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Incidence and morphological characteristics of the reversed halo sign in patients with acute pulmonary embolism and pulmonary infarction undergoing computed tomography angiography of the pulmonary arteries

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ABSTRACT

Objective: To determine the incidence of the reversed halo sign (RHS) in patients with pulmonary infarction (PI) due to acute pulmonary embolism (PE), detected by computed tomography angiography (CTA) of the pulmonary arteries, and to describe the main morphological features of the RHS. **Methods:** We evaluated 993 CTA scans, stratified by the risk of PE, performed between January of 2010 and December of 2014. Although PE was detected in 164 scans (16.5%), three of those scans were excluded because of respiratory motion artifacts. Of the remaining 161 scans, 75 (46.6%) showed lesions consistent with PI, totaling 86 lesions. Among those lesions, the RHS was seen in 33 (38.4%, in 29 patients). **Results:** Among the 29 patients with scans showing lesions characteristic of PI with the RHS, 25 (86.2%) had a single lesion and 4 (13.8%) had two, totaling 33 lesions. In all cases, the RHS was in a subpleural location. To standardize the analysis, all images were interpreted in the axial plane. Among those 33 lesions, the RHS was in the right lower lobe in 17 (51.5%), in the left lower lobe in 10 (30.3%), in the lingula in 5 (15.2%), and in the right upper lobe in 1 (3.0%). Among those same 33 lesions, areas of low attenuation were seen in 29 (87.9%). The RHS was oval in 24 (72.7%) of the cases and round in 9 (27.3%). Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS. **Conclusions:** A diagnosis of PE should be considered when there are findings such as those described here, even in patients with nonspecific clinical symptoms.

Keywords: Pulmonary embolism; Pulmonary infarction; Computed tomography angiography.

INTRODUCTION

Acute pulmonary embolism (PE) is a major cause of morbidity and mortality, requiring early diagnosis to enable appropriate treatment. PE is the third leading cause of morbidity and mortality among acute cardiovascular diseases, and is the most common cause of death in inpatients. However, it is believed that PE was suspected in only 30% of the patients who eventually died of the disease.[1-3]

It is estimated that approximately 5 million patients present with deep vein thrombosis in the United States every year.[4,5] Of those, approximately 650,000 (13%) develop PE and 100,000 to 200,000 (15.3-30.7%) die of the disease.[4,6] Epidemiological studies on PE in Brazil are few, almost all of which were based on autopsy findings, and show that the prevalence of the disease ranges from 3.9% to 16.6%.[3]

The signs and symptoms of PE are often nonspecific, requiring a high degree of suspicion. Early diagnosis to enable the institution of appropriate treatment is essential for preventing major complications, including death. A diagnosis of PE cannot be based solely on clinical data, and imaging studies, especially computed tomography angiography (CTA) of the pulmonary arteries, play a key role in this investigation. Detection of arterial luminal filling defects by CTA is the key finding for making the diagnosis. In addition, CT allows analysis of the lung parenchyma, mediastinum, and pleural cavity, with excellent spatial resolution.

Recent studies in the literature have focused on PE-related parenchymal signs[4,7,8] that, in special situations, such as inconclusive studies, could be important for diagnosis. Balakrishnan et al.[7] identified areas of reduced attenuation within the pulmonary infarction (PI) in up to 58% of the patients. He et al.[4] used the term "internal air lucencies" to describe the sign they identified within the PI in 32% of the cases evaluated, whereas Revel et al.[8] identified central lucencies within the PI in 46% of their patients. In those studies, the findings

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described are similar to the reversed halo sign (RHS), although the RHS was not identified by the authors.

