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The bullseye sign: A variant of the reverse halo sign in COVID-19 pneumonia☆

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ABSTRACT

The predominant pulmonary imaging findings on chest CT in the novel 2019 coronavirus infection (COVID-19) are bilateral ground glass opacities. The reverse halo sign is uncommon. This is a report of the new "bullseye sign," which is considered a variant of the reverse halo sign and favored to represent a focus of organizing pneumonia. The specificity of this finding is unclear, however its presence should alert radiologists to the possibility of COVID-19 infection.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for COVID-19 infection, has infected millions of people worldwide [1]. Although it is increasingly recognized as a multisystem disease, the main source of morbidity and mortality is respiratory failure. Imaging findings include ground glass opacities as the predominant pulmonary finding on CT [2–8]. A less common finding is the reverse halo sign (RHS), a region of consolidation with central ground glass or normal parenchyma [8–10]. This case series describes a CT finding – which we believe is a variant of the RHS and have referred to as the "bullseye sign" – that has not been previously reported in COVID-19 pneumonia or any other pulmonary disease of which we are aware.

2. Case 1

A 59 year-old Hispanic woman with no significant past medical history presented to the Emergency Department with new onset of severe chest pain and two weeks of cough, fatigue, and subjective fever. On physical examination, she was tachypneic without hypoxia, wheezing, or stridor. Body temperature was 38.6 °C (101.5 °F), and blood oxygen saturation was 97% with 2 L of supplemental oxygen by nasal cannula. A contrast-enhanced chest CT was negative for pulmonary embolus and instead showed patchy, multifocal ground glass opacities in both lungs. Nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) was positive for COVID-19 infection. Respiratory viral panel was otherwise negative, and no organisms were later identified on sputum culture. White blood cell count was 6.5 × 10^9/L, D-dimer was 880 ng/mL, and C-reactive protein was 166 mg/L.

About 8 h after initial presentation, the patient began to experience worsening dyspnea, hypotension, and deteriorating mental status, requiring intubation and vasopressors. The treating team started hydroxychloroquine and intravenous vitamin C for COVID-19 infection and ceftriaxone and doxycycline for potential superimposed community-acquired pneumonia.

With subsequent supportive management, inflammatory markers progressively declined, fever resolved, and the patient's condition improved enough to allow extubation on hospital day 10 despite several chest radiographs over that time showing increasing bilateral pulmonary opacities. No repeat chest CT was obtained, and bronchoscopy or tissue sampling was not indicated.

On hospital day 11, she developed a fever of 38.8 °C (101.8 °F), with increased white blood cell count of 11.5 × 10^9/L. Blood cultures grew *Enterococcus faecalis*, presumed to be due to an intravenous line infection, and vancomycin was added as treatment. She later developed right hand swelling and a D-dimer of 3060 ng/mL on hospital day 16, and a subsequent upper extremity duplex ultrasound showed thrombus within a brachial vein. With no additional complication and earlier resolution of respiratory symptoms, she was discharged home the following day.

