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Case Report

Case Report: Macrophage Activation Syndrome in Two Patients with Moderate COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing a devastating pandemic. Although infection may be asymptomatic or cause only mild symptoms in most of the cases, immunologic complications such as macrophage activation syndrome (MAS) and cytokine storm may occur in some cases.

We report the case of two patients having SARS-CoV-2 infection without severe respiratory involvement and who developed MAS with favorable outcomes after treatment with intravenous immunoglobulin.

Keywords: Covid-19; SARS-CoV-2; Macrophage Activation Syndrome

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing a devastating pandemic. Although infection may be asymptomatic or cause only mild symptoms in most of the cases, immunologic complications such as macrophage activation syndrome (MAS) and cytokine storm may occur in some cases.

We report the case of two patients having SARS-CoV-2 infection with no severe respiratory involvement and who developed MAS with favorable outcomes.

Case 1

A 47 year-old man who presented with dry cough and headache evolving for 10 days prior to admission. He has a history of end-stage renal failure, hypertension and hemodialysis since 4 years.

Physical Examination revealed pallor and pale conjunctivae, dyspnea, tachypnea, and bilateral mild crackles in the bases on lung auscultation. Blood pressure was 130/75 mmHg, pulse of 102 beats per minute, respiratory rate 20 breaths per minute, Sat O_2 96% on room oxygen and a temperature of 39 °C (102.2 F). No further relevant information was found except a splenomegaly. Reverse transcription polymerase chain reaction (rtPCR) COVID-19 in nasopharyngeal swab was positive. Laboratory findings are summarized in table 1.

The patient was put on antibiotics (ceftriaxone 1g twice a day), preventive anticoagulation (calciparin 5000 UI twice a day) and supportive treatment (paracetamol according to fever, vitamine C 1000 mg/day and zinc 30 mg/day).

We noted sustained high fever and cough with dyspnea. Whole body CT scan showed peripheral bilateral ground glass opacities in 50% of the lung parenchyma and splenomegaly with no other abnormalities.

A bone marrow aspiration was performed and revealed heamophagocyte. The diagnosis of secondary hemophagocytic lymphohistiocytosis (macrophagic activation syndrom (MAS)) was es-

Biological findings	Case 1	Case 2	Normal range
Blood pressure(mmHg)	130/75	130-70	120-129/80-84
Heart rate(bpm)	102	104	60-100
respiratory rate(bpm)	20	19	12-16
Temperature(°C)	39	37.8	36.2-37.7
SaO_2(%)on roomOxygen	94	95	95-100
Hemoglobin g/dl	9	14	13-16
Leukocytes(x10^9/l)	9.5	2.67	4-10
Lymphocytes(x10^9/l)	0.6	0,91	1 - 4
Platlets (x10^9/l)	350	58, 5	150-350
ALT(UI/l)	11	16	5-45
AST(UI/l)	19	22	5-45
ALP(UI/l)	107	186	50-150
GGT	34	184	7-64
Bilirubin (µmol/l)	5	8	<17
PT(%)	90	65	70-100
CRP (mg/l)	520	129	<5
Procalcitonin(ng/ml)	6.2	-	<0.5
LDH(UI/l)	850	540	20-200
Ferritin(µg/l)	3300	2761	18-440
Triglycirid (mmol/l)	4.6	4	1.8-2.2
D-dimers(ng/ml)	2200	700	<250
Troponin(ng/ml)	0.02	0.01	0-0.4
Creatinin(µmol/l)	1200	74	50-120
Albumin(g/l)	42	23	35-45
Blood Culture	Negative	Negative	
Proteinuria	-	negative	
Hematuria(cells/mm^3)	-	170	
Leukocyturia(cells/mm^3)	8	10	
Urine culture	Negative	Negative	

Table 1: Clinical and Biological finding at presentation. ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl Transferase; PT : Prothrombin Time; CRP: C Reactive Protein; LDH: Lactate Deshydrogenase; rt-PCR COVID 19: Reverse Transcription Polymerase Chain Reaction COVID 19.

tablished. He had a high Hscore score of 227. The patient received 0,4g/kg intravenous immunoglobulin for five days with 50 mg twice a day of hemisuccinate hydrocortisone. This therapy lead to the improvement of symptoms and biological parameters and the patient was discharged on day fifteen.

Case 2

A 63 year-old man who manifested with limbs oedema and microscopic hematuria. He developed fever, dry cough and dyspnea three weeks before admission and he was diagnosed with SARS cov-2 infection. He was put on antibiotics (azithromycin) and supportive treatment (paracetamol, vitamin C and zinc). Initially the patient responded well within 7 days of treatment, then his condition worsened with reappearence of persistant high fever, arthralgia myalgia, diffuse skin rush, limb oedema with no cough nor dyspnea. Neurological, cardiac and abdominal examinations were normal with mild crackles in the lung bases and mild limb oedema. Blood pressure on admission was 130/70 mmHg, heart rate was 104 beats/minute and the patient had a temperature of 37.5°C. Respiratory rate was 18 breaths/minute and SatO2 was 95% on room oxygen. Laboratory findings are summarized in table 1.

A second nasopharyngal swab for SARS-CoV-2 was always positive. The scan images revealed diffuse ground glass infiltrates in over 25% of lung fields.

