Clinical Radiology 73 (2018) 503.e7–503.e13

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Morphological characteristics of the reversed halo sign that may strongly suggest pulmonary infarction

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ARTICLE INFORMATION

Article history:
Received 28 June 2017
Accepted 20 November 2017

AIM: To analyse the morphological characteristics of the reversed halo sign (RHS) on unenhanced chest computed tomography (CT), which raise suspicion of pulmonary infarction (PI) associated with pulmonary embolism (PE), and to compare these characteristics with those observed in the RHS caused by other diseases.

MATERIAL AND METHODS: CT images of 145 patients (250 RHSs) were reviewed retrospectively. Sixty-four patients had the RHS due to PI; in 81 immunocompetent patients, the RHS was caused by alternative pulmonary diseases. All PIs secondary to PE were confirmed at CT angiography. Other diagnoses were confirmed using published criteria. Two independent thoracic radiologists, who were blinded patient demographics, clinical data, and final diagnoses, analysed the morphological CT features of the RHSs.

RESULTS: Seventy-four RHSs were found in the PI group and 176 RHSs in the group of other diseases. Single RHSs were associated more frequently with PI compared with the group without PIs; three or more lesions were seen only in patients with other diseases. Low-attenuation areas inside the RHS, with or without reticulation, were observed in 94.59% of PI-associated lesions, and in no patient in the group without PI ($p<0.001$). Subpleural involvement ($p<0.001$) and lower-lung predominance ($p=0.001$) were also associated more frequently with PI. Pleural effusion was observed in 64.06% of patients with PI and in only 6.17% of those with other diseases ($p<0.001$).

CONCLUSIONS: A single RHS with low-attenuation areas inside the halo, with or without reticulation, is highly suggestive of PI. Lower-lung predominance and pleural effusion also suggest PI.

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https://doi.org/10.1016/j.crad.2017.11.022
0009-9260/

Introduction

Pulmonary embolism (PE) is a common, potentially fatal condition associated with high morbidity and mortality. Early diagnosis of PE followed by adequate treatment reduces the risk of major complications, making the institution of effective therapy as quickly as possible imperative. Patients with acute PE, however, often have non-specific symptoms, and prompt recognition of PE remains a challenge.[1–5]

Imaging plays a critical role in the early diagnosis of PE. Computed tomography (CT) pulmonary angiography (PA) has been established as a first-line diagnostic technique in patients suspected of having PE. Although the diagnosis of PE is based on direct arterial findings, indirect parenchymal signs suggestive of pulmonary infarction (PI) are occasionally detected at unenhanced CT, increasing the diagnosis of unexpected PE.[5]

Although a variety of parenchymal CT signs suggesting PI have been reported,[5–7] the reversed halo sign (RHS) has seldom been included among them.[8–10] The RHS has been defined as a focal, rounded area of ground-glass opacity surrounded by a nearly complete ring of consolidation.[11] Voloudaki *et al.*[12] first described the RHS in patients with cryptogenic organising pneumonia (COP), and this sign was once considered to be specific to COP[13]; however, it was subsequently reported in association with a wide spectrum of diseases[14,15] and is now regarded as a non-specific sign.

The recognition of specific morphological CT characteristics of the RHS due to PI may raise the possibility of PE and indicate the need for urgent definitive investigations, such as CTPA. The aims of this study were to describe the characteristics of the RHS on unenhanced chest CT associated with PI, and compare them with those caused by diseases other than PI, with the ultimate aim of identifying CT characteristics that may raise the suspicion of PE.

Materials and methods

Patient selection

The institutional review board approved this study and waived the requirement for informed patient consent. All data used in this study were anonymised. Patients with the RHS caused by PI were selected retrospectively from a total of 2,482 consecutive patients who underwent CTPA between January 2011 and December 2015 in three tertiary hospitals in Brazil. PE was detected in 410 (16.52%) of these patients, but eight cases were discarded because of movement artefacts that impaired parenchymal evaluation. In the remaining 402 studies, 64 (15.9%) patients demonstrated the RHS. To identify patients with the RHS related to diseases other than PE, a search tool was used to select reports containing the words “reversed halo sign”; a total of 81 patients were identified. Medical records and CT images of 64 patients with PI (34 men, 30 women; mean age 50.1 years, range 31–77 years) and 81 immunocompetent patients (46 men, 35 women; mean age 46.4 years, range 27–74 years) with other infectious and non-infectious diseases (organising pneumonia, n=30; paracoccidioidomycosis, n=23; tuberculosis, n=15; sarcoidosis, n=5; adenocarcinoma, n=3; granulomatosis with polyangiitis, n=2; histoplasmosis, n=1; cryptococcosis, n=1; and schistosomiasis, n=1) who presented the RHS were reviewed retrospectively.

