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Case series

Is Standard Oral Dose Dexamethasone (6mg Once Daily) Prescribed For COVID-19 Pneumonitis Treating Autoimmune Haemolytic Anaemia Associated with COVID-19? A Case Series of Five Patients Providing Us with the Answer

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Abstract

Initially originating as an epidemic respiratory illness in Wuhan, China, COVID-19 eventually spread around the world and has now been declared as a global pandemic disease by the WHO. Our understanding of the pathophysiology of SARS-CoV-2 is evolving with each passage of days. Previously thought to be a respiratory illness resulting in pulmonary complications such as pneumonia, respiratory failure, and acute respiratory distress syndrome now have been found to be causing multiple extra-pulmonary pathologies which includes various degree of autoimmune disorders. Certain group of patients have been found to have autoimmune haemolytic anaemia triggered by COVID-19. We report a case series of five patients who developed COVID-19 induced AIHA which responded dramatically to oral dexamethasone (6mg once daily) initially prescribed for the deteriorating pulmonary function. Therefore, our intuition is dexamethasone prescribed for COVID-19 pneumonitis is beneficial for the rapid recovery of AIHA associated with COVID-19.

Keywords: ***COVID-19, Autoimmune Haemolytic Anaemia,***

Introduction

Human history entered a new era with the unfolding and spread of a novel coronavirus towards the end of 2019. Since its declaration as a pandemic crisis by WHO in March, 2020 a plethora of spectrum of pathophysiology have been identified to be associated with COVID-19 infection. Although initially thought to be a respiratory illness resulting in commonly encountered pulmonary complications such as pneumonia, respiratory failure, and acute respiratory distress syndrome but with passage of time we have found multiple extra-pulmonary involvement caused by COVID-19 infection. Autoimmune pathologies such as autoimmune haemolytic anaemia, auto-immune thrombocytopenia, Guillain-Barre, and anti-phospholipid syndrome have been found to be linked with SARS-COV-2 [1,2,3]. In this report we describe 5 patients who developed a first episode of autoimmune haemolytic anaemia (AIHA) which was found to be improving during a COVID-19 infection with oral standard dexamethasone dose (6mg once daily) initially prescribed for COVID-19 pneumonitis as recommended by Oxford recovery trial for COVID-19 patients requiring oxygen supplementation [4].

Case Presentation

Patient characteristics are detailed in Table 01. All of the 5 patients were admitted in the hospital for non-respiratory illness and later caught the virus during their hospital stay (after at least 10days of hospital stay). They started developing viral prodrome features and later found to have positive SARS-CoV-2 swab test taken on the day of onset of symptoms. All of them became hypoxic after at least 6 days of a positive covid-19 swab test results requiring transfer to COVID-19 HDU ward for higher oxygen supplementation in the form of continuous positive pressure ventilation (CPAP). Interesting point to note was all of them started to drop their haemoglobin level from their baseline after at least 4 days from the point of having positive covid-19 swab test which again started to elevate and reach the baseline within 3-days of onset of dexamethasone (6mg once daily). Haemoglobin level was found to be decreased by more than 20g/L for all of them on day-4

from a positive SARS-CoV-2 swab and continued to drop further till initiation of dexamethasone. Characteristics of haemoglobin are detailed in Table 02. First dose of steroid was prescribed after a minimal interval of 6-days from the positive SARS-CoV-2 swab result as they started to deteriorate in terms of pulmonary function and began to require oxygen supplementation (One patient was started steroid on day-6 of a positive COVID-19 swab test whereas 2 patients had the first dose on day-7 of the positive swab result. Remaining two patients received their first dose of steroid on day 9 and day 10 respectively). All five patients were found to have anti-erythrocytes antibodies (warm antibodies) as direct antiglobulin test (DAT) was positive in all cases either for IgG or both IgG and C3d. They were also noted to develop higher levels of inflammatory markers during the same time frame. (I.e. C-reactive protein, D-dimmers, and fibrinogen). Amongst other haemolytic parameters all of them were noted to develop high levels of unconjugated bilirubin, high reticulocyte count, and high LDH which all regained normal levels within 3days of onset of dexamethasone along with haemoglobin level. All of them had a negative antinuclear antibody (ANA) along with negative influenza, respiratory syncytial virus (RSV), and viral respiratory polymerase chain reaction (PCR) panel. Blood cultures and mycoplasma serology were negative. Urine antigens for streptococcal and legionella were unremarkable. Hepatitis viral screen too was negative. There was no clinical indication to perform an HIV test. All of them had bi-lateral opacities on their chest X-ray (Figure 1,2,3,4,5).

