Open Journal of
Clinical & Medical
Case Reports

Volume 6 (2020)
Issue 14

ISSN: 2379-1039

Myasthenic crisis in a patient with COVID-19 taking hydroxychloroquine and azithromycin

James Greenan-Barrett*; Teodros Truneh; Deven Ramoutar

***Corresponding Author: James Greenan-Barrett**
Department of Emergency Medicine, Royal Free Hospital, Pond Street, Hampstead, London, NW3 2QG.
Email: james.greenan@nhs.net

Abstract

A 61-year-old man with a history of myasthenia gravis presented to the emergency department with fever, coryza and dyspnoea two days after being prescribed hydroxychloroquine and azithromycin off-license in the community. His blood tests and imaging were consistent with COVID-19 and had a positive nasopharyngeal swab for COVID-19. He was in type 1 respiratory failure initially but subsequently developed type 2 respiratory failure and hypophonia suggestive of a myasthenic crisis triggered either by COVID-19 infection or hydroxychloroquine and azithromycin use. He was intubated and ventilated and treated with intravenous immunoglobulin and prednisolone. Two weeks after discharge he represented with syncope and dyspnoea. A CT demonstrated a pulmonary embolus, loculated pneumothorax and pneumomediastinum. This case illustrates the importance of considering alternate or coexisting pathology in patients with suspected COVID-19 who present atypically and demonstrates the dangers of prescribing off-licence medication.

Keywords

COVID-19; myasthenia gravis; pulmonary embolus; pneumothorax; hydroxychloroquine; azithromycin.

Background

The first confirmed case in the United Kingdom of COVID-19, a disease caused by a novel respiratory coronavirus (SARS-CoV-2), was on the 31st January 2020. Four months later, there had been almost 40,000 COVID-19 associated deaths and 300,000 lab-confirmed cases [1]. At its peak, there were large volumes of patients attending the emergency department with similar presentations- fever, respiratory symptoms and hypoxaemia. Whilst most of these patients had COVID-19, alternate diagnoses or atypical disease patterns may be overlooked. This case report illustrates the importance of considering differential diagnoses during this pandemic.

Case Presentation

Clinical findings

A 61-year-old man presented to the emergency department with six days of fever and coryzal symptoms and a one day history of exertional dyspnoea. He denied cough, chest pain or dyspnoea at rest. He had seen a doctor in the community two days previously who had been concerned that he had COVID-19 and prescribed him hydroxychloroquine and azithromycin off-license. He had a history of myasthenia gravis for which he took pyridostigmine and azathioprine; he was diagnosed by a neurologist in 2016 with a positive anti-acetylcholine receptor antibody test and had a history of 2 previous myasthenic crises. He had type 2 diabetes and hypercholesterolaemia for which he took metformin and atorvastatin respectively. He had never smoked, was previously entirely independent and had a Rockwood frailty score of 3 [2].

On assessment he had a respiratory rate of 30 breaths/min, was hypoxaemic with SpO_2 of 71% on air and 96% on 40% FiO_2 and had a clear chest to auscultation. He had a blood pressure of 161/92 mmHg, a heart rate of 130 beats/min and a capillary refill time of <2 seconds. He had a temperature of 39.3 degrees and was orientated entirely. He had a normal neurological examination of the limbs with normal power and reflexes and no evidence of ptosis, facial droop, swallowing difficulty or speech impediment. A forced-vital capacity could not be performed as it was classed as an aerosol generating procedure.

9 hours after arrival to the emergency department, the patient developed increased respiratory distress and he desaturated to an SpO_2 of 80% on 40% FiO_2. On 60% FiO_2 his SpO_2 was 93% and he developed hypophonia.

Investigations

A chest radiograph showed significant bilateral mid- and lower-zone patchy consolidation (Figure 1). A 12-lead ECG showed sinus tachycardia with a rate of 124 beats/min.

An initial arterial blood gas on 40% FiO_2 demonstrated a pO_2 of 13.7 kPA, pCO_2 of 5.2 kPA, pH of 7.38, HCO_3 of 22.7 mmol/L, base excess of -2 mmol/L and a lactate of 3.25 mmol/L. This is consistent with type 1 respiratory failure and tissue hypoxia. A repeat arterial blood gas on 60% FiO_2 demonstrated a pO_2 of 7.12kPA, pCO_2 of 6.55 kPa, pH of 7.27, HCO_3 of 20.3 mmol/L, base excess of -4.8 mmol/L and a lactate of 8.25 mmol/L. This is consistent with type 2 respiratory failure, mixed respiratory and metabolic acidosis with severe tissue hypoxia.