Image acquisition

Chest CT examinations were performed using a variety of helical scanners, as different hospitals were involved in this study. CT acquisition parameters were 0.625–2.5 mm section thickness, 0.9–1.75 pitch, 120 kV, 80–350 mA/s or automatic tube current adjustment, and 0.6–0.8 seconds per gantry rotation. All CTPA examinations were performed with 16- to 64-detector row CT systems using a peak voltage of 120 kV, exposure of approximately 300 mA/s per section, and 50–100 ml of 350 mg non-ionic iso-osmolar contrast medium. In the authors’ institutions, the routine procedure for CTPA examination includes scanning without contrast medium administration before performing a study with intravenous contrast medium. Image reconstruction included contiguous 1.25- or 2-mm-thick sections with high-resolution and standard algorithms for evaluation of the lung parenchyma and mediastinum. Patients were examined using the single breath-hold technique.

Image analysis

Two board-certified radiologists, both with >17 years of experience in chest imaging, analysed all CT images, and final assessment was achieved in consensus. The radiologists were blinded to patient demographics, clinical data, and final diagnoses. All chest CT images were analysed initially using parenchymal window settings (1200–1600 HU width; −500 to −700 HU level), and subsequently, reviewed using mediastinal window settings (350–450 HU width; 20–50 HU level). For patients with PI, only unenhanced images were reviewed. Various studies[10,16–18] have shown that the central area of the RHS may consist not only of ground-glass opacities, but also of small nodules, the reticulated pattern, or low-density areas. Images were displayed with standard mediastinal and parenchymal window settings, and each observer adjusted to an intermediate modified setting that enabled more accurate analysis of the various characteristics of the central RHS area. CT evaluation with mediastinal or intermediate windows may be important in depicting different aspects inside the halo.

The readers were asked to assess the internal features of the RHS, such as low attenuation areas, reticulation, small nodules, and ground-glass opacities, and to determine the number of lesions. Low attenuation areas were evaluated in lung, mediastinal, and intermediate window settings. For patients with more than three lesions, only the largest three lesions were analysed, as the presence of many RHSs in the same patient sometimes hindered individual analysis of each lesion.[16]

The anatomical distribution was noted to be peripheral (subpleural) when a predominance of abnormalities were detected in the outer third of the lung periphery, in contact with the pleural surface, and central when a predominance of abnormalities were detected in the inner two-thirds of the transverse plane. In the craniocaudal direction, lung zones were determined to be upper (abnormality above the level of the aortic arch), middle between the aortic arch and carina), and lower (below the level of the carina). Pleural effusions were also investigated.

All patients in the PI group had PE confirmed at CTPA. The criterion for PE diagnosis was the presence of intraluminal filling defects causing partial or total obliteration of lumen arteries, with or without a corresponding increase in the diameter of the affected vessel. PI was diagnosed based on the presence of an RHS in the vascular territory of a thrombosed artery, with or without clinical signs suggesting PI. PI was also diagnosed by the presence of arterial filling defects in arteries supplying segments other than those showing the RHS, associated with signs of PI, such as pleuritic chest pain, and/or haemoptysis.[3,5] In the other group, the RHS was associated with various infectious and non-infectious conditions, including granulomatous pulmonary diseases. The diagnoses of these other diseases were confirmed by the identification of bacilli or fungi on direct examination, culture, or histopathological specimens, or by the typical findings of laboratory or histopathological studies.[9,16,17]

Statistical analysis

Demographic data were presented as mean values. The number, morphological characteristics, and distribution of RHSs and the presence of pleural effusion were compared between patient groups using the chi-squared test. The interobserver agreement between the two chest radiologists regarding the 64 patients with PI was determined using the kappa coefficient. Observer agreement was categorised by kappa values as poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or almost perfect (>0.81). Statistical analyses were performed using the PRISM Statistical Software Package (version 6.04; GraphPad Software, La Jolla, CA, USA). A value of $p<0.05$ was considered to indicate a statistically significant difference.

