Radiation Induced Lung Injury (RILI) and COVID-19 Pneumonia: Are There Similarities by The Radiation Oncologist's Point of View?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), is a novel infectious disease responsible for a severe acute respiratory syndrome due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, which was firstly reported in January 2020 in Wuhan, Hubei Province, China, and then rapidly spread to other countries beyond China with a pandemic proportion in these last two years. In its severe lung expression, disease onset may result in death due to massive alveolar damage and progressive respiratory failure due to acute lung injury (ALI) which predisposes to fatal acute respiratory distress syndrome (ARDS). Autopsies reports describe a diffuse alveolar damage with vascular congestion, inflammatory cell population entrapped, thrombosis with hyaline membrane formation in the alveolar walls allowing to an irreversible lung destruction.

Altogether these findings remind the radiation oncologists many similarities with radiation induced lung injury which is a well-known side effect of radiotherapy for lung cancer. A fascinating hypothesis is that a common inflammatory paradoxical response of lung could be underlying the injury whatever the causes may be, virus, drugs or ionizing radiation. In this paper we will review the similarities between these two illnesses just going through the mechanisms of ALI-ARDS and the role of the most important immune cells and cytokines involved.

Introduction and Background

Radiation induced lung injury (RILI) and COVID-19 pneumonia could yield a fatal lung injury. The incidence of RILI is near 25% in lung cancer, 10% in mediastinal lymphoma and 5% in breast cancer [1,2]. It is well acknowledged that RILI is driven by the direct cytotoxic action of ionizing radiation on lung cells activating a self-sustaining inflammatory cascade. This last amplifies the alveolar damage leading to a lung failure which is related to its functional structure. In fact, lung shows a parallel like organ structure for which injury is related to damaged volume in terms of the amount of functional units involved in, regardless of the cause [3].

In RILI two variants have been described: the classic and the sporadic type. In the classic type, the damage is related to radiation altered variables as Mean Lung dose and the percentage of lung volume receiving 30 Gy, 20 Gy, 10 Gy, 5 Gy [4,5]. Furthermore, even patient related factor risks, as older age and comorbidities (diabetes, lung and heart disease and smoking) are accounted for [6].

As described in COVID-19 pneumonia process, also RILI evolves through 3 phases (latent, acute, chronic) [7]. Fibrosis occurs

within a few months after radiotherapy, leading to a respiratory impairment depending on its grade severity. This pneumonitis usually involves only the irradiated lung unlike the sporadic variety [8]. The sporadic type of RILI is a rare acute phenomenon occurring a few weeks after thoracic radiotherapy in less than 10% of treated patients. In this case, the inflammatory features occur outside the radiation fields, involving both lungs and mainly evolving in fatal acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). As hypothesized by Morgan et al, this event seems to be related to a hypersensitivity mechanism which amplify the lung damage over the irradiated lung [9]. However, in both cases an extensive inflammatory damage may lead to a fatal and severe pneumonitis with similar findings of COVID-19 pneumonia as we describe below.

Laboratory findings

In RILI patients in the early stage may have a normal or decreased total white blood cell count and a decreased lymphocyte count. Subsequently, neutrophils arise with lymphopenia which is considered a negative prognostic factor. Moreover, increased values of lactic dehydrogenase (LDH) and muscle enzymes could be observed. Anemia or thrombocytopenia could develop later.

In critical patients, the thrombogenic biomarker D-dimer may increase a lot, the counts of blood lymphocytes back down persistently, platelet count is reduced and laboratory alterations in biomarkers of multi-organ injury become prominent. Bronchoalveolar lavage (BAL) fluid shows inflammatory cells with activated lymphocytes, while pyrogenic cytokines such as interleukin-6 (IL-6), IL-10 could be also detectable [10]. Clearly swab and BAL are negative for opportunistics or viruses.

In most patients with COVID-19 infection, standard blood investigations reveal normal or decreased leucocytes, and lymphocytopenia. As in RILI, in COVID-19 pneumonia it can be found increased level of LDH, indicating a poor prognosis [11]. Similarly, in severe COVID-19 pneumonia elevated D-dimer can be observed. This finding has been found as an accurate biomarker for predicting mortality [12]. Furthermore, in the inflammatory phase, there is a systemic elevation of the pyrogenic cytokines such as IL-6, IL-10, and tumor necrosis factor α (TNF-α), whereas IL6 is an adequate predictor of severe disease [13]. In critical infected patients, neutrophilia, thrombocytopenia, increased plasma blood urea nitrogen and creatinine are also documented. Swab, real time polimerase chain reaction or BAL fluid are mandatory to improve accuracy of virus detection [7].