A full blood count demonstrated lymphopenia (0.18 x 10^9/L) with a normal neutrophil count (4.9 x 10^9/L). Biochemical markers demonstrated an elevated C-reactive protein (CRP) (478 mg/L), transaminases (alanine aminotransferase 71 units/L, aspartate aminotransferase 72 units/L), creatinine kinase (1413 units/L), ferritin (2410 units/L), troponin (19 ng/L) and procalcitonin (1.55 micrograms/L) but normal renal function (eGFR 79 mL/minute), sodium (137 mmol/L) and potassium (4.4 mmol/L). A coagulation screen demonstrated an elevated d-dimer (1490 ng/L). These results are supportive of infection with COVID-19 and the significantly elevated CRP and elevated procalcitonin suggested there was a super-

added bacterial infection. A nasopharyngeal PCR swab was positive for COVID-19 and negative for other respiratory viruses, blood cultures were negative and a legionella/pneumococcal urine antigen test was negative.

Treatment

The patient was initially treated with high flow oxygen via a Venturi mask but after developing type 2 respiratory failure, he was subsequently intubated and ventilated before being transferred to the intensive care unit (ICU). To reverse the myasthenic crisis he was treated with intravenous immunoglobulin (IVIG) over 5 days (4 mg/kg/day) and prednisolone. The suspected superadded bacterial infection was treated with intravenous antibiotics and his azathioprine was stopped. He was given a prophylactic dose of low-molecular weight heparin to prevent venous thromboembolism. After 7 days in ICU, he was extubated and transferred to a ward where he was weaned off oxygen. He was discharged 16 days after admission when he was asymptomatic and had normal observations.

Outcome

The patient was discharged on a weaning regime of prednisolone and advice to restart azathioprine one week later. During follow-up the patient was asymptomatic with an improvement in exercise tolerance. However, two weeks later he had an episode of syncope and developed dyspnoea. He was tachypnoeic (respiratory rate 24/min) and tachycardic (heart rate 130/min). Bloods showed a significantly elevated d-dimer (13,763 ng/L) and a mildly elevated CRP (17 m/L) but were otherwise normal. A chest radiograph demonstrated a left lower zone loculated hydropneumothorax and persistent bilateral patchy consolidation consistent with known COVID-19 infection (Figure 2). A CT pulmonary angiogram demonstrated a right upper lobe pulmonary embolus, a left-sided loculated pneumothorax confined to the oblique fissure, pneumomediastinum and bilateral airspace opacification (Figure 3,4). The patient was treated with treatment dose low-molecular-weight heparin before being switched to a novel oral anticoagulant. A chest drain was inserted under CT guidance- a repeat CT scan showed resolution of the pneumomediastinum but persistence of the pneumothorax. As the appearance was loculated and stable, the patient's symptoms had resolved and he did not require oxygen, it was decided that further intervention was not indicated. He was discharged and a follow-up chest radiograph four weeks later showed resolution of the pneumothorax.

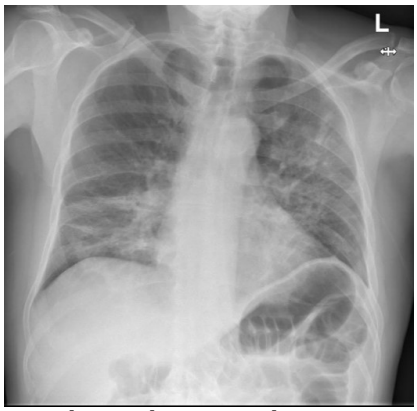

Figure 1: Chest radiograph on initial presentation showing significant bilateral mid- and lower-zone patchy consolidation classical for COVID-19.

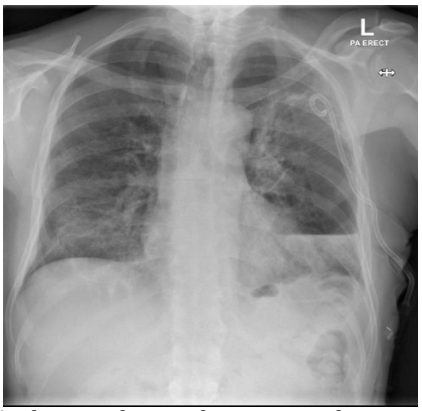

Figure 2: A chest radiograph on second presentation showing a left sided hydropneumothorax and an intercostal drain in situ.

