

'Long COVID' syndrome

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SUMMARY

SARS-CoV-2 has resulted in a global pandemic and an unprecedented public health crisis. Recent literature suggests the emergence of a novel syndrome known as 'long COVID', a term used to describe a diverse set of symptoms that persist after a minimum of 4 weeks from the onset of a diagnosed COVID-19 infection. Common symptoms include persistent breathlessness, fatigue and cough. Other symptoms reported include chest pain, palpitations, neurological and cognitive deficits, rashes, and gastrointestinal dysfunction. We present a complex case of a previously well 28-year-old woman who was diagnosed with COVID-19. After resolution of her acute symptoms, she continued to experience retrosternal discomfort, shortness of breath, poor memory and severe myalgia. Investigations yielded no significant findings. Given no alternative diagnosis, she was diagnosed with 'long COVID'.

BACKGROUND

SARS-CoV-2 has resulted in a global pandemic and an unprecedented public health crisis. It has infected more than 75 million people worldwide.¹ Clinical features vary from a mild asymptomatic state to a severe state with respiratory dysfunction, thrombotic complications and multiorgan failure.² A large degree of uncertainty remains regarding disease progression; however, individuals with pre-existing chronic cardiac, respiratory and metabolic diseases are at risk of developing a greater disease burden.³

Recent literature suggests the emergence of a novel syndrome known as 'long COVID/post-COVID-19 syndrome', a term used to describe a diverse set of symptoms that persist after a diagnosed COVID-19 infection.⁴ Current estimates suggest that 10% of patients in the UK have persistent or progressive symptoms after resolution of the acute viral infection.⁵ Researchers in Italy report that 60 days after the disease onset, 87.1% of discharged patients with COVID-19 still experience at least one symptom and 55% experience three or more symptoms, such as dyspnoea, chest pain, fatigue and reduced quality of life.⁶

Until now, there has been an absence of agreed definitions for the syndrome. The terms 'long COVID' and 'post-COVID-19 syndrome' have been used interchangeably across the literature. Four potential domains have been identified, which include postintensive care syndrome, post-viral fatigue syndrome, long-term COVID-19 syndrome and permanent organ damage.⁷ Recent National Institute for Health and Care Excellence (NICE) guidelines effectively define and clarify the terminology that can be used to describe the

condition. 'Post-COVID-19 syndrome' is defined as a persistence of symptoms beyond 12 weeks from date of onset. These are not explained by an alternative diagnosis. Ongoing symptomatic COVID-19 is defined as signs and symptoms that persist between 4 and 12 weeks from onset of the infection. The term 'long COVID' includes both ongoing symptomatic COVID-19 (4–12 weeks) and post-COVID-19 syndrome (>12 weeks).⁸

CASE PRESENTATION

We present a previously healthy 28-year-old woman who was diagnosed with COVID-19 in the community in August 2020. She initially presented with fever, cough, myalgia, anosmia and rash, symptoms in keeping with her diagnosis. As per national guidance, she was instructed to self-quarantine at home and received supportive care. Despite her initial efforts, she continued to experience persistent symptoms of fatigue, lethargy, intermittent dizziness, and tachycardia. She experienced a degree of positional retrosternal chest discomfort, which was alleviated by sitting forward. She also experienced increasing back pain, chest tightness, and persistent dyspnoea. The symptoms appeared to fluctuate unpredictably over the weeks with no aggravating or alleviating factors identified. She had no significant medical history other than a previous Epstein-Barr virus infection, whereby she developed postviral fatigue for a duration of 3–4 months. No significant drug history was noted.

She attended accident and emergency twice due to increasing concerns regarding her symptoms. During both visits she was noted to have persistent tachycardia and overt shortness of breath. She underwent a number of investigations, including blood tests, ECG and chest X-rays, which were insignificant; she was later discharged home with appropriate safety netting advice.