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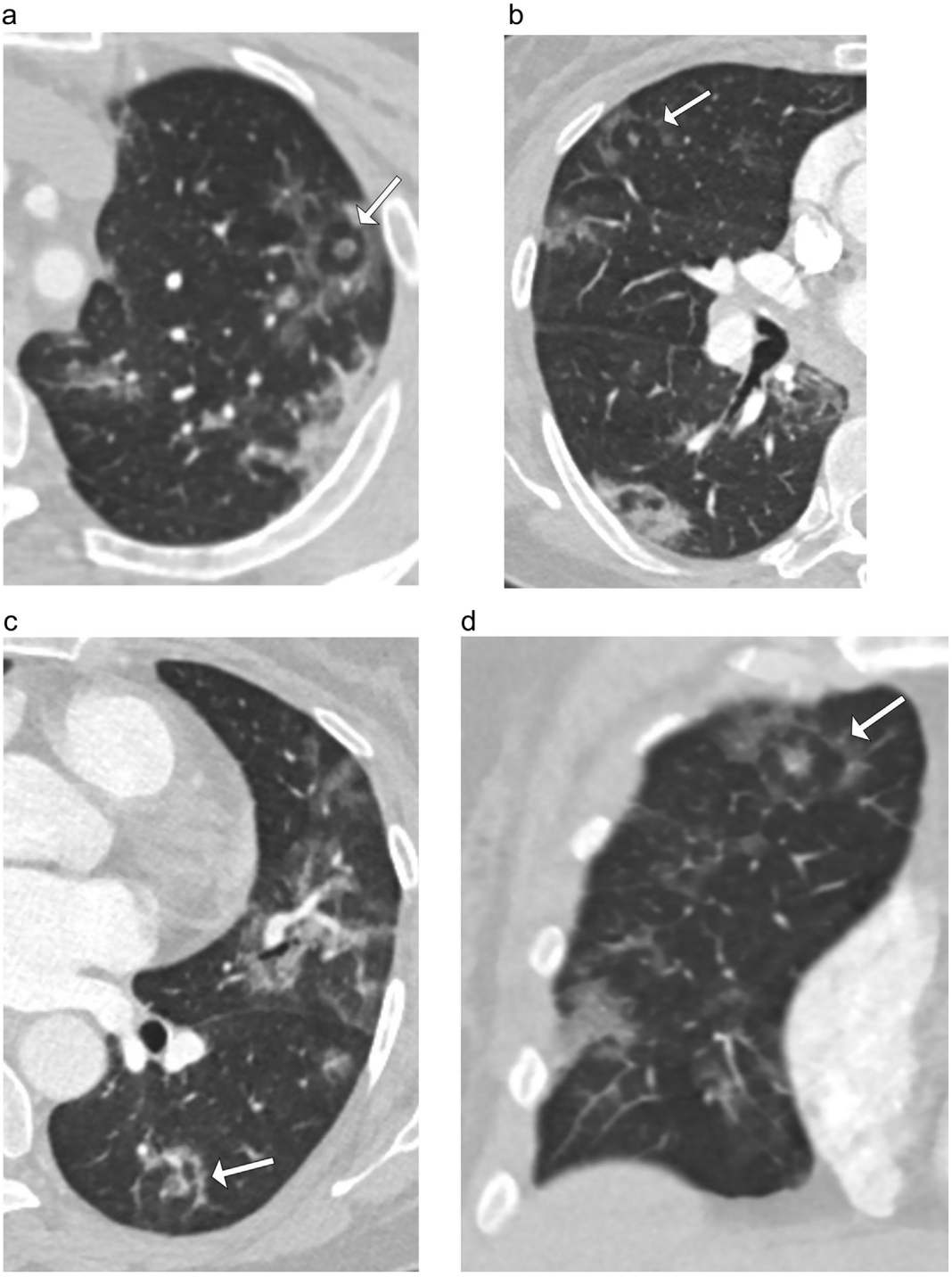

Fig. 1. The "bullseye sign" in a 59 year-old woman presenting with fever, cough, and chest pain. Axial (a, b, and c) and coronal (d and e) CT images and an axial minimum intensity projection CT image (f) show foci of central ground glass nodules surrounded by an inner ring of air and an outer ring of ground glass (white arrows). This appearance resembles a bullseye. An axial CT image (g) also shows classic reverse halo signs (black arrows). More patchy, ill-defined ground glass opacities are also present in the lungs.

3. Case 2

A 28 year-old obese woman with history of sleep apnea, asthma, and pulmonary embolus presented with seven days of progressive shortness of breath, cough, scant hemoptysis, and subjective fever. She was hypoxic on room air with blood oxygenation saturation of 91%. A contrast-enhanced chest CT showed patchy, bilateral, multifocal ground glass opacities and no pulmonary embolus. Nasopharyngeal RT-PCR confirmed COVID-19 infection.

She was then admitted and treated with supportive care including acetaminophen, anti-tussive medication, albuterol as needed, and enoxaparin prophylaxis. With 1 L/min oxygen by nasal cannula, blood oxygen saturation improved to > 95%. White blood cell count was 5.7×10^9/L, D-dimer was 680 ng/mL, and C-reactive protein was 26.5 mg/L on admission. Within three days, she began breathing comfortably on room air and was discharged home. No additional imaging was performed.

