



Non-pulmonary manifestations of coronavirus disease 2019 (COVID-19): case report

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Abstract: Doctors from various specialties across the world are faced with the management of coronavirus disease 2019 (COVID-19). The typical presentation is one of viral pneumonia, with a large spectrum of disease severity. Increasingly, extra-pulmonary manifestations are being reported, often in those with significant pulmonary pathology. Here we discuss a novel presentation of COVID-19, with no pulmonary involvement and the challenges faced by clinicians in achieving the correct diagnosis. A previously fit and well 30-year-old female presented with gastroenteritis, pyrexias, myalgia, rashes, conjunctivitis, and myocarditis. There were no respiratory features, either from her history or clinical examination. Initial and subsequent reverse transcription polymerase chain reaction (RT-PCR) swabs were negative for severe acute respiratory failure coronavirus 2 (SARS-CoV-2), alongside normal appearances of her lungs on computed tomography scans. Her third and final COVID-19 RT-PCR swab was positive, just prior to transfer for her ongoing myocarditis management, at a specialist cardiac critical care. She went on to make a full recovery. Novel presentations of COVID-19 signify a new challenge to clinicians. Correct diagnosis is important for the patient, as well as staff safety. Atypical presentations often have non-specific clinical features, and so a strong index of suspicion, appropriate exclusion of differentials and a multi-disciplinary approach are needed.

Keywords: Case report; coronavirus disease 2019 (COVID-19); atypical; extra-pulmonary manifestations; myocarditis

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Introduction

The 2019 novel coronavirus [now called severe acute respiratory failure coronavirus 2 (SARS-CoV-2), causing the disease coronavirus disease 2019 (COVID-19)] was declared a global pandemic by the World Health Organisation (WHO) on 11th March 2020. Early reports from China suggested that COVID-19 resulted in a viral pneumonia. Patients present with the cardinal features of fever (88.7%), cough (67.8%) and variable shortness of breath (18.7%) (1).

Alternative clinical features, such as diarrhoea (3.7%), rashes (0.2%) and conjunctivitis (0.9%) were rare (1). The vast majority of patients presented with the aforementioned cardinal features, in keeping with pulmonary COVID-19, thus allowing for easier triage, diagnosis and management. The disease spectrum ranges from asymptomatic carriage through to multi-organ failure. Complications were primarily single organ, pneumonia (91.1%) and in those with extra-pulmonary manifestations, such as myocarditis,

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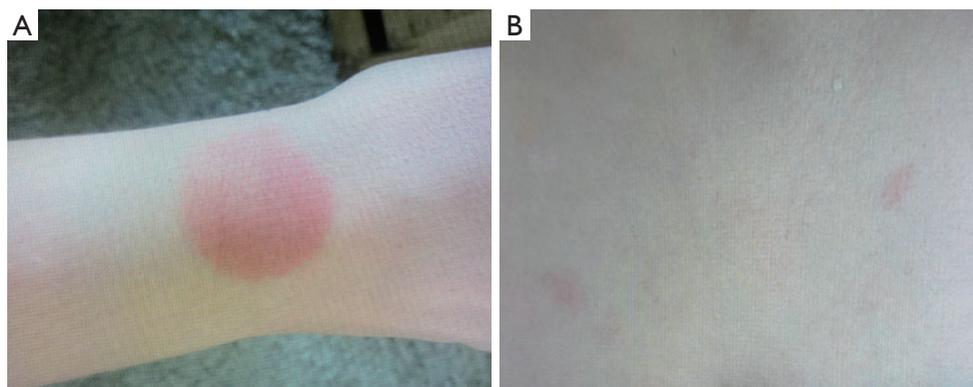


Figure 1 Photographs taken of the rashes on admission. (A) Patient's left forearm. It is a circular (diameter 3 cm), erythematous, slightly indurated plaque without epidermal change. The best description would be of an urticarial rash, but unlike true urticaria, there is an absence of surrounding oedema. (B) Patient's lower back. There were 3–4 lesion macules, slightly raised, with no specific texture or temperature difference.

patients often had significant COVID-19 lung disease (2).

