

Reversed Halo Sign in Active Pulmonary Tuberculosis: Criteria for Differentiation From Cryptogenic Organizing Pneumonia

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OBJECTIVE. The purpose of this study was to compare the morphologic characteristics of the “reversed halo” sign caused by tuberculosis with those caused by cryptogenic organizing pneumonia (COP) and to determine whether high-resolution CT (HRCT) can differentiate between these two conditions.

MATERIALS AND METHODS. We retrospectively reviewed the HRCT scans of patients with the reversed halo sign caused by active tuberculosis and HRCT scans of patients with the reversed halo sign caused by COP. The study included 12 patients with active pulmonary tuberculosis (10 women and two men) and 10 patients with biopsy-proven COP (five women and five men). Tuberculosis was diagnosed by culture of sputum, bronchoalveolar lavage, or biopsy specimen. All patients underwent HRCT, and the images were reviewed by two chest radiologists who reached decisions by consensus.

RESULTS. HRCT scans of all patients with active tuberculosis showed reversed halos with nodular walls; in most cases (10/12), we also observed nodules inside the halos. None of the HRCT scans of the COP cases reviewed had halos with nodular walls or nodules inside them. We also observed parenchymal abnormalities, such as consolidation, ground-glass, and linear opacities, associated with the reversed halo sign. Neither the number of reversed halo sign lesions nor the associated parenchymal lesions discriminated between tuberculosis and COP. Nevertheless, the association of the reversed halo sign with nodular walls or nodules inside the halo was seen only in tuberculosis patients.

CONCLUSION. Although COP is considered the most frequent cause of the reversed halo sign, the presence of nodular walls or nodules inside the reversed halo strongly favors a diagnosis of active pulmonary tuberculosis rather than COP.

The “reversed halo” sign shown by high-resolution CT (HRCT) is defined as a focal, rounded area of ground-glass opacity surrounded by a nearly complete ring of consolidation [1]. This lung lesion pattern was first described by Voloudaki et al. [2] as a crescent- or ring-shaped opacity surrounding areas of ground-glass attenuation in patients with cryptogenic organizing pneumonia (COP). The term “reversed halo sign” was first suggested by Kim et al. [3] who regarded the reversed halo sign as specific for COP. Subsequently, various authors have reported the presence of the sign in a wide spectrum of diseases including infectious and noninfectious conditions [4, 5].

The presence of reversed halo sign-type lesions in patients with pulmonary tuberculosis was described only recently [6, 7]. The importance of identifying imaging pat-

terns that could raise the possibility of active tuberculosis has long been recognized as highly relevant for public health and for ensuring that infected patients receive the appropriate therapy. Acid-fast bacilli are found in the sputum in only a limited number of patients with active pulmonary tuberculosis. For this reason, antituberculosis treatment is frequently initiated and anti-communicating exposure measures such as isolation are taken on the basis of imaging findings that are suggestive of active tuberculosis before bacteriologic confirmation is possible [8]. Although different HRCT signs have been reported in pulmonary tuberculosis [8–11], the reversed halo sign has not been included among these signs. With the exception of the two articles mentioned [6, 7], no other article in the literature to our knowledge has described the reversed halo sign in patients with active tuberculosis.

Reversed Halo Sign in Active Pulmonary Tuberculosis

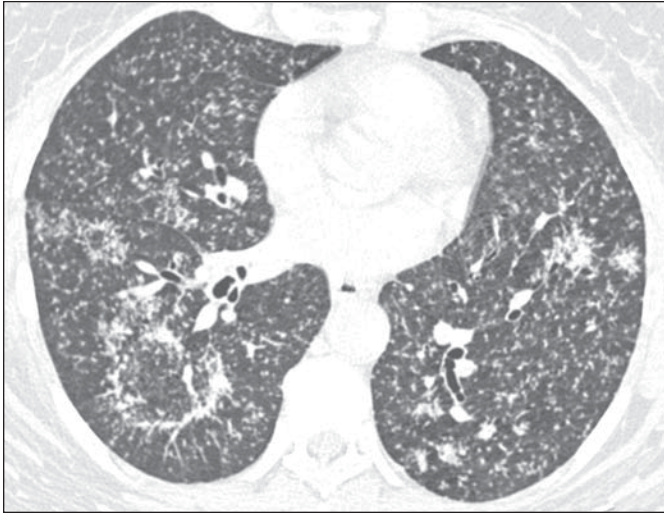


Fig. 1—59-year-old woman with pulmonary tuberculosis. High-resolution CT scan of lower pulmonary regions shows bilateral random nodules and two reversed halo signs on right lung. Note that walls of halos are nodular.

