Case report

Silent hypoxia: a frequently overlooked clinical entity in patients with COVID-19

Atanu Chandra, Uddalak Chakraborty, Jyotirmoy Pal, Parthasarathi Karmakar

SUMMARY

COVID-19 caused by SARS-CoV-2 may present with a wide spectrum of symptoms ranging from mild upper respiratory tract infection like illness to severe pneumonia and death. Patients may have severe hypoxaemia without proportional features of respiratory distress, also known as ‘silent’ or ‘apathetic’ hypoxia. We present a case of a 56-year-old man with COVID-19 who presented to the fever clinic of our institution with fever and cough without any respiratory distress but low oxygen saturation. The patient deteriorated over the next 2 days but eventually recovered of his illness in due course of time. This case demonstrates ‘silent hypoxia’ as a possible presentation in COVID-19 and emphasises the importance of meticulous clinical examination including oxygen saturation measurements in suspected or confirmed patients.

BACKGROUND

Coronaviruses (CoVs) are spherical or pleomorphic positive-sense, enveloped, single-stranded RNA viruses with club shaped spikes on surface. Since December 2019, a new strain of CoV also known as ‘novel coronavirus (2019-nCoV/ SARS-CoV-2)’ emerged in the Wuhan city of China and has spread rapidly throughout most of the countries placing a substantial burden on healthcare services. The clinical spectrum of SARS-CoV-2 infection varies from mild self-limiting upper respiratory tract infection to the severe form of illness like severe pneumonia and acute respiratory distress syndrome (ARDS). Some patients with COVID-19 may have significantly reduced pulse oximetry readings without signs of respiratory distress. This entity has been described as ‘silent’ or ‘apathetic’ hypoxia. However, sudden and rapid deterioration may occur in this subset of patients. The patients of suspected COVID-19 are often evaluated by general practitioners or paramedics in a prehospital context. To assess the severity of pulmonary involvement, clinical examination should be meticulous and adequate emphasis should be given to pulse oximetry, rate/depth of respiration and use of accessory muscles. As SARS-CoV-2 infection has become a major public health problem, many guidelines and standardised protocols are being followed to efficiently manage the cases. Though they are very important clinical tools, there is no substitution for good history taking and clinical examination especially in developing countries such as India.

In the following case report, we describe a 56-year-old male patient with COVID-19 who presented with fever and dry cough without any shortness of breath, but had a dramatic decrease in oxygen saturation. The patient had further respiratory decompensation after admission, but eventually recovered within next few days. The purpose of this report is to highlight the importance of ‘silent hypoxia’ and the rationale behind our decision-making process which could be useful to other clinicians and paramedics managing patients with COVID-19.

CASE PRESENTATION

A 56-year-old man presented to the fever clinic of our institution on 23 April 2020, with a history of low-grade fever and dry cough for 6 days. There was also problem of fatigue and loss of appetite for the same duration. Notably, he did not have any shortness of breath, expectoration, haemoptysis, chest pain, orthopnoea, diarrhoea and loss of smell or taste sensation. He had been diagnosed with type 2 diabetes mellitus 11 years ago and was on regular oral antidiabetic medications (metformin and glimepride) along with atorvastatin since then. He was a smoker with 10 pack-year history of smoking. He had no history of contact to any suspected or confirmed patient of COVID-19. On examination, he was febrile (37.8°C) with tachycardia (pulse rate—110/min). His blood pressure was 100/60 mm Hg and respiratory rate was 30/min. Pulse oximetry revealed oxygen saturation of 78% on room air. There was no clinical evidence of heart failure such as raised jugular venous pressure, pedal oedema or gallop rhythm on cardiac auscultation. On auscultation of the chest, rales and wheezes were audible bilaterally, most predominantly on the lung bases.