In a study published in 2012, Marchiori et al.[9] evaluated 79 cases of RHS, describing infectious and noninfectious causes, and, in 7 of those cases, the RHS was caused by PI. Subsequently, in a study published in 2013, Casullo and Semionov[10] conducted a retrospective analysis of 12 cases of PE and PI in which the RHS was detected, showing that this sign could be clinically relevant in the diagnosis of PE. Therefore, the analysis of parenchymal findings on CT may be critical in patients with silent or unsuspected PE, in patients undergoing unenhanced imaging for the investigation of nonspecific clinical symptoms, or when CTA does not achieve adequate contrast of the pulmonary arteries, which can occur in up to 3% of cases.[8]

The objective of the present study was to determine the incidence of the RHS in patients with PI due to acute PE, detected by CTA of the pulmonary arteries, and to describe the main morphological features of the RHS.

METHODS

This was a cross-sectional, retrospective, observational study of PE-protocol CTA scans of the chest performed between January of 2010 and December of 2014 in the radiology department of a private hospital in Taguatinga, Brazil. The patients, who had been clinically suspected of having PE and had been stratified by the Wells score,[11] were referred from the hospital emergency room, inpatient units, and outpatient clinics to the Radiology Department of the same hospital for dedicated PE-protocol CTA of the chest. The study was approved by the Ethics Committee of the Cardiology Institute of the Federal District of Brasília (Ruling no. 844,585).

The scans were obtained in two 16-channel multidetector CT scanners (Activion; Toshiba, Tokyo, Japan), with intravenous injection of nonionic iodinated contrast (Omnipaque 300; GE Healthcare, Chicago, IL, USA), using a contrast injection pump (Stellant D; Medrad, Warrendale, PA, USA), at a flow rate of 3-5 mL/s and a total injected volume of 100-150 mL.

Images were reconstructed in a 512 × 512 pixel matrix, with a slice thickness of 1 mm and an interslice gap of 1 mm. The lungs were assessed with window widths ranging from 1,200 to 2,000 HU and center levels ranging from −300 to −700 HU. The mediastinum was assessed with window widths ranging from 350 to 500 HU and center levels ranging from 10 to 50 HU. In addition, coronal and sagittal multiplanar reconstructions were performed.

The scans were independently reevaluated by three thoracic radiologists, and disagreements were resolved by consensus. An imaging study was considered positive if at least two radiologists agreed. The criteria used to define the CT findings were those reported in the 2010 illustrated Brazilian consensus.[12]

PI was defined as the presence of peripheral consolidations on CT, with a pleural base and little contrast uptake, in patients with CTA-confirmed PE[4,8,13]; in addition, whenever possible, its lobar/segmental location was determined according to the occluded arterial branch. Patients with PI were assessed for the presence of the RHS, defined as an area of central ground-glass opacity surrounded by a peripheral halo of crescent-shaped consolidation, forming more than three quarters of a circle, or a peripheral halo of ring-shaped consolidation, forming a complete circle.[14,15]

Each scan from a patient with CTA-confirmed PE was initially analyzed for the presence of lesions consistent with PI. Contiguous lesions were considered a single lesion for statistical purposes, and, for standardization purposes and by consensus among the examiners, positive images were interpreted only in the axial plane. Subsequently, the positive images were evaluated for the presence of lesions consistent with the RHS and due to PI, and then the following characteristics were assessed: number of lesions characteristic of PI with the RHS per patient; lobar location of the lesions; presence or absence of heterogeneous areas of low attenuation within the central ground-glass opacity, with or without reticulation, in the lesions; and presence or absence of pleural effusion in the patients with the RHS.

RESULTS

In the present study, we evaluated 993 consecutive PE-protocol CTA scans, obtained between January of 2010 and December of 2014, which were stratified by the risk of PE by the hospital medical teams. PE was detected in 164 scans (16.5%). Three of those scans were excluded from the sample because of respiratory motion artifacts that impaired the analysis of the lung parenchyma, leaving a total of 161 scans in the study sample. Of the remaining scans, 75 (46.6%) showed lesions consistent with PI, totaling 86 lesions. Among those lesions, the RHS was identified in 33 (38.4%, in 29 patients). Therefore, the RHS was detected in 18% of the patients with CTA-confirmed PE. Figure 1 shows the selection of patients.

