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Hypothesis

Clinical evidence and therapeutic treatments at the time of the coronaviruses responsible for SARS: a perspective point of view.

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Abstract: The clinical evolution of the COVID-19 patients highlights a significant minority of subjects with very rapid lethal outcomes with respect to the almost complete healing after coronavirus infections for most of the subjects involved. In addition, the reckless use of some drugs and therapeutic protocols that have not shown any efficacy in reducing mortality in those patients where the progression of the disease was unstoppable suggests a different interpretative way in the pathogenesis of severe cases. Starting from the clinical data already known for almost twenty years on the behavior of human SARS coronaviruses it is possible to advance a new hypothesis. The reference points taken into consideration are: i) the comparison of the histological evidence of the autoptic material; ii) the poor pharmacological response in subjects with severe phenotype of the pathology; iii) the common elements of endotheliitis that a subgroup of the population characterized by the unfortunate clinical outcome expresses during the evolution of the pathology. The tendency to develop a widespread, massive endothelial lesions not responding to any drug therapy or health treatment necessarily play a crucial role in the onset of the systemic and severe stage of the disease. The present hypothesis opens the door to a different therapeutic approach both to the full-blown phase of COVID-19 and to the preventive phase or the very first manifestations of the disease, suggesting greater attention to the protection of the vascular endothelium in subjects who already have it predisposed to the severe evolution of this ailment than to simple antiviral defense.

Keywords: Coronavirus; SARS-CoV-2; COVID-19; Lymphocytopenia; Endothelial cells; Endotheliitis; Prescriptive appropriateness; Personalized medicine

1. Introduction

The COVID-19 pandemic took the world's population by surprise, starting with the top decision-makers. The originality of the causal infectious agent (SARS-CoV-2 or 2019-nCoV) has ensured that each of us looks to the future with the presumption of a journey into the unknown with the sharpest technological and pharmaceutical weapons available. Despite this, apart from the initial hesitation of some political leaders, the answer was the lockdown. But what if this pathogen wasn't so completely unfamiliar? But what if such a new positive sense RNA betacoronavirus had left any clue of itself and its etiopathogenesis in any of its ancestors?

In late 2002, an unknown, highly virulent respiratory infection originally described as an outbreak of a severe atypical pneumonia appeared in the Guangdong Province of southern China. Such a severe acute respiratory syndrome (SARS) rapidly spread through Southeast Asia, Europe, and North America [1]. Even in that circumstance the state of pandemic was declared and the pathogen belonging to the coronavirus family (namely SARS-CoV) was held responsible.

Even if we grant for the sake of argument that there may be translational reasons justifying the substantial difference in size between the two infections [2,3], this is not the purpose of this note. The questions we will try to answer are: i) What scientific evidence have we inherited from previous human coronavirus-mediated diseases? ii) What is the current state-of-the art? iii) What approach will we take to best treat patients with COVID-19?

2. What scientific evidence have we inherited from previous human coronavirus-mediated diseases?

From the first cases of SARS, the clinical evidence revealed "worsening in week 2 is unrelated to uncontrolled viral replication but may be related to immunopathological damage" [4]. Going forward, a standard treatment protocol comprising antibiotics, a combination of ribavirin, and a 3-week step-down course of corticosteroids resulted in overall satisfactory outcomes [5]. To understanding SARS pathogenesis, manifestations include systemic vasculitis, apoptosis and swelling of endothelial cells and inflammation in various organs like heart, kidney, liver and adrenal glands. However, the absence of SARS-CoV in these organs where there is an abundant expression of ACE2 allows us concluding that the vascular abnormalities and inflammatory changes in various organs might be related to systemic toxic effects of immunopathological in nature elicited by SARS-CoV infection [4,6]. Therefore, patterns of disease progression in terms of response to different corticosteroid doses [7] and about the quality rather than magnitude of immune response [8] were of interest. To support the latter aspect, the predisposition of the host suffering of Kawasaki disease resulting in the vasculitis from an abnormal clonal expansion of CD8+ T cells in response to the viral agent [9,10].