Results

The study population comprised 145 patients with the RHS on chest CT. A total of 250 RHSs were identified. Single lesions were observed in 81 (55.9%) patients, two RHSs were present in each of 22 (15.2%) patients, and three or more RHSs were present in each of 42 (28.9%) patients. Low-attenuation areas were observed in 70 of 250 (28%) RHSs, but not in 180 (72%) RHSs. Reticulation inside the halo was found in 26 (10.4%) RHSs and ground-glass opacities were present in 148 (59.2%) RHSs. Sixty-six (26.4%) RHSs were located in the upper third, 70 (28%) in the middle third, and 114 (45.6%) in the lower third of the lungs. Preferential distribution was central for 106 (42.4%) RHSs and peripheral for 144 (57.6%). Associated pleural effusion was present in 45 (31.7%) patients.

Among the 64 patients in the PI group (Figs 1–3), 54 (84.38%) presented with single RHS lesions and the remaining 10 (15.62%) had two lesions each with RHS morphology. No patient in this group had three or more RHS lesions. In cases with more than one lesion, the morphological characteristics of the lesions were similar. A total of 74 RHS lesions were found in the PI group. Among these, low-attenuation areas were observed in 70 (94.59%; 44 [59.46%] without reticulation, 26 [35.13%] with reticulation). The remaining four (5.41%) RHSs showed central ground-glass opacities. Sixty-nine (93.24%) lesions occupied the lower third and five (6.76%) were located in the upper third of the lung. Seventy-one (95.95%) lesions were peripheral (subpleural) and only three (4.05%) were central. Pleural effusion occurred in 41 (64.06%) cases of PI. The interobserver agreement between the two chest radiologists for the presence of the RHS was good, with a kappa value of 0.79 (95% confidence interval [CI]: 0.6–1.0).

Among the 81 immunocompetent patients with other diseases, 176 RHSs were analysed (paracoccidioidomycosis, $n=64$; organising pneumonia, $n=58$, Fig 4; tuberculosis, $n=27$, Fig 5; sarcoidosis, $n=11$; granulomatosis with polyangiitis, $n=4$; adenocarcinoma, $n=3$; histoplasmosis, $n=3$; cryptococcosis, $n=3$; schistosomiasis, $n=3$). Twenty-eight (34.57%) patients presented single RHSs, 11 (13.58%) presented two lesions, and 42 (51.85%) presented with three or more lesions with this sign. Ground-glass opacities were found as the internal features of 144 (81.82%) RHSs, and small nodules were detected in 32 (18.18%) RHSs in this group. No low-attenuation area (with or without reticulation) inside the RHS was observed in patients with diseases other than PI. Sixty-one (34.66%) lesions occurred in the upper third, 70 (39.77%) in the middle third, and 45 (25.57%) in the lower third of the lung. In this group, 103 (58.52%) RHSs occurred in the central region and 73 (41.48%) occurred in the peripheral (subpleural) region. Only five (6.17%) patients in this group showed pleural effusion.

When the two groups were compared, the presence of more than two lesions strongly suggested diseases other than PI ($p<0.001$). The presence of low-attenuation areas, with or without reticulation, inside the halo was associated strongly with the diagnosis of PI ($p<0.001$). Peripheral (subpleural) RHSs and those located in the lower third of the lung occurred mostly in patients with PI, as did pleural effusion (all $p<0.001$). The CT findings of patients with PI and other diseases are summarised in Table 1.

Discussion

In this series of patients with the RHS caused by PI and other diseases, the main morphological characteristics of the RHS that favoured PI were the presence of internal areas of low attenuation (with or without reticulation) and predominance in the peripheral regions of the lower lobes.