Of the 29 patients with PI and the RHS, 22 (75.9%) were female and 7 (24.1%) were male. The mean age was 43 years and 3 months, ranging from 21 to 84 years. Patients in the fourth decade of life were most often affected (13 patients).

Of those same 29 patients, 25 (86.2%) had a single lesion consistent with the RHS and 4 (13.8%) had two (Figures 2 through 5). No more than two lesions were detected per patient in our study sample. It is of note that all lesions consistent with the RHS (n = 33) were in a subpleural location. Of those 33 lesions, 17 (51.5%) were in the right lower lobe (RLL), 10 (30.3%) were in the left lower lobe (LLL), 5 (15.2%) were in the lingula, and 1 (3.0%) was in the right upper lobe (RUL). Therefore, the RHS was in the lower lobes in 81.8% of the cases.

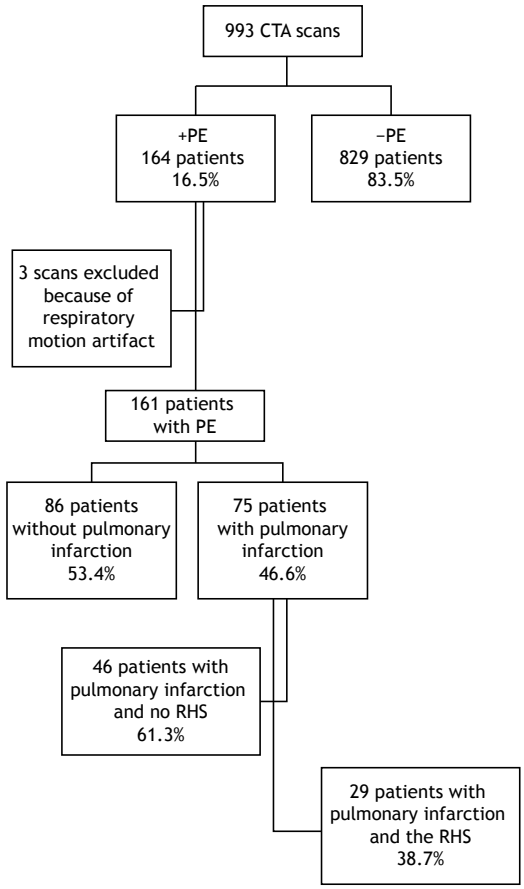

Figure 1. Patient selection process. CTA: CT angiography; PE: pulmonary embolism; and RHS: reversed halo sign.

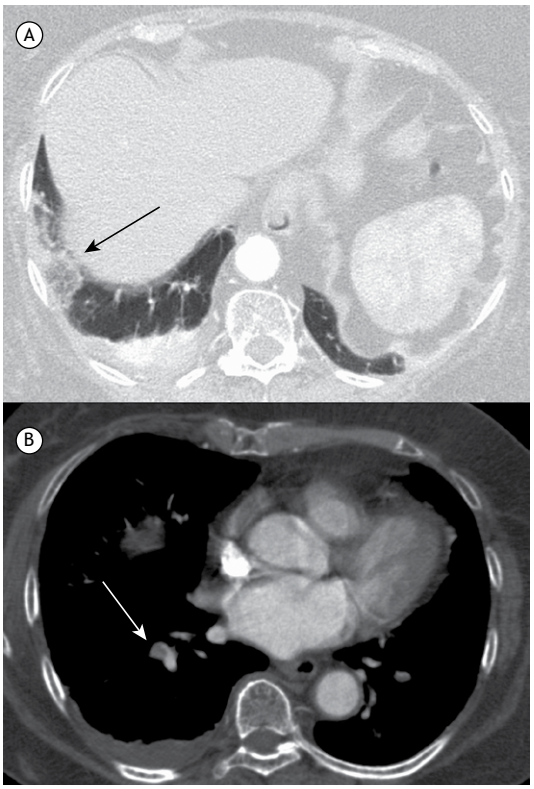

Figure 2. In A, computed tomography angiography image, with lung window settings, showing a lesion characteristic of pulmonary infarction with the reversed halo sign (black arrow) in the subpleural region of the right lower lobe, comprising heterogeneous areas of low attenuation. A small pleural effusion is also seen on this side. In B, computed tomography angiography image, with mediastinal window settings, showing a small filling defect (white arrow) at the emergence of the segmental branch that connects the right pulmonary artery to the lateral basal segment of the lower lobe.

