Editorial

Potential mechanisms of mediastinum involvement in SARS-COV-2 infection

Maria Giannaki,
Antonis Antoniadis

Pneumonology Department of General Hospital of Serres, Greece

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Correspondence:
Dr Antonis Antoniadis,
Director of Pneumonology Clinic,
General Hospital of Serres, Greece,
Tel.: +30 23210-94607,
Fax: +30 23210-94624,
e-mail: antonisant100@gmail.com

The last two decades humanity has experienced three significant outbreaks of coronaviruses starting from 2002 with SARS-CoV, then MERS-CoV (2012) and currently SARS-CoV-2 (COVID-19). Due to the rapid spread from Wuhan to all over the globe, the current disease has been characterized as pandemic by WHO on 11 March 2020.

Coronaviruses are positive-stranded RNA viruses, whose genetic analysis has revealed that they cluster with the genus Betacoronavirus. All available evidence for COVID-19 suggests that SARS-CoV-2 has a zoonotic source suggesting an ecological origin in bat populations. The clinical spectrum of COVID-19 varies from asymptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an ICU, to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS).

The wide-ranging systemic effects of the virus remain a challenge for the scientific community in order to identify the specific impact on each organ system. Among them, mediastinum is of special interest due to the vital organs that houses, even if it is not often reported so far.

The mediastinum is the central compartment of the thoracic cavity between the pleural sacs of the lungs. It is typically discussed based on the four-compartment model, that divides the mediastinum into the superior, anterior, middle, and posterior portions. The mediastinum houses many vital structures including the heart and its vessels, esophagus, trachea, thymus gland, thoracic duct, lymph nodes of the central chest and essential nerves. The mediastinum is also clinically significant due to the variety of physical anomalies and pathologies that can occur in this region. Viral infections, have been suggested as etiogenic factors in several of mediastinal pathologies.

Among mediastinal structures, there is a strong association between SARS-COV2 and the thymus, mediastinal lymph nodes and the heart and pericardium. In addition, mediastinum is involved in SARS-COV2 infection through serious complications that arise from pulmonary involvement, such as spontaneous pneumomediastinum. The impact of COVID-19 in the heart and cardiovascular system is an extended and distinct entity that would not be discussed.

The thymus gland is a primary lymphoid organ, located in anterior mediastinum. It is responsible for generating mature T cells that eventually colonize secondary lymphoid organs such as the spleen, lymph nodes and

the mucosa associated lymphoid tissue. It is predominantly consisted of epithelial cells and lymphocytes. Anatomically it is consisted of two lobes, which are further divided into lobules. Each lobule consists of an outer cortex, occupied by mature T lymphocytes and an inner medulla, occupied by immature lymphocytes. Thymus responses to endogenous or exogenous factors are highly sensitive and lead to impaired peripheral export of mature cells.

The first theory on the beneficial role of the thymus gland regarding SARS-COV-2 infection derives from the observation that children have milder symptoms or are completely asymptomatic even if they have equal chances of becoming infected.[1] The resident plasma cells of the thymus secrete functional antibodies fixing complements, which highly promote the immunity in the starting of early age and this has been established as a possible explanation.[2]

In adults, evidence derived from studies performed in common viral infections, introduce the beneficial role of the thymus gland. The majority of those studies refers to HIV infected humans and animal models, due to the limited availability of thymus from infected patients, as the thymus is difficult to biopsy.

Pathogens seem to disrupt thymic structure and function, and alter T cell selection and export and this procedure takes place through local or systemic way. Local refers to the direct presence of the pathogen in the thymus and systemic to the effects of soluble factors that are released into the blood stream, involving glucocorticoids and other pro-inflammatory mediators.[3-6]

A common feature observed in a variety of infections -mostly viral- is significant atrophy of the thymus regarding both lymphoid and microenvironmental compartments. It particularly concerns cortical lymphocytes, as it has been shown in AIDS.[7] The pathways through the apoptosis takes place are not yet completely understood but there is evidence to highlight the involvement of glucocorticoid hormone levels in the blood stream and TNF-α. It seems that infected cells are phagocyted by intrathymic macrophages.

The microenvironmental compartment of the thymus is also affected, particularly in acute infectious diseases, by disorganization of the epithelial network and an increase in the deposition of extracellular matrix.