Chest computed tomography (CT) scan findings

Chest CT scan plays a key role in detecting the damage of these pneumonia in all phases. CT findings change over time showing different patterns according to the severity and phase of evolution. In classic RILI, chest CT scan shows well determined signs in the irradiated field involving the irradiated lung along the beam pathways. In sporadic RILI, the patterns of CT findings are spread in both lungs and outside the radiation ports. Findings vary from homogeneously increased density, patchy consolidation, to a combination of homogeneously increased density and patchy consolidation. However, the radiological characteristics in the initial phase of RILI remain the ground glass opacities (GGOs) with the patchy areas of consolidation in the peak phase [14,15].

In severe RILI, the thickened pulmonary interstitium and the crazy paving pattern are the main described features leading to a linear scar when fibrosis is consolidated. Air bronchograms are also accounted. In cases evolving into ARDS the finding of whited out lung has been described (Figure 1) [16].
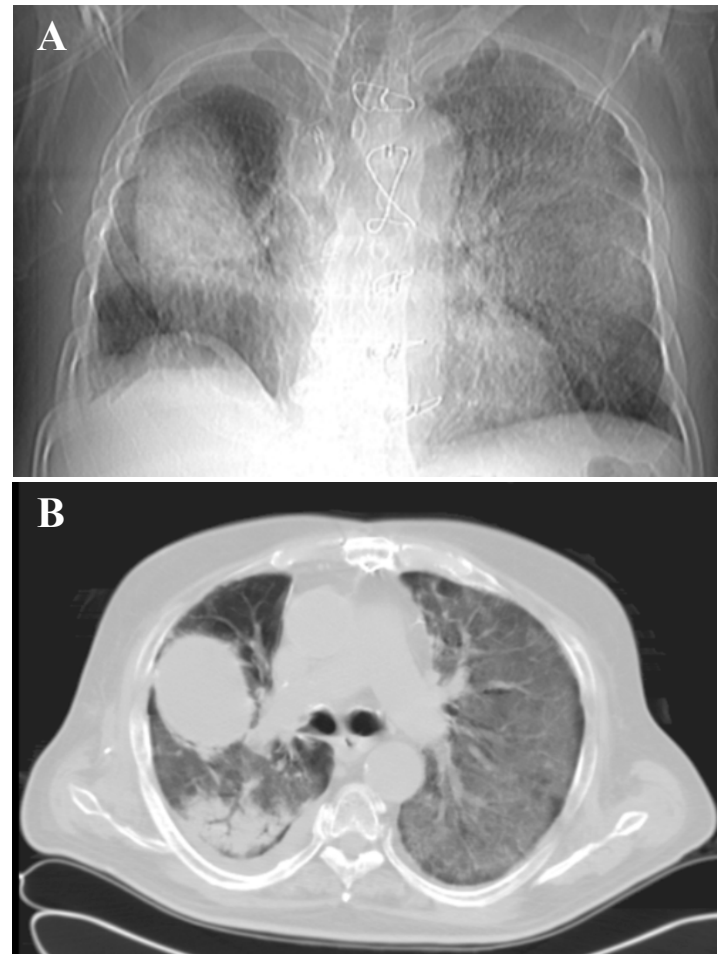
Figure 1: Whited out lung in ARDS related to RILI after radiotherapy, panel **A** – Chest Xray, panel **B** - CT scan.

As in RILI, among typical and atypical CT findings in COVID-19 pneumonia, GGOs and consolidations areas have been found as the predominant signs [17].

Recently Carotti et al. have provided an interesting summary of the main aspects and evolution of pulmonary lesions in this disease [18]. As a result, the hallmark of COVID-19 has been considered the bilateral presence of patchy GGOs that may coalesce into dense, consolidative lesions, with a predominantly peripheral distribution under the pleura and along the bronchovascular bundles. As in RILI, with the disease progression, in the severe stages, chest CT shows diffused consolidation including linear opacities, "crazy-

