Editorial

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The post-COVID lung

Pulmón post-COVID

Pulmão pós-COVID

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One year after the beginning of the worst pandemic known to humanity in the 21st century, we are approaching 100 million infected globally and two million deaths, with new waves in the horizon and the worst of the epidemic yet to come soon this winter, although with the hope of an upcoming universal vaccine.

Many problems threaten contemporary society in the very near future in the economic, labor, social, educational and family fields, among others.

However, being this a fundamentally respiratory disease, it is the lung *per se* that is most threatened; the respiratory system as a shock organ, is the most favored target of infectious diseases as much as of noncommunicable diseases. It is clear that limited lung function is associated with poor quality of life and a heavy burden on society and health systems regardless of the cause.

We know that in the SARS pandemic in 2003, a milder version of lung disease, 4.6% of survivors developed chronic forms of lung disease and more than 30% did it after the MERS outbreak, a more serious version of respiratory infection produced by coronavirus.

The basic physiopathological mechanisms of multiorganic injury are complex and incompletely understood but include a direct cytotoxic effect after the coupling to specific hACE2 receptors and/or αvβ3 and αvβ6 integrins, with multisystemic expression, dysregulation of the renin angiotensin aldosterone system (RAAS), as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II, with effects of tissue injury and remodeling, inflammation, vasoconstriction and an increase in microvascular permeability, endothelial cell damage resulting in endothelitis, apoptosis and thromboinflammation with a decreased fibrinolysis and an increase in the thrombin production, complement activation and NET's formation, and finally a dysregulation in the immune response with over-activation of the innate immunity in a setting of lymphodepletion characterized by a profound T cell lymphopenia, inhibition of interferon signaling, hypereactive innate immunity with the consequent cytocine-release syndrome. All of this results in serious cellular damage and loss of physiological balance as ARDS progressively develops, with its pathological equivalent diffuse alveolar damage (DAD).

A large part, perhaps even the majority, of inflammatory diseases of the respiratory tract are caused by viral infection, but in COVID-19 other histological patterns have been described in addition to DAD, such as acute lymphocytic pneumonia, non-specific interstitial pneumonia and a type of organized pneumonia, and at the same time, different clinical-functional phenotypes (H&L) of interest for the management of mechanical ventilation in the ICU have been described, as well as more recently two different histological phenotypes of SARS-CoV-2 induced ARDS. One of severe viral infection, associated with alveolar damage, interstitial thickening, and increased αvβ6 alveolar integrins and other with few viral proteins but with a huge inflammatory and immune reaction, leading to severe alveolar damage, increased collagen deposition and finally fibrosis.

The histologic and cytologic phenotypes of viral diseases of the lung appear extremely diverse, depending mainly on the specific type of virus involved, and on the immunological responsiveness of the infected organism. In 1965, Liebow *et al* described the clinical and histologic picture of desquamative interstitial pneumonia (DIP). Histologically, DIP is manifested as diffuse interstitial infiltration of plasma cells and in follicular lymphocytic infiltration into predominantly peribronchial and subpleural lung tissue. This chronic interstitial inflammatory reaction parallels to some extent, the forms of peribronchitis we know from paramyxoviral infections, and therefore, a viral etiology was suspected, but never proven; although viral-like intranuclear inclusions were observed in some cases. Follow-up studies have shown that DIP, though initially unconnected with interstitial fibrosis, may show a progressive picture of diffuse fibrosing alveolitis (diffuse interstitial fibrosis), during its prolonged and often fatal course turning eventually into the known honey-comb pattern. SARS-CoV-2 by severely affecting the endothelial cell, it produces a greater amount of thrombosis compared to the rest of ARDS of viral or other origin.

Long-term disability imposed by usual ARDS has been documented for years in survivors, with only 80% of their expected FVC and 60% of distance covered in the 6-minute walk at 6 and 12 months, but perhaps

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the data with the greatest impact is that only 30 and 49% return to a working life at 6 and 12 months post-ARDS respectively, which clearly shows an incomplete recovery. Fatigue and dyspnea are the symptoms that show the highest prevalence percentage at discharge in both general ward and ICU patients in recent cross sectional evaluations of COVID-19 survivors, with almost 80% and 66% respectively. These symptoms persist in a large number of cases in the post-COVID follow-up, being the question why.