Heterogeneous areas of low attenuation, with or without reticulation, were seen in 29 (87.9%) of the lesions characteristic of PI with the RHS; only 5 lesions (12.1%) did not show reticulation. The RHS was oval (greater diameter parallel to the pleural surface) in 24 (72.7%) of the cases and round (equivalent diameters) in 9 (27.3%). Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS.

DISCUSSION

We analyzed 993 PE-protocol CTA scans of clinically stratified patients, and PE was confirmed in 164 (16.5%). Stein et al.[16,17] analyzed 824 PE-protocol CTA scans, and PE was confirmed in 192 patients (23%), a proportion slightly higher than that found in the present study. This difference might be due to the fact that the study conducted by Stein et al.[16,17] was a prospective multicenter study conducted to validate CTA as a diagnostic method for PE, probably with better patient selection and stratification. In contrast, the present study is retrospective in nature, and the patients selected, despite having been clinically evaluated and stratified, were referred for CTA from various hospital units, such as the emergency room, inpatient units, outpatient clinics, and ICUs, by various physicians. Therefore, our inclusion criteria might not have been as stringent as those of the Stein et al. study.[17]

PI in cases of PE occurs despite the fact that the lungs have a double arterial blood supply from the pulmonary and bronchial arteries[6,18,19]; in addition, it is of note that the lung tissue is oxygenated by the alveoli.[20] PI is more common when the peripheral pulmonary artery branches are occluded,[4,20-22] because the bronchial arteries are believed to play a minor role in the parenchymal perfusion of the lung periphery.[4]

The incidence of PI in patients diagnosed with PE in the present study was 46.6%, higher than that found by He et al. (32%).[4] A comparative analysis of the two studies reveals large methodological differences. In their study, He et al.[4] analyzed 74 CTA scans that were positive for PE, whereas, in our study, we analyzed 161. In addition, the selection of positive cases in the study conducted by He et al. was based on final imaging reports, and only in cases in which the reports were positive for PE were the images assessed for PI, whereas, in the present study, positive cases were identified by studying the images from all patients who underwent PE-protocol

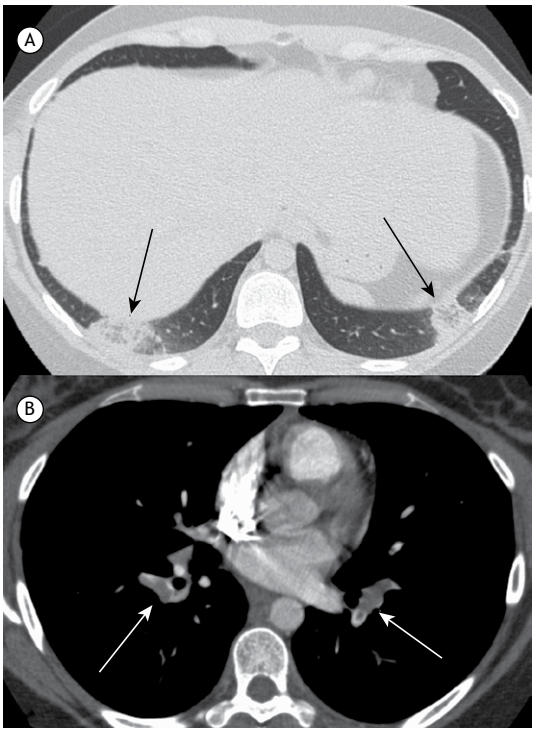

Figure 3. In A, computed tomography angiography image, with lung window settings, showing lesions characteristic of pulmonary infarction with the reversed halo sign (black arrows) in the subpleural region of the lower lobes, containing reticulation; the lesion in the right lower lobe is oval, and the one in the left lower lobe is round. In B, computed tomography angiography image, with mediastinal window settings, showing filling defects (white arrows) at the emergence of the pulmonary arteries.