paving" pattern, "reversed halo" sign and vascular enlargement. Nonconsolidated areas of the lung appear as patchy ground glass opacity. When most of the lungs are involved, a "whited out lung" may occur (Figure 2) [17,18].
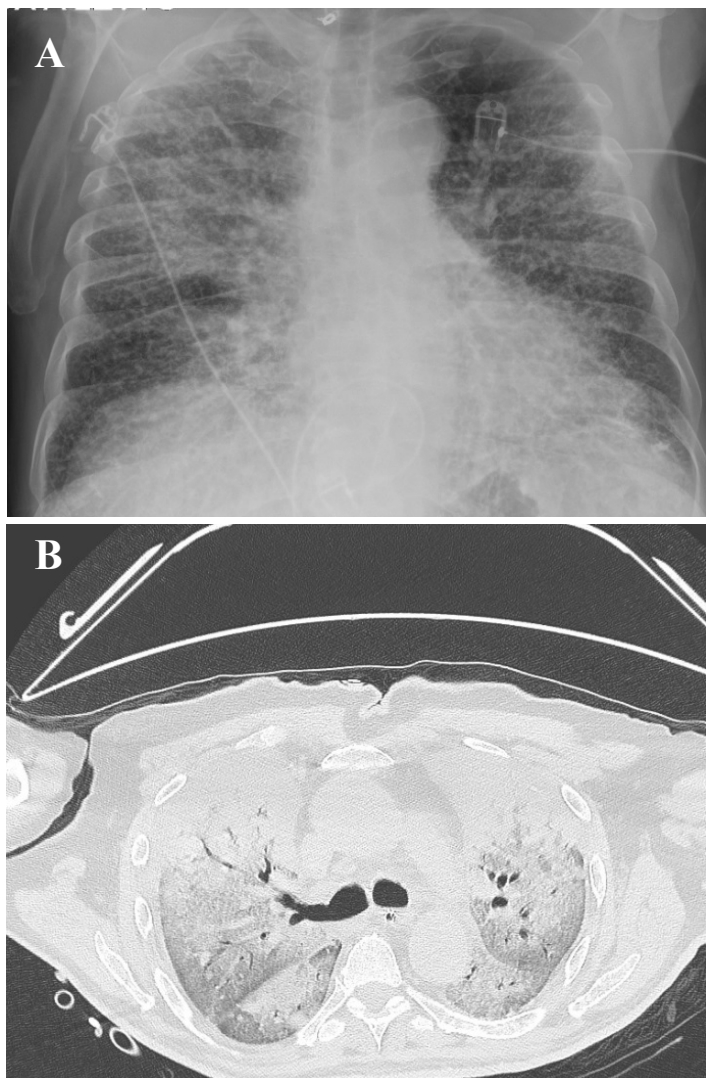

Figure 2: Whited out lung in ARDS related to COVID-19 pneumonia, panel **A** – Chest Xray, panel **B** – CT scan.

After pneumonia remission, residual lung injury could be detected on CT scan, such as architectural distortion, reticular lesions, traction bronchiolectasis, GGOs, mosaic attenuation, and honey combing [19], showing a similarity with radiation induced pulmonary fibrosis.

Autopsy reports
Lung autopsies show a pictorial variety of findings with lung architectural damage, oedema, hemorrhages, thrombosis with destroyed cellular stromas and inflammatory entrapped cells.

Concerning RILI, animal models and reports on a series of open-lung biopsies taken from within the field of irradiation in irradiated patients with clinical pneumonitis have shown edematous pulmonary interstitium with many cellular elements as the dominant finding in RILI acute-phase pneumonitis.

The neutrophil load is the dominant inflammatory cell pattern in radiation lung damage, but in biopsy samples from patients who had radiation pneumonitis at various times after treatment, a large amount of mononuclear cells rather than neutrophils has been found living in the pulmonary interstitium. Septal fibrosis and alveolar congestion are the main findings at the time of completion of the radiotherapy and at six months post irradiation [20].

In the chronic phase the development of fibrosis is characterized by the presence of hyaline membranes, marked cytological atypia within hyperplastic pneumocytes, and vascular changes with clots and microthrombi in the vessels [21].

Going to the inflammatory lung damage by SARS-CoV-2, in biopsy samples taken from lung of deceased patients, histological examinations have shown bilateral diffuse alveolar damage with cellular fibromyxoid exudates. In both lungs massive exfoliation of pneumocytes and hyaline membrane formation have been found typically in the case of ARDS. Further, diffuse microvascular thrombosis has been widely described [22]. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli have been identified in the intra-alveolar spaces, showing viral cytopathic-like changes. Viral traces have been found inside these cells [23,24].

As a conclusion the lung damage seems to be the result of the cytopatic effector cause (radiation or virus) and the lung inflammatory up front high response [23,24].