In this case report, we discuss the diagnostic difficulties of COVID-19 in a previously well 30-year-old female, who presented with a 1-week history of atypical symptoms and subsequently developed new onset acute cardiac failure. She had no pulmonary involvement, making the diagnosis of COVID-19 challenging. She was the first patient to present atypically to our hospital. Confounding factors were the lack of the classic pulmonary COVID-19 symptoms, no COVID-19 specific radiological findings and serial negative reverse transcriptase-polymerase chain reaction (RT-PCR) tests. A chronological clinical course will be presented, alongside the various investigations, advice from complimentary specialties and subsequent management. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/jeccm-20-81>).

Case presentation

A 30-year-old female presented to Accident & Emergency (A&E) with a 5-day history of diarrhoea, vomiting, muscle aches and intermittent fevers. She also complained of red eyes for 2 days which had resolved by admission. She denied any cough, dyspnoea and had no history of recent travel or unwell contacts. Her past medical history was of coeliac disease and a thoracic scoliosis, managed conservatively. She was on no regular medication and had no allergies. She did not smoke, had minimal alcohol intake and an unlimited exercise tolerance.

On initial examination, she was shocked, hypotensive

(blood pressure 68/46) and tachycardic (sinus at 133 beats per minute) with cool peripheries, and no oedema. Her respiratory examination (saturations 99% on room air, respiratory rate 16 breaths/minute, with a clear chest on auscultation) and abdominal examination were unremarkable. Of note, one distinct rash was noticed, and another found incidentally on examination (*Figure 1*). She was lucid with no focal neurology, but with intermittent pyrexias.

Initial significant investigations are displayed in *Table 1*.

A chest X-ray (CXR), and then a computerised tomography (CT) chest/abdomen/pelvis (C/A/P) was performed to identify the source of sepsis (*Figure 2*).

The working diagnosis was atypical COVID-19; however, her initial RT-PCR swab was negative. Based on the evidence thus far, she was treated with antibiotics for infective gastroenteritis. The shock responded to fluid therapy and was attributed to hypovolaemia, combined with an element of distributive shock (sepsis). Despite adequate resuscitation, she remained hypotensive and was escalated to critical care for vasopressors. A summary of the differential diagnoses alongside the patient's systems are demonstrated in *Table 2*.

On critical care, she developed rapidly worsening dyspnoea and hypotension, although her diarrhoea had settled. COVID-19 was still suspected, however the repeat swab, the following day, was negative. Repeat CT imaging was requested, suspecting evolving COVID-19 lung involvement or a pulmonary embolism (PE) (*Figure 3*). The findings were consistent with acute heart failure, with no classic COVID-19 lung changes or PE. The repeat troponin

Table 1 Initial investigations on admission

Investigations	Results
Arterial blood gas (ABG)	pH 7.37, pO ₂ 11 kPa, pCO ₂ 3.4 kPa, lactate 1.7 mmol/L, base excess 10 mmol/L, HCO ₃ 15 mmol/L, conducted on air
Bloods	WBC 14.3×10 ⁹ /L (0.7 lymphocytes), CRP 468 mg/L, Na 125 mmol/L, K 3.2 mmol/L, urea 8.5 mmol/L, creatinine 195 µmol/L (baseline 70), troponin (116 ng/L), B-type natriuretic peptide (BNP) (1,670 ng/L), D-dimer (1,058 µg/L), ferritin (702 µg/L) and normal thyroid function tests (TFTs)
Electrocardiogram (ECG)	Sinus tachycardia with no evidence of ischaemia

pH, power of hydrogen; pO₂, partial pressure of oxygen; pCO₂, partial pressure of carbon dioxide; HCO₃, bicarbonate; WBC, white blood cells; CRP, C-reactive protein; Na, sodium; K, potassium.