CTA rather than by studying imaging reports, and there was therefore no risk of omitting images whose reports were negative for PE and might be wrong. Most patients in the study conducted by He et al.[4] (n = 45) underwent imaging in a 4-channel scanner; in the present study, all scans were performed in 16-channel scanners. In the study conducted by He et al.,[4] some of the patients were injected with contrast medium without bolus tracking or correct calculation of delay time, which may have reduced the accuracy of the diagnosis of PE; in contrast, in the present study, bolus tracking was performed in all patients. We believe that these differences had an impact on the incidence of PI, which was higher in the present study. It is also of note that the major predisposing factors for PI are left heart failure, pneumonia, septicemia, and malignancy.[4,23] In our study, all patients came from a hospital setting comprising a regional referral center for cancer. Although we could not clinically assess all of the patients included, which would go beyond the scope of the present study, we believe that, because they were hospitalized patients, they had more comorbidities and predisposing factors for PI, which would further contribute to a higher incidence of PI in the present study.

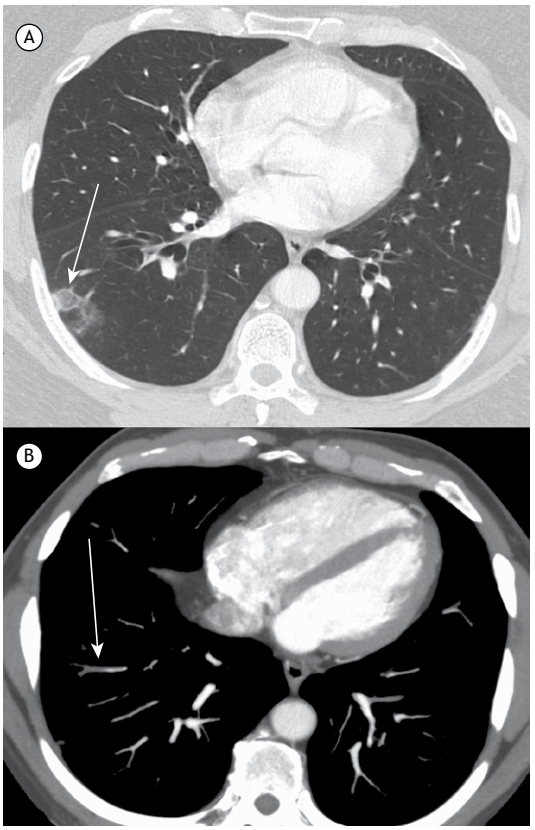

Figure 4. In A, computed tomography angiography image, with lung window settings, showing a round lesion characteristic of subpleural pulmonary infarction with the reversed halo sign (white arrow) in the right lower lobe, comprising heterogeneous areas of low attenuation and no evident reticulation. In B, computed tomography angiography image, with mediastinal window settings, showing a small filling defect (white arrow) in the segmental branch that connects the right pulmonary artery to the lower lobe.

Although the RHS is considered a finding with low specificity, the presence of nodules on the wall of or within the halo (nodular RHS) and the presence of a reticular pattern within the halo (reticular RHS) are morphological features that can narrow the differential diagnosis.[24-26] The nodular RHS is found in active granulomatous diseases, especially tuberculosis and sarcoidosis.[27] With regard to the reticular RHS, the primary diagnostic hypothesis in immunocompromised patients is that of invasive fungal diseases.[28] In immunocompetent patients, the reticular RHS usually corresponds to PI, usually secondary to thromboembolic disease.[29]

There are few studies in the literature discussing the RHS in patients with PI. However, an analysis of CT images obtained from previously published studies about the morphological features of thromboembolic PI reveal imaging patterns similar to those of the RHS,[4,7,8] although the RHS itself was not identified by the authors.