ALI and ARDS as a common fate of both diseases
Thus, regardless of the cause, inflammation and alveolar damage are the common features in both cases. ALI and its more severe form ARDS are syndromes of acute hypoxemic respiratory failure resulting from a variety of direct and indirect injuries to the lungs [25]. Inflammation due to neutrophil and platelets activation is the key in the pathogenesis of ARDS with the increased capillary permeability as the hallmark [26]. Many other factors released from damaged cell plasma membranes may have a role such as endothelin-1, angiotensin-2 and phospholipase A-2 [27]. All these factors increase the vascular permeability destroying the micro-vascular architecture, thus enhancing the lung damage and its functional failure.

Damage of the capillary endothelium and alveolar epithelium in correlation to impaired fluid removed from the alveolar space result in accumulation of protein-rich fluid inside the alveoli. Thereby a diffuse alveolar damage, with a release of pro-inflammatory cytokines, such as TNF, IL-1 and IL-6 occurs [28]. In this context, the Renin-Angiotensin-Aldosterone system (RAAS) seems to impact on vascular functions in the organ damage and pathologic tissue remodeling, which includes cellular hypertrophy, proliferation and/or migration, and extracellular

matrix proliferation. In turn a surfactant dysfunction, endoplasmic reticulum stress. Cell death is the common consequence of lung damage involving the cytokine and chemokine released from activated innate and adaptive immune cells, including neutrophil-attracting chemokines. As a result, proinflammatory cytokines and tissue-infiltrated neutrophils continue to sustain the lung injury as in vicious circle [29]. Injured cells in turn release danger signals such as uric acid and activate the inflammasomes, further promoting inflammatory responses and aggravating lung injury leading to a massive lung involvement. At last, barotrauma due to inappropriate ventilation therapy protocols may enhance the lung injury leading to a complicated clinical picture and autopsy reports as occurs in ventilation induced lung injury [30].

The damage in the RILI model

The RILI model is based on the theory by Rubin et al reporting a radiation induced orchestrated pulmonary response, scattered by the reactive oxygen species (ROS) generation, followed by various activations of signal transduction pathways inducing processes, leading to a replacement of damaged cells, influx of inflammatory cells from peripheral blood and cytokine production, and development of radiation complications due to fibrosis [21].

Ionizing radiation is known to generate tissue ROS that damage DNA molecules and cause clonogenic death in alveolar epithelial cells through the release of damage-associated molecular patterns (DAMPs), irrespective if the dying cells are malignant or not. Thus these events trigger a distinct state of activation in endothelial cells as characterized by upregulation of adhesion molecules and a cytokine/chemokine expression pattern dominated by IL-6 and specific chemokine ligands, leading to sequential recruitment of neutrophils and monocytic cells in vivo [31].

Then follows the antigen presenting cells activities, T-lymphocytes chemiotaxis and subsequent immune-modulation and a dysregulation of a number of fibro-inflammatory molecules.

In addition, adhesion molecules, other cytokines (such as transforming growth factor-β – TGF-β), growth factors, transcription factors, ROS and reactive nitrogen species are involved with a dangerous effect for lung cells. Among cytokines, TGF-β1 roles in RILI evolving into fibrosis [32].

All these molecular dysregulations and the lethality of ionizing radiation to type 1 pneumocytes, alveolar epithelial and endothelial cells could trigger loss of barrier function and structural denudation to promote recruitment of inflammatory cells, activated alveolar macrophages and platelets, uncontrolled matrix turnover, and aberrant repair evolving into ALI and then ARDS [33].

The damage in the Virus Induced Lung Injury (VrILI) model

A similar orchestrated response could sustain the COVID-19 pneumonia evolution. In the VrILI, it has been speculated that SARS-CoV-2 infects lung alveolar epithelial cells by receptor-mediated endocytosis in association with angiotensin converting enzyme II (ACE2) through the Spike (S) protein [34]. The S protein of Coronavirus binds to the host cells by ACE2 receptors, fusing to the membrane and releasing the viral RNA. This step promotes the pathogen-associated molecular patterns (PAMPs) that are detected by the pattern recognition receptors, then the viral RNA enters the cell trough the endosome [35].

Virus-cell interaction produces the host's immune system activation, inducing the recruitment of inflammatory cells with subsequent production of pro-inflammatory cytokines and chemokines, as well as the maturation of dendritic cells. Furthemore, the immune system is repeatedly activated, due to the rapid viral replication, culminating in an uncontrolled and exacerbated response [36].

Several cytokines and chemokines have been found in the plasma of observed COVID-19 patients, including IL-6, IL-10, macrophage colony-stimulating factor, hepatocyte growth factor, interferon-γ (IFN-γ) and TNF-α.

Among these cytokines the release of IFN dependent on TNF-α induces pneumocytes apoptosis, activating cell death receptors [37].