Over the subsequent few weeks, the cumulative effect of her symptoms became so debilitating that she remained bedbound and was unable to resume her professional work. In September, she went on to seek further advice and assessment from her respiratory physician due to concerns about potential persistent bronchial inflammation and disordered breathing. A follow-up assessment 1 month later showed no significant improvement in her clinical condition, despite normal repeat investigations. A cardiology review concluded there was no evidence of pericarditis, but she continued to experience severe retrosternal discomfort refractory to treatment with anti-inflammatory agents and antihistamines.

Furthermore, the patient experienced a number of multifaceted cognitive symptoms including reduction in concentration, poor memory, 'non-specific



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head buzzing', worsening anxiety, and brain fog. Musculoskeletal symptoms included restless legs, non-specific paraesthesia across her hands and feet, and generalised body ache. She was reviewed by a rheumatology specialist for these symptoms.

INVESTIGATIONS

Multiple blood tests showed normal full blood count (haemoglobin 131 g/L, white cell count 8×10^9 /L, platelets 262×10^9 /L), clotting profile, liver function test (alanine aminotransferase 24 U/L, alkaline phosphatase 56 U/L) and lactate dehydrogenase (187 U/L). D-dimer was mildly elevated (466 ng/mL; normal <400 ng/mL); however, Wells' score for pulmonary embolism (PE) was insignificant. C reactive protein (CRP) (<1 mg/L) and creatine kinase (59 U/L) were within normal limits, along with negative troponin (<3 µg/L) and negative brain natriuretic peptide (BNP). B₁₂, folate and ferritin values were insignificant. Autoantibodies including antinuclear antibody, extractable nuclear antigen, double-stranded DNA, rheumatoid factor, and anticyclic citrullinated peptide were negative. Thyroid function tests and cortisol levels were within normal range.

Multiple imaging investigations were also noted to be normal. Chest X-ray films identified normal clear lung fields. CT scan of the thorax was normal with the presence of a 5 mm left lower lobe intrapulmonary lymph node, which was of no clinical relevance.

An outpatient respiratory clinical assessment demonstrated normal respiratory examination. Peak flow was 450 L/min (94% predicted). She had an occasional deep sighing respiration consistent with a breathing pattern disorder. Her persistent respiratory symptoms were thought to be consistent with bronchial inflammation. Cardiovascular assessment and examination were unremarkable with normal ECG and echocardiogram report.

TREATMENT

The treatment provided was aimed at symptom control. She was commenced on low-dose propranolol to reduce her persistent tachycardia. As per respiratory guidance, she was started on regular inhaler therapy in order to reduce her bronchial inflammation. This included regular Fostair (beclomethasone, formoterol) 6/100 metered dose inhaler two times per day.

Rheumatology recommendations included graded aerobic exercises, yoga and Pilates, mindfulness, and improved sleep hygiene. Pharmacotherapy with duloxetine was prescribed to improve her chronic fatigue, pain and anxiety symptoms. She was prescribed promethazine to improve insomnia.

OUTCOME AND FOLLOW-UP

The patient in this case study presented with a variety of symptoms. As per the NICE guidance, it is important to rule out other organic, acute or life-threatening diagnoses that may provide an explanation for the clinical presentation. Key differentials include PE, angina, and pericarditis. Electrolyte abnormalities, hormonal imbalances, haematological conditions such as iron deficiency and anaemia, and a number of rheumatological conditions may offer an alternative diagnosis.

Respiratory complications such as PEs are frequently observed post-COVID-19 infection. The clinical history of shortness of breath appears more gradual and fluctuant in nature; neither characteristic was suggestive of a PE. The patient had normal observations and no new oxygen requirement. D-dimer was mildly elevated; however, the Wells' score was 0. A respiratory clinical follow-up highlighted normal

peak flow values, ruling out the possibility of underlying undiagnosed asthma. CT imaging showed no evidence of lung fibrosis.

The retrosternal chest discomfort and tightness raised concerns of a possible pericarditis or myocarditis. However, normal ECG and echocardiogram findings ruled this out, in addition to negative troponin values. B₁₂, folate and thyroid function tests were also insignificant. Haematinics including ferritin were within normal ranges, ruling out the possibility of an underlying anaemia. An autoantibody screen and cortisol levels were not significant, ruling out any rheumatological or endocrine disorders.

