CASE REPORT

The use of contrast-enhanced ultrasound in COVID-19 lung imaging

Gibran Timothy Yusuf[1] · Adrian Wong[2] · Deepak Rao[3] · Alice Tee[1] · Cheng Fang[1] · Paul Singh Sidhu[1]

Abstract

Lung ultrasound has become an essential tool for rapid bedside assessment in critically unwell patients, proving helpful in assessment of COVID-19 due to logistics of cross-sectional imaging. Contrast enhanced ultrasound (CEUS) further characterizes sonographic features of COVID-19 as multiple areas of infarction, a finding not reproducible on other widely available imaging modalities. CEUS also has the benefit of being cheap, radiation-free, without risk of nephrotoxicity, and can be performed at the bedside. It is predicted that lung CEUS in COVID-19 may help guide prognosis and management. We describe three cases of CEUS in COVID-19.

Keywords COVID-19 · Contrast-enhanced ultrasound · Lung ultrasound · POCUS

Abbreviations

CEUS	Contrast enhanced ultrasound
LUS	Lung ultrasound
COVID-19	Novel Coronavirus 19
CTPA	Computer tomography pulmonary angiogram
ACE-2	Angiotensin converting enzyme 2

Background

An increase in thromboembolic events in COVID-19 is reported, supported by lung microinfarcts found at autopsy [1, 2]. The etiology remains unclear but there is growing acceptance of an immune-mediated thrombosis [2]. Diagnosis of pulmonary embolus traditionally relies on computed tomography pulmonary angiography (CTPA), but CTPA cannot visualize the microvasculature. CTPA also requires transferring a critically unwell, infected patient to radiology, with the added nephrotoxic effects of iodinated-contrast media and radiation exposure.

✉ Gibran Timothy Yusuf
   Gibran.yusuf@nhs.net

1   Department of Radiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK

2   Department of Intensive Care, King's College Hospital, Denmark Hill, London SE5 9RS, UK

3   Department of Respiratory Medicine, Princess Royal University Hospital, Farnborough, Kent BR6 8ND, UK

The current COVID-19 pandemic has brought point-of-care ultrasound (POCUS) to the forefront with the ability to rapidly, safely and repeatedly assess patients with proposed grading systems [3]. Contrast enhanced ultrasound (CEUS) is an adjunctive ultrasound technique with a range of applications [4]. Microbubbles consist of sulfur hexafluoride encased in a phospholipid shell, approximately the size of a red cell. These undergo non-linear oscillation with acoustic pressure and are detectable in a contrast-specific mode, resulting in a purely intravascular image to a capillary bed level. Critically, there is the ability to differentiate perfused, ischemic and avascular tissue.

Methods

Sonographic technique

Conventional B-mode imaging was undertaken using either Siemens Redwood™ (Siemens Acuson, Mountain View, CA) or GE Logiq E9™ (GE Healthcare, Milwaukee, WI) with a curvilinear transducer (5C1 or C1-6, respectively). Conventional six-point sonography of the lungs was conducted [5].

Once a target area for CEUS was selected, a split-screen mode was initiated to allow a simultaneous B-mode and contrast specific image. Low mechanical index imaging was used, < 0.2. CEUS was performed with 2.4 mL Sonovue/Lumason™ (Bracco SpA, Milan) via a venous line with cine

clips and still images obtained. The contrast agent persisted for several minutes, allowing re-imaging of all areas.

All operators were experienced sonographers with specific focused training in CEUS by an operator with 10 years' experience.

Image interpretation

All images were reviewed live and retrospectively by a reviewer. Each zone was evaluated for pleural thickening and irregularity. B-lines were categorized as <3, >3 or confluent. Hypoechoic areas were a key finding defined as focal (≤ 2 per single ultrasound field) or multiple (≥ 2). The largest or most visible lesion was the target for CEUS, but all lesions were evaluated.