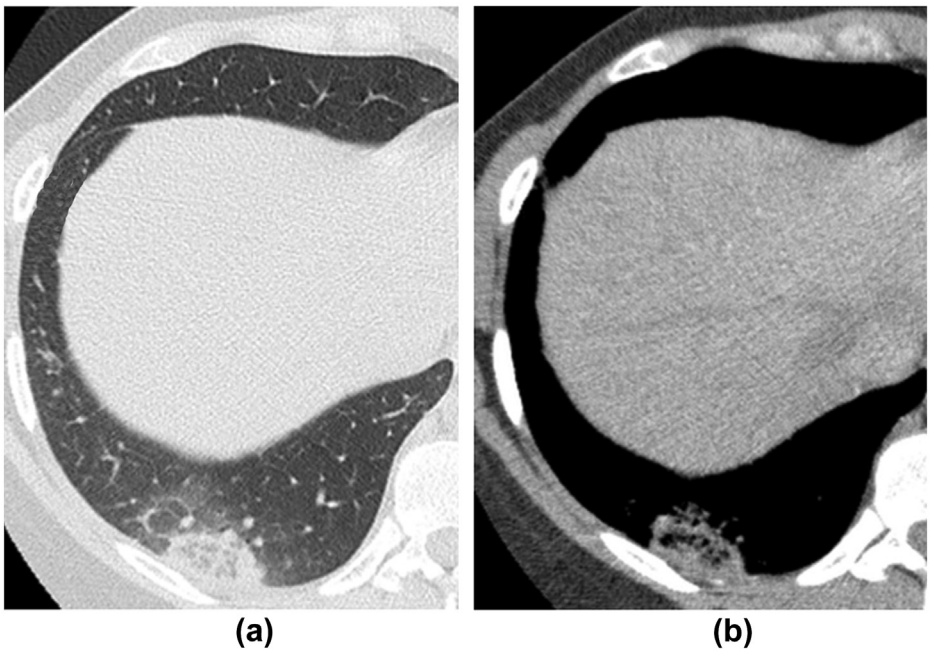

Figure 1 A 54-year-old man with PE. Axial unenhanced CT images obtained with the lung (a) and mediastinal (b) window settings demonstrate a subpleural RHS in the lower lobe of the right lung. Note in (b) the presence of low-attenuation areas (central lucencies) inside the halo.

Lung ischaemia may lead to a spectrum of injuries involving damage to the pulmonary and alveolar epithelial cells, resulting in haemorrhage and infarction in an area distal to the embolic obstruction.[3,6] Ischaemic injury to the lung with infarction is not inevitable in patients with acute PE because the lung has a dual blood supply via the pulmonary and bronchial arteries.[6] PI has been identified in 10–45% of patients with PE in autopsy studies,[3,6] but its clinical presentation may be elusive and up to 70% of major PE may be unsuspected by clinicians.[19] The diagnosis of PI caused by PE is based on clinicoradiological grounds, and little information regarding the pathological description of the RHS due to PI is available.

The RHS has increasingly been recognised as a valuable imaging finding in several diseases; however, few RHS morphological features that may help to narrow the range

