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RAPID RESEARCH IN COVID-19 PROGRAMME

Inflammation in Covid-19: Exploration of Critical Aspects of Pathogenesis (ICECAP)

AIMS

The COVID-19 pandemic is causing widespread illness and death, with lung damage characterising severe disease. How the virus causes lung injury is poorly understood. By performing hospital post-mortems of those dying from severe COVID-19 we aimed to describe the presence of the coronavirus in multiple organs in the body and also understand how the immune system responds.

KEY FINDINGS

- Coronavirus was found in multiple organs within patients who died from COVID-19.
- Activation of the immune response was most commonly observed in lung tissue and organs of the immune system.
- Analysis of the immune response showed the main abnormalities were in macrophages (cells that respond to infection and organ damage) and also plasma cells (involved in producing antibodies).
- Tissue banking for further ongoing analyses is allowing maximal utility of the post-mortems and the tissue gifted.

WHAT DID THE STUDY INVOLVE?

Tissue was collected and analysed from patients who died from severe COVID-19. These tissues were then analysed by a large multidisciplinary team of expert clinicians, virologists, pathologists and immune system experts. This consortium involved researchers at numerous sites including University. Of Edinburgh, University of St Andrews, University of Liverpool and Stanford University.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Severe COVID-19 leads to life-threatening lung damage and a high risk of death despite life support on a ventilator. COVID-19 is a new disease and we do not fully understand the process leading to lung damage: is it directly due to the presence of virus, or is the body's immune system also causing damaging inflammation? Our ability to design and test specific treatments is improved by answering this question.

Many studies of the immune system in COVID-19 have used blood or lung washing samples. Whilst useful, these might not be representative of what is going on deep inside the lung tissue where the disease is most active. The virus has also been detected in organs other than the lung. Investigating the mechanism of lung tissue damage, and involvement of other organs, is an urgent unmet need in understanding COVID-19. Hospital post-mortem examinations of people who have died from COVID-19 provide an opportunity to study the whole body in a level of detail not possible during life and answer important clinical questions.

We found evidence of the coronavirus in multiple sampled organs and tissues, most frequently in the lungs, but also from the gastrointestinal tract, heart and muscle, and less often from the liver, kidney and other organs. Generally, we found virus in the lining cells of these organs (epithelial cells). Interestingly, outside of the lung, the presence of virus was not associated with adjacent tissue damage or clinical features of organ damage. For example, within the kidney the presence of virus was not associated with local inflammation, nor blood test evidence of kidney failure.

As we expected, tissue damage was mainly found in the lung, but we also found a universally abnormal response in organs of the immune system (including the lymph nodes, spleen and bone marrow). In the lung, in addition to damage to the air sacs (alveoli), we identified blood vessel inflammation (vasculitis), which could contribute to the high frequency of blood clots seen in the lungs of patients with COVID-19. Significant findings in the immune system organs included abnormal macrophages (white blood cells involved in sensing infection and tissue repair) and strikingly increased numbers of abnormal plasma cells (usually involved in producing antibodies). Whilst the consequences of these abnormalities are currently unknown, they identify specific cell types for further investigation. Detailed studies of cell types present within badly damaged lung tissue confirmed that macrophages and macrophage-like cells were increased in number and likely to be important.

WHAT IMPACT COULD THE FINDINGS HAVE?

Overall, our findings:

- Provide a detailed atlas of where in the body the virus is present and how this associates with organ injury and abnormality.

- Demonstrate a mismatch between the presence of virus and evidence of tissue damage and inflammation outside the lung.
- Report new types of inflammation in the lung that could contribute to lung failure in fatal COVID-19 (vasculitis) and identify specific immune cell types involved in the disease.

Overall, our findings suggest that treatments that reduce inflammation could be particularly effective in severe cases, since the virus may not be causing all of the tissue damage. This is consistent with the beneficial effect of dexamethasone (a broad-spectrum anti-inflammatory drug) reported in recent clinical trials.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Our initial findings were released as a pre-print on the website medRxiv (a website for open access health sciences manuscripts before peer review, to accelerate dissemination of findings https://www.medrxiv.org/content/10.1101/2020.07.02.20145003v1), fed into UK health policy via NERVTAG (New and Emerging Respiratory Virus Threats Advisory Group) and is currently submitted for publication. A lay summary of our research appears under our ICECAP specific website at https://www.ed.ac.uk/inflammation-research/research/icecap/research-outputs and has been picked up by the scientific press. Our individual patient findings are also fed back to the patient's relatives by our research team.

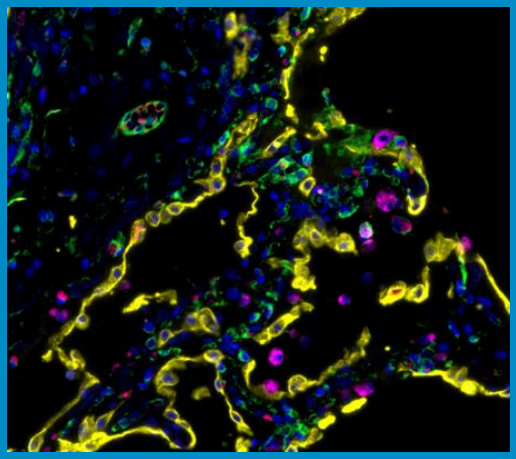
Our ongoing work to delineate the viral and immune response to coronavirus, to improve our ability to design and test specific treatments, has recently been awarded additional funding by UK Research and Innovation.

CONCLUSION

Consequences of the presence of the coronavirus differs between different tissues, with inflammation and organ damage likely to be significantly mediated by the immune system. Understanding the reasons behind this may lead to new treatments in severe disease.

Lung tissue cellular localization of Coronavirus protein.

Lung lining cells (epithelium) in yellow, blood vessel cells (endothelium) in green, immune cells (macrophages) in pink, and coronavirus in red.



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ADDITIONAL INFORMATION

This project ran from 1st May – 31st October 2020, and was awarded £160,000.