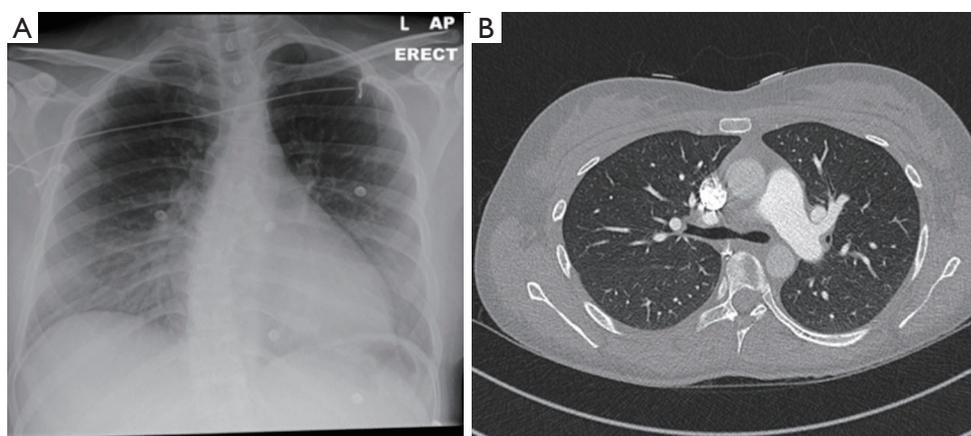


Figure 2 X-rays and CT taken on admission. (A) Admission anterior-posterior (AP) chest X-ray (CXR), taken in the Accident and Emergency department (A&E). The consultant radiologist reported “the heart is not enlarged. Normal cardiomeastinal contour. The lungs and pleural spaces are clear. A note of a thoracic scoliosis convexed to the right.” (B) Admission computerised tomography (CT) chest/abdomen/pelvis. Consultant radiologist’s report “No pulmonary embolism, no specific imaging features of COVID-19, there is some non-specific mesenteric lymph nodes in keeping with an enteritis, possibly infective.” Note abdominal cross-sections not shown.

increased (from 116 to 705 ng/L), despite normal renal function with no new electrocardiogram (ECG) changes. A formal transthoracic echocardiogram (TTE) revealed new biventricular failure with a dilated, impaired right ventricle [tricuspid annular plane systolic excursion (TAPSE) 0.9 cm] and global left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) 44%] with severe tricuspid regurgitation. She required the addition of an inotrope (milrinone), alongside low dose noradrenaline. The combination of careful diuresis and continuous positive airway pressure (CPAP) allowed safe offloading and she improved quickly. The addition of cardiogenic shock to her clinical picture required her to be discussed and subsequently transferred to our tertiary cardiac centre for suspected COVID-19 myocarditis, despite the negative tests thus far.

Whilst awaiting transfer, screens for autoimmune, vasculitis, blood borne viruses and atypical respiratory infections (including legionella) were reviewed and all negative. All her microbiological samples were negative. She was reviewed by multiple specialties: gastroenterology; dermatology; cardiology; and rheumatology. With no clear unifying diagnosis or underlying medical history and a lingering suspicion of COVID-19 a third swab was performed, despite improving oxygenation, which was positive.

After transfer, she spent two nights in cardiac critical care and was weaned off noradrenaline and milrinone. Her myocarditis screen was negative and a computed tomography coronary angiogram (CTCA) excluded an acute coronary syndrome. Her other symptoms had resolved and her serial TTE showed progression towards normal cardiac

Table 2 Summary of differentials and investigations

Clinical system	Differentials	Investigations
Cardiorespiratory (dyspnoea; hypotension; oedema; shock)	Acute heart failure; myocarditis; acute coronary syndrome; arrhythmias; pulmonary embolus; ARDS/COVID-19	Troponin, B-natriuretic peptide; electrocardiogram/chest X-ray arterial blood gas; echocardiography; CTCA/CTPA; cMRI
Gastrointestinal (diarrhoea & vomiting, anorexia)	Infective colitis; coeliac disease; inflammatory bowel disease; COVID-19	Coeliac serology; faecal <i>C. difficile</i> toxin; stool MC&S, viral screen and parasites; CT abdomen & pelvis; endoscopy
Dermatology/rheumatology (rashes; conjunctivitis; myalgia)	Drug reaction; vasculitis; autoimmune; connective tissue disorders; blood borne viruses COVID-19	CRP/ESR; vasculitis screen (ANA/ANCA/RF); blood borne virus screen; autoimmune screen; skin biopsy

CTCA, computerised tomography coronary angiography; CTPA, computerised tomography pulmonary artery; cMRI, cardiac magnetic resonance imaging; ARDS, acute respiratory distress syndrome; MC&S, microscopy culture and sensitivity; CRP, C-related protein; ESR, erythrocyte sedimentation rate; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor. References (3-5).