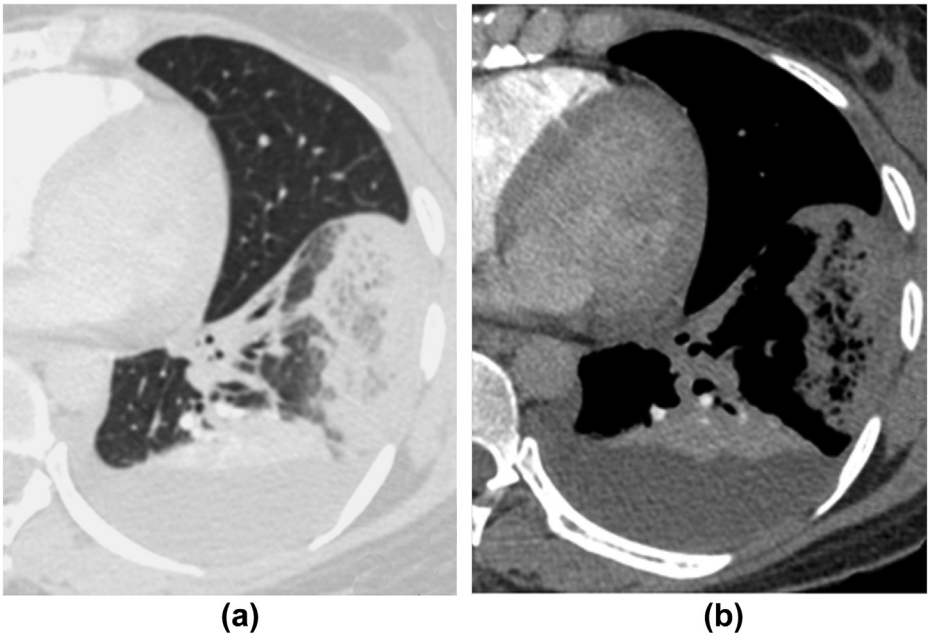

Figure 2 A 32-year-old woman with acute PE and PI. Axial contrast-enhanced CT images obtained with the lung (a) and mediastinal (b) window settings show an oval, subpleural RHS in the lateral segment of the left lower lobe of the lung (arrows). Note in (b) the reticulation inside the halo. A posterior atelectasis is also visible, outlined against a pleural effusion. The patient had clots involving several segmentary and non-segmentary pulmonary arteries (not shown).

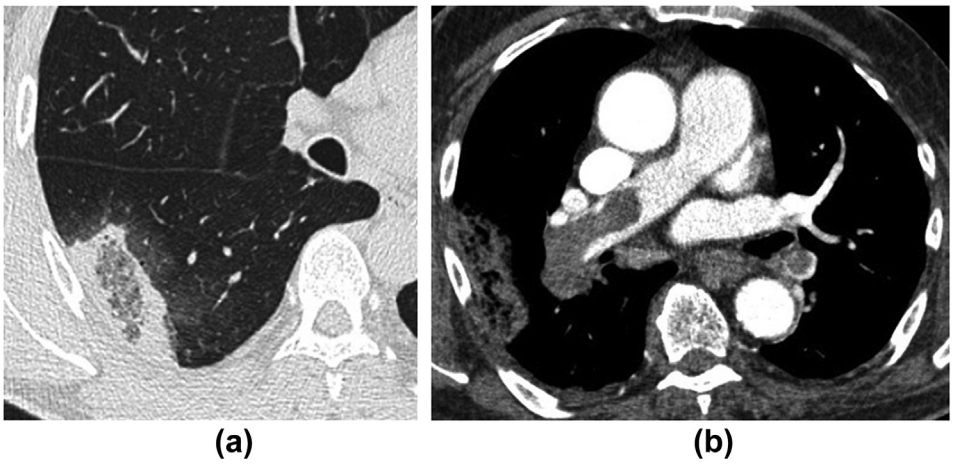

Figure 3 A 42-year-old man with PE. (a) Axial unenhanced CT image obtained with the lung window setting demonstrates a subpleural RHS in the right lower lobe of the lung. (b) CTPA shows the presence of intraluminal filling defects (emboli) in the right main pulmonary artery and left lower lobar artery.

of diseases considered in differential diagnosis have been described. Most PI cases described in the literature have presented with single lesions. Two infarctions have been observed in some patients, and the presence of three or more infarctions is rare.[3,7,8] In the present study, single RHSs occurred in 84.38% of patients with PI and in 33.33% of those with other diseases. Single and multiple (more than two) RHSs were seen in association with diseases other than PI, as in the literature[9]; however, no patient with PI presented three or more lesions.

In the present series, low-attenuation areas inside the halo, with or without reticulation, occurred in almost all (94.59%) PI lesions and were not found in patients with other diseases. CT aspects similar to the RHS have been described in patients with PI.[5–7,10] Balakrishnan *et al.*[7] reported the presence of "low-attenuation areas" within peripheral consolidations in 58% of such patients, He *et al.*[6] observed "internal air lucencies" in 32% of patients, and Revel *et al.*[5] found "centrally located lucencies" within peripheral consolidations in 46% of patients with PI. The data from the present study suggest that low-attenuation areas inside the halo, with or without reticulation, are highly suggestive of PI.