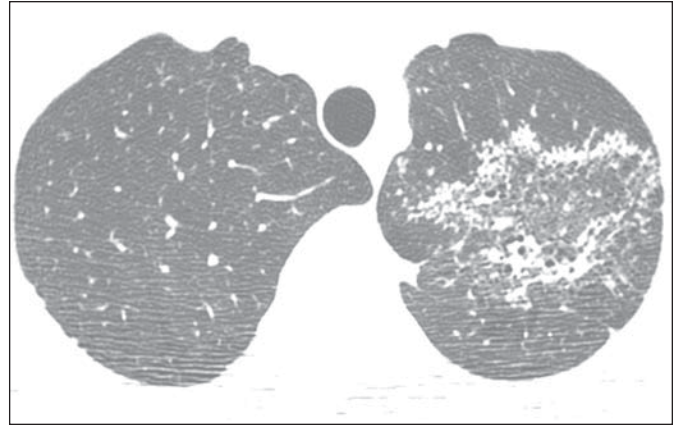


Fig. 2—36-year-old man with pulmonary tuberculosis. High-resolution CT scan of upper pulmonary regions shows reversed halo sign in left upper lobe with nodular walls and nodules inside halo.

Because COP is described as the most common cause of the reversed halo sign and because this pattern can also occur in active tuberculosis, the aim of this study was to compare the morphologic findings of the reversed halo sign in patients with COP and in those with tuberculosis and to determine whether COP and active tuberculosis cases showing this tomographic sign can be differentiated with the aid of HRCT.

Materials and Methods

This study was approved by the institutional review board of our institution, and the requirement for informed patient consent was waived. We retrospectively reviewed the medical records of 12 patients with active pulmonary tuberculosis and of 10 patients with COP who presented the reversed halo sign by HRCT. These patients were evaluated in seven tertiary hospitals in Brazil between 2005 and 2010.

The tuberculosis patients were 10 women and two men ranging in age from 31 to 59 years old (mean age, 40.1 years). The patients with COP were five women and five men ranging in age from 25 to 68 years old (mean age, 46.3 years).

The COP diagnosis in all cases was made by open lung biopsy. The active tuberculosis diagnosis was based on the presence of acid-fast bacilli identified by means of a culture of bronchoalveolar lavage ($n = 7$) or sputum ($n = 4$) and histologic visualization of caseating granulomas typical of tuberculosis with culture of biopsy specimen ($n = 1$). Direct sputum microscopy was negative for acid-fast bacilli in six tuberculosis patients. No tuberculosis patients had diabetes mellitus or AIDS

or a history of steroid medication or alcoholism. An extensive diagnostic workup did not reveal any other reason for the symptoms or radiologic abnormalities in any of the tuberculosis patients.

High-Resolution CT

HRCT lung scans were obtained using different CT scanners because patients from different hospitals were involved in this study. Nevertheless, the technical parameters for HRCT were similar: 1- to 2-mm collimation and 5- to 10-mm interval using a high-spatial-frequency recon-

struction algorithm. Images were acquired at mediastinal (width, 350–450 HU; level, 10–20 HU) and parenchymal (width, 1200–1600 HU; level, –500 to –700 HU) window settings.

Two chest radiologists with more than 15 years of experience independently reviewed the scans, and decisions concerning the findings were reached by consensus. The observers were blinded to patient demographics, the clinical findings, and the final diagnosis. The HRCT scans were assessed for morphologic characteristics and the number of lesions. We also studied the HRCT scans for the