As with many of the most common illnesses in clinical practice, including fibromyalgia, migraine and irritable bowel syndrome, the diagnosis rests on documenting a number of subjective symptoms and excluding other conditions that could account for those symptoms. There are no confirmatory tests or biomarkers which are being used in clinical practice. Therefore, the clinician's familiarity with the diagnosis and a comprehensive clinical encounter are pivotal in making a timely diagnosis.

Given that all the investigations and imaging recommended by the NICE guidelines were not able to explain the clinical condition, the most plausible diagnosis here is 'long COVID' syndrome.

DISCUSSION

'Long COVID' is a complex, multifactorial illness that describes the residual effects of the acute COVID-19 infection. While thousands of patients experienced 'mild' COVID-19 symptoms not requiring hospital admission, a large proportion are collectively suffering from post-COVID-19 sequelae. These symptoms were not commonly acknowledged within healthcare policy making during the start of the pandemic but have emerged as tremendous challenges for clinicians and the healthcare system.

NICE have published new guidance defining post-COVID-19 syndrome as signs and symptoms that develop during or after a COVID-19 infection, continuing for more than 12 weeks, and are not explained by an alternative diagnosis. These symptoms, as noted in the case report, can affect any system in the body and fluctuate over time. 'Long COVID-19' is used to describe both patients with symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).⁹

The guidance recommends offering medical consultations to patients who are concerned about persistent symptoms lasting more than 4 weeks from the onset of acute COVID-19. This is particularly important in vulnerable groups. Patients who have been admitted to hospital should receive a 6-week follow-up appointment after discharge to assess their symptom progression.⁹ Tests and investigations should be offered to rule out acute or life-threatening differentials in order support the diagnosis of 'long COVID-19'. This includes blood tests-full blood count, liver and kidney function tests, CRP, ferritin, BNP, and thyroid function tests. Exercise tolerance tests have also been recommended.

Diverse arrays of symptom presentation have been identified across multiple studies. Mandal *et al*¹⁰ demonstrated that patients most commonly present with persistent breathlessness, fatigue and cough. Of the individuals, 30% were noted to have a persistently elevated D-dimer and 9.5% had a raised CRP up to 90 days after discharge. These are in keeping with the case report we have discussed. Other symptoms noted were chest pain, palpitations, neurological symptoms, rashes, gastrointestinal dysfunction and cognitive blunting.^{9 11 12} The large variety

of presentations contributes to a degree of diagnostic uncertainty, making the management challenging.

Those who are diagnosed with 'long COVID' should receive additional medical, psychological and emotional support as part of a multidisciplinary approach. Referral to further multidisciplinary rehabilitation services (occupational therapy, psychological therapies, physiotherapy) should also be considered.

Patient's perspective

During the first 3 months I was completely debilitated, mostly bedbound, and unable to socialise, exercise, or partake in any hobbies. When I pushed myself, I ended up spending days in bed. As someone who has always been very healthy and active this has been difficult for me. My symptoms have tremendously affected my quality of life.

Furthermore, the uncertainty has made the whole process significantly worse. Finding out that most of my investigations were normal increased my level of anxiety because it felt as if there was no explanation for the way I was feeling. Getting the diagnosis of 'Long COVID' has helped me to come to terms with my condition and accept my symptoms. Life is still anything but normal, but I am glad to have received a diagnosis. I have been told my recovery is likely to be very gradual and currently I am trying to set realistic goals with an attempted phased return to work. I have also been recommended to start physiotherapy, yoga, and Pilates, which seem to be having a positive effect on my health.

Learning points

- ▶ 'Long COVID' is used to describe patients with both symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).
- ▶ Presentation can vary greatly between individuals, making diagnosis and treatment challenging.
- ▶ Management of patients with 'long COVID' should include a multidisciplinary team.

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