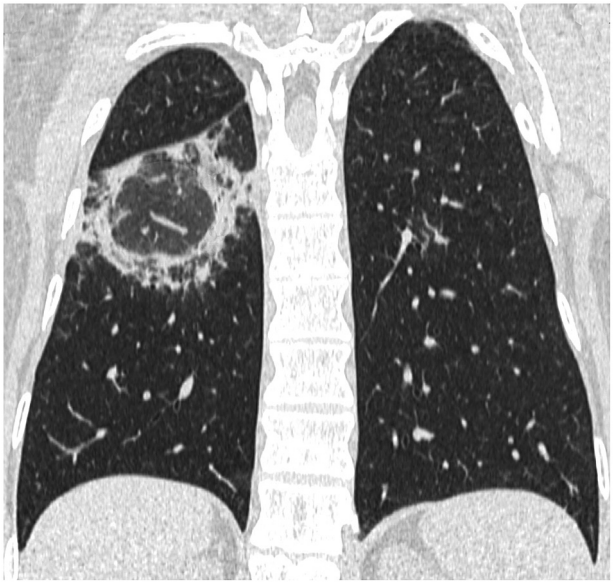

Figure 4 A 47-year-old woman with biopsy-proven organising pneumonia. A coronal reformatted CT image obtained with the lung window setting demonstrates a round RHS in the superior segment of the right lower lobe. Mild ground-glass opacities are visible inside the halo.

Published criteria for the characterisation of the RHS caused by invasive fungal infection (IFI) indicate that reticulation inside the halo is also very common (in 93% of patients) and associated pleural effusion was present in 73% of affected patients.[18] This similarity of appearance may be due to the same pathophysiological mechanism underlying both diseases: the PI is caused by thromboembolic occlusion and IFI infarcts occur due to intravascular thrombi containing fungal hyphae. Reticulation inside the RHS halo, however, should be interpreted with consideration of the overall clinical presentation and the patient's immune status. In an immunocompromised patient, the RHS with reticulation is highly suggestive of IFI, particularly pulmonary zygomycosis or angioinvasive pulmonary aspergillosis.[9,20–23] In an immunocompetent patient, this feature is highly suggestive of PI. In this context, careful investigation for PE should be initiated, as any delay significantly increases mortality. In the present study, reticulation inside the halo occurred in one-third of cases of PI.

In the present study, RHS predominance in the lower lung regions was significantly more frequent in association with PI than with other diseases. The present data are consistent with the literature concerning the craniocaudal distribution of the RHS due to PI. Casullo *et al.*[8] described the occurrence of the RHS due to PI more frequently in the lower lobes than in other lung regions, and Kim *et al.*[13] showed no predominance in the craniocaudal distribution of the RHS caused by organising pneumonia, which is the most frequent cause of this sign.