The absence of contrast enhancement was documented as avascular and any contrast enhancement was documented by comparison to surrounding structures, i.e. hypo or hyper enhancement. The dominant lesion enhancement was described, along with any differing lesional enhancement.

Cases

Case 1: (Fig. 1)

A 61-year old female with reflux esophagitis and fatty liver presented with typical clinical features of COVID-19 confirmed on PCR. She developed progressive type one

respiratory failure escalating to non-invasive ventilation alongside regular proning. Serological markers showed: CRP 179 mg/L, serum ferritin of 4476 ng/mL, D-dimer 916mcg/mL, lymphocytes $0.7*10^9$/L. Lung ultrasound (LUS) performed on day 3 demonstrated pleural thickening and irregularity, diffuse confluent B-lines and multiple hypoechoic areas throughout. A hypoechoic lesion within the right zone 3 lesion showed no enhancement on CEUS. Multiple further areas were also avascular, including tiny areas manifesting as pleural irregularity. CT confirmed typical severe features of COVID-19 with bilateral ground glass opacity and early organization.

The patient required intubation and ventilation in the prone position later on day 3. Follow-up LUS on days 9 and 20 showed progression with CEUS demonstrating avascularity in an increased number and volume of hypoechoic areas correlating to raised inflammatory markers and increasing ventilatory support via tracheostomy. She was extubated on day 30 and discharged.

Case 2 (Fig. 2)

A 67-year old male with a history of multiple pulmonary emboli, pulmonary hypertension, type-2 diabetes, peripheral vascular disease and anemia of chronic disease presented with a 3-day history of typical COVID-19 symptoms. He was subsequently tested positive for SARS-CoV-2 on RT-PCR. CTPA confirmed severe COVID-19 and there were
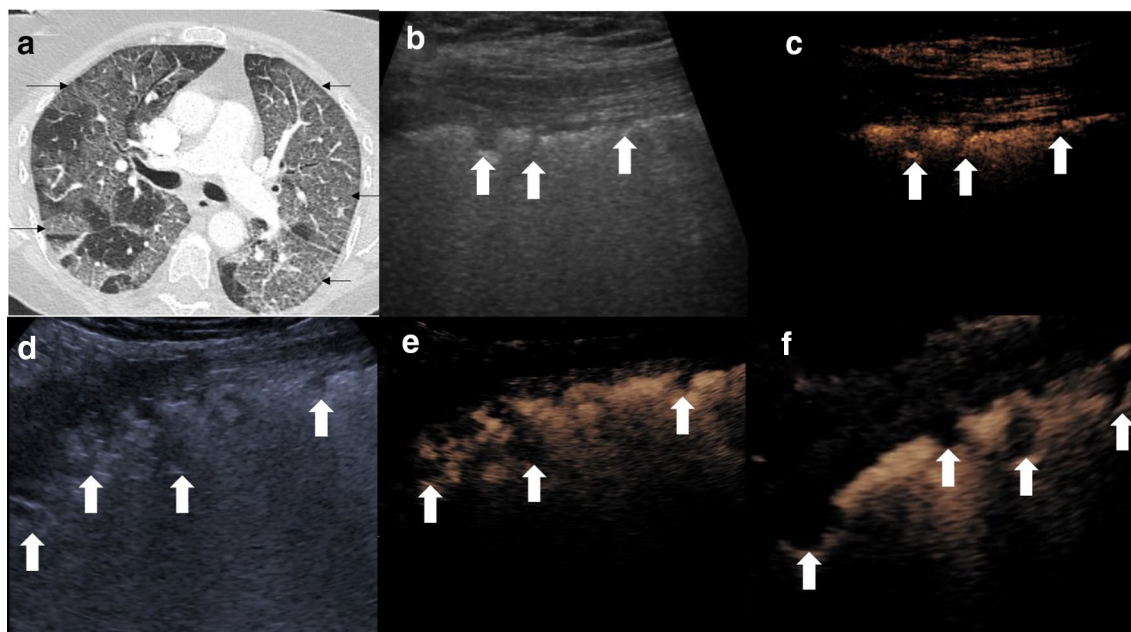