As previously mentioned, He et al.[4] used the term "internal air lucencies" to describe the sign observed

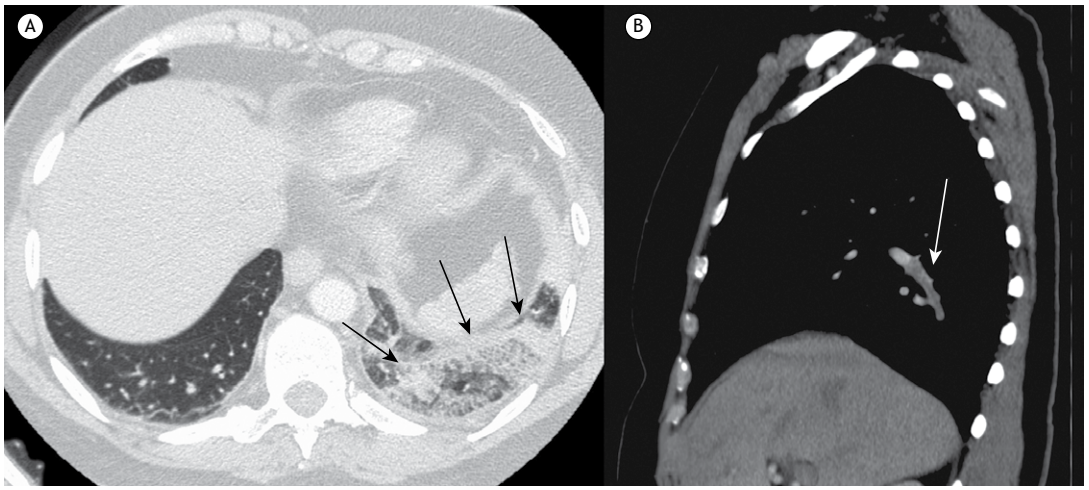

Figure 5. In A, computed tomography angiography image, with lung window settings, showing oval lesions characteristic of pulmonary infarction with the reversed halo sign (black arrows) in the subpleural region of the left lower lobe, comprising heterogeneous areas of low attenuation. In B, sagittal reconstruction, with mediastinal window settings, showing an extensive filling defect (white arrow) in the segmental branch that connects the left pulmonary artery to the posterior basal segment of the lower lobe.

in 32% of patients with PI. Revel et al.[8] described PI comprising central lucencies with peripheral consolidations in up to 46% of their patients. Balakrishnan et al.[7] reported that areas of reduced attenuation within peripheral consolidations could be seen in up to 58% of the patients with PI. In none of those three studies is there any mention of the RHS.

In the previously mentioned study published in 2012, Marchiori et al.[9] reported that the RHS was found in infectious and noninfectious diseases, and that, among the noninfectious causes, PI with imaging findings consistent with the RHS was seen in 7 cases. In the previously mentioned study published in 2013, Casullo and Semionov[10] identified the RHS in PI in a retrospective analysis of 12 cases. Those authors described the morphology, location, and number of lesions per patient, showing that this sign could have some clinical relevance in the diagnosis of PE, despite the small sample. However, the incidence and morphological features of the RHS in thromboembolic PI, as well as its true association with PE, have not been fully elucidated, and clarifying that was one of the objectives of the present study.

In the present study, we found 75 patients with PI, and, in 29 of those patients, the RHS was detected, which corresponds to approximately 39% of the patients with PI involved in the study. In those 75 patients, we found a total of 86 lesions consistent with PI, and, in 33 of those lesions, the RHS was identified, which corresponds to 38.4% of that total; in all cases, the RHS was in a subpleural location. This proportion is slightly higher than that found in the study conducted by He et al.,[4] who identified internal air lucencies in 32% of the PIs, although, as previously discussed, those authors did not use the term "RHS" to describe their findings. This proportion difference might be due to the methodologies used, because the primary objective of our study was to identify only the RHS in PI.

