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COVID-19: Cytokine Storm - The Egyptian Integrated Medicine

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History

By 1930s, the family of coronaviruses was initially detected whilst produced severe respiratory infection of hens. By 1940s, another two variants (animal) were isolated; the spreadable gastroenteritis virus (SGEV) and mice hepatitis virus (MHV) [1]. By 1960s,the human strains were revealed [2]. The first was isolated from influenza patients [3].

Human coronaviruses

So far six human species had been verified, with one type sub-classified into two various strains, leading overall to seven strains. Out of those, four strains yield to mild symptoms of the periodic flu:-

i. Type 1 coronavirus OC43, from the betacoronavirus class (β-CoV).

ii. Type 2 coronavirus HKU1, from the class with high resemblance to type1 (β-CoV) [4].

iii. Type 3 coronavirus 229E, from the alphacoronavirus class (α-CoV).

iv. Type 4 coronavirus NL63, from the alphacoronavirus class (α-CoV) [5].

The other three strains create potentially more severe manifestations; wholly are β-CoV strains:-

a. Severe acute respiratory syndrome coronavirus (SARS-CoV-1) 2003

b. Middle East respiratory syndrome-related coronavirus (MERS-CoV), 2012

c. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as "novel coronavirus 2019"

The death rate varies from 30% of those involved by (MERS-CoV-1 2012), to 0.1% of seasonal influenza affected patients [6].

Nomenclature & Morphology

"Coronavirus" is originated from the Latin word "corona", that means "Crown", indicating to the distinctive electron microscopic look of the infective form of this virus , which have a large spherical surface with a villous like projections creating a crown-like image or a solar corona [7,8] (Figure 1) Covered by a two lipid layers [9,10]. Surrounding a multiple copy of nucleocapsid (N) protein. Those double layers in addition to the membrane proteins and nucleocapsid guard the virus whenever outside the host cell [6,11]. It is a single-stranded RNA., one of the largest among RNA viruses, where the size ranges from 27 – 34 kilobases [1].

Transmission

Spreading of coronaviruses from person to other is thought to be through respiratory drizzle generated by sneezing or coughing amongst adjacent dealings [9] the interaction of the coronavirus spike proteins with the host cell receptor is crucial in defining the virulence and contagion of this virus [12,13].

Plagues of coronavirus

Severe Acute Respiratory Syndrome (SARS)

By 2003, the pandemic of severe acute respiratory syndrome (SARS) had been started in Asia; at that time, the virus was publically called SARS coronavirus (SARS-CoV), upsetting ≥ 8,000 persons with 10% fatality rate [14].

Middle East Respiratory Syndrome (MERS)

By September 2012, a novel variety of coronavirus was

recognized, primarily so-called Novel Coronavirus 2012, and currently named (MERS-CoV) [15]. By 28th September 2012, WHO apprised that virus did not seem to pass easily from person to person.17 But, later at 12th May 2013, a case of person-to-person spread was confirmed in France. By the end of October 2013, more than 124 cases and 52 deaths were recorded in Saudi Arabia [16]. In May 2015, another pandemic of MERS-CoV had occurred in the Republic of Korea, when a traveller from the Middle East, went to more than hospital appealing to manage his illness leading to one of the biggest outbursts of MERS-CoV outer the Middle East [17]. By the end of 2019, about 2,468 cases of MERS-CoV infectivity had been established, with a fatality rate 34.5% [18].

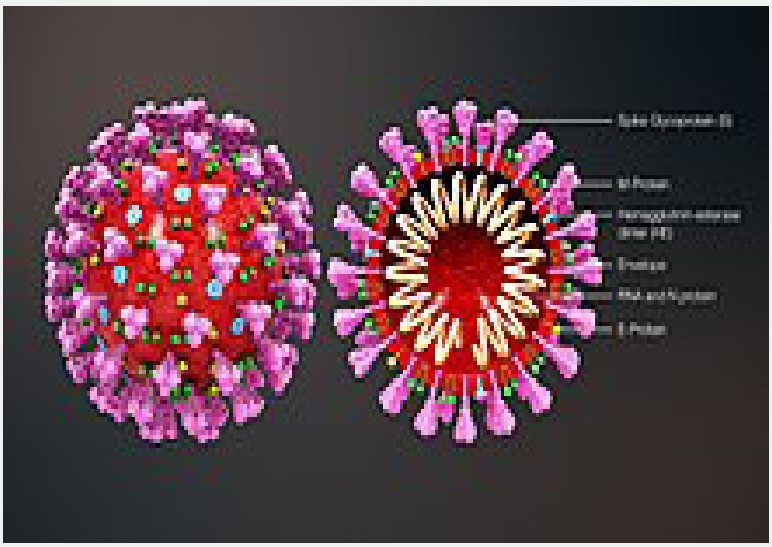

Figure 1: Cross-sectional model of a coronavirus 3. The diameter varies from 80 -160 nm.