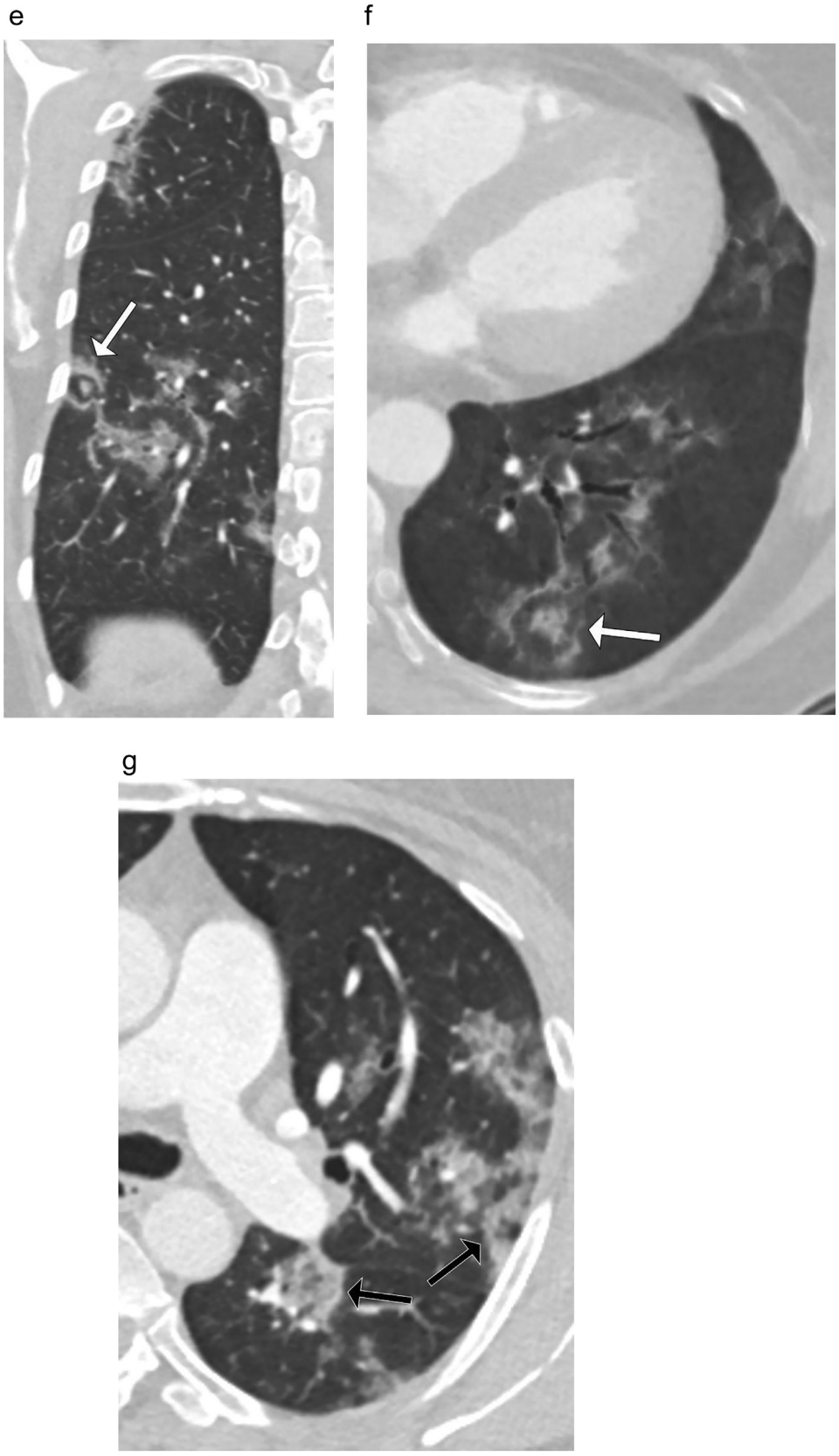

Fig. 1. (*continued*)

4. Chest CT findings

The predominant findings on the two patients' chest CT scans were ground glass opacities in both lungs with peripheral and basilar predominance. Among the ground glass opacities were focal areas we have referred to as “bullseyes” — central ground glass nodules surrounded by an inner ring of air and an outer ring of ground glass. In case 1, nine “bullseyes” were present in both lungs (seven in the lower