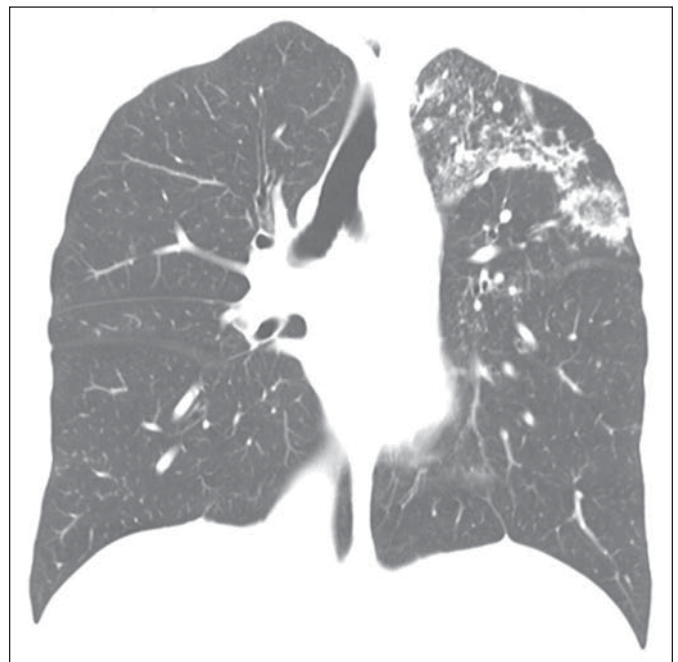


Fig. 3—38-year-old woman with pulmonary tuberculosis. Coronal reformatted image shows reversed halo sign with nodular walls in left upper lobe. Also seen are consolidations, ground-glass opacities, and nodules in upper portion of this lobe.

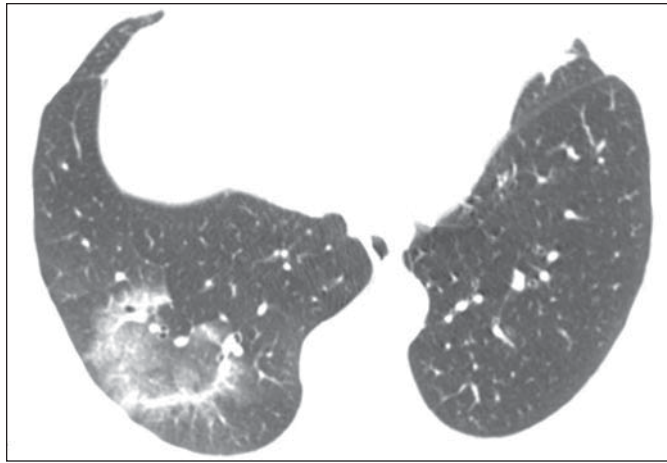


Fig. 4—39-year-old woman with cryptogenic organizing pneumonia. High-resolution CT scan shows reversed halo sign in right lower lobe. Note also absence of nodules on walls or inside halo.

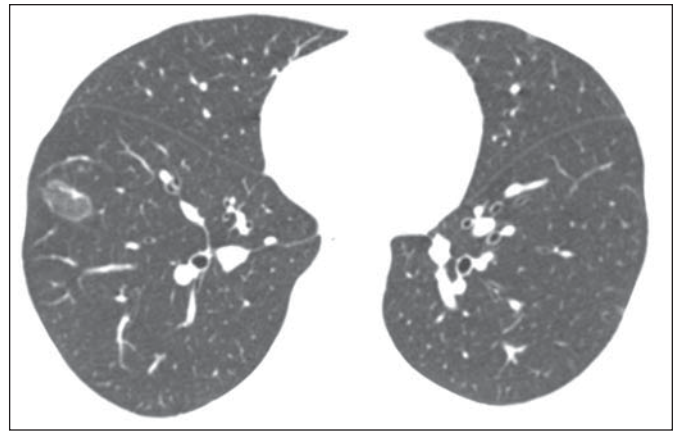


Fig. 5—36-year-old woman with cryptogenic organizing pneumonia. High-resolution CT scan of lower pulmonary regions shows localized oval area containing central homogeneous ground-glass opacities and smooth ring of consolidation (reversed halo sign) in right lower lobe. Again, note absence of nodules.

presence of the associated findings of airspace consolidation, ground-glass attenuation, linear opacities, and nodules. The definitions of these patterns followed the “Glossary of Terms for Thoracic Imaging” proposed by the Fleischner Society [1]. Lymph node enlargement, pleural effusions, and any other lung abnormalities were also investigated.

Statistical Analysis

The two patient groups were compared with respect to the number of patients with HRCT images showing the reversed halo sign, other associated lesions, a nodular wall, and nodules inside the reversed halo sign. The presence of significant differences was statistically evaluated by means of the Fisher exact test. A p value < 0.05 was considered to indicate a statistically significant difference. Data analyses were performed using SPSS software (version 10.0, SPSS).

Results

Of the 12 patients with active pulmonary tuberculosis, six patients had a single lesion, three had two lesions (Figs. 1–3), and the remaining three had three or more lesions. Other parenchymal abnormalities were found in association with the reversed halo sign in six patients and were characterized as consolidations ($n = 5$), clusters of small nodules ($n = 5$), sparse nodules ($n = 3$), linear opacities ($n = 2$), ground-glass opacities ($n = 1$), and cavitation ($n = 1$).