In addition, an increased capillary permeability occurs due to chemokines and others cytokines released by macrophages and responsible for neutrophils recruitment [38].

The continuous neutrophil degranulation produces permanent damage into pneumocytes and endothelial cells, breaking alveolar-capillary barrier [39-41].

In summary, the virus particles invade the respiratory mucosa firstly and infect other cells, triggering a damage to the barrier with a series of immune responses and the production of cytokine storm in the body, which may be associated with the critical condition of COVID-19 patient leading to a severe respiratory failure like ALI - ARDS.

Repair mechanisms and main features in the paradoxical response to lung injury

Lung is functionally considered a parallel-like organ [42]. Indeed, the functional impairment is related to the volume of damaged lung because of a low cell turnover rate and facultative post-injury regeneration capacity of adult lung epithelial cells. As a matter of fact, the alveolar epithelial cells have membrane lipid folds that partially mitigate the likelihood of cell breakage at non-injurious lung volume changes, or in case of fix small disruptions at the plasma membrane [33]. But when cell stress failures occur at high lung parenchymal units or when exposed to excessive biotoxins as could be in radiation or viral infection, as a result, the alveolar epithelial and endothelial cells are highly wounded. As a paradoxical effect, in attempt to contain the lung damage, all these events consequently trigger an extensive cell death without an effective repairs so cellular and membrane debris spread a paradoxical self-sustaining inflammatory response as a vicious circle which could have systemic involvement [32].

In brief, the lung repair machinery starts by the alveolar wall which is a part of the gas-exchanging region, so called the alveolar–capillary barrier which comprises pneumocytes types I and II, alveolar macrophages and the endothelial cells of the capillaries, as the basement membrane between these cells. The interstitium of the alveoli is occupied by resident fibroblasts and forms an extracellular matrix. Once the barrier of lung tissue is damaged, a large number of blood exudate and inflammatory cells accumulate in the alveolar cavity, which then aggregates numerous fibroblasts and induces their differentiation into myofibroblasts [43].

Activated myofibroblasts then secret angiotensin and hydrogen peroxide, which in turn induces apoptosis of alveolar epithelial cells. In the early stages of tissue injury, damaged epithelial and endothelial cells release high amounts of inflammatory mediators that promote the activation of a coagulation cascade through platelet activation and aggregation. This process triggers the formation of clots to obtain a fast hemostasis. Platelet degranulation improves vasodilation, increasing blood vessel permeability and permitting the recruitment of inflammatory cells to the site of injury. The leucocytes also secrete cytokines and chemokines such as IL-1, IL-6 and TNF that amplify inflammatory response and promote the recruitment and proliferation of both endothelial cells and fibroblasts useful in the late repair mechanisms [32].

Renin-Angiotensin II-aldosterone system

About the RAAS role in lung damage, angiotensin II has been considered as a pro-inflammatory mediator that stimulates the production of other growth factors and vasoconstrictors, trans activates several growth factor receptors, and influences cell contraction, cell growth, apoptosis, differentiation, and gene expression [44].

By rat's models in the early phase of RILI, it has been shown an increase of the local angiotensin II levels which seem to have a more important function than the circulating angiotensin II in the regulation of tissue injury, due to a strong bind to high-affinity receptors on the cell surface, as the angiotensin receptor [45]. Moreover, angiotensin II stimulated TGF-β1 secretion and activation and enhanced TGF-β1 signaling [46,47].

As a confirmation, treatment with aldosterone-salt seems to be able to induce a proinflammatory/fibrogenic phenotype, it consists of a coupling of an inflammatory response and the release of several proinflammatory mediators, which include an adhesion molecule, a chemokine, and a proinflammatory cytokine. In addition, the aldosterone-salt-induced proinflammatory phenotype seems a necessary requisite to the accumulation of fibrous tissue at vascular and non-vascular sites of injury to the heart [48].

With this regard, is reported that vascular cells are steroidogenic with their own responding system by detecting the specific mRNA that encodes the key enzyme for the biosynthesis of aldosterone in both endothelial and smooth muscle cells cultivated from a human pulmonary artery [49]. Thus, therapies targeting RAAS or TGF-β1 pathways might provide effective strategies to treat the inflammation or slow the progression of fibrosis in RILI.

Alveolar Epitelium

The epithelium is the first line of defense. Following the epithelial death, injured epithelial cells respond rapidly in attempt to close the developing wounds through a process that involves cell proliferation, spreading and migration. Loss of epithelial cells may occur via apoptosis or necrosis [35]. Apoptosis is characterized by DNA fragmentation and cellular involution and can be triggered by external pathways mediated by a family of death receptors.