Again, the response has physiological bases, a restrictive syndrome of varying magnitude, with decreased lung compliance and increased work of breathing, limitation of the diffusion capacity, and alteration of the V/Q ratio, with a neuromechanical dissociation produced by a disproportionately high mechanical effort for the poor mechanical response obtained, which is the base of dyspnea, in a scenario of generalized muscle weakness and physical deconditioning, not to mention possible associated cardiovascular alterations and pulmonary hypertension, as well as relevant psychological aspects, where anxiety and insomnia stand out.

Some preliminary data suggest in COVID-19 survivors, a 30% of fibrotic changes, 47% limitation to gas diffusion and 25% with pulmonary restriction, being the functional impact greater in those with severe pneumonia compared to mild coronavirus disease; however, tomographic and functional sequelae have been demonstrated even in patients managed completely at home for apparently presenting with pictures of acute respiratory failure classified as less severe and that therefore were not generally exposed to high FiO_2.

There are several mechanisms described to explain the damage of the alveolar epithelial cell induced by viruses, that help to understand the evolution of some cases towards pulmonary fibrosis, a term commonly used to refer to interstitial lung disease. The viral replication that happens in the acute and chronic phase of the infection can cause epithelial injury by a cytophatic effect already mentioned or by inducing the production of cytokines, chemokines and growth factors. These soluble factors may be involved in the recruitment of fibrocytes (MCP-1 and SDF-1) or alternative activated macrophages (MCP-1, CCL-18), and like TGF-β, mediate the direct stimulation of fibroblast proliferation, production of extracelular matrix components, and induction of epitelial mesenchymal transition (EMT). Besides, increased viral protein synthesis may trigger endoplasmic reticulum stress, a process associated with apoptosis and expression of oxidants and inflammatory mediators; this stress may result from increased viral protein synthesis and the accumulation of misfolded proteins that provoke the so-called unfolded protein response.

In addition, the collapse and apposition of the alveolar walls due to a failure in the production of surfactant secondary to the destruction of epitelial cells by the virus, prevents re-epithelialization, a critical step in the process of repair and reconstitution of the alveolar epithelium by type II cell differentiation.

So, based on current knowledge about the functions of these mediators, there is enough evidence to suggest that viruses have in effect the ability of initiating or promoting processes that end in the development of interstitial lung disease, and might also serve as cofactors that increase susceptibility to other injurious agents in the form of a second hit, explaining why some responses persist long after the transient acute viral infection waned, a common observation in COVID-19 critically ill patients, where a natural history has been modeled based on the observation of multiple cases that can be hyperacute with a serious respiratory functional impact or follow an indolent course, which can eventually become biphasic or triphasic with devastating cellular and functional consequences that sometimes but not always end with death.

These facts give rise to the possibility of having a significant increase in cases of symptomatic progressive pulmonary fibrosis in the near future on a scale never before known, something like a COVID-22 pandemic.

Based on the experience of SARS and MERS at the beginning of the century, the impact could encompass an important number of cases with a severe and sustained alveolar inflammatory component, not necessarily limited to patients under mechanical ventilation; it is a fact that even some home-managed patients are developing this problem.

We know from the ARDS lessons that less than a week of severe inflammation is accompanied by approximately 4% of damage to the alveolar epithelium, although if the process lasts up to three weeks (as occurs in a significant number of patients with SARS-CoV-2 infection), this damage increases up to 24%, while if it extends beyond three weeks, there will be alveolar epitelial damage in up almost two thirds of all theses cases, even in absence of substantial parenchymal infection and promoting pulmonary fibrosis, the production of bronchiectasis and vascular damage.

This will surely place a significant burden on health systems throughout the world, also affecting the society quality of life, requiring due care and attention and research.

Humanity still has much to learn from this virus and reduce the margin for future surprises and misfortunes.

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