In 2013, the published series ''From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses'' originated with the stated purpose "that more research is urgently needed to elucidate their replication mechanisms, identify potential drug targets, and develop effective countermeasures" taught us many lessons. However, the hope to change the attitude of researchers and funding policy makers this time around the expected return of a coronavirus pandemic remained in vain, at least until the COVID-19 pandemic state has been declared [11].

Eventually, it is worth noticing that over imposable pulmonary CT scan findings were described in SARS patients in 2003 [12], as well as the principal pathological findings associated with acute respiratory distress syndrome [13].

3. What is the current state-of-the art?

Today we are witnessing redundancy in research and reporting in COVID-19, many of which for the sake of publishing [14]. COVID-19 is a viral disease with multi-organ clinical expression where lung injury represents only the first phase of the disease. Nevertheless, in some subgroups of the human population COVID-19 dramatically evolves into a multisystemic disease [15] At this regard, an increasing awareness about COVID-19 immunity, inflammation and intervention is taking shape [16]. Moreover, different respiratory treatments for different phenotypes have been proposed [17], together with prediction models for diagnosis and prognosis [18].

From a cell biology perspective, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease [19]. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion [20]. This step, which is crucial in assessing the hazard of the disease in a subgroup of infected people, appears increasingly linked to an alteration of the endothelial cells that cover the entire circulatory tree, at an arterial, capillary and venous level [21]. Therefore, the claim suggesting "expanding our understanding of processes that mediate endothelial cell-cell communication is an important step in the approach to treatment of disease processes" is of paramount importance [22].

4. What approach will we take to best treat COVID-19 patients?

Starting from an acquired individual predisposition, it is precisely the ubiquitous presence of vascular endothelial cells in all the parenchyma and tissues of the body to determine modifications of their physiological pattern when they are attacked by the circulating virus [23]. In our opinion, among these changes, an increased degree of molecular freedom at level of membrane bilayer and endothelial cilia structures represents the key to interpretation [24]. From a clinical, laboratory and histopathological viewpoint the altered signal transduction events are the most important factor for the development of these widespread organ, polysystemic lesions and which also involve vascular parietal microthrombosis. Such a cellular adaptation generates an increase in the attraction and uptake stage with firm adhesion to the endothelial surface of the circulating blood bodies [25]. Among these, the lymphocytes and platelets are noteworthy: the former, responsible for a massive transendothelial transmigration and the latter through an induction to the phenomena of micro adhesion and the beginning of the thrombotic phases [26]. The first mechanism justifies the phenomenon of lymphocytopenia especially affecting the CD8 + (cytotoxic) and CD4 + subpopulations. In fact, despite the intense lymph node and bone marrow production of leukocytes, compared to a significant increase in circulating neutrophils which rapidly rise up to 90% of the white blood cells present in the blood, and temporary increases also in the circulating lymphocytes, the latter decrease both in percentage and in absolute numbers at values comparable to an acquired immunodeficiency syndrome. The drop is prevalent in the T lymphocyte line. This immediately has two effects:

1) The first is to have an intense perivascular lymphocellular infiltrate spread in all organs, with toxic effects on tissue parenchyma both for immediate hypoxemia which prevents organ cells from continuing to perform their normal functions and for direct damage by cytotoxic CD8 + lymphocytes at the level of the same parenchymal cells [4,16]. In fact, the function of these immune cells is to attack cancer and virus infected cells.

2) The second is an immunosuppression effect, also by reducing T helper lymphocytes and circulating natural killer cells. So, the response times of the immune system to COVID-19 are longer than the time expected for the body's normal antibody reaction to infections [27].

In this context, it is not clear why glucocorticoid drugs continue to be administered even at massive doses which further reduce the antiviral capacity of the residual lymphocyte population [28].

