Contrast-Enhanced Ultrasound in Patients With COVID-19
Pneumonia, Acute Respiratory Distress Syndrome, or Something Else?

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Coronavirus disease 2019 (COVID-19) represents a very heterogeneous disease. Some aspects of COVID-19 pneumonia question the real nature of ground glass opacities and its consolidative lesions. It has been hypothesized that COVID-19 lung involvement could represent not only a viral effect but also an immune response induced by the infection, causing epithelial/endothelial lesions and coagulation disorders. We report 3 cases of COVID-19 pneumonia in which contrast-enhanced ultrasound was suggestive of consolidations with perfusion defects, at least in part caused by ischemic or necrotic changes and not only by inflammatory or atelectasis events.

Key Words—contrast-enhanced ultrasound; COVID-19; lung ultrasound

Coronavirus disease 2019 (COVID-19) causes clusters of severe pneumonia, evolving into respiratory failure and death through bilateral pulmonary involvement. Respiratory failure requiring intensive support is similar to ARDS. The wide and simultaneous spread of the infection, with the need for advanced health care support, makes this pandemic a real health emergency.

COVID-19 is a heterogeneous disease. Not all people exposed are infected; not all people infected show important symptoms, and not all symptomatic patients develop respiratory failure. COVID-19 can be divided into 3 stages: (1) an asymptomatic period, with or without 2019 novel coronavirus polymerase chain reaction swab positivity; (2) a nonsevere symptomatic period; and (3) a severe symptomatic stage with respiratory failure. The first period is probably the most important from an epidemiologic point of view because the finding from the viral RNA swab can fail. The stage with severe respiratory failure seems to represent a time-related spectrum within phenotypes.

Computed tomography is the reference standard for identifying lung involvement in patients with COVID-19, with sensitivity of 97.2% at presentation, showing bilateral patchy lesions with a mainly peripheral parenchymal pattern. Ground glass opacities are present in the early stage, whereas consolidation and a mixed pattern (47.0%) are noted from the second week. Ground glass opacities plus interlobular septal thickening (crazy-paving pattern) seem to be the main pattern in third week.
These phenomena may be attributed to the fact that consolidations may regress to small areas of irregular linear opacities. When the clinical course is favorable, the disease improves in the third week. When the disease progresses, lung infiltrates spread, and consolidative areas in the posterior segments of the lower lobes appear.

Although some features of COVID-19 resemble those described for the usual viral pneumonia, some morphologic aspects of the lung involvement question the real nature of the consolidative lesions. This is particularly intriguing in light of the hypothesis that COVID-19 could represent not only a viral effect but also an immune response induced by the infection. In this series, we describe 3 cases of confirmed COVID-19 with pulmonary consolidations in which studies with contrast-enhanced ultrasound (CEUS) showed large perfusion defects in the lung.

**Case Descriptions**

Three male patients were admitted for fever (>39°C), and symptoms compatible with COVID-19. Severe acute respiratory syndrome (SARS) coronavirus 2 polymerase chain reaction nasal and pharyngeal swab results were positive, and hematologic findings were in accord with the diagnosis of COVID-19. Some clinical characteristics of the patients at admission are summarized in Table 1. All patients underwent radiographic and chest ultrasound (US) examinations within 3 hours of admission, according to the guidelines approved at our center, and all signed an informed consent form. The chest US examination was performed with an RS85 system equipped with a 3.5–5-MHz transducer (Samsung Medison, Seoul, Korea), exploring the patients in a sitting position, scanning the bases and the posterior and lateral regions of the chest. The anterior chest was explored in the supine position. The results of the chest radiographic and US examinations are summarized in Table 2.

All patients showed radiographic interstitial and consolidative abnormalities. Ultrasound findings were characterized by vertical artifacts (B-lines), often grouped and confluent in white lung areas, and with a patchy appearance. All patients had echographic parenchymal consolidations at the bases, in a gravitational position (Table 2), whereas only 1 subject had minimal bilateral pleural effusion. In each patient, there was more than 1 nonbasal subpleural consolidation, less than 2 cm in diameter, with a wedge-shaped...
or angular aspect, containing central air artifacts. The US findings of COVID-19 lung involvement were comparable with the descriptions found in the literature.8,9

The patients required noninvasive respiratory support but had an uneventful recovery. The symptoms improved after combined treatment with sarilumab, azithromycin, and enoxaparin, allowing discharge of the patients in 10 to 12 days.