Morphological analysis of the PIs with the RHS revealed that the lesion was oval in 24 (72.7%) of the cases, a finding similar to what was reported by Casullo and Semionov,[10] who found this same characteristic in 71% of the cases. The oval shape was markedly predominant in that study[10] and in ours, which could contribute to the diagnosis.

Heterogeneous areas of low attenuation within the ground-glass opacity, which were possibly due to coagulation necrosis, edema, and inflammation, as discussed above, were identified in 87.9% of the cases in the present study, a proportion that is similar to that reported by Marchiori et al.[29] (94.6% of the cases), showing the importance of this morphological feature in the diagnosis of PI with the RHS.

Among the 29 patients with scans showing lesions characteristic of PI with the RHS, 25 (86.2%) had a single lesion and 4 (13.8%) had two. None of the patients had more than two lesions consistent with the RHS. In the study conducted by Casullo and Semionov,[10] 83% had a single such lesion, compared with 84.4% in the study conducted by Marchiori et al.[29]; both proportions are similar to that found in our study. Another important point is that we did not detect more than two lesions consistent with the RHS per patient, a finding also reported by Marchiori et al.[29]; this supports the notion that the finding of more than three such lesions in the same patient makes the diagnosis of PI due to PE unlikely.

Cha et al.[20] found that 53.1% of the PIs were in the RLL and 20.4% were in the LLL. In the sample studied by He et al.,[4] 73% of the PIs were in the lower lobes, 49% of which were in the RLL and 24% of which were in the LLL. Casullo and Semionov,[10] specifically evaluating the RHS in PI, found that 50%

of the lesions were in the RLL and 36% were in the LLL. Marchiori et al.[29] found that 93.2% of the imaging findings characteristic of PI with the RHS were in the lower thirds of the lungs. In the present study, we found similar results, with 17 (51.5%) of the PIs with the RHS being in the RLL and 10 (30.3%) being in the LLL. In summary, 81.8% of the lesions characteristic of PI with the RHS were detected in the lower lobes in the present study, a finding similar to what has been reported in the literature.[10,29]

Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS in the present study. In the study conducted by Casullo and Semionov,[10] there is no mention of the presence or absence of pleural effusion. In contrast, Marchiori et al.[29] reported finding pleural effusion in 64.1% of the patients with PI. The presence of pleural effusion in patients with PI could be explained by the subpleural location of the PI, accompanied by the presence of ischemia and hemorrhage, leading to pleural irritation and, consequently, to the onset of effusion. The slightly higher incidence of pleural effusion in our study might be due to the fact that our study sample consisted only of hospitalized patients, who potentially have more comorbidities.

The present study has some limitations, such as the fact that it was a retrospective observational study involving a sample of patients drawn from a single hospital and that it lacked histopathological confirmation of the PIs with the RHS. However, all patients included in the study had unequivocal CTA signs of PE, and the scans showing lesions characteristic of PI with the RHS were analyzed by three thoracic radiologists, an imaging study being considered positive if at least two examiners agreed. In addition, obtaining histopathological material from patients with PE with signs of PI is ethically unacceptable in daily practice. However, the examiners agreed that the images analyzed were consistent with PI.

In summary, the RHS was detected in 29 (18%) of the 161 patients with CTA-confirmed PE. Most (86.2%) of the patients with PI and the RHS had a single lesion, although 13.8% had two. None of the patients had more than two lesions. The RHS was oval in 72.7% of the cases, and reticulation within the ground-glass opacity was present in 87.9%. We found a higher incidence of lesions characteristic of PI with the RHS in the lower lobes (81.8%), and, in all cases, the lesions were in a subpleural location. In conclusion, attending physicians should consider a diagnosis of PE when there are incidental findings such as those described here, even in patients with nonspecific clinical symptoms.

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