COVID-19 revolution: a new challenge for the internist

Pulmonary involvement and cytochemical storm: beyond SARS-CoV-2 pneumoniae

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ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, *etc*.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with pulmonary involvement and cytochemical storm.

According to some studies, in many patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection the sudden respiratory deterioration seen around 7-8 days after initial symptoms onset seems to be due to a cytokine storm similar to that implied in macrophage activation syndrome (MAS).[1,2] In these patients high levels of ferritin, interleukin (IL)-1 and IL-6 could correlate both with a higher probability of developing acute respiratory distress syndrome and mortality increase. In coronavirus infection disease (COVID-19) patients the proinflammatory state and the consequent end organ damage seem to be confined to lung parenchyma, lacking other classical systemic clinical features.[3,4]

Severe COVID-19 may show features of systemic hyper-inflammation like MAS.[5] MAS represents a prototype of cytokine storm syndrome, characterized by hyperinflammatory response leading to organs damage. It has traditionally been classified into primary and secondary forms: the secondary forms may be triggered by infections, cancer, or inflammatory diseases.[6]

As other conditions leading to the clinical phenotype of cytokine storm syndrome, severe COVID-19 is characterized by elevated levels of IL-6. From the point of view of rheumatologists, the critical COVID-19 patients have common features such as sudden deterioration of disease around one to two weeks after onset, much lower level of lymphocytes in peripheral blood, extremely high inflammatory parameters associated to hypercoagulability, destroyed immune system revealed by atrophy of spleen and lymph nodes. Moreover, the majority of infiltrated immune cells in

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lung lesion are monocytes and macrophages, with minimal lymphocytes infiltration.[7]

In the context of lack of vaccine and specific antiviral agents, the testing of immunomodulatory agents to reduce excessive or uncontrolled inflammation before it results in irreversible multi-organ dysfunction infection has received increasing research attention.[8]

Since T cells, inflammatory monocytes and IL-6 play a central role in sudden worsening of COVID-19 pneumonia, monoclonal antibody that targets the IL-6 pathways may potentially curb inflammatory storm. Tocilizumab, an IL-6 receptor blocker, may effectively block the IL-6 signal transduction pathway and it could be an effective treatment in severe patients of COVID-19 to calm the inflammatory storm and reduce mortality.[9]

The common physio-pathogenetic basis with the MAS could reveal a significant therapeutic role for steroids in the early phase, immediately after the viremic one. In addition, ruxolitinib may also play a therapeutic role: it is a JAK1/2 inhibitor approved for the treatment of polycythemia vera and myelofibrosis and it could be a promising option in the treatment of secondary hemophagocytic lymphohistiocytosis.[8]

All recent studies agree that the lung is the organ most affected by COVID-19[10,11] and a recent report shows that discharged patients with COVID-19 pneumonia are still having residual abnormalities in chest computed tomographic scans, with ground-glass opacity as the most common pattern.[12] Previously it has been observed that persistent impairment of pulmonary function and exercise capacity for months or even years was typical in the recovered survivors with other coronavirus pneumonia (SARS and Middle East respiratory syndrome, MERS). In the follow-up studies going from half a year to two years in the rehabilitating SARS patients, impaired carbon monoxide diffusing capacity (DLCO) was the most common abnormality, ranging from 15.5% to 43.6%, followed by defected total lung capacity (TLC), ranging from 5.2% to 10.9%. Wan *et al.* showed that 37% of MERS survivors still presented with an impairment of DLCO, but normal TLC at 12 months.[1,13-15] Now there are still no certain data regarding pulmonary function in discharged COVID-19 survivors. An interesting recently published work of Mo *et al*.[16] has highlighted a greater decline in DLCO *vs* DLCO/alveolar volume (DLCO corrected for alveolar volume), which suggests that altered diffusion membrane may be more causative of the pulmonary dysfunction compared to lowered lung volume. The low proportion and severity of small airway dysfunction in this cohort of patients also suggests that COVID-19 is more likely associated with diffuse lung epithelial damage and small airway congestion. These data are confirmed by the first autopsy results in literature. A study by Buja *et al*.[17] based on clinicopathological correlation from 23 autopsy cases, summarized following observations: i) acute COVID19 pneumonia is a viral interstitial pneumonia characterized by the early exudative phase of diffuse alveolar damage with endothelial and epithelial injury, hyaline membranes, reactive pneumocytes with viral cytopathic effect, and mild combined lymphocytic and histiocytic intra-alveolar inflammation;[18-20] ii) In the following stages (illness of several days) there is a different pulmonary pathology pattern that can be associated with a lymphocytic interstitial pneumonitis with intra-alveolar fibrin deposits, which may represent an early stage of acute fibrinous and organizing pneumonia;[21,22] iii) although not universally found, pulmonary microthrombi are common, consistently with the frequent development of a SARS-CoV-2-induced hypercoagulable state, and major pulmonary thromboembolism is a common fatal complication;[23] iv) cardiovascular disease is a frequent co-morbidity in fatal cases; individual cardiomyocyte damage is frequent, probably as a result of infection of endothelial cells and/or perivascular cells.[22]

In discharged survivors with COVID-19, impairment of diffusion capacity (DLCO) is the most common abnormality of lung function followed by restrictive ventilatory defect, which are both associated with the severity of the disease as shown by autopsy studies; therefore pulmonary function test should be performed in routine clinical follow-up of this patients.

In conclusion, deeper knowledge of the pathogenic mechanisms, the genetic background, and the inflammatory pathways of the host are still needed to identify the hyper-inflammatory clinical picture of COVID-19. Immunomodulatory agents with good safety profiles may be considered for use in combination with antiviral drugs for the treatment of severe or critical cases of COVID-19 but physicians will need to rely on a unified approach to treating these ill individuals. In addition, many of the current and emerging antifibrotic drugs could have therapeutic potential for treating severe COVID-19 and preventing the long-term fibrotic consequences that might follow this pandemic.

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