Because of the presence of small cuneiform lung consolidations with a central echogenic spot (a US sign described in patients with pulmonary embolism), the finding of high level of D-dimer, and the impossibility of performing chest computed tomography with a contrast medium, a CEUS examination in accordance with European Federation of Societies for Ultrasound in Medicine and Biology guidelines7 was performed at the bedside, after acquisition of written consent.

**Figure 1.** A, Ultrasound image of left basal pneumonia (arrows). The parenchyma of the lower lung lobe is consolidated. B, Contrast-enhanced US 8 seconds from the injection of 2.4 mL of SonoVue. Arterial enhancement with a segmental appearance is shown. C, Initial parenchymal phase. D, Perfusion parenchymal phase. The whole lobe is enhanced. E, Right, Ultrasound image of compressive pulmonary atelectasis. Left, Same image at 30 seconds from the injection of 2.4 mL of SonoVue. The compressed and airless parenchyma is strongly enhanced.
Figure 2. Contrast-enhanced US (left) and grayscale B-mode (right) images of left basal consolidation (arrows) in patient 2. **A**, Enhancement after 9 seconds from the injection of 2.4 mL of SonoVue. Consolidation shows partial and uneven perfusion. **B**, after 40 seconds, part of the coconsolidation shows a rather homogeneous parenchymal phase, whereas part of the consolidation does not show enhancement.

Figure 3. Detail of a small cuneiform subpleural consolidation (arrows). Contrast-enhanced US (left) and grayscale B-mode (right) images were acquired at 20 seconds from the injection of 2.4 mL of SonoVue. An obvious defect of perfusion of the lesion is shown.
informed consent. The patients were in a supine position with the sides alternately raised to explore the rear bases. Video sequences were acquired in the dual mode (basal and CEUS protocol) after rapid intravenous administration of 2.4 mL of a suspension of sulfur hexafluoride microbubbles (SonoVue; Bracco SpA, Milan, Italy), followed by bolus of 5 mL of normal saline. The enhancement was continuously observed for 5 minutes.

After intravenous injection of SonoVue, the major consolidations showed abnormal early arterial enhancement within 9 seconds from the administration (Figure 2). The enhancement was partial, often inhomogeneous, without evidence of pulmonary arteries in a segmentary arrangement. In particular, incomplete enhancement of the major consolidations was achieved, especially in part of the pulmonary cortex, whereas little or no perfusion of large deep parts was observed. The boundaries between perfused and nonperfused areas were sharp. Consolidations of less than 2 cm did not show enhancement (Figure 3). Early wash-out phenomena were not noticed.

Discussion

Contrast-enhanced US imaging of the lung is proposed in the assessment of pulmonary consolidations.7 Pneumonia shows ready and complete enhancement starting 8 seconds after the injection, with a treelike pulmonary arterial vascular pattern (Figure 1B), appearing as linear hyperechoic images with greater enhancement compared with the parenchyma. Compressive atelectasis behaves in a similar way (Figure 1E), whereas obstructive atelectasis can show avascular fluid channels (fluid bronchograms) inside homogeneous parenchymal enhancement. Embolic consolidations show absent or inhomogeneous enhancement.10 In a case of long-lasting atelectasis or pneumonia, perfuse patchy inhomogeneity, due to hypoxic vasoconstriction phenomena, may appear.11

Our patients showed large perfusion defects, delimited with respect to the perfused parenchyma, which often appeared only as a shell of enhanced tissue. This pattern is not typical of pneumonia and atelectasis. Inhomogeneous enhancement in the first 10 to 15 seconds was noted. The small cuneiform consolidations showed no enhancement, thus behaving as ischemic or infarct regions.

Figure 1 illustrates the perfusion stages of pneumonia and the CEUS appearance of a compressive atelectasis within a pleural effusion. Figure 2 shows some phases of the CEUS enhancement of basal macroconsolidations related to patient 2. Figure 3 shows the perfusion pattern of a small subpleural consolidation in patient 1.

Our findings may have importance in the pathogenetic interpretation of the consolidations in COVID-19 and, consequently, in the ventilatory and medical treatments of patients with COVID-19.