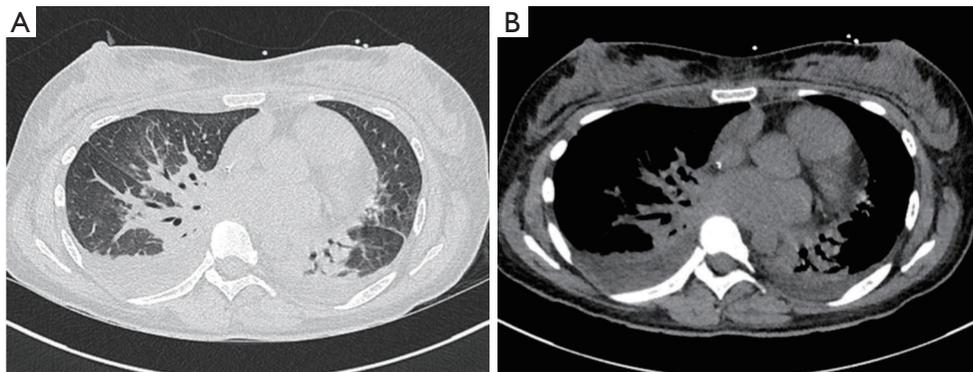


Figure 3 Repeat computerised tomography (CT) chest shown in two different windows, lung window (A) and mediastinal window (B). Left: lung window. This CT scan was performed a day after the chest X-ray and CT scan. There is an acute deterioration in lung changes compared to the first CT scan (*Figure 2*). This subsequent study demonstrates bilateral pleural effusions, associated compressive atelectasis and pronounced bilateral perihilar infiltrates, most suggestive of cardiac failure. These features are not typical for COVID-19, normally manifesting as bilateral peripheral ground glass opacities with a “crazy-paving” pattern and the absence of effusions.

function. The cardiac magnetic resonance imaging (cMRI) was performed once she was COVID-19 negative on swab; this was three weeks after her symptoms. The result was essentially normal by the time it had been performed. Despite this the diagnosis was still considered COVID-19 myocarditis, with no other identifiable cause found. The patient’s symptoms continued to resolve, and she was successfully discharged home, after making a good recovery, after a total of 29 days in hospital (*Figure 4*). There were no concerns over compliance to treatment or adverse events we were aware of, throughout her hospital stay.

All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The patient’s consent was obtained, in writing, for the use of identifiable data related to this manuscript.

Discussion

As the evidence emerges, COVID-19 appears to be a more heterogeneous disease, making the diagnosis difficult, especially in those with a paucity of pulmonary involvement (6). Published case reports comment on extra-pulmonary manifestations, however often these patients have the classic acute severe respiratory failure caused by COVID-19. To

