharged after 37 days in hospital. After being well at home initially, he gradually became more short of breath, fevers returned and he was readmitted 19 days later. A COVID-19 rRT-PCR swab on readmission was positive, but a SARS-CoV-2 antibody test was negative. He was treated with dexamethasone, intravenous antibiotics and prophylactic anticoagulation; and although he initially improved on this regime and the fevers settled, he became more oxygen dependant and at the patient's request he was discharged home with palliative care support. He died at home soon after discharge.

INVESTIGATIONS

Blood results

TREATMENT

During the admissions, along with standard severe chest infection therapies, he received prednisolone,



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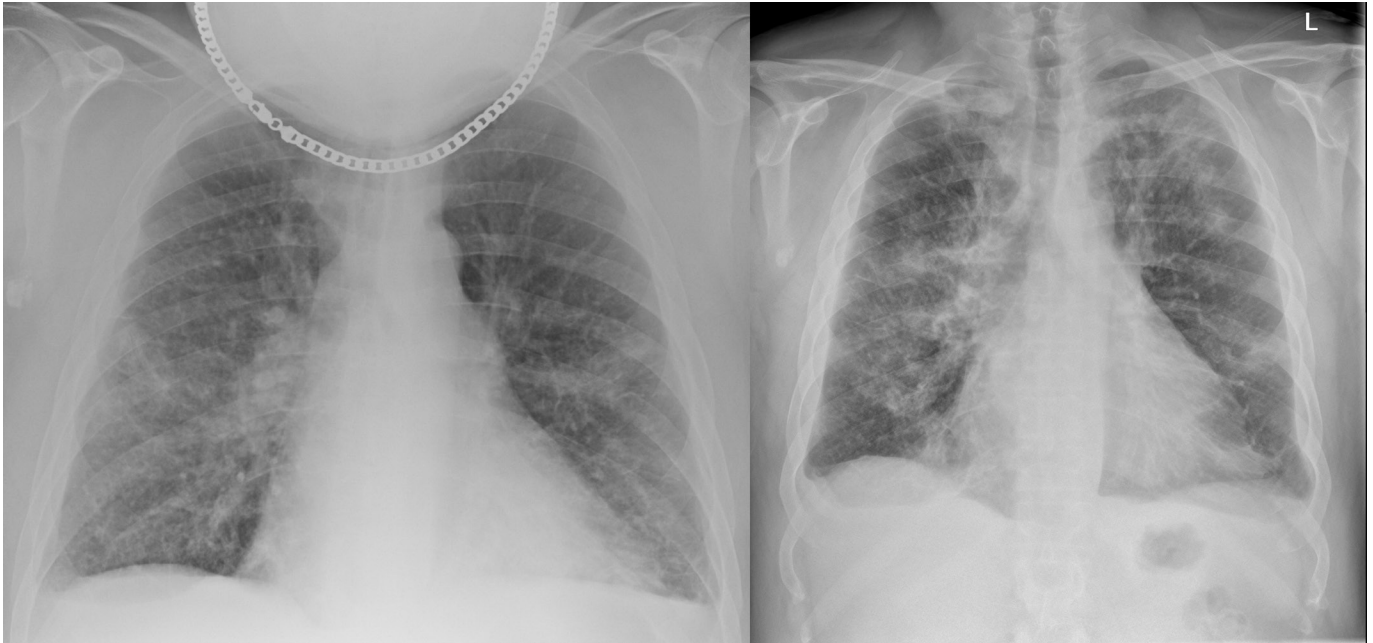


Figure 1 Plain film chest X-ray for patient taken on 20 April 2020 and 14 June 2020, respectively, demonstrating the progressive mid-zone COVID-19-related changes.

prophylactic anticoagulation, dexamethasone and oral azithromycin targeted towards COVID-19.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient died at home shortly after the second discharge from hospital.

