SARS-CoV-2 Infection: Not Just The Lungs

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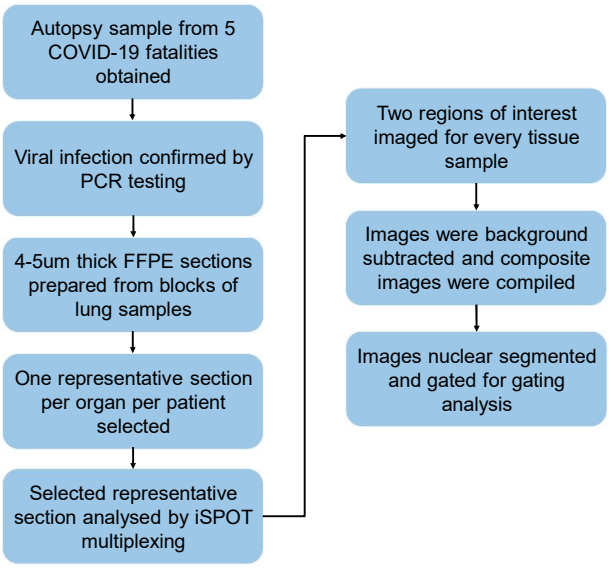
BACKGROUND

- The COVID-19 pandemic first broke out in China in December 2019. This has led to over 6 million deaths and continues to pose a huge public health risk.
- Most patients experience mild flu-like symptoms, but a reported 19% of patients experience severe symptoms. This disease has culminated in multi-organ failure and death in severe cases.
- Many studies have investigated systemic immune responses to the SARS-CoV 2 infection through analysis of peripheral blood. These revealed proinflammatory cytokines, specifically TNF-α, IL-6 and IFN-γ, to be important markers for severity and prognosis of the disease.
- However, peripheral responses do not adequately represent compartment-specific responses as demonstrated by the bronchoalveolar extracts (BAL), which under-represented the resident cells in the pulmonary parenchyma.
- This highlighted the need for analysing disease correlates in situ for a better understanding of the pathology in the specific tissues.

RESEARCH QUESTION

What is the organ-specific immunopathology in lethal COVID-19 cases?

MATERIALS AND METHODS



AIMS

- This study aims to characterise the organ-specific immunopathology through detection of immune, cytokine and stromal cell status in lethal COVID-19 cases.
- This is achieved through a tyramide signal amplification (TSA)-IHC based deep-phenotyping technique, iSPOT (immunoSpatial histoPhenOmics) of lung, heart and intestinal autopsy samples from five young adult COVID-19 fatalities.

RESULTS

PULMONARY

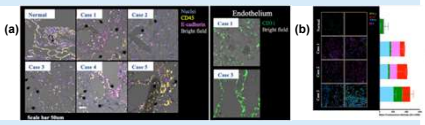


Figure 2: (a) Germinal centres of the gastrointestinal tract indicated in blue-dotted contour in normal and SARS-CoV-2 infected samples. The presence of varying numbers of CD3 cells across all the cases, as compared to normal, in the originally CD20-dominated germinal center indicates a disruption of germinal center architecture with SARS-CoV-2 infection. (b) Global cytokine profiles, of acquired field of view, in SARS-CoV-2-infected pulmonary tissue. The increase in pro-inflammatory cytokines with SARS-CoV-2 infection of pulmonary tissues suggests a virus-induced hyperinflammation which could contribute to tissue damage.

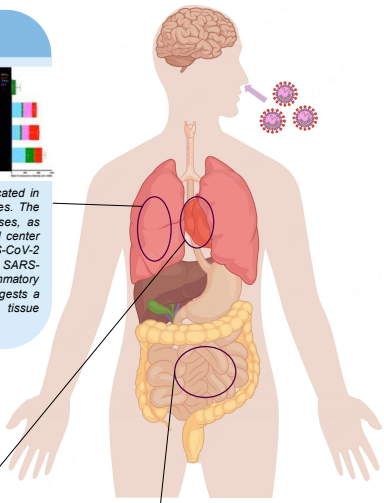


Figure 1: Figure of Simplified Human Anatomy with Areas Investigated in Study Circled with Simplified COVID-19 Particles.[1,2]

CARDIAC

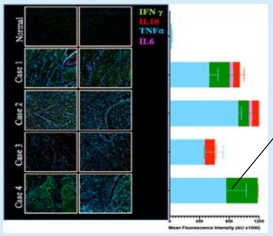


Figure 3: Global cytokine profiles, of acquired field of view, in SARS-CoV-2-infected cardiac tissue. The infected cardiac tissue demonstrate an increase in pro-inflammatory cytokines, such as IFN- γ, IL-10, TNF- α and IL-6. TNF- α, is especially raised.

ENTERIC

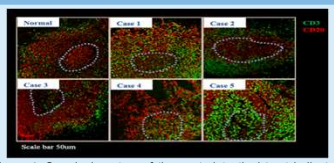


Figure 4: Germinal centres of the gastrointestinal tract indicated in blue-dotted contour in normal and SARS-CoV-2 infected samples. The presence of varying numbers of CD3 cells across all the cases, as compared to normal, in the originally CD20-dominated germinal center indicates a disruption of germinal center architecture with SARS-CoV-2 infection.

DISCUSSION

- SARS-CoV-2 infected pulmonary tissues showed altered tissue architecture and elevated cytokine levels with persistent viral pathogen. These can have synergistic maladaptive effects leading to lethality.
- SARS-CoV-2 infected cardiac tissues showed a decrease in macrophages, essential homeostatic regulators of cardiac health[3], and an increase in vimentin+ cells, which suggests cardiac injury leading to myofibroblast differentiation[4]. Additionally, SARS-CoV-2 infected cardiac tissues showed an elevation of proinflammatory cytokines, in particular TNF-α, a prognostic indicator of a failing heart[5].
- Lastly, ileal tissues showed poor formation of germinal centres across all infected Peyer's patches. These are important structures for eliminating gut-associated pathogens[6]. Failure to eradicate these gut-associated pathogens may contribute to gastrointestinal symptoms observed in SARS-CoV-2 infected patients.

CONCLUSION

- This study examined the immune response in the lungs, heart and intestines of 5 patients with lethal SARS-CoV-2 infections using iSPOT, a novel IHC method that enables detection, localisation and quantification of large numbers of targets by fluorescence imaging across tissue types.
- This study demonstrated that even in young patients without pre-existing comorbidities, SARS-CoV-2 infection can potentiate possibly lethal pulmonary and cardiac dysfunction due to dysregulation of proinflammatory cytokines. Hence, target specific cytokine therapy may be beneficial for young patient groups with severe SARS-CoV-2 infections.

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