Timeline of clinical course and management

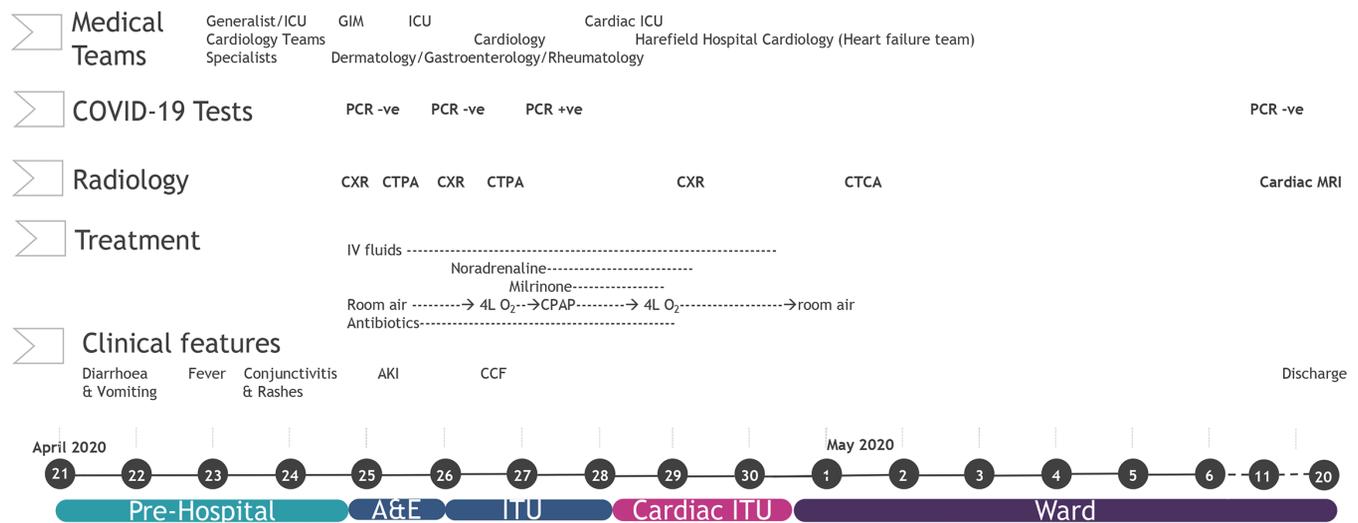


Figure 4 Timeline of the patient's clinical course and management. GIM, general internal medicine; ICU, intensive care unit; PCR, polymerase chain reaction (COVID-19 swab test); -ve, negative; +ve, positive; CXR, chest X-ray; CTPA, computerised tomography pulmonary angiogram; CTCA, computerised tomography coronary arteries; cardiac MRI, cardiac magnetic resonance imaging; O₂, oxygen; CPAP, continuous positive airway pressure.

improve awareness of extra-pulmonary COVID-19, we aim to discuss the incidence, investigations and specific management, using this case as an example.

A recent review of 2,023 patients found the incidence of diarrhoea (49.5%) and vomiting (66.7%) to be much higher than initially thought. Other gastrointestinal symptoms reported included anorexia (up to 50.2%), nausea (up to 29.4%), abdominal pain (up to 6%) and gastrointestinal bleeding (up to 13.7%). Gastrointestinal symptoms were even occasionally the first symptom, sometimes in the absence of fever or cough, leading to potential delays and difficulties in diagnosis, such as in this case (7). Similar findings, from the USA, found that gastrointestinal symptoms were the predominant presenting complaint in 20.3% of patients and the initial presenting symptom in 14.2% of patients (3).

Coronavirus can be detected in faeces by RT-PCR (8). A meta-analysis revealed that 48.1% of stool samples were positive for virus ribonucleic acid (RNA), and they often remained positive, even once respiratory specimens were negative (8). In our centre, like many others, testing stool samples in this manner is not possible. Therefore, an appropriate knowledge of the COVID-19 gastrointestinal presentations, exclusion of differentials (*Table 2*) and advice from gastroenterologists is required.

The largest study of COVID-19 cutaneous manifestations, by Casas *et al.*, reviewed 375 patients with suspected or confirmed COVID-19. Rashes were categorised into five major groups: urticarial lesions (19%); livedo or necrosis (6%); vesicular eruptions (9%); pseudo-chilblain (19%); and other maculopapules (47%). Maculopapular lesions, as demonstrated by this patient, were associated with more severe COVID-19 illness (4). However, it was noted that urticarial and maculopapular lesions may not aid diagnostics, due to their commonality and multiple potential causes (4).

Another method of categorising cutaneous lesions are by splitting them up into two groups: viral exanthems (an immune response to viral nucleotides); and cutaneous lesions (a systemic consequence of COVID-19) in particular vasculitis and thrombotic vasculopathy (9). Ideally, a biopsy is required to further classify and investigate rashes, however this was not feasible in our case.

Most rashes in critical care are manifestations of underlying systemic disease. This patient has a predisposition to one autoimmune disease (coeliac disease) and should be investigated for others. Drug reactions with rashes are common in critical care; however, in this case the rashes were noticed prior to admission. No new rashes or evolution of the existing rashes were noted. The differential diagnosis required exclusion of allergic reactions, autoimmune,

vasculitis and connective tissue diseases (*Table 2*).

The patient's sudden respiratory deterioration, rising troponin and B-type natriuretic peptide (BNP) levels, and new biventricular failure, suggested this was a new cardiac event. However, initial bloods were confounded by shock and acute kidney injury (AKI). The difficulty here is the timing of the myocarditis. It is possible that the pre-hospital fluid losses (diarrhoea, vomiting and pyrexia) may have concealed any clinical evidence of acute cardiac failure. The fluids she received, although significant in volume, were felt to be appropriate in a 30-year-old, with no known cardiac disease. The appearances on the CT scan were in keeping with pulmonary oedema rather than pulmonary COVID-19. The acute cardiac failure could have been myocarditis or decompensation of a pre-existing undiagnosed cardiomyopathy. This combined with cardiogenic shock was the rationale for specialist centre referral. With a normal ECG, no cardiac risk factors and the absence of chest pain, an acute coronary syndrome was felt to be unlikely.