DISCUSSION

The development of natural immunity to an infecting pathogen takes place over 1–2 weeks. Initially, non-specific innate responses to viral infections occur, in which macrophages, neutrophils and dendritic cells slow the progress of the virus and may prevent symptoms. This is followed by the production of antibodies (immunoglobulins) which target the virus, and subsequent cellular immunity conferred by the production of T-cells, recognise which destroy other infected cells. This combined adaptive response may clear the virus and prevent progression or reinfection, and can be measured by the presence of antibodies in the blood.⁶ Primary immunodeficiency disorder is a heterogeneous group of disorders that affects the immune system and can be divided into adaptive immunity (T-cell, B cell or combined immunodeficiencies) or of innate immunity (eg, phagocyte and complement disorders).⁷ In XLA, mutation of the gene that encodes for Burton tyrosine kinase causes inability of B cells to mature and differentiate such that antibody production is deficient with impaired humoral immunity. In our patient, his white cell count differential revealed a total lack of CD19 receptors (see [table 1](#) and [table 2](#)). Although the mechanism of immune response in

COVID-19 is still not well understood, it is known COVID-19 elicits a robust B cell response, as evidenced by the rapid and near-universal detection of virus-specific IgM, IgG and IgA, and neutralising IgG antibodies (nAbs) in 1–2 weeks of infection.⁸ In one study where CD19+ IgG+ memory B cells were single-cell sorted from a cohort of eight COVID-19 donors between days 9 and 28 after the onset of symptoms, 209 SARS-CoV-2-specific monoclonal antibodies were produced.⁹ Although there are reports of nAbs being present 54 days after symptom onset,¹⁰ other coronaviruses such as 229E, NL63 and OC43 do not confer long-term immunity.¹¹ As regards

Table 1 Clinical chemistry value of the patient

	21 April (first admission)	14 June (second admission)	Normal values
Lymphocytes ($\times 10^9/L$)	0.6, 1.0 (26 April)	0.6	1.0–3.5
C reactive protein (mg/L)	86, 63 (26 April)	258	<5
Lactate dehydrogenase (U/L)	233 (26 April)	–	<250
D-dimer (ng/mL)	364 (7 May)	777 (17 June)	0–500
Alanine transaminase (U/L)	28, 59 (26 April)	25	<35

Table 2 Lymphocyte subsets of the patient 16 June 2017

	Result	Normal values
Lymphocyte subsets (immunophenotyping)		
CD3 (%)	88	47–79
CD3 count	$1.328 \times 10^9/L$	0.630–3.000
CD4 (%)	75	28–48
CD4 count	$1.135 \times 10^9/L$	0.430–1.820
CD8 (%)	13	17–33
CD8 count	$0.205 \times 10^9/L$	0.250–1.200
CD4: CD8 ratio	5.53	
CD19		
CD19 (%)	0	0.120–0.670
CD19 count	$0.000 \times 10^9/L$	
CD56/CD16 (NK cells)		
CD56/CD16 (%)	12	0.200–1.200
CD56/CD16 (NK cells)	$0.183 \times 10^9/L$	

NK, natural killer.

Patient's perspective

I am grateful for the care given by the hospital, especially the physiotherapy team who encouraged me greatly during my stay at the hospital.

Learning points

- ▶ Patients with X-linked agammaglobulinaemia may be unable to produce antibodies against COVID-19 causing persistent infection.
- ▶ Patients should have two COVID-19 swabs taken to lower the chance of one being a false negative.
- ▶ This underlines the importance of shielding vulnerable patients from COVID-19 until a long-term immunity solution is achieved.
- ▶ It is hoped that more studies will be a platform so that a common criteria for identification of reinfection of SARS-CoV-2 can be developed.
- ▶ Further studies on reinfection could pave the way for the development of an effective vaccine against SARS-CoV-2.

're-positive' cases, where there is a further positive test after recovery from COVID-19 and a subsequent negative nasopharyngeal swab, an analysis of 285 re-positive cases did not find them to be infectious.¹² A study in three paediatric patients showed that clearance of SARS-CoV-2 in the respiratory tract occurred within 2 weeks after resolution of fever, whereas viral RNA remained detectable in stools of the patients for longer than 4 weeks.¹³

Twenty-nine cases of suspected reinfection with SARS-CoV-2 have been reported to date, of which two were known to be immunocompromised due to daily steroid use.^{14–17} There are reports of patients with XLA recovering from COVID-19 infection,¹⁸ but none of recurrence. As regards recurrence, in previous studies there was speculation as to whether it was true reinfection or that the PCR test had remained positive for a period of time following initial infection, whether tests may be intermittently negative if the viral concentration is low in the sampled material, and finally that variability in the number of swabs taken between the first and suspected second infection may have contributed.^{14–16} In keeping with this, common criteria for the definition of reinfection have yet to be ascertained.¹⁴ In our patient, given that his immune system was deficient, persistence of viral excretion is always possible but the negative swab and improvement in symptoms and clinical condition prior to first discharge make this less likely. Likewise, although there is an algorithm for investigation and treatment of pneumonia in the immunocompromised, the insidious onset coupled with typical imaging and clinical features make COVID-19 more likely. We therefore believe that this is the first report of possible reinfection with COVID-19 in a patient with the XLA. However, reinfection could only be confirmed through viral sequencing, indicating that this manoeuvre should be considered in cases of possible reinfection with this virus.