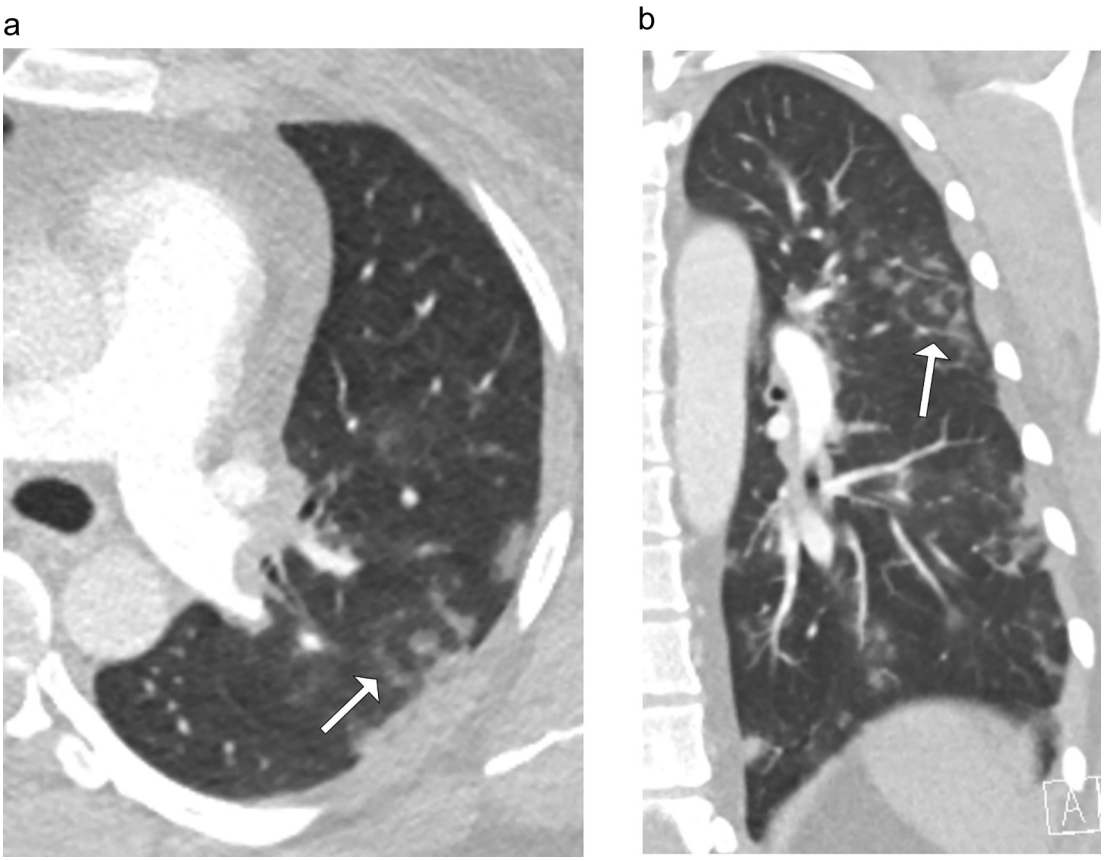

Fig. 2. The "bullseye sign" in a 28 year-old woman presenting with progressive shortness of breath, cough, scant hemoptysis, and subjective fever. Axial (a) and coronal (b) CT images show a centrilobular ground glass nodule surrounded by an inner ring of air and an outer ring of ground glass (white arrows) amidst more patchy ground glass opacities. This appearance resembles a bullseye.

lobes and two in the upper lobes), and all were located peripherally [Fig. 1]. Some "bullseyes" were more evident on minimum intensity projection images. There were also a few scattered areas of the classic RHS, although these were less numerous and conspicuous. In case 2, there was one "bullseye" in the peripheral left upper lobe [Fig. 2].

Anatomically, the central ground glass nodules of the "bullseyes" were centrilobular and the outer rings of ground glass were perilobular. The inner rings of air corresponded to sparing of the remainder of the pulmonary lobules. Adjacent pulmonary lobules tended to be spared as well. The centrilobular ground glass component was favored to be airway-related, noting that a normal pulmonary artery branch could be seen coursing through one "bullseye" in the left lower lobe in case 1. Pulmonary artery branches were otherwise not clearly identified within the other "bullseyes" due to their peripheral locations. No pulmonary embolus was identified in either case. There were no additional findings such as consolidation, interlobular septal thickening, cavitation, bronchiectasis, pleural effusion, or lymphadenopathy.

5. Discussion

Ground glass opacities are the most frequent pulmonary manifestation on CT in COVID-19 infection [2–8]. The distribution is most often bilateral, multilobar, peripheral, and basilar. Consolidation and interlobular septal thickening may be present in more advanced cases. The RHS is an infrequently reported finding [8–10].

The classic RHS consists of central ground glass or normal parenchyma with peripheral ring-like consolidation. We presume the "bullseyes" in the above cases represent variants of the RHS, presenting as centrilobular and perilobular inflammation with sparing of the remainder of the pulmonary lobule. To our knowledge, the "bullseye" appearance has not previously been described before the COVID-19 pandemic. An early case of COVID-19 pneumonia presented by Wu et al. seems to demonstrate evolution of a round consolidation into a "bullseye" [11]. A more recent case report of COVID-19 pneumonia describes a similar finding and refers to it as "target-shaped" [12].