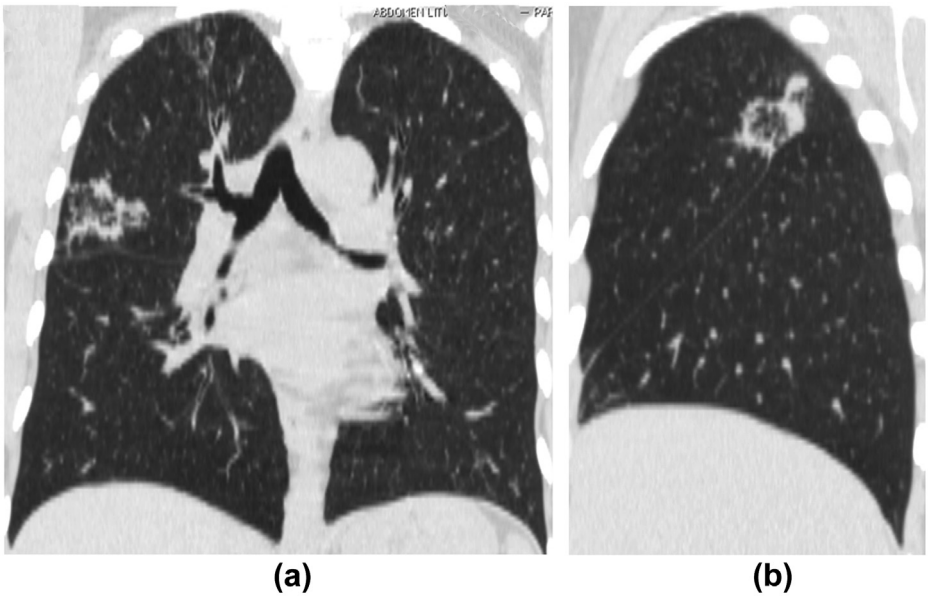

Figure 5 A 53-year-old man with pulmonary tuberculosis. (a) Axial and (b) coronal unenhanced CT images obtained with the lung window setting show a RHS with nodular walls in the apicoposterior segment of the right upper lobe.

Pleural effusion is often present in patients with acute PE, occurring in about 50% of cases.[6,24] The pathogenesis of pleural effusion in the setting of PE remains unclear, but seems to be related to the presence of PI.[24] In contrast, pleural effusion is seldom seen in patients with the RHS caused by other diseases.[6] In the present series, pleural effusion was present in more than half (64.06%) of patients with PI and was rarely seen in patients with other diseases (6.17%), contributing to the diagnosis of PI.

PE is a major health problem and a potentially fatal condition that should be treated effectively once diagnosed; however, due to the non-specific clinical signs and symptoms in a high percentage of cases, early diagnosis may be difficult.[1–5] The recognition of radiological signs suggesting PI on unenhanced CT has clinical utility, as it raises suspicion of PE and indicates the need for CTPA, with important clinical implications in patients with no known risk factor.[8]

Table 1
Morphological characteristics and distribution of reversed halo signs in patients with pulmonary infarction and other diseases.

Morphological characteristics and distribution	PI (n=64 patients; 74 RHS)	Non-embolic diseases (n=81 patients; 176 RHS)	p-Value
Number of lesions[a]			<0.001
1	54 (84.38%)	28 (34.57%)	
2	10 (15.62%)	11 (13.58%)	
≥3	0 (0%)	42 (51.85%)	
Low-attenuation areas[b]			<0.001
Yes	70 (94.59%)	0 (0%)	
No	4 (5.41)	176 (100%)	
Ground-glass opacities[b]			<0.001
Yes	4 (5.41%)	144 (81.82%)	
No	70 (94.59%)	32 (18.18%)	
Craniocaudal distribution[b]			<0.001
Upper third	5 (6.76%)	61 (34.66%)	
Middle third	0 (0%)	70 (39.77%)	
Lower third	69 (93.24%)	45 (25.57%)	
Axial predominance[b]			<0.001
Central	3 (4.05%)	103 (58.52%)	
Peripheral/subpleural	71 (95.95%)	73 (41.48%)	
Associated findings			
Pleural effusion[a]			<0.001
Yes	41 (64.06%)	5 (6.17%)	
No	23 (35.94%)	76 (93.83%)	

Data are presented as n (%).
PI, pulmonary infarction; RHS, reversed halo sign.
[a] Based on 64 patients with PI and 81 patients with non-embolic diseases.
[b] Based on 74 RHSs caused by PI and 176 RHSs caused by non-embolic diseases.

This study has some limitations, including the retrospective design and the relatively small sample. Despite the limitations inherent to retrospective studies, this study is the first to systematically analyse the morphological characteristics of the RHS in patients with PI due to PE. In addition, although the cases were obtained from different institutions with small differences in the equipment used to perform examinations, this variation is unlikely to have impacted the results. Finally, no histopathological correlation was obtained in patients with PI, although all patients in this series had unequivocal CT findings of PE; however, even in a prospective study, it would be ethically controversial to obtain histopathological diagnoses for parenchymal lesions in the clinical setting of PE.

In conclusion, the RHS is increasingly recognised as a valuable imaging finding in several lung diseases. Morphological characteristics of the RHS may help to narrow the differential diagnosis. Low-attenuation areas inside the halo, with or without reticulation, strongly suggest PI. Subpleural and lower-lung localisation, as well as pleural effusion in association with the RHS, may also favour PI. These chest CT findings should indicate the need for additional CTPA examination in patients with unsuspected PE.

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