Fig. 1 Patient 1 (**a**) CTPA showed typical features of severe COVID-19 with peripheral ground glass opacity and no pulmonary emboli. (**b**, **c**) Simultaneous B-mode and CEUS showed the multiple hypoechoic areas (arrows) with no enhancement in keeping with infarction. **d–f** Follow-up ultrasound performed after intubation showed progressive number of hypoechoic areas throughout all 6 zones, all of which showed no enhancement
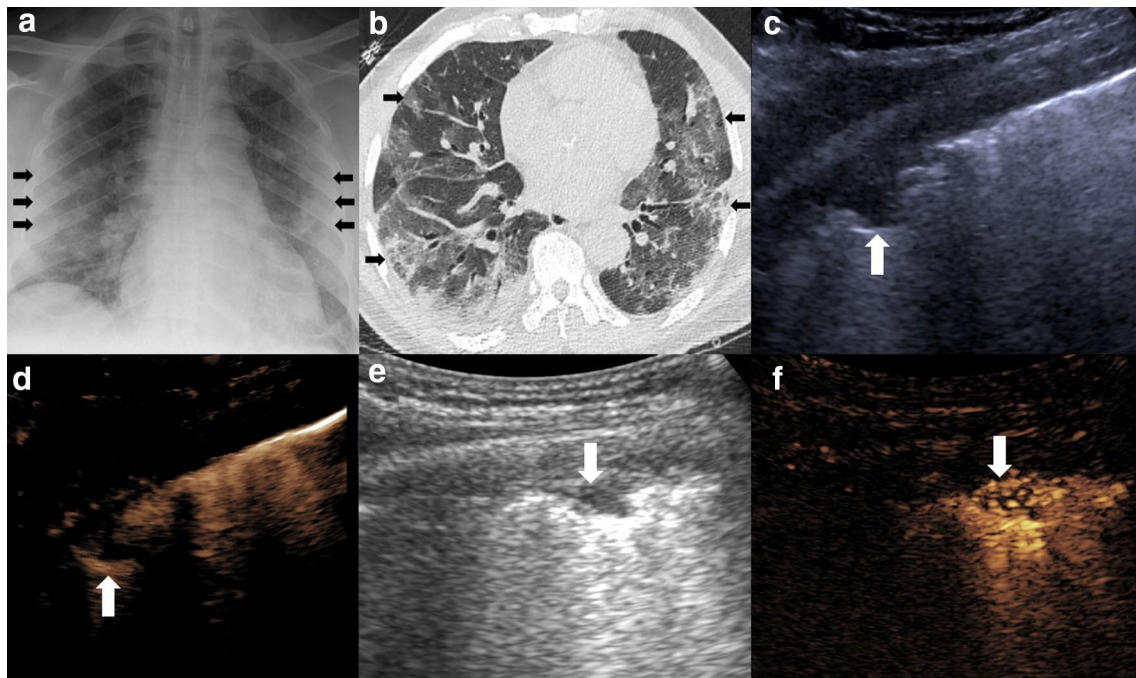
Fig. 2 Patient 2 (**a**) Plain radiograph shows typical features of COVID-19 with peripheral basal consolidation (arrows). **b** CT demonstrated findings of severe disease. **c** B-mode ultrasound and **d** simultaneous CEUS confirmed avascular wedge-shaped hypoechoic areas in multiple zones (arrows). **e**, **f** B-mode and CEUS follow-up after clinical improvement showed many hypoechoic areas had resolved, one previously seen had retracted of consolidation had retracted and had delayed hypoenhancement with signal seen from individual microbubbles in the capillary bed implying reperfusion (arrows)

raised inflammatory markers (CRP 260 mg/L, D-dimer 2610 mcg/mL, lymphocytes $0.9*10^9$/L). Due to progressive respiratory failure, he was transferred to high dependency unit. LUS on day 5 demonstrated pleural thickening, confluent B-lines and multiple hypoechoic areas in all zones. All hypoechoic lesions were avascular on CEUS, including areas not seen on B-mode.