Coronavirus disease 2019 (COVID-19)

At December 2019, a pneumonia outburst was recorded in Wuhan, China [19]. By the end of December 2019, this pandemic was tracked to a novel variant of coronavirus, [18] which was termed temporally by WHO as 2019-nCoV [20]. then renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. By 12th May 2020, there have been almost four million confirmed cases by coronavirus pandemic and about 282,000 confirmed deaths with fatality rate 6.89% [21]. This new variant has been known as a new strain of β-CoV with about 70% resemblance to the SARS-CoV. This virus almost identical to the bat corona strain, so it is broadly assumed to originate from bats. [25] This plague has resulted in travel limitations and countrywide lockdowns in numerous nations.

Cytokine Storm

57 years old physician, hypertensive, asthmatic with history of controlled rheumatoid arthritis. Contacted with a foreigner worker that presented to the physician' clinic by fever, pharyngitis and dry cough (later turned out to be corona positive by PCR). 2 days later our colleague started to develop high fever, cough that rapidly deteriorated to Acute Respiratory Distress Syndrome (later turned out to be Cytokine Storm Syndrome).and died within 48 hours.

It is a form of systemic inflammatory reaction that can be triggered by a diversity of reasons for instance; infections and some drugs [22]. it arises once huge amounts of leukocytes are stimulated by diseased cells that die by apoptosis or mortification overproducing inflammatory cytokines, which sequentially stimulate more leukocytes [23]. COVID-19 virus looks to motivate the inflammatory reaction through over stimulation of the pulmonary macrophages, across numerous processes [23].

NETs and Cytokine storm

While leukocytosis and neutrophilia are features of severe infection, COVID-19 is associated with neutrophilia that could be a cause of additional neutrophil extracellular traps (NETs). NETs are mesh structures of DNA and proteins ejected from the neutrophil that entrap pathogens. However, ejection of DNA to the extracellular space is not commonly well-known as a serious immune function. Severe COVID-19 is accompanied by a cytokine storm stamped by elevated cytokine plasma levels particularly IL1β,IL6, IFNγ, and TNFα. These inflammatory cytokines adjust neutrophil activity and encourage the release of chemoattractant. It is remarkable that NETs are capable of enhancing macrophages to produce IL1 β that augments NET formation. If a NET–IL1β. circle is triggered in severe COVID- 19, this will augment NETs and IL1 β. creation that might hasten the formation of microthrombi ,respiratory decompensation, and abnormal immune reaction. Therefore, blocking IL-6 trans-signaling and/or IL1β. might be an advantageous approach to target neutrophils and NETs in severe COVID-19 [24].

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NETs and extreme thrombosis

High blood levels of NETs have been revealed to play a crucial position in introducing and accumulating arterial and venous thrombosis. Severe cardiac and renal damages are frequent in patients with severe COVID-19 promoting the mortality incidence [25]. Once elevated intravascular levels of NETs disseminated, be able to initiate small vessels obstruction, causing multi organ injury [26]. however, the most prominent detection is the presence of platelet-fibrin thrombi in tiny arterial blood vessels; this vital inspection is acceptable with the clinical situation of coagulopathy which predominate in such cases and represents one of the focal objectives of treatment [27].

Signs and Symptoms

The chief manifestations are high fever, extreme fatigue, and nausea. In some cases this immune reaction may leads to multiple organ dysfunction syndrome (MODS) and eventually death, in addition to loss of appetite, myalgia and arthralgia, sickness, emitting, loose stool, skin eruptions, tachypnea, tachycardia, hypotension, seizures, headache, ambiguity, disorientation, illusions, shivering, and coordination deficit [23,28].

Lab Tests

Patients often show leukopenia, lymphopenia, thrombocytopenia, hypo-albuminemia and extensively elevated C-reactive protein (CRP), thrombin time, fibrinogen, blood sugar, lactic dehydrogenase (LDH) and liver enzymes. Moreover, excessive levels of IL6 (>24.3 pg/mL) and D dimer (>0.28 μg/L) were predictive of incident of terrible pneumonia; with a sensitivity of 93.3% when the two parameters were combined by parallel testing (IL6 or D-dimer) and a specificity of 96.4% when using a cyclic assessment (IL6 and D-dimer). High nitrogen levels in blood, elevated Serum ferritin, factor I deficiency, higher than-normal level of bilirubin is also prognostic (Table 1) [29].

Table 1: Comparison of coronavirus pandemics.