This event could be evocated in the influenza viruses (IV) pneumonia. Indeed, it has been found that IFN-β produced by alveolar macrophages significantly contributes to IV-induced alveolar epithelial cell injury by autocrine induction of the proapoptotic factor TNF-related apoptosis-inducing ligand [50].

The epithelial cell death via necrosis results in the liberation of cellular contents into the environment, which can lead to further injury and inflammation. A frequent cause of necrotic cell death is disruption of the plasma membrane by toxic agents or by stress failure of the plasma membrane. This latter mechanism has been identified in lungs ventilated with high tidal volumes [51].

Plasma membrane injury results in intracellular components escaping the cell, and poisonous extracellular components flushing into the cell, leading to compromised cellular functions or even cell death. Inflammation is propagated from the initial site of tissue injury or infection by the diffusion of small molecules that act locally and more distantly.

The pulmonary epithelium also produces several proinflammatory cytokines and chemokines [52]. *In vitro*, type II epithelial cells can produce greater chemoattractant signals than alveolar macrophages dependent on TNF-α and IL-1β [53]. Furthermore, the epithelium also expresses other proteins, such as heparin sulphate proteoglycans, which help bind and restrain chemokines to aid in leukocyte retention and migration [54].

Chemokines family is further subdivided based on the presence or absence of a Glu-Leu-Arg (ELR) motif preceding the first cysteine residue. In general, ELR-positive chemokines regulate neutrophil migration, and the ELR-negative chemokines modulate mononuclear leukocyte migration [55].

Migration and proliferation of type II alveolar epithelium is required for regeneration of the alveolar architecture, and several mediators are critical for proper, rapid re-epithelialization of the alveolus like the matrix metalloproteinase-7 [56]. This is a metalloproteinase with a role in facilitating neutrophil efflux. In the absence of this proteinase, alveolar and airway repair is markedly impaired. Furthermore, some cytokines promote epithelial cell migration and alveolar epithelial repair (including TGF-α and keratinocyte growth factor – KGF). KGF has been shown to induce alveolar type II proliferation *in vitro* and *in vivo,* and it reduces disease severity and mortality of murine models of ALI [57].

Platelets

Despite their morphology, platelets have not only hemostatic functions, but they share other activities like inflammatory and immune capabilities. Recent observations have demonstrated that activated platelets are critical links between the hemostatic and immune systems, with the capacity to carry out recognition and signaling functions, transfer biologic information, and orchestrate complex physiological and pathological inflammatory responses [58]. Platelets have intimate interactions with the pulmonary vasculature in the healthy and diseased lung. There is evidence that mammalian lungs contain an intravascular pool of "marginated" platelets that can be released into the systemic circulation by ventilatory and pharmacological maneuvers. It is likely, however, that most platelets pass unimpeded through alveolar capillaries in tidal breathing under physiological conditions because of differences in size of platelets and the vessels (in humans, the mean platelet diameter is ~2.25 μm; the mean alveolar capillary diameter is 7.5 μm) [59]. In contrast, activated platelets interact with alveolar capillaries, endothelium in larger pulmonary vessels, with other platelets, and with leukocytes in the pulmonary blood in lung and systemic inflammation and injury, initiating or amplifying lung dysfunction and damage [60].

Observations from experiments with cultured endothelium and isolated lungs have provided evidence that the pool of resident platelets are involved in maintenance of basal pulmonary endothelial barrier integrity and are required for preservation of an element of restricted alveolar capillary barrier permeability to protein in inflammatory or injury states. Paradoxically, however, they also contribute to disruption of endothelial barriers and vascular leak [61]. In fact the accumulation of platelet-leukocyte aggregates and free platelets in inflamed or injured alveoli could have multiple consequences, including fibrin deposition and amplification of inflammation through the DAMPs or PAMPs pathways [62]. A recent experimental study reported that chemokine C-C ligand 5 (CCL5) released from platelets triggers alveolar macrophage activation, macrophage secretion of IL-8, and neutrophil recruitment to the alveoli in a sepsis model [63]. Signals to alveolar macrophages by CCL5 or other soluble mediators may be delivered by platelets in the alveolar space, by intravascular platelets, or by platelets in both compartments [64].