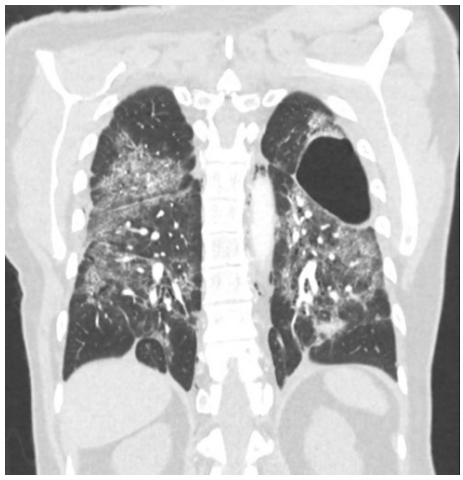

Figure 3: A CT showing a left sided pneumothorax confined to the oblique fissure and extensive bilateral airspace opacification in keeping with COVID-19 infection.

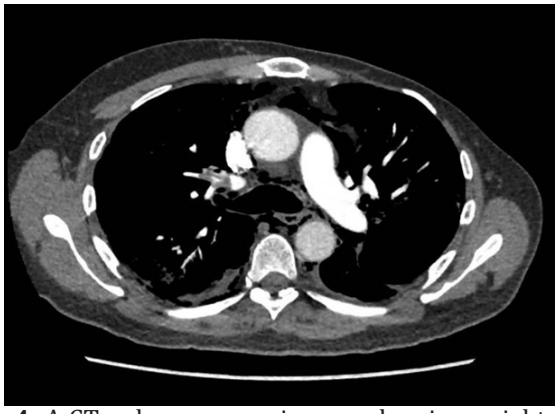

Figure 4: A CT pulmonary angiogram showing a right sided pulmonary embolism.

Discussion

This is an unusual case of a patient with a myasthenic crisis triggered by COVID-19 infection or hydroxychloroquine and azithromycin use, who recovered after treatment with steroids and IVIG but subsequently developed a pulmonary embolus and a loculated pneumothorax. The is the first case of its kind in the literature, although there has been a single report of a patient who was intubated with COVID-19 infection who subsequently developed a myasthenic crisis [4]. In this case, a patient with myasthenia gravis who took hydroxychloroquine daily for mixed connective tissue disease developed COVID-19 infection and was intubated and ventilated for type 1 respiratory failure. She was treated with azithromycin and 6 days later developed proximal muscle weakness and worsening respiratory function which was successfully treated with IVIG.

Infection is the most common precipitant of myasthenic crises, causing 38% of cases [5]. 29% of myasthenic crises are triggered by respiratory tract infections, thus it is possible that COVID-19 infection was a precipitant in this case, although it is impossible to ascertain causality in the absence of further research. Additionally, there are many drugs that are known precipitants; both hydroxychloroquine and azithromycin have been reported to trigger myasthenic crises [6,7]. As such, it is also possible that the myasthenic crisis was precipitated by treatment with these drugs in the community. Guidance from the International MG/COVID-19 Working Group advises against use of these drugs in myasthenic patients [8].

This case highlights the dangers of prescribing off-licence drugs in a community setting. Whilst the US Food and Drug Administration (FDA) has licensed the use of hydroxychloroquine as treatment for COVID-19 and high-profile advocates in the US have endorsed its use, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has not licensed its use outside of a clinical trial, stating a lack of definitive evidence [9,10]. In fact, a recent randomised control trial demonstrated that hydroxychloroquine did not result in a significantly higher probability of negative conversion when compared to standard supportive care in COVID-19 patients and stated a higher rate of adverse events [11]. Likewise, a recent review concluded that there is no evidence to support the use of azithromycin for COVID-19 unless used to treat a

superadded bacterial infection [12]. In addition to precipitating a myasthenic crisis, these medications can cause a number of serious adverse effects such as a cardiac arrhythmias. As such, the authors would recommend following current national advice and not prescribing these medications off-license.

This case also highlights the importance of considering alternate or coexisting pathology in patients presenting with respiratory symptoms during the COVID-19 pandemic, especially in those with underlying medical problems that can affect ventilation such as myasthenia gravis. COVID-19 infection predominantly causes hypoxaemic respiratory failure so presence of type 2 respiratory failure should prompt further diagnostic consideration [13].