Cardiac complications are a common feature amongst COVID-19 patients and can present in numerous ways: acute coronary event; acute heart failure; arrhythmias; and myocarditis (10). A study of 416 patients with COVID-19 showed that cardiac injury was present in 19.7% of cases. These patients had higher levels of complications (58.5% *vs.* 14.7%), and significantly higher mortality (51.2% *vs.* 4.5%) compared to patients without cardiac injury respectively (11). Another study identified that 27.8% of patients exhibited myocardial injury, as indicated by raised troponin levels, as in this case (12). Of those with acute cardiac injury, 94% had CT features consistent with COVID-19 lung infiltration. This suggests isolated myocarditis without significant pulmonary involvement is rare (5).

At present, the incidence of COVID-19 myocarditis is not evident in the literature. Our patient had no cardiac family history or past medical history, and a myocarditis screen was negative. She had normal coronary arteries, and a cMRI was normal, however, this was performed for logistic reasons after she was RT-PCR negative (active transplant centre). It is possible if the cMRI was performed earlier it may have shown myocarditis.

Radiological changes, primarily on CT, have been shown to be more sensitive (98%) than RT-PCR (71%) (13). Potential sources of error are: sampling technique; specimen source; and sampling timing, ideally within 2 to 7 days of symptom onset (14). In this case the timing of testing was within the ideal range, and a possible cause for the negative

results could be sampling technique or site.

The CT scans taken after the patient's respiratory deterioration are shown and reported in *Figure 3*.

The potential pitfalls in the case report are as follows. Firstly, as the evidence base expands for COVID-19, clinicians are becoming more aware of the various presentations. At the time of writing this was our first case of extra-pulmonary COVID-19, and the evidence base at the time (May 2020) was still expanding, making the diagnosis challenging. Secondly the potential errors from COVID-19 swab testing are now more apparent. False negatives from inappropriate sampling techniques and timing are now more defined (14). It is possible this could have occurred with the first two swabs, and that she may have indeed been positive for COVID-19 on presentation. The use of CXR/CT scans as a screening tool for COVID-19 is widespread, however, the use in those without pulmonary symptoms, as in this case is less defined, however, combined with negative swab results we believed at the time she was initially COVID-19 negative. The underlying myocarditis may have been masked by sepsis and hypovolaemia on admission. Bedside screening tests, such as lung ultrasound or echocardiography may have helped identify the cardiogenic component sooner, for example whilst in A&E. Thirdly, although it is the consensus opinion of multiple specialists, without histological samples, it is not possible to categorically confirm this case report as COVID-19 myocarditis.

A correct diagnosis of COVID-19 has significant implications for the patient, staff and the institution. For the patient, although no targeted effective treatment is currently available, as research progresses a potential drug treatment may be developed. Early diagnosis also avoids unnecessary investigation and treatments, which may have side effects. Additionally, a positive diagnosis has a psychological impact on the patient and alters isolating guidelines for relatives.

For staff, appropriate personal protective equipment (PPE) is essential for health and safety. This relies on an accurate diagnosis of COVID-19 and depends on the procedures performed, e.g., CPAP which is an aerosol generating procedure. This is especially important during a pandemic to minimise staff shortages through sickness.

Institutionally, many hospitals have COVID-19 and non-COVID-19 wards, and therefore appropriate placement depends upon correct early diagnosis. The risk of cross infection to staff and other patients is a significant consideration, especially for those with risk factors for COVID-19.

The original, classic pulmonary COVID-19, will remain the most common clinical presentation, however clinicians may be faced with atypical, extra-pulmonary COVID-19 presentations. As the numbers of cases reduce, making this infrequent atypical diagnosis will become increasingly challenging. Methodical clinical assessment, appropriate exclusion of differential diagnoses and early involvement of appropriate medical specialties is essential. A strong index of suspicion for atypical COVID-19 remains imperative for correct patient management and staff safety.

Patient perspective

Following discharge the patient was re-united with her family and expressed her utmost gratitude to the care that she had received. A thank you card was received addressed to all the staff at Chelsea and Westminster Hospital, involved with her care.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/jecm-20-81>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jecm-20-81>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in

accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The case report was written during the COVID-19 infection outbreak as part of the clinical care the patient received at Chelsea & Westminster NHS Foundation Trust. As the case report involves routinely collected non-identifiable clinical data, no ethical approval was required under the UK policy framework for Health and Social Care. The patient's consent was obtained, in writing, for the use of identifiable data related to this manuscript.

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