In the COP cases (Figs. 4 and 5), five patients had only one halo, and three or more lesions were seen in the five remaining patients. Associated parenchymal abnormalities were detected in six patients and were characterized as consolidations ($n = 5$),

ground-glass opacities ($n = 2$), and linear opacities ($n = 1$).

Regarding the morphology of the reversed halo, all active tuberculosis cases showed nodularities in the halo wall. In 10 of the 12 tuberculosis cases, nodules were also seen inside the reversed halo lesions. None of the 10 COP cases showed nodules on the walls or inside the halos. No patients presented with lymph node enlargement or pleural effusion. The main CT patterns of both diseases are summarized and compared in Table 1.

Discussion

Well-recognized HRCT findings in post-primary pulmonary tuberculosis include centrilobular or airspace nodules, branching linear and nodular opacities (tree-in-bud sign), areas of consolidation, cavitations, bronchial wall thickening, miliary nodules, tuberculomas, calcifications, parenchymal bands, interlobular septal thickening, ground-glass opacities, pericatricial emphysema, and fibrotic

changes [8–11]. Clusters of small nodules have been described as a possible manifestation of pulmonary tuberculosis on HRCT examinations [9].

Organizing pneumonia can be primary (COP) or secondary. COP is classified as an idiopathic interstitial pneumonia, whereas secondary organizing pneumonia is associated with radiation injury, organ transplantation, aspiration, certain drugs and a variety of entities that include connective tissue diseases, infections, and malignancies, among others [12]. Consolidation involving subpleural and peribronchial areas is the most common HRCT finding observed in COP patients, followed by ground-glass opacities, nodules or masses, and linear opacities [12–15]. Lung lesions with the reversed halo sign pattern have also been regarded as highly suggestive of COP [3].

In our series, we observed solitary or multiple lesions with the reversed halo sign pattern in both tuberculosis and COP cases, frequently in association with parenchymal

TABLE 1: Main High-Resolution CT (HRCT) Characteristics of Patients With Tuberculosis and Patients With Cryptogenic Organizing Pneumonia (COP) Showing the Reversed Halo Sign on HRCT

Tomographic Characteristic	No. of Patients		p^a
	Tuberculosis ($n = 12$)	COP ($n = 10$)	
Solitary reversed halo sign	6	5	NS
Other associated parenchymal lesions ^b	6	6	NS
Reversed halo sign with nodular wall	12	0	< 0.001
Nodules inside the reversed halo sign	10	0	< 0.001

Note—NS = not significant.

^aFisher exact test.

^bSuch as consolidation, ground-glass, and linear opacities.

abnormalities such as consolidation, multifocal ground-glass opacities, or linear opacities. The morphologic characteristics of the reversed halos included nodular walls detected in all the active tuberculosis cases and nodules observed inside the reversed halos in most cases (10/12). Neither pattern—nodular walls or internal nodularity—was detected in any of the COP patients.

The nodular pattern of the ring component of the reversed halo sign lesions has been described in other granulomatous diseases especially sarcoidosis [16]. Histopathologic study of those specimens revealed that the nodular aspect noted in the ring component was related to the presence of multiple granulomas. However, the investigators found that this association was not true for cases diagnosed as COP. Thus, they concluded that the nodular appearance of the ring in the reversed halo sign is a useful finding because it indicates the presence of active granulomatous disease rather than COP [16]. Therefore, we should emphasize that the reversed halo with nodular walls—despite having an important role in the differential diagnosis between tuberculosis and COP—is not an exclusive tuberculosis finding and also can be seen in cases of sarcoidosis [4, 16].

This study has several limitations. The design was retrospective, and the number of patients included was relatively small. For this reason, the results could not be statistically validated. The fact that only one tuberculosis case was studied by histopathology is another limitation, but we could not justify or expect open lung biopsy because the procedure is rarely indicated for tuberculosis cases. This difficulty limited the possibility of correlating the HRCT findings with pathologic findings. Nevertheless, we believe that we achieved our main goal in the study, which was to compare for the first time the morphologic characteristics of the reversed halo sign

caused by tuberculosis with those caused by COP and look for findings that could be useful in the differential diagnosis. This study was justified because treatments prescribed for these two diseases differ and cannot be given concurrently: Steroids are the treatment of choice for patients with COP but can have very deleterious effects in patients with pulmonary tuberculosis.

In conclusion, the presence of nodular walls or nodules inside the halo of the reversed halo sign is highly suggestive of granulomatous diseases, especially tuberculosis, rather than of COP. The nodular reversed halo sign should be included among the HRCT findings that are suggestive of active tuberculosis.

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