The patient subsequently represented with a pulmonary embolus (PE). Although there has been a single case report of a myasthenic crisis causing a PE [14], there is a known association between IVIG and PE; in one study 7% of patients receiving IVIG developed a PE [15]. Emerging evidence has also demonstrated a high rate of PE in COVID-19 patients, suggestive of a pro-thrombotic state [16]. The authors suggest that, in the absence of contraindications, prophylactic anticoagulation should be used in all inpatients with COVID-19 and all inpatients receiving IVIG and clinicians should have a low threshold for suspecting venous thromboembolism in these patients who subsequently deteriorate.

When the patient represented he also had a loculated pneumothorax and pneumomediastinum. There have been a handful of cases of pneumothoraces and pneumomediastinum in COVID-19 reported in the literature, although no cases of a loculated pneumothorax [17,18]. Loculated pneumothoraces are a known complication of acute respiratory distress syndrome, occurring in 32% of patients [19]. This may be caused by positive end-expiratory pressure used in ventilation or inflammation-induced adhesions between parietal and visceral pleura.

Learning points

- Alternate or coexisting pathology should be considered in patients with suspected COVID-19 who present atypically, such as with type 2 respiratory failure
- Hydroxychloroquine and azithromycin should not be prescribed off-licence for COVID-19 by community practitioners
- Both COVID-19 infection and drugs used to treat COVID-19 (hydroxychloroquine and azithromycin) may precipitate a myasthenic crisis
- Pulmonary emboli, pneumothoraces and pneumomediastinum should be considered as a cause of clinical deterioration in patients with COVID-19

References

1. Public Health England. Coronavirus (COVID-19) in the UK. 2020.

2. Rockwood K, Song X, MacKnight C, Bergman H, Hogan D, McDowell I et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005; 173: 489-495.

3. Ottestad W, Søvik S. COVID-19 patients with respiratory failure: what can we learn from aviation medicine? Br J Anaesth. 2020.

4. Delly F, Syed M, Lisak R and Zutchi D. Myasthenic crisis in COVID-19. J Neurol Sci. 2020; 414: 116888.

5. Thomas CE, Mayer SA, Gungor Y, Swarup R, Webster EA et al. Myasthenic crisis: Clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology. 1997; 48: 1253-1260.

6. Cadisch R, Streit E, Hartmann K. Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax). Schweiz Med Wochenschr. 1996; 126: 308-310.

7. Varan O, Kucuk H, Tufan A. Myasthenia gravis due to hydroxychloroquine. Reumatismo. 2016; 67: 125.

8. International MG/COVID-19 Working Group, Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020; 412: 116803.

9. Hinton DM. Food and Drug Administration. FDA Emergency use authorization (EUA) of chloroquine and hydroxychloroquine. 2020.

10. Medicine and Healthcare products Regulatory Agency (MHRA). Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment. 2020.

11. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020; m1849.

12. Gbinigie K and Frie K. Should azithromycin be used to treat COVID-19? A rapid review. BJGP Open. 2020.

13. World Health Organisation (WHO). Clinical management of COVID-19. 2020.

14. Lin S, Wang Y, Guan W and Shi Y. Pulmonary embolism caused by myasthenia gravis. Medicine. 2018; 97: e13578.

15. Marie I, Maurey G, Herve F, Hellot MF, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. Br J Dermatol. 2006; 155: 714-721.

16. Klok F, Kruip M, van der Meer, Arbous M, Gommers D, Kaptein J et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020; 191: 148-150.

17. Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 2020; 20: 510.

18. Wang W, Gao R, Zheng Y, Jiang L. COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. J Travel Med. 2020.

19. Tagliabue M, Casella T, Zincone G, Fumagalli R, Salvini E. CT and Chest Radiography in the Evaluation of Adult Respiratory Distress Syndrome. Acta Radiologica. 1994; 35: 230-234.

Manuscript Information: Received: July 22, 2020; Accepted: September 25, 2020; Published: September 30, 2020

Authors Information: James Greenan-Barrett[1]*; Teodros Truneh[2]; Deven Ramoutar[2]
[1]Department of Emergency Medicine, Royal Free Hospital, London, UK.
[2]Oxford University Hospitals, NHS Foundation Trust, Oxford, UK.

Citation: Greenan-Barrett J, Truneh T, Ramoutar D. Myasthenic crisis in a patient with COVID-19 taking hydroxychloroquine and azithromycin. Open J Clin Med Case Rep. 2020; 1695.

About the Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.
Visit the journal website at www.jclinmedcasereports.com
For reprints and other information, contact info@jclinmedcasereports.com