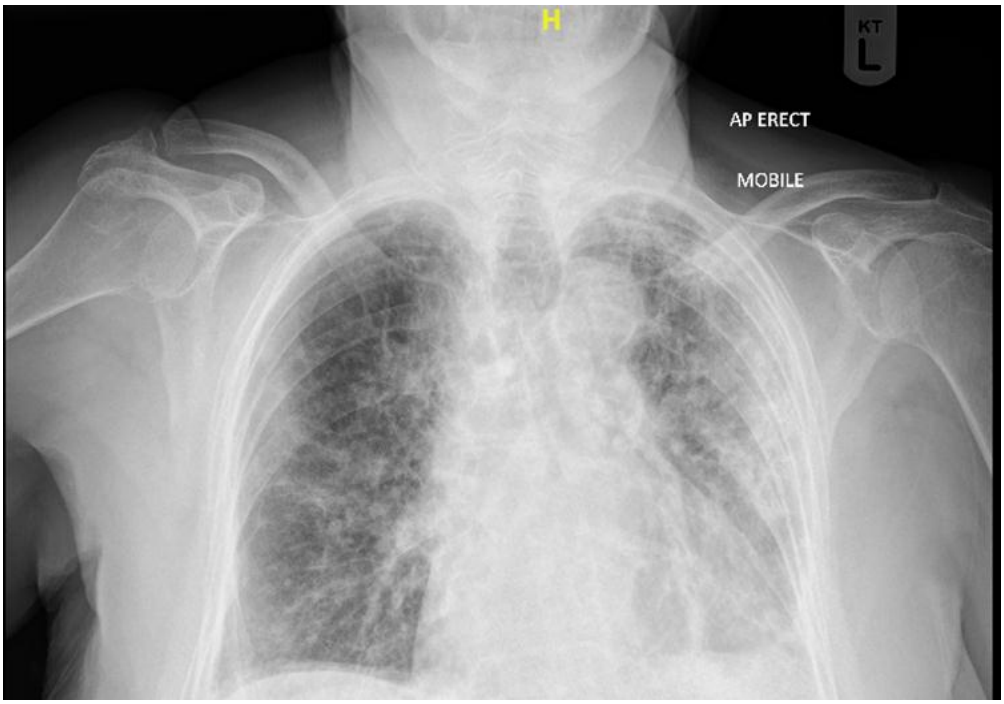

Figure 01: Bi-lateral opacities more on the left lung

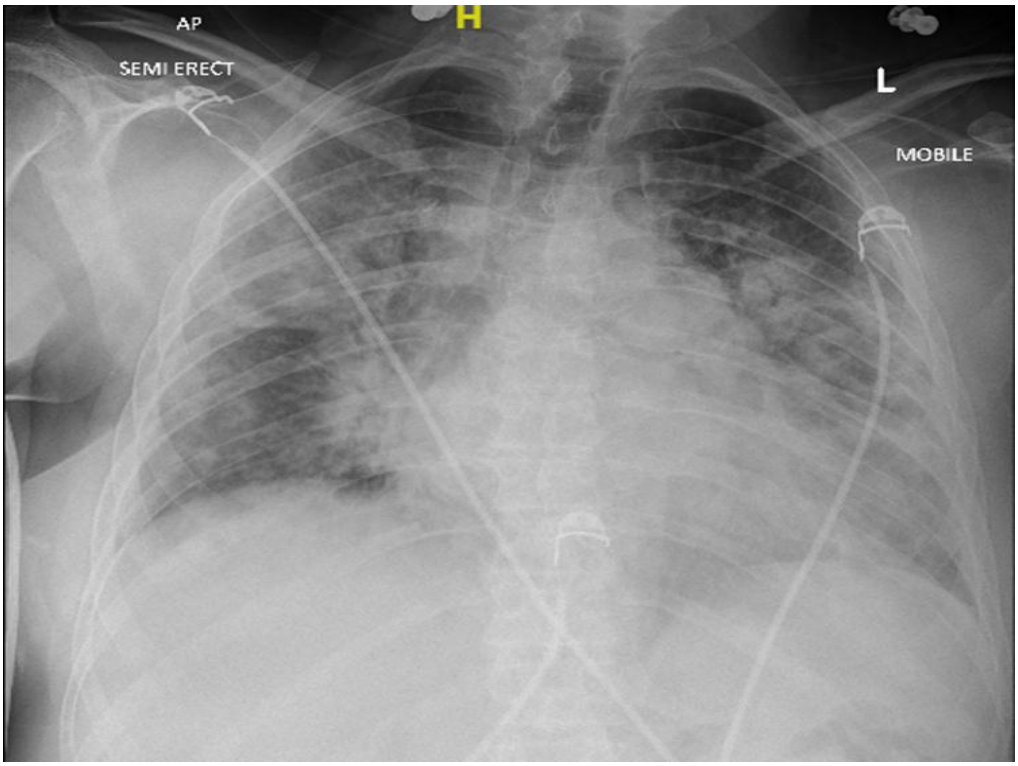

Figure 02: Extensive bi-lateral opacities

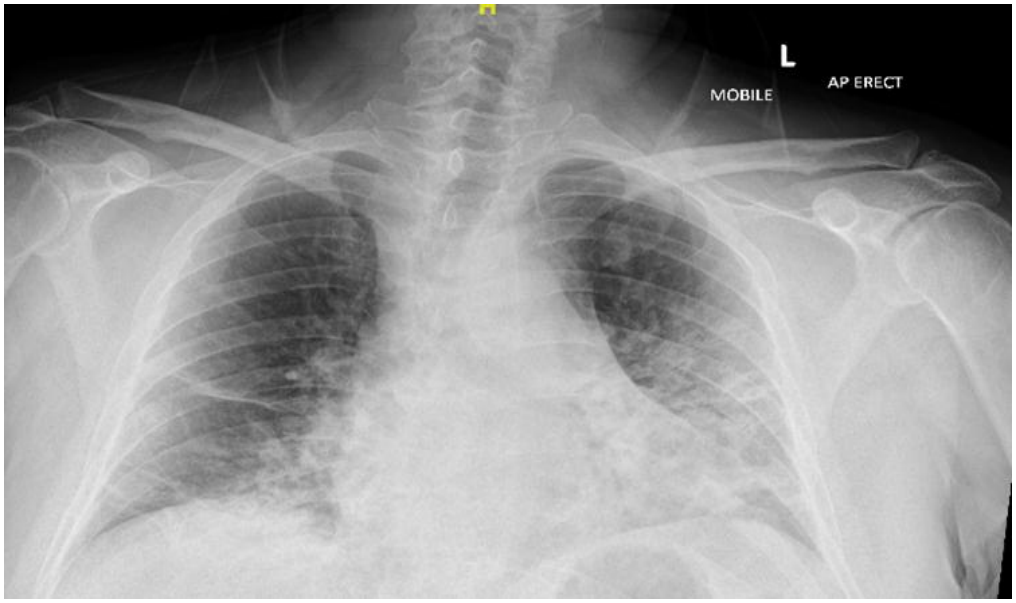

Figure 03: Bi-lateral opacities

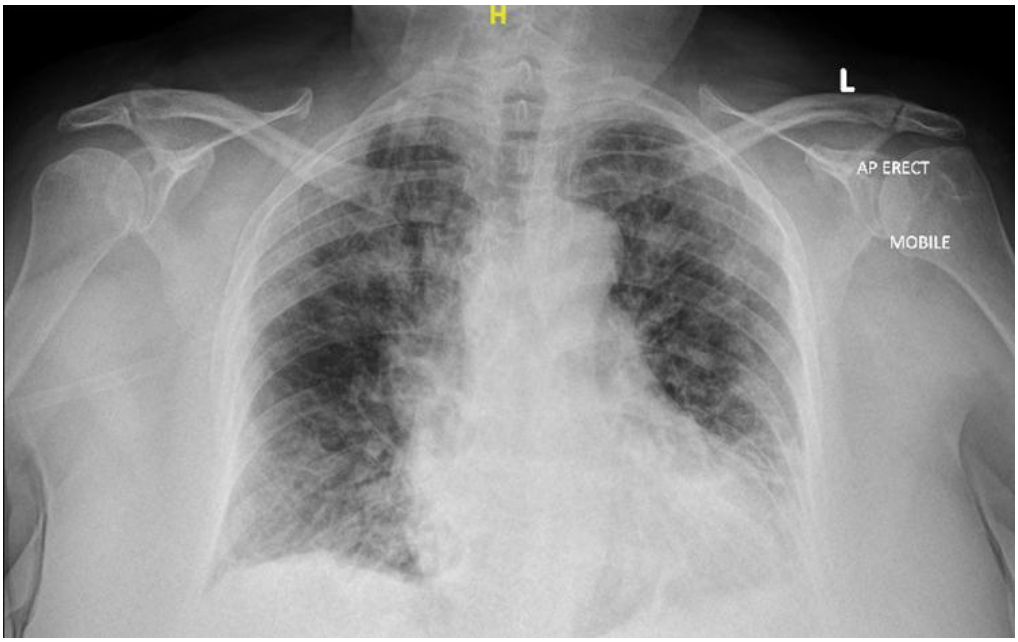

Figure 04: Bi-lateral opacities

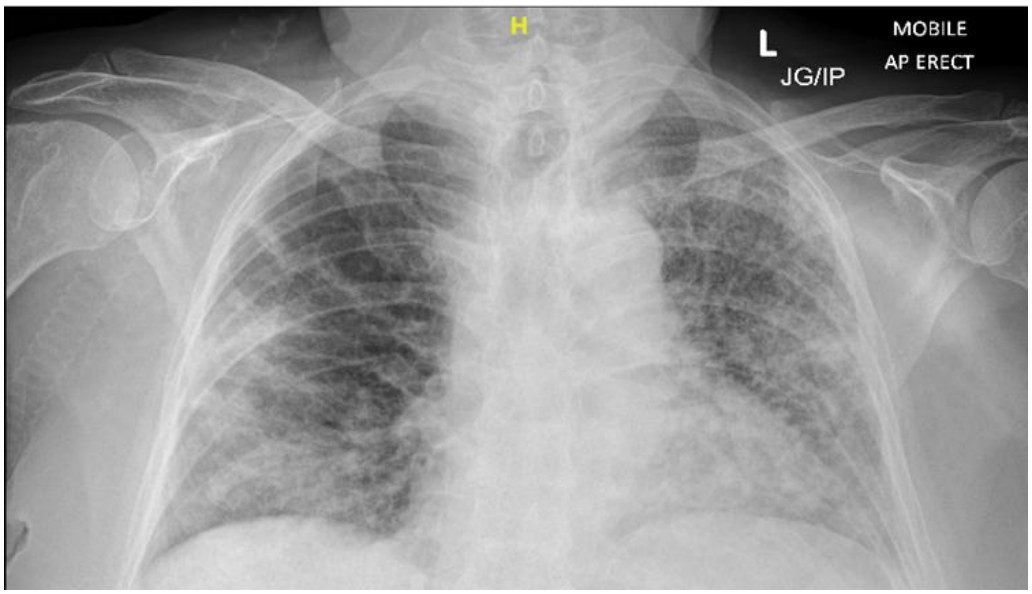

Figure 05: extensive bi-lateral opacities

The patients were all treated with adequate oxygen supplementation in the form of Venturi device and later by continuous positive airway pressure (CPAP) due to higher oxygen requirement along with the course of the illness. All of them received antibiotics (amoxicillin and clarithromycin). They were reviewed by the nutritionist to maintain adequate nutritional status and received 6mg once daily dose of dexamethasone as standard protocol for COVID-19 pneumonia requiring oxygen support as per Oxford Recovery trial recommendation (Two of them received steroids for total 10days whereas other three of them required it for less than 10 days as we were successful in weaning off oxygen due to quicker recovery compared to other two patients). None required red blood cell infusions as haemoglobin levels significantly peaked up with the onset of dexamethasone treatment. All the patients were found to have their haemoglobin elevated to 30g/L or higher after the 4rd dose of dexamethasone. Prior to discharge all of them continued to maintain normal haemoglobin level along with a normal haemolytic profile (Reticulocyte count, LDH, unconjugated bilirubin). As resolution of viral illness and initiation of steroid showed significant improvement of the haemolytic anaemia, we came into conclusion that AIHA was related to COVID-19 and dexamethasone dose (6mg once daily) used in COVID-19 pneumonia is concomitantly treating AIHA associated with SARS-CoV-2infection.