Although the RHS is rare in most studies of COVID-19 pneumonia, it was found in 11% of cases in a study by Bai et al., who suggested its presence could distinguish COVID-19 pneumonia from non-COVID-19 pneumonias, which demonstrate a RHS in only 1% of patients [13–15]. Early in the SARS-CoV-2 outbreak, a study evaluating imaging findings of COVID-19 pneumonia suggested the RHS as a late finding (6–12 days after symptom onset) [16]. Other case reports demonstrated progression of a focus of ground glass to RHS over the course of three days and a new RHS three days after a normal chest CT [17,18].

A currently unpublished study found the RHS to be present in 25% of patients with COVID-19 pneumonia [19]. The majority were located in the periphery of the lower lobes and appeared 5–9 days of symptom onset. The RHS was also more common in patients with moderate disease than severe or critical disease with most improving or resolving on subsequent CT. The "bullseyes" in the presented cases likewise were all peripherally located and late findings (the chest CT scans were obtained 1–2 weeks after symptom onset). The patient in case 1, however, had critical disease requiring intubation and a prolonged hospitalization with progressively worsening chest radiograph findings. The patient in case 2 had mild disease requiring supplemental oxygen by nasal cannula only and a short hospitalization.

We theorize that these "bullseyes" represent regions of organizing pneumonia, the most common cause of the RHS (although it can be found in several pulmonary diseases) [20]. Other features these "bullseyes" share with organizing pneumonia are perilobular involvement

and a tendency to be located peripherally within the lung parenchyma [21]. The late presentation and evolution of the RHS and "bullseyes" on imaging also correlate with the onset of organization in patients with prolonged disease courses. The presented patients unfortunately did not have follow-up CT imaging to evaluate the evolving appearance of "bullseyes."

Autopsy series of decedent patients with COVID-19 infection show a predominant pathologic finding of diffuse alveolar damage with varying degrees of hyaline membrane formation, cellular infiltration, and organization [22–26]. These features are similar to those reported in the SARS outbreak of the early 2000s with acute exudation and hyaline membrane formation in the first 10 days and fibroblast proliferation and organizing pneumonia occurring in cases lasting longer than 20 days [24]. Within this timeframe, it is likely that ground glass opacities on CT correspond to the early exudative phase, and the RHS and "bullseyes" correspond to the later organizing phase.

Although the predominant autopsy finding in SARS patients was diffuse alveolar damage and organizing pneumonia, patients were also found to have pulmonary thrombi and hemorrhagic infarcts as well as multiorgan failure due to microthrombi [27]. While vascular injury was an important pathologic finding in SARS patients, these features can also be seen generally in ARDS [28,29].

There is growing clinical and pathologic evidence that in addition to targeting the lungs, COVID-19 infection is an endothelial disease with pulmonary features distinct from ARDS [30]. SARS-CoV-2 infects hosts through the angiotensin converting enzyme 2 receptor, which is expressed in the lungs, heart, kidneys, intestines, and throughout the vascular endothelium. Many COVID-19 patients have elevated D-dimer levels and are at increased risk of arterial and venous thrombosis [31]. Physiological features of respiratory failure in COVID-19 such as normal compliance and increased dead-space are suggestive of pulmonary endothelial dysfunction [32].

Autopsy series in COVID-19 infection have similarly shown severe pulmonary endothelial injury with widespread microangiopathy and associated hemorrhage in the periphery of the lungs [25,26], and these thrombi may play a role in gas exchange abnormalities [32]. This also raises the possibility that the RHS and "bullseyes" on imaging could represent areas of infarct and/or hemorrhage, and this may explain the preferential involvement of the lung bases, where perfusion is more prevalent [33]. Although autopsies in the early stages of the COVID-19 outbreak were limited due to biosafety concerns, future pathologic studies should be helpful in determining the precise etiology and significance of the RHS and "bullseye sign" [24].

Further study into the presence of the "bullseye sign" on CT could determine the degree of specificity for COVID-19 pneumonia. If more cases are identified, this appearance could potentially distinguish COVID-19 pneumonia from other viral pneumonias such as influenza as we enter the fall of 2020.

6. Conclusion

This case report describes the "bullseye sign" on CT, which we believe is a variant of the RHS and most likely represents the organizing phase of COVID-19 pneumonia. Although the specificity of this finding and its association with clinical outcomes are unclear, its presence should alert radiologists to the possibility of COVID-19 infection.

Declaration of competing interest

Thomas A. McLaren does not have any disclosures of possible conflict of interest and/or commercial involvement.

James F. Gruden does not have any disclosures of possible conflict of interest and/or commercial involvement.

Daniel B. Green does not have any disclosures of possible conflict of interest and/or commercial involvement.

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