Platelet-leukocyte aggregates in the peripheral blood, in pulmonary microvessels or in the alveolar compartment, have the potential to further amplify and drive inflammation by mediating synthesis of additional mediators. It is well acknowledged that the changes in the plasma membranes of deposited spread platelets facilitate steps in the biochemical coagulation cascade, amplifying thrombin generation and conversion of fibrinogen to fibrin. Recent in vitro observations demonstrate that human platelets can synthesize tissue factor, a key procoagulant protein, and B-cell lymphoma-3, an intracellular protein that influences fibrin retraction [65].

Another component appears to be interactions of activated platelets with leukocytes in inflamed vessels, triggering a release or generation of barrier-destabilizing factors by platelet-dependent activation of the leukocytes or by reciprocal signaling as demonstrated in murine models. In these models, platelet depletion seemed to improve indexes of increased alveolar capillary permeability while neutrophil depletion or interruption of platelet-neutrophil interactions also had a similar effect [66]. Further myeloid leukocytes (neutrophils and monocytes), which are critical innate immune effector cells, are recruited into clots exerting multiple prothrombotic activities. These include tissue factor synthesis, synthesis of IL-1β and TNF-α, and formation of neutrophil extracellular traps, which paradoxically amplify the lung injury [67].

Macrophages

Macrophages represent an essential host immune defense mechanism against xenobiotics. This population consists of two different types: alveolar macrophages and inflammatory macrophages. The alveolar macrophages are resident tissue elements which originate mainly from embryonic precursors during development and self-renew during adulthood [68]. They play a key role in recycling of surfactant and in the pulmonary immune defense, acting as sentinels, strategically located to respond to invading pathogens and inhaled toxicants. In healthy lung, alveolar macrophages are sustained in a restrained state by their interaction with the alveolar epithelium and molecules such as surfactant protein D, IL-10, TGFβ [69].

Evidence suggests that alveolar macrophages play a role in triggering acute inflammatory responses to noxious stimuli through their death, which is thought to be key in triggering the recruitment of circulating monocytes and neutrophils to sites of injury and infection and initiating inflammatory responses [70]. There is increasing recognition that macrophage death and inflammation reciprocally affect one another, forming an autoamplification loop which exaggerates inflammation.

They have the capacity to recognize danger signals (as DAMPs) released from injured and/or necrotic epithelial cells and initiate the inflammatory phase of wound healing. DAMPs are recognized by macrophage receptors. Binding to these receptors a signaling process starts. resulting in the release of inflammatory mediators and chemokines and the recruitment of inflammatory cells to sites of injury [71].

Alveolar macrophage activation following pulmonary exposure to noxious stimuli can also occur via inflammasomes. The inflammatory macrophages are largely derived from blood and bone marrow precursors, showing specific chemokine receptors and accumulating in tissues in response to chemokines released from injured cells and tissues [72].

Once localized at sites of tissue injury, these newly recruited macrophages become activated by mediators they encounter in the tissue microenvironment developing into subpopulations, exhibiting varying levels of pro-inflammatory/cytotoxic (M1) or anti-inflammatory/wound repair (M2) activity [73].

The process of macrophage activation into M1 and M2 subsets is tightly controlled and involves specific signaling pathways and transcription factors, and posttranslational regulatory networks.

The activity of M1 macrophages is balanced by M2 macrophages, which downregulate inflammation and initiate wound repair. These actions are mediated by anti-inflammatory cytokines (as IL-4, IL-10, IL-13), pro-resolving eicosanoids (as lipoxins and resolvins), and growth factors (as TGFβ, vascular endothelial growth factor, fibroblast growth factor, platelet derived growth factor) [74].

The resolution of acute injury and the return to normal lung structure and function is an active coordinated process, largely mediated by M2, through counter-regulatory mechanisms, suppressing the release of proinflammatory mediators and activating tissue repair processes. M2 have been reported to increase in the lung following exposure of animals to ozone, mustards, bleomycin, particulate matter, radiation, endotoxin, cigarette smoke, silica and asbestos. M2 macrophages are also involved in the development of T helper type-2 lymphocytes which produce pro-fibrotic cytokines and suppress T helper type-1 response. Moreover, they express immunosuppressive molecules such as IL-10 and arginase-1, the latter being especially important for the synthesis of l-proline, an amino acid required for the production of collagen by activated myofibroblasts [69].

Neutrophilis
Neutrophils seem to play a key role in the progression of ALI and ARDS [25]. In patients with ARDS, the concentration of neutrophils in BAL fluid correlates with severity of ARDS and outcome, whereas the severity of lung injury seems to be reduced by neutrophil depletion as observed in mice model [75]. The neutrophil recruitment into the lung takes place in the small capillaries in a sequence of activation, sequestration from blood to interstitium and transepithelial migration. After activation, recruited neutrophils are able to egress from the vasculature and migrate through the interstitium into the alveolar space through the alveolar-capillary barrier [76].