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REFERENCES

- 1 Chan JF-W, Yuan S, Kok K-H, *et al*. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395:514–23 <https://pubmed.ncbi.nlm.nih.gov/31986261/>
- 2 Younes N, Al-Sadeq DW, Al-Jighefee H, *et al*. Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. *Viruses* 2020;12:E582 <https://pubmed.ncbi.nlm.nih.gov/32466458/>
- 3 Rothe C, Schunk M, Sothmann P, *et al*. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970–1 <https://www.nejm.org/doi/full/>
- 4 Bai Y, Yao L, Wei T, *et al*. Presumed asymptomatic carrier transmission of COVID-19. *JAMA* 2020;323:1406–7 <https://jamanetwork.com/journals/jama/fullarticle/2762028>
- 5 Xu J, Wu R, Huang H, *et al*. Computed tomographic imaging of 3 patients with coronavirus disease 2019 pneumonia with negative virus real-time reverse-transcription polymerase chain reaction test. *Clin Infect Dis* 2020;71:850–2 <https://academic.oup.com/cid/article/71/15/850/5814104>
- 6 World Health Organization. Immunity passports in the context of COVID-19. *World Health Organisation*, 2020. Available: <https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19> [Accessed 19 Jun 2020].
- 7 McCusker C, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* 2011;7 Suppl 1:S11 <https://www.ncbi.nlm.nih.gov/pmc/articles/>
- 8 Vabret N, Britton GJ, Gruber C, *et al*. Immunology of COVID-19: current state of the science. *Immunity* 2020;52:910–41 <https://pubmed.ncbi.nlm.nih.gov/32505227/>
- 9 Ju B, Zhang Q, Ge J, *et al*. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 2020;584:115–9 <https://www.nature.com/articles/s41586-020-2380-z>
- 10 Wu J, Liu X, Liu J, *et al*. Coronavirus disease 2019 test results after clinical recovery and hospital discharge among patients in China. *JAMA Netw Open* 2020;3:e209759 <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766230>
- 11 Cavanaugh D. Coronaviruses and toroviruses. In: Zuckerman AJ, Banatvala JE, Pattinson JR, *et al*, eds. *Principles and practice of clinical virology*. 5th edn. John Wiley & Sons Ltd, 2004: 379–97.
- 12 Health Information and Quality Authority. Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses. *Health and Quality Authority* 2020 https://www.hiqa.ie/sites/default/files/2020-08/Evidence-summary_SARS-CoV-2-immune-response.pdf
- 13 Xing Y-H, Ni W, Wu Q, *et al*. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. *J Microbiol Immunol Infect* 2020;53:473–80 <https://www.ncbi.nlm.nih.gov/pmc/articles/>
- 14 European Centre for Disease Prevention and Control. Reinfection with SARS-CoV: considerations for public health response. *European Centre for Disease Prevention and Control* 2020 <https://www.ecdc.europa.eu/sites/default/files/documents/Reinfection-and-viral-shedding-threat-assessment-brief.pdf>
- 15 Tillett RL, Sevinsky JR, Hartley PD, *et al*. Genomic evidence for reinfection with SARS-CoV-2: a case study. *Lancet Infect Dis* 2021;21:52–8 [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30764-7/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30764-7/fulltext)
- 16 Lafaie L, C el arier T, Goethals L, *et al*. Recurrence or relapse of COVID-19 in older patients: a description of three cases. *J Am Geriatr Soc* 2020;68:2179–83 <https://onlinelibrary.wiley.com/doi/full/>
- 17 Yuan B, Liu H-Q, Yang Z-R, *et al*. Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation. *Sci Rep* 2020;10:11887 <https://www.ncbi.nlm.nih.gov/pmc/articles/>
- 18 Soresina A, Moratto D, Chiarini M, *et al*. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. *Pediatr Allergy Immunol* 2020;31:565–9 <https://onlinelibrary.wiley.com/doi/full/>

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