		MERS-CoV	SARS-CoV-1	SARS-CoV-2
Pandemic		2012, 2015, 2018	2002–2004	2019 – 2020
Origin		Jeddah, Saudi Arabia	Shunde, China	Wuhan, China
Established Cases		2494	8096 [29]	≥Two million [29]
Mortality rate		37%	9.2% [29]	6.4% [29]
Manifestations	**Fever**	98%	99–100%	87.9% [39]
	Pharyngitis	47%	29–75%	67.7% [39]
	Dry cough	72%	40–42%	18.6% [39]
	Difficult breathing	26%	20–25%	3.7% [39]
	Loose stools	21%	13–25%	13.9% [39]
	Artificial Ventilation	24.5% [41]	14–20%	4.1% [40]

Management

Along with the extremely infectious nature of SARS-CoV-2, Intensive endeavors have been and still paid to abort the SARS-CoV-2 spreading with its subsequent disaster; all are centralized on vaccine invention and/or unique antiviral treatments. Prior to this tools will be available, possibly more or less one year from now, lots of persons worldwide may developed infection due to nominal early manifestations in more than 80% of those affected; with concomitant progression of the fatal Cytokine Storm Syndromes (CSS) in some cases [29]. While waiting this vaccine and the novel antiviral treatment, as rheumatologists, we have abundant to present on the battlefront to identify and treat our patients with the available tool that we have to support their survives [30].

Cytokine storm seems to be a major cause of fatality in the "Spanish flu 1918" that murdered up to 100 million people globally and more recently the " hogs flu H1N1" and " chicken flu H5N1". Where, the fatality rate was commonly among youthful adults with seemingly robust immune responses to this virus infection [31]. The hemophagocytic disorders; macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) signify two clinically related CSS with an unidentified point of pathogenic commonality. The clinical demonstrations of wholly CSS could be extremely analogous, producing diagnostic ambiguity. However, physicians must escape the advocate to treat all CSS similarly, as their provoking inflammatory causes are very different. However, failure to recognize and determine the triggering factors may lead to possible lethal outcomes [32]. The dealing with CSS should be started by evaluation of hemodynamic constancy and the suitable intervention for each separate situation. Seriously followed by evaluation of coagulopathy state and organ dysfunction that seldom delivers definite diagnostic approach. Serum ferritin seems to be reliable biomarker for diagnosis and monitoring

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response to therapy in CSS patients [33].

Antioxidants such as N-acetylcysteine can suppress viral duplication, and sequentially diminishes inflammatory mediator's secretions. Corticosteroids have miscellaneous outcomes, due to the augmented hazard of hospital-acquired infections and its fatal sequences. However, the usefulness of corticosteroids in treatment of COVID-19 infected patients still debatable [34]. According to WHO regulations, corticosteroids are not compulsory only in patients with septic shock. The Italian Society of Rheumatology (SIR), ACR and EULAR recommend not to stop/reduce immunosuppressive treatment unless physician indication [34]. CytoSorb plasma sanitization 250 mL/min for six hours daily for one week, improving renal functions for dialyzed patients within 24 hours of CytoSorb therapy with prompt corrections of hemodynamic constancy, IL-6 levels, halted vasopressors, and full retrieving within 72 hours [35]. Cytokine targeting therapy as (IL-6) (IL-1), (IL-18) and interferon-gamma inhibitors have been described for some Chines patients with promising results in different forms of CSS [36].

IL-1 inhibitor has been reported as a highly effective treatment for many causes of CSS, predominantly rheumaticlogical disorder-related CSS treat children and adults. IL-6 inhibitor has been promoted for CSS management as a result of chimeric antigen receptor (CART)T cell treatment for resistant leukemia. Early data denoted encouraging results in a series of Chinese patients with extremely ill COVID-19 status treated with IL-6 blocker with high corticosteroid doses [37]. IL-18 inhibitors were described for a child with seldom autoinflammatory disease convoluted by CSS. IFNγ blocker was permitted by FDA for the management of familial hemophagocytic lymphohistiocytosis with secondary features of CSS. Finally, inhibition of JAK-STAT signaling as a line of management for CSS is recently studied [30].

The Italian Society of Rheumatology (SIR), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Thoracic Society (AIPO) have lately endorsed an open-label, phase-2 study for patients with COVID-19 to assess the effectiveness of colchicine as a part therapeutic algorithm. This trial ("Treatment with Colchicine of patients affected by COVID-19: a Pilot Study – COLVID-19") is currently under evaluation by the Italian Medicines Agency (AIFA) [34]. IVIg is extremely costly, however from the rheumatological point of view its anti-inflammatory influences prevail above its immunosuppressive efficacy rendering IVIg therapy valuable in some COVID-19 patients with bacterial infection and everywhere the autoinflammatory and autoimmune disorders are suspicious. IVIg could be strategic in some conditions with early seroconversion to suppress the FcR-induced antibody-related boosting and inflammatory cytokines release by macrophages. Heparin treatment seems to be accompanied by improved outcomes in COVID-19 patients with coagulopathy. 28-day fatality of heparin consumers were less than non-heparinised patients [37-40].

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