Neutrophil infiltration of the lung is controlled by a complex network of chemokines that are released by a variety of cell types. Among them, alveolar macrophages are a major source of chemokines in the alveolar space, producing IL-8, growth-regulated oncogene related peptides and CXC chemokine lingand 5 (also known as epithelial neutrophil-activating protein) [77].

Neutrophils contain four granule subsets: azurophilic (also known as primary) granules, specific (also known as secondary), gelatinase granules (also known as tertiary) and secretory vesicles [77].

Primary and secondary granules are discharged once the neutrophil has entered the tissue. Secretory vesicles are rich in membrane-bound receptors, but granules released at later stages mainly contain proteases and antimicrobial polypeptides. Besides its important antimicrobial functions, the neutrophil elastase holds

an evident role during the pathogenesis of lung injury in the recruitment of them. For example, elastase levels are increased in BAL fluid and plasma of patients with ALI and ARDS. These elevated levels correlate with the severity of the lung injury [78].

Mononuclear stem cells (MSCs)
MSCs are a heterogeneous population of differentiated cells, committed-progenitors and stem cells with different multi-potential properties and several diversified roles in tissue repair [79]. Their role, in tissue repair is replacing damaged cells and modulating immune and stromal cells functions. They also promote cell survival and repair of damaged resident cells, thus enhancing the regeneration of injured tissue. In addition, they exert documented immune-regulatory effects on the immune system, acting on both adaptive and innate responses. MSCs suppress T cells, reduce B cell activation and proliferation and actively interact with macrophages, exerting both anti-inflammatory and pro-inflammatory effects [80]. Finally, MSCs are highly metabolically active and are able to secrete chemokines, cytokines growth factors and paracrine molecules as exosomes delivering soluble factors, which appears to play a key role in repairing injured tissue caused by different pathological conditions [81].

A population of c-kit positive stem cells in the human lung located in the distal lung, the bronchioles and to a lesser extent the alveoli have been recently identified, demonstrating the ability to regenerate all components of an injured mouse lung [82]. It is not known whether the regenerative capacity demonstrated by these c-kit-positive stem cells can be replicated in human lung, and indeed whether the tissue produced will function as normal lung. This finding might have a therapeutic silver lining [83].

IL-6
High levels of IL-6 are found in ALI-ARDS but its role remains controversial. It is acknowledged that in patients with ARDS, the elevation in baseline plasma levels of IL-6 predicted a poor survival [84]. A higher BAL fluid levels indicate a pulmonary, rather than systemic origin for these cytokines in ARDS pathology. IL-6 is a multifunctional pleiotropic cytokine with multiple functions during inflammation as stimulating growth and differentiation of B and T lymphocytes, driving leukocyte trafficking and activation, and inducing production of acute phase proteins by hepatocytes [85].

It is synthesized by a variety of cells in the lung parenchyma, including alveolar macrophages, lung fibroblasts, and type II pneumocytes. IL-6 is also produced in response to the production of various other cytokines (IL-1, IL-17 and TNF-α) [86].

The precise role of high levels of IL-6 in predicting radiation pneumonitis and therefore its value as a biomarker have been debated as a significant predictor factor. To this concern, Chen et al. consider IL-6 to be an important and valuable biomarker in connection with radiation-induced pneumonitis as they found significantly higher pretreatment levels of IL-6 in blood specimens of patients who subsequently developed radiation pneumonitis [87].

A recent study founds IL-6 levels to be a good prognosticator for progression to severe disease and in-hospital mortality, and probably the best prognosticator for negative outcome [88,89].

At the same way a meta-analysis published in 2021 considers IL6 as an adequate predictor of severe disease [13].

Therefore, these studies support the hypothesis that the cytokine storm induced by SARS-CoV-2 could be strictly related to IL-6 and confirm the hypothesis the anti IL6 drugs could be a valid therapeutic option, for improving outcomes in COVID-19 patients.

Conclusions

Assuming that ALI-ARDS is a paradoxical response triggered by lung injury, RILI and in VrILI should be considered as two sides of the same coin. Knowledge of the main repair mechanisms and main actors in answer to the alveolar damage could be useful in the attempt to find targets therapies like nebulised heparin, [90,91] elastase inhibitors [92], inhibitors of Il-6 signal transduction [93, 94] and as more recently aimed, MCSs cell therapy [95].

Acknowledgments

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