After clinical improvement, LUS on day 12 showed a solitary hypoechoic area with delayed hypovascularity on CEUS after several minutes. The patient was discharged on day 17.

Case 3 (Fig. 3)

A 52-year old female with hypercholesterolaemia presented with a 14-day history of typical COVID-19 confirmed on PCR. In addition to acute kidney injury (AKI), her inflammatory markers were elevated: CRP of 349 mg/L, D-dimer 5951 mcg/mL, lymphopenia of $0.4*10^9$/L.

LUS on day 2: B-mode demonstrated pleural thickening, multiple B-lines in zone 3 bilaterally and scattered focal hypoechoic areas in zone 3 bilaterally. A lesion in left zone 3 demonstrated no enhancement, and all further areas were avascular, including areas of presumed pleural irregularity. A CTPA (negative for embolus) done concurrently was consistent with moderate COVID-19. Worsening AKI and

respiratory failure led to intensive care admission without need for mechanical ventilation or dialysis. On day 7 she recovered, inflammatory markers normalized and she had a normal LUS.

Discussion

Our series demonstrates that bedside CEUS in COVID-19 patients is able to define the presence of avascular peripheral lung infarcts and permits disease monitoring, as findings echo the clinical course. Previous studies are limited in their ability to demonstrate lung infarcts in COVID-19 due to challenging patient logistics, inability of CT to image to a microvascular level with sufficient spatial resolution, and lack of ability to monitor the illness in a continuous fashion [1, 2]. CEUS offers improved spatial and temporal resolution that is able to detect smaller infarcts than on conventional CTPA, shown in both our case series and a similar one recently [6].

There has been debate regarding the etiology of thrombus within COVID-19, whether secondary to embolic phenomena or immune-mediated thrombus secondary to severe inflammation. There is, however, a hypercoagulable state and clear increased risk of thrombotic/embolic disease, resulting in revelation of occult cardiovascular disease [1,
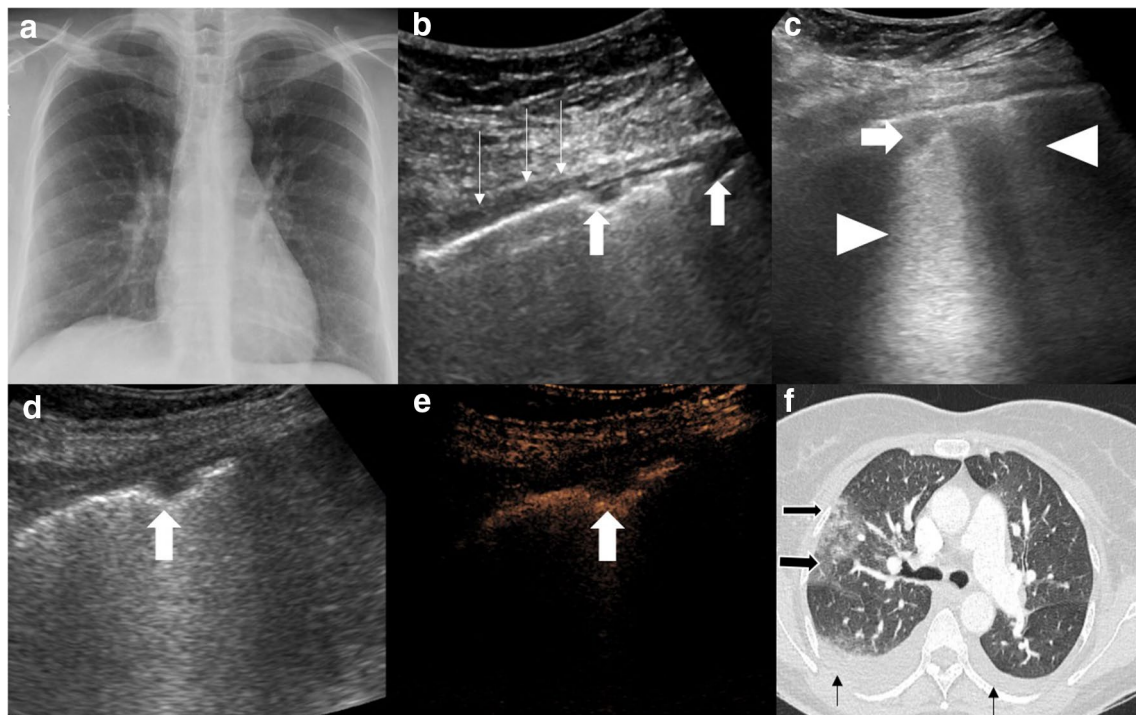
Fig. 3 Patient 3 (**a**) Normal initial chest radiograph. **b** LUS showed small consolidations (thick arrows), pleural thickening (thin arrows) and **c** confluent B-lines bilaterally (arrowheads), and hypoechoic areas (thick arrow). **d**, **e** B-mode and CEUS show a non-enhancing hypoechoic area indicating infarction (thick arrows). **f** CT performed the same day shows typical peripheral ground glass (thick arrows) with less common bilateral pleural effusions (thin arrows) but no pulmonary embolus