Data from animal model studies has shown that direct thymic infections by viruses can alter T-cell selection and induce tolerance against invading pathogens and thus leading to chronic infections.[8,9]

The close genetic relations between SARS-CoV-1 and SARS-CoV-2 could probably offer significant data on the understanding of the involvement of COVID-19 in the thymus since SARS-COV-1 has been studied in animal models. Coronaviruses investigated in the past, failed to replicate in other species rather their hosts. SARS-COV family however seems to differ since it is an animal virus that infects humans. Subbarao et al after the SARS-COV-1 spread in 2004, reported high titers of the virus in the respiratory tract of BALB/c infected mice. According to thymus gland, no histopathologic changes were observed.[10] In addition, the knowledge that a metallopeptidase named angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor for SARS-CoV, excluded the direct infection of the thymus, since thymic cells were found negative for ACE2.[11] Based on the previous data, the indirect involvement of the thymus related to systematic effects was suggested. The current knowledge on SARS-COV2 comes to introduce new receptors, such as CD147, as possible mediators through which the virus could enter the thymus gland.[12] Another theory, involves the transfer of the virus to the thymus through T cells and Dendritic cells that circulate from periphery to the thymus according to "Trojan Horse" model.[13]

A significant observational study that was conducted in the Intensive Care Unit of the Clinique Ambroise Paré (Neuilly, France) comes to bring some light in the involvement of thymus in SARS-COV2 infection by noticing thymus enlargement at CT-scan in adult patients admitted for COVID-19 associated SARS. Thymus enlargement was more frequent in the COVID-19 group than in control, except the elderly, and was associated with more severe pulmonary involvement but lower mortality. They also concluded that it is related to enhanced thymic function that is beneficial to COVID-19 induced lymphopenia through increased production of T-cell precursors as was quantified through PCR TRECS.

Lymphadenopathy refers to the abnormality of lymph node size, density, and/or number.[14] Computed tomography (CT) is the gold standard method for the assessment of these features. Frequent causes of lymphadenopathy are inflammatory and neoplastic conditions, as well as several infections. The most common infections that result in thoracic lymphadenopathy are TB, fungal diseases and several viruses, including Epstein–Barr virus, Varicella-Zoster virus and Influenza viruses, which can cause lower respiratory tract Infections in adults.

Lymphadenopathy has been established as part of protective immunity to a viral infection and is dependent on initiating events in a primary immune response to the

virus. Dendritic cells present viral antigens and induce naive T cells to proliferate and to become effectors. Hamilton et al detected influenza virus in the draining mediastinal lymph nodes early after intranasal inoculation, with peak virus titers in this tissue measured at 2 days postinfection in infected mice.[15]

Mediastinal lymphadenopathy has already been reported in several SARS-COV-2 infected patients. Large systematic reviews on the current published studies, which provide a summary of evidence on detection of COVID-19 by chest CT, report a prevalence of 3.4% and 5.4% of lymphadenopathy.[16,17] Xavier Valette and colleagues reported a high (66%) prevalence of mediastinal lymphadenopathy in 15 patients with COVID-19 admitted to their intensive care unit (ICU).[18] Microbiological samples ruled out bacterial or fungal coinfections in all of them. Sardanelli et al in a larger cohort study with 410 patients with COVID-19, reported 19% prevalence of mediastinal lymphadenopathy in CTs at the emergency department during admission. In this study, researchers tried to correlate lymphadenopathy with worse prognosis, since it was reported more frequently in patients with crazy paving pattern on CT and in those who died.[19] The discrepancy among prevalence in those studies (ICU and non) suggests the disease severity as a probable explanation.

Spontaneous pneumomediastinum (SPM) is defined by the presence of air in the mediastinum without evident causes such as traumatic, iatrogenic, organ perforation, surgery or gas producing infections. Clinical symptoms include chest pain, dyspnea, cough and dysphagia.

The pathophysiology underlying spontaneous pneumomediastinum is the presence of a pressure gradient between the alveoli and the lung interstitium resulting in alveolar rupture and circulation of air through the venous sheaths to the mediastinum. Conditions that provoke Valsava maneuver such as coughing, sneezing, defecation, vomiting and others during extreme respiratory effort, marijuana smoking, diabetic ketosis, rapid reduction in atmospheric pressure are considered as causing factors.[20,21] Viral pulmonary infections are rarely associated with SPM and are mostly detected in influenza.[22]

To our current knowledge, several cases of spontaneous pneumomediastinum have been reported in COVID-19 patients with pulmonary involvement.[23-25] In case of pulmonary infections due to SARS-COV, the virus causes breakdown of the alveolar membrane integrity as it infects both type I and II pneumocytes and this can be one of the mechanism leading to alveolar rupture and spontaneous pneumomediastinum.[26,27] Thus, spontaneous pneumomediastinum is more likely to occur in cases of extensive pulmonary lesions on CT, according to the severity of alveolar damage.

In conclusion, mediastinum is a field of special interest in the effort of the scientific community to collect data on the pathophysiology of SARS-COV2. Thymus gland is a major lymphoid organ that is required for optimal immunity to infection throughout life and not only until puberty, as it was thought for several years. The understanding of involvement and protective role of thymus gland during SARS-COV-2 infection as well as the contribution of mediastinal lymph nodes, are of crucial role in research of the pathogenesis and organization of strategies and vaccination against the virus.[28] A systematic review of thymus and lymphoid tissue virology in combination with the current knowledge on SARS-COV-2 pathogenesis could lead to useful conclusions in this field. More studies on animal models, as well as observational studies on hospitalized patients need to be carried in order to export useful data.

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