Our patient developed a systemic severe inflammatory response to SARS-CoV-2 infection in absence of other infections pathogens. A bone marrow aspiration was performed and heamophagocytes were abudantly present. The patient fulfilled most of hallmarks of secondary MAS (HScore=240). His clinical status as well as his biological features resolved quickly with hydrocortisone hemisuccinate 50mgx2/day, intravenous Immunoglobulins 0.4g/kg for five day, preventive anticoagulation (enoxaparin 4000 UI/day), and supportive therapy (paracetamol according to fever, vitamin C 1000 mg/day and zinc 30 mg/day). The patient was discharged on day seven.

Discussion

Coronavirus disease 2019 (covid-19) is a clinical syndrome, caused by a mutational RNA virus named as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2).

We reported two cases of moderate symptomatic covid-19 with immunological complication: MAS but a favorable outcome. To our knowledge only one publication reported the same findings [1].

Our first patient was on hemodialysis, at presentation he had moderate respiratory symptoms but severe biological inflamma-

tory syndrome: hyperferritinemia, elevated C Reactive Protein and procalcitonin. The others biologicals findings were: anemia, lymphopenia without thrombocytopenia, hypertriglyceridemia and medullary hemophagocytosis.

Our second patient had also the same presentation with almost the same biologicals finding except: no anemia, thrombocytopenia, and low prothrombin ratio.

None of our patients had respiratory distress. Times from the onset of symptoms to the diagnosis were respectively thirteen and twenty-three days. Patients were treated by corticosteroid and immunoglobulin with favorable outcome.

It has been clearly established so far that SARS-Cov-2 may be asymptomatic or cause only mild symptoms in the majority of the cases or may progress to interstitial pneumonia and acute respiratory distress syndrome in nearly 10–20% of the cases, especially in those having older age and co-morbidities. This subgroup of patients is notable with having very high levels of serum ferritin and D-dimer levels, hepatic dysfunction, thrombotic tendency, and disseminated intravascular coagulation implicating occurrence of macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH) [2,3].

The first particularity of our observations was that our patients were not elderly (respectively aged 47 and 63-year-old). The second one was their relatively preserved general condition and the absence of comorbidities except for the first patient who was under hemodialysis.

Third particularity was that our patients were paucisymptomatic, they didn't develop severe respiratory symptoms nor cardiac or thromboembolic complications but they developed a MAS witch considered as severe life threatening complication.

The diagnosis of MAS in our cases was made according to the HScore: a validated score devoted to the diagnosis of MAS based on clinical, biological and cytological criterias [4,5]. The HScore were respectively 227 and 240 for our two cases. Infact, the clinical features for our first patient were: underlying immunosuppression, high temperature, splenomegaly, biological criteria were: anemia, lymphopenia, hypertriglyceridemia and hyperferritinemia. The cytological criteria was medullary hemophagocytosis. The same findings were noted in the second patient namely: fever, leukopenia with lymphopenia, thrombocytopenia, hypertriglyceridemia, hyperferritinemia and finally medullary hemophagocytosis.

Time to diagnosis of MAS was respectively three and two days after admission in nephrology department. Persistent fever, the significant inflammatory syndrome and hypertriglyceridemia led to the suspicion of the MAS. Among patients initially reported in Wuhan, the occurrence of MAS, cytokine storm, and acute respiratory distress syndrome were heralded by very high levels of serum pro-inflammatory cytokines and ferritin [6].

Although present in our two patients, lymphopenia may not be linked only to MAS. Infact, lymphopenia is a common disturbance and early sign in Covid-19, preceding pulmonary problems, and tends to normalize as the patient improves. It's also one of the diagnostic criteria for COVID-19 in China [7]. Zhang., *et al*. reported that the number of T lymphocytes including both CD4 and CD8 subtypes and especially NK cells as well as regulatory T cells are much lower than expected in patients with severe disease course [8]. On the other hand, the great majority of the inflammatory cells infiltrating the lungs are monocytes and macrophages. Autopsy findings showed the presence of monocytes and macrophages and a moderate amount of multinucleated giant cells associated with a diffuse alveolar injury [9].

Our first patient had moderate elevated D-Dimer (2200 µg/l), the second one had moderate thrombocytopenia (58500 E/µl) and low prothrombin time ratio. It is currently admitted that elevated D-Dimer levels are important and persistent elevation confers to poor prognosis. Development of disseminated intravascular coagulation is another problem, characterized by prolongation of prothrombin time and activated partial thromboplastin time, high fibrin degradation products, and severe thrombocytopenia, which may be life-threatening [10]. Why disease course is variable ranging from asymptomatic to lethal may be explained by genetic and host factors [11].

Both of our patients received immunoglobulin (0,4g/kg) administred over five days with hydrocortisone hemisuccinate (50mg x 2/day) intravenously. Infact, previous favorable experience from patients with SARS suggested the use of a high dose of intravenous immunoglobulin in patients with serious COVID-19 infection in the early phase of the disease [12]. Anticoagulation and hydration should not be overlooked for increased tendency to thrombosis during IVIG treatment for COVID-19 patients.

Conclusion

In summary, our patient developed systemic inflammatory response to SARS-CoV-2 infection despite moderate respiratory symptoms and in absence of other infectious pathogens.

The disease starts as a simple viral infection but may goes out of control after a while and progresses towards a deadly result with development of the cytokine storm and serious organ damage. Thus, the main prognostic factor in our cases may be early recognition of MAS and prompt treatment witch lead to improvement of clinical symptoms with full recovery.

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