2, 7]. A mechanism in COVID-19 coagulopathy is thought due to ubiquitous expression of Angiotensin-2-converting enzyme (ACE-2) within type II pneumocytes and macrophage activation syndrome-like response, releasing pro-inflammatory/procoagulants and causing endothelial damage leading to thrombosis [7]. This propagates cyclically faster than lysis can occur, resulting in widespread areas of in situ pulmonary thrombosis and subsequent infarction—the areas of avascularity seen on CEUS.

The use of lung POCUS to assess acutely unwell patients by non-radiologists has become routine and has led to several accreditation pathways [5, 8]. Given the logistical and clinical issues facing healthcare professionals during the COVID-19 pandemic, the use of lung POCUS has increased exponentially [9]. The key benefits are the ability to repeatedly scan the patient without the need to transfer outside the ward/ICU and, crucially, the sensitivity and specificity is comparable to CT scans [8].

Although novel territory within POCUS, CEUS has gained popularity in adults and pediatrics, particularly in the trauma setting, where it is able to identify avascular laceration planes as well as pseudoaneurysms and active bleeding [4, 10]. CEUS has proved useful in distinguishing testicular hematoma from tumors and identifying cortical necrosis in kidneys, among other uses [4, 11, 12]. As a blood pool agent, CEUS can accurately determine ischemia, infarction or preserved vascularity.

In all patients, the degree of infarction correlated with clinical status, supporting the theory of immunothrombus [7]. Early recognition of hypoechoic areas as lung infarction rather than pure inflammatory consolidation with CEUS may provide prognostic and diagnostic information to guide early management. Our patients showed multiple avascular areas lung infarcts, but CEUS also allowed us to demonstrate revascularization with recovery.

The role of LUS in COVID-19 is developing, as there is expectation of recurrent peaks of the disease. We postulate the addition of CEUS may help determine degree of infarction, risk stratify, and monitor patients in a similar way to thrombotic degradation products such as D-dimer. It is possible fibrosis, pulmonary hypertension or as yet unknown long term effects are related to the degree of infarction.

Conclusion

CEUS in LUS confirms hypoechoic areas seen in COVID-19 as micropulmonary infarction not seen on any other imaging modality, and it can potentially guide early management and determine prognosis. Given the widespread utility of LUS,

CEUS is of use in the point-of-care setting and aiding long term follow-up.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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