Simple skin biopsy can assess tissue damage related to COVID-19

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Using skin biopsy samples, investigators found that patients with severe COVID-19 had clots in small venous and arterial blood vessels in skin that appears normal. This was not seen in the skin of patents with other types of severe infectious lung disease, or in individuals with only mild or moderate COVID-19. Their findings appear in *The American Journal of Pathology*.

The researchers document, for the first time in premortem evidence, that a minimally invasive skin biopsy can help assess tissue damage related to COVID-19 as well as help distinguish this blood vessel pathology from other forms of severe respiratory illnesses. Prior to this study, invasive procedures such as nerve, kidney, or lung biopsy would have been required.

"We were the first group to recognize that the lung disease of acute COVID-19 was different from other severe critical respiratory infections, and that the unusual pathology was systemic," explained lead investigator Jeffrey Laurence, MD, Department of Medicine, Division of Hematology and Medical Oncology, Weill Cornell Medicine, New York, NY, USA.

The investigators collected simple 4mm punch biopsy samples of normal-appearing deltoid skin from 15 patients who were in intensive care with COVID-19 and six patients with mild to moderate COVID-19 symptoms, such as fever, chills, cough, or shortness of breath. Biopsy samples from nine hospitalized patients with severe or critical respiratory or kidney disease who died before the COVID-19 era were also included in the study.

Microthrombi were detected in 13 of the 15 patients with severe or critical COVID-19. No microthrombi were detected in the biopsies of patients who had mild to moderate COVID-19 or the pre-COVID-19 era patients with severe respiratory illness or kidney diseases. It is likely that these microvascular changes may be a unique characteristic of COVID-19 respiratory disorder compared to other acute respiratory diseases.

An antiviral protein capable of blocking SARS-CoV-2 growth, MxA, was found in all six mild to moderate COVID-19 patients, indicating that their immune systems were actively fighting the virus, versus only two patients with severe to critical disease.

An interferon-induced inflammatory protein, SIN3A, was prominent in the microvascular of normal-appearing skin from patients with severe or critical COVID-19, but not in similar samples from normal control subjects. Increased SN3A levels in plasma and expression in skin microvasculature were associated with the severity of the patient's disease and could contribute to the cytokine storm characteristic in such patients.

Dr. Laurence notes that these results have clinical implications. "Although anticoagulants were used in the pre-COVID-19 era in sepsis-associated pneumonias to reduce macrovessel thromboembolism, most randomized trials to date

have not found this treatment benefits hospitalized patients who are critically ill with COVID-19 acute respiratory distress syndrome. These drugs may not be capable of reducing the microvessel thrombosis found with SARS-CoV-2 infection."

The investigators acknowledge that their work is limited by its nonrandomized referral process, and before the clinical significance of these findings as actionable correlates of disease progression can be established, a prospective study using serial biopsy samples of normal-looking skin is required. However, they emphasize that the simple punch skin biopsy allows tissue-based assessment for microvascular thrombosis, complement disposition, and MxA and SN3A levels at different time points.

"If validated in a longitudinal cohort, earlier identification of factors linked to severe COVID-19 using a simple skin biopsy in patients at early stages of SARS-CoV-2 infection may help identify individuals at risk of acute disease progression and long COVID and enable early targeted interventions," Dr. Laurence said.

More information: Jeffrey Laurence et al, Premortem Skin Biopsy Assessing Microthrombi, Interferon Type I Antiviral and Regulatory Proteins, and Complement Deposition Correlates with Coronavirus Disease 2019 Clinical Stage, *The American Journal of Pathology* (2022). DOI: 10.1016/j.ajpath.2022.05.006