Among patients with COVID-19 studied in Wuhan, China, about 15% progressed to severe cases.12 Therefore, an important question is why only a subgroup of infected patients develop severe pulmonary impairment and others not. It is conceivable that in many patients with COVID-19, during the initial stages of the disease, an adaptive immune response to limit the progression to severe stages is achieved. However, when the protective immune response is impaired, or, in particular, when aberrant inflammation mediated by proinflammatory macrophages, granulocytes, and cytokines is activated, secondary organ damage is possible. The cytokine release syndrome is a form of a systemic inflammatory response featured by interferons, interleukin 2, interleukin 6, and other mediators.13 This overreaction was described in SARS, Middle East respiratory syndrome, and severe influenza (H1N1 and HSN1). The cytokine storm causes severe capillary damage and organ dysfunction. In the lung, diffuse alveolar damage, hyaline membrane formation, interstitial infiltration of inflammatory cells, fibrin exudate, and fibrotic changes were observed. Thrombosis of venules was noted in some cases, with infarction, hemorrhage, and fibrin thrombi. Systemic vasculitis was observed in one report of SARS.14 Histopathologic findings in COVID-19 are limited, but its features resemble those seen in SARS and Middle East respiratory syndrome.15,16 Microscopic findings are described as nonspecific and include edema, pneumocyte hyperplasia, cellular infiltrates, multinucleate giant cell formation, and hemorrhagic necrosis.

Viral diseases are associated with coagulation disorders. Thrombosis, disseminated intravascular coagulation, and hemorrhage can occur. These pathologic findings and microembolism are complications described in influenza A infections.17 Recently Tang et al18 showed that in
183 patients with confirmed COVID-19, the non-survivors had significantly higher D-dimer and fibrin degradation product levels compared with survivors. In 2013, it was suggested that an abnormal urokinase pathway during SARS progression could contribute to more severe lung lesions.\(^9\) Finally, COVID-19 cases complicated by acute pulmonary embolism were described.\(^20\) According to these reports, consolidations with perfusion defects observed in our patients could be supported, at least in part, by ischemic and necrotic changes and not only by inflammatory or atelectasis events. Moreover, small subpleural consolidations could be small embolic or thrombotic events.

Recently, Magro et al\(^{21}\) examined skin and lung tissue from 5 patients with COVID-19 who had respiratory failure and a purpuric skin rash. Histopathologic patterns were characterized by pauci-inflammatory septal capillary injury but substantial fibrin deposition inside the capillary lumen. These vascular findings were accompanied by vascular deposits of terminal complement components (C5b9, C4d, and mannan-binding lectin serine protease 2), suggesting systemic activation of the alternative and lectin-based complement pathways. It is interesting to note that excessive complement activation may lead to the activation of a clotting pathway and diffuse thrombotic microangiopathy and is responsible for a massive local release of proinflammatory cytokines.\(^{22,23}\)

Although consolidations are commonly observed in patients with acute respiratory distress syndrome (ARDS), not all patients with severe respiratory failure from COVID-19 have the characteristics of ARDS. Gattinoni et al\(^3\) noted that patients with COVID-19 who had respiratory failure showed severe hypoxemia associated with near-normal respiratory system compliance: a combination rarely seen in ARDS. This pattern is seen at the beginning of the lung involvement, and it may improve, increase, or remain unchanged. It has been hypothesized that the worsening of these patients represents an evolution toward a picture similar to ARDS, characterized by low compliance and a decrease in the pulmonary gas volume. Our and other observations\(^{22,23}\) suggest that there also may be an ulterior pattern of COVID-19 lung involvement in which the consolidations do not represent atelectasis or easily recruitable areas but tissue with large perfusion defects. This possibility could be important for managing the ventilatory support of patients with respiratory failure. Ventilatory parameters could be rationally modulated according to the pattern of pulmonary impairment initially estimated with bedside lung US and CEUS.

Our findings require further confirmatory studies. However, if confirmed, they should lead to rethinking of the therapeutic approaches to COVID-19, including the immunomodulatory therapy for the cytokine storm, but, above all, a direct intervention on the mechanisms of complement activation\(^3\) and, consequently, on the coagulation/fibrinolysis cascade.

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