Table 01:

Patient	Age	Comorbidity	X-Ray Chest	Nasal & Oropharyngeal Swab (Tested By PCR)	Direct Agglutination Test (DAT)	Reticulocyte Count (0.2-2.2%)	LDH (125-220u/L)
01	67	Hypertension, T2dm, Ckd	Bi-Lateral Opacities	Positive	Positive For Igg	13.7	699
02	62	T2dm, High Cholesterol	Bi-Lateral Opacities	Positive	Positive For IgG And C3d	08.1	414
03	57	None	Bi-Lateral Opacities	Positive	Positive For IgG And C3d	10.1	597
04	68	Ckd, Atrial Fibrillation	Bi-Lateral Opacities	Positive	Positive For IgG And C3d	14.9	765
05	77	Ihd, Htn, T2dm	Bi-Lateral Opacities	Positive	Positive For IgG And C3d	11.8	605

Table 02

Haemoglobin (Day of admission) [110-150g/L]	Haemoglobin (4 days after positive SARS-CoV-2 swab) [110-150g/L]	Haemoglobin (After 3rd dose of dexamethasone)
124	88	120
137	91	135
146	103	144
119	79	112
139	98	128

Discussion

Autoimmune haemolytic anaemia (AIHA) occurs as a result of autoantibody induced destruction of erythrocytes. While many causes remain idiopathic, others have been associated with certain drugs, auto-immune diseases, malignancies or viral illness (Epstein-Barr virus, cytomegalovirus) [5].

The British Journal of Haematology has published two papers describing auto-immune haemolytic anaemia (AIHA) associated with COVID-19 [6,7]. AIHA is characterised by auto-immune destruction of red blood cells. Previously published studies suggest molecular mimicry could be responsible for COVID-19 associated autoimmune disorders [8,9]. Structural similarity between ANK-1 and viral Spike protein have been suggested to be the trigger behind red blood cell haemolysis. Defective ANK-1 have been found in hereditary spherocytosis too [10]. Ankyrin 1 (ANK-1) is a red blood cell membrane protein which provides linkage between the membrane skeletal and plasma membrane. Any defect in such protein results in defective and weaker erythrocytes membranes which later can be easily haemolysed. Francesca Angileri study revealed structural similarity between ANK-1 and SARS-CoV-2 surface glycoprotein called Spike protein [9]. Amino acids LLLQY an immunogenicity-antigenic epitope shared by ANK-1 was found to have a 100% identical match with Spike protein [9,10]. This explains the likely mechanism of formation of antibodies against SARS-CoV-2 virus affecting the erythrocytes membrane resulting in haemolytic anaemia.

Diagnosis of haemolytic is based on the serological evidence of haemolysis in the form of anti-erythrocyte antibodies, detected by direct agglutination test (DAT). DAT is usually positive with anti-IgG and anti-C3d in cases of Warm AIHA whereas IgM antibodies are commonly found in Cold AIHA [11]. Traditional therapeutic options for treating warm AIHA includes corticosteroids and if fails requires splenectomy, immunosuppressive drugs such as rituximab, intravenous immunoglobulins, plasma exchange, synthetic anabolic steroid such as Danazol [11]. Usual choice of corticosteroid in cases of warm AIHA is prednisone whereas our case report reveals dexamethasone 6mg once daily dose was found to be sufficient to improve haemoglobin levels in COVID-19 induced haemolytic anaemia. Infection induced AIHA have been found to be resolved with the resolution of the infection; therefore, as we do think haemoglobin levels in our patients remained within normal limit along with resolution of the viral illness, but significant improvement of haemoglobin levels was noted with the commencement of dexamethasone therapy whereas all five patients were noted to regain normal haemoglobin levels with maximum 3 doses of dexamethasone 6mg once daily dose. Although complete resolution from viral illness took many days ranging from 9 to 13 days.

Conclusion

To conclude, we report 5 cases of warm AIHA associated with COVID-19 disease all responding in terms of resolution of haemolytic anaemia within 3-days of onset of 6mg once daily

dexamethasone which was prescribed for COVID-19 pneumonitis induced respiratory failure.

Ethics approval and consent to participate

Our manuscript did not require ethical approval

List of abbreviations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

LDH: Lactate dehydrogenase

Conflict of interest

The authors do not disclose a conflict of interest regarding the publication of this article.

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Author's contributions

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