The thrombotic phenomena will then determine consequent diffuse microembolies since the attraction and surface ligands of the shear stress endothelial cells may or may not retain the thrombotic structures formed. This hypothesis is supported by the fact that despite the intense and sometimes preventive administration of heparin even in large doses, this does not prevent or limit the dramatic effects of the intravascular disseminated coagulation [29,30]. The precapillary terminal arterial vessels are extremely widespread, and they are necessarily present in all parts of the body because the microcirculation must touch all the cells of the body since the need of oxygen to survive. They have an endothelium consisting of simple monolayer paved epithelial tissue of mesenchymal origin whose functions are multiple. In addition to those of constituting an important blood pressure regulation organs actively participating in the changes of the blood flow at the terminal level through the phenomena of dilation and contraction of the vascular lumen, they also perform two important functions strictly connected to each other by the ability of their cytoplasmic membrane to easily adapt to these purposes: i) the mitotic function of cell duplication linked to neoangiogenesis and ii) the structural modification that occurs in the phase of the transcellular passage of lymphocytes from the vascular lumen to the perivascular parenchymal tissue. These two phases are necessarily regulated by physiological regulatory mechanisms. However, they can be modified and altered by various agents such as the toxic action generated by both infectious, especially viral, and autoimmune diseases, by chemical stress related to the metabolic or/and pharmacological action, by cellular senescence, just to name the most important [31-33].

According to the pathogenetic mechanism proposed by us for COVID-19, the clinical manifestations of the pathological pictures resulting from these endothelial alterations are mainly linked to the exaggerated lymphopenia that we find in phase 2, that is, in the phase of the multi-

organ tissue damage of which we have previously reported [21]. In this regard, it should be reiterated that this pathological situation cannot occur without an active participation of endothelial cells and therefore we will have to talk about endotheliitis, where the occasional binding phase of circulating lymphocytes immediately turns into a close adhesion of the former and in the subsequent passage transendothelial of the latter.

The accelerated migration stage is necessarily related to a mechanism of reduction of membrane rigidity in analogy to the rearrangement of molecules in the cholesteric, smectic, nematic phases of liquid crystals [34-36]. It allows rapid penetration of the large lymphocyte corpus (6-8 μm in diameter) through the thin barrier of the endothelial cell whose thickness does not exceed 1 μm [37]. Such a phase transition could occur due to the changes in the apical cell polarity that the mechanical force of shear stress, exerted by the blood flow on the lymphocyte closely attached to the endothelium, is plausibly capable of generating [38]. By doing so, the structure of the endothelial cytoplasmic membrane is modified, initiating a phagocytosis/exocytosis process and allowing a mitotic-like membrane separation [39]. These phenomena are functional and physiological in endothelial cells, but in this step of the pathology they instead become exaggerated and out of control, hence the rapid and massive passage of T-lymphocytes through the endothelial cell body into the perivascular tissue with all resulting pathological consequences [40].

Moreover, to further confirm the phase of "tight" adhesion between lymphocyte and endothelium there are some parameters that during COVID-19 should always be carefully monitored. They are the blood values of the calcium ion and haptoglobin. Ca^{2+} is also responsible for molecular adhesion when the relationship concerns actin filaments such as those present in the cilia present on the surfaces of endothelial cells [24,41]. In COVID-19 patients, calcemia is always below normal values. On the contrary, the presence of high haptoglobin values even in the absence of haemolysis phenomena suggest a liver release during the pathogenic challenge [42]. The role of haptoglobin in the genesis of thrombotic phenomena needs more in-depth studies.

5. Conclusions

On the basis of clinical observations from COVID-19 patients, the severity of COVID-19 is determined by the viral attack but becomes truly dramatic when it is associated with endotheliitis triggered by the presence of risk factors at level of vascular endothelium such as aging, and/or concomitant pathologies, therapies and immune-based diseases [43]. For this reason, we suggest that the therapeutic action in COVID-19 cannot ignore personalized medicine. The elderly, patients subjected for a long time to pharmacological treatments with a potential degree of endothelial toxicity and patients with diseases that act heavily on the endothelium and which generally manifest themselves as microangiopathies are at risk. In addition to both trying to limit the viral action with the use of effective antiretrovirals for RNA viruses and improving the antibody response with immunostimulation using specific monoclonal antibodies, it should mainly focus on the defense of patients with diabetes, scleroderma microangiopathy, Raynaud disease, obliterating arteritis, Kawasaki disease.

We are also convinced that if COVID-19 is observed with this attention to its deeper etiopathogenetic mechanisms, the social protection measures currently in place in this pandemic can be tailored and re-evaluated.

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