INVESTIGATIONS

Laboratory workup revealed normal blood counts except lymphopenia and slightly elevated erythrocyte sedimentation rate. Biochemical markers demonstrated a mildly raised C-reactive protein, lactate dehydrogenase and hepatic transaminases. Rest of the liver function and renal function tests were normal. No significant elevation of D-dimer, N-terminal pro-brain natriuretic peptide or cardiac troponin-T was found. Arterial blood gas analysis on admission revealed features of type 1 respiratory failure (pH—7.44, pCO2—28 mm Hg, pO2—54 mm Hg, arterial oxygen saturation—83% and alveolar–arterial gradient of 60 mm Hg).
A 12-lead ECG showed sinus tachycardia. Chest radiograph demonstrated patchy airspace opacities bilaterally occupying the mid and lower radiological zones (figure 1). CT scan of thorax revealed diffuse bilateral patchy ground glass opacities in the aforementioned areas with predominant subpleural involvement and crazy-paving appearance (figure 2). CT angiogram revealed no evidence of pulmonary embolism.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis in our patient was broad and included viral pneumonia, pneumonia caused by atypical infection, cardiogenic pulmonary oedema and acute/subacute hypersensitivity pneumonitis. The differential diagnosis of patients with fever, cough and type 1 respiratory failure in recent times is so much influenced by the COVID-19 pandemic that such patients can be considered as COVID-19 cases until proved otherwise. The nasopharyngeal and oropharyngeal swab for SARS-CoV-2 can be considered as COVID-19 cases until proved otherwise. Much influenced by the COVID-19 pandemic, that such patients were sent for RT-PCR assay. On day 3, the RT-PCR report came as positive.

OUTCOME AND FOLLOW-UP
The patient remained in ICU for 3 days and was then shifted to general isolation ward as the respiratory status improved markedly. From day 6, he became afebrile and was able to maintain oxygen saturation of above 94% without supplemental oxygen. His cough subsided on day 8. On day 10, repeat oropharyngeal and nasopharyngeal swab specimens were sent which came as negative. He was discharged with advice to remain quarantined for 14 days. He was also instructed to return to the emergency department if he experienced any respiratory distress or fever. The patient contacted us over telephone after 14 days and reported that he had no new symptoms. At present, he is on regular antidiabetic medications.

DISCUSSION
Throughout the recent weeks, there have been many discussions on silent hypoxia. Though it is not unique to COVID-19, adequate scientific data on this topic are lacking. This case demonstrates the importance of history taking and thorough clinical examination including the measurement of oxygen saturation to diagnose pulmonary involvement of COVID-19 at an early stage.

The mechanism of hypoxia in general can be explained in two ways—ventilation–perfusion mismatch and right to left shunt (intracardiac or intrapulmonary). Type 1 pneumocytes form the lining layer of alveoli and type 2 pneumocytes produce surfactant which regulates alveolar surface tension thereby maintaining the compliance of lung. SARS-CoV-2 spike protein mainly uses the ACE2 receptors as the attachment site to enter pneumocytes. The binding of SARS-CoV-2 spike protein to ACE2 receptors causes downregulation of the enzyme, resulting in ARDS due to the detrimental action of ACE (by mediating vasoconstriction, inflammation and apoptosis). Gattinoni et al have proposed

Table 1 Summary of relevant laboratory investigations

| Tests          | Results   | Normal range |
|----------------|-----------|--------------|
| Haemoglobin    | 12.8      | 12–16 g/dL   |
| WBC            | 7.8×10⁹   | 4–11×10⁹/L   |
| Lymphocyte     | 940 (12%) | 20%–40% of WBC |
| Platelet count | 290×10⁹   | 150–450×10⁹/L|
| Creatinine     | 100       | 59–104 µmol/L|
| Fasting blood glucose | 112 | <126 mg/dL |
| ESR            | 44        | <20 mm (first hour) |
| CRP            | 1.8       | Up to 0.8 mg/dL |
| AST            | 84        | <37 U/L      |
| ALT            | 96        | <41 U/L      |
| Serum LDH      | 324       | <248 U/L     |
| NT-pro BNP     | 204       | <130 pg/mL   |
| D-dimer        | 422       | ≤500 ng/mL   |
| Troponin T     | 11        | ≤15 ng/mL    |

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; NT-pro BNP, N-terminal pro-brain natriuretic peptide; WBC, white blood count.

Reminder of important clinical lesson

along with azithromycin 500 mg/day for 5 days. Low molecular weight heparin (enoxaparin) was started in the dose of 60 mg/day through subcutaneous injection. Additionally, he was given some antitussives for his cough. He was put on moist oxygen at 5 L/min. However, he was shifted to intensive care unit (ICU) for persistent desaturation and respiratory distress despite supplemental oxygen delivered via nasal cannula. He was placed on a non-rebreather mask at 15 L/min supplemental oxygen. His oxygen saturation improved to 94% subsequently. As the patient expressed his wish of not being intubated at the time of admission, invasive ventilation was not an option to us. On the very next day, oropharyngeal and nasopharyngeal swab specimens were sent for RT-PCR assay. On day 3, the RT-PCR report came as positive.

Figure 1 Chest X-ray showing bilateral patchy airspace opacities in mid and lower zone.

Figure 2 CT thorax revealed bilateral ground glass opacities with predominant subpleural involvement and crazy-paving appearance.
two primary phenotypes of ARDS in COVID-19: type L is characterised by low elastance or high compliance, low ventilation-to-perfusion ratio, low recruitability and low lung weight; type H is characterised by high elastance, high right to left shunt, high lung weight and high recruitability. Type L is seen at initial stages of COVID-19 when silent hypoxaemia occurs. The type L patient may remain unchanged for a few days followed by improvement or worsening to type H. Published reports of histopathology from lung tissue describe diffuse alveolar damage and interstitial inflammation with predominance of inflammatory cells like macrophage and monocytes.

Patients with COVID-19 are often seen to have severe hypoxaemia without proportional features of respiratory distress, which is known as silent or apathetic hypoxia. The exact mechanism of silent hypoxia is unknown; however, different hypothesis including idiosyncratic effect of COVID-19 on the respiratory control system has been proposed.

In the initial phase of infection with SARS-CoV-2, there is alveolar and interstitial inflammation resulting in impaired gas exchange. But as long as the surfactant production is normal, there is preserved lung compliance. Due to more solubility, the diffusion capacity of CO₂ is 20 times more than that of oxygen. So, in this stage, there is hypocapnic hypoxia. Experimental models have shown that hypocapnic hypoxia is not usually associated with air hunger. These patients are seen to have severe hypoxaemia without proportional features of respiratory distress which occurs mainly due to a significant discrepancy between almost well-preserved lung compliance and much affected pulmonary gas exchange. A rapid respiratory rate may be the sole clinical presentation in those patients. But silent hypoxaemia as a result of preserved compliance due to normal surfactant production at initial stages of infection is an unapproved hypothesis. Though the entry of the virus into the pneumocytes occurs through ACE2 receptors, whether they have any significant role in blunted respiratory drive is not known. Some researchers propose that silent hypoxia is linked to the developmental pulmonary thrombi formation in COVID-19. The respiratory centres are too much sensitive to CO₂. On the other hand, hypoxia produces dyspnoea by stimulating carotid bodies, which in turn send signals to the medulla oblongata. Advancing age and diabetes are the two factors which are seen to blunt the response of the respiratory regulatory system to hypoxia. Moreover, a wide variability in respiratory drive is seen between normal individuals in response to hypoxia and hypercapnia.

Our patient also had tachypnoea and low peripheral oxygen saturation without respiratory distress at presentation. The patient had pulse oximetry reading of 78%, arterial oxygen saturation (SaO₂) —83% and PaO₂ —54 mm Hg. Pulse oximetry reading can differ from the arterial oxygen saturation in arterial blood gas (ABG) by as much as 4%. The discrepancy between PaO₂ and oxygen saturation in our case may be due to inaccuracy of pulse oximeters at lower oxygen saturation or due to a right shift in the oxygen-dissociation curve in the presence of fever or both. The right shift of the oxygen-dissociation curve may be a possible mechanism of silent hypoxia, because the receptors in the carotid bodies are only sensitive to PaO₂ and not to O₂ saturation.

Ottestad et al first reported this entity in an elderly man with COVID-19 who developed rapidly progressive respiratory failure with severe hypoxia, although having no significant respiratory distress at presentation. Later, Wilkerson et al described a 72-year-old man with COVID-19 who presented with minimal respiratory symptoms and very low oxygen saturation; the patient eventually died due to progressive respiratory decompensation and multiorgan dysfunction.

The unusual clinical picture of hypoxia out of proportion to the respiratory distress in our patient and the aforementioned review of literature emphasise the importance of identifying the subtle clinical signs which are often missed. However, more peer-reviewed scientific literature is needed for better understanding of this clinical entity.

**Learning points**

- Proper understanding of ‘silent hypoxia’ and measurement of oxygen saturation in suspected or confirmed patient of COVID-19 in outpatient or emergency department will help physicians in early diagnosis of hypoxaemia and manage accordingly.
- Patients of COVID-19 often present without fever. Identification of silent hypoxia in those patients may lead to appropriate diagnosis and management.
- During community surveillance by paramedics, use of pulse oximetry can identify hypoxia in apparently clinically healthy persons with fever and cough. This can be a clue to COVID-19 infection and they can be brought to healthcare facilities earlier.
- The patients with silent hypoxia are seen to have rapid respiratory decompensation often. Therefore, early identification of this subset of patients can limit mortality in COVID-19 to a large extent.
Reminder of important clinical lesson

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