Atypical distribution of small nodules on high resolution CT studies: Patterns and differentials

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Summary
Accurate diagnosis of lung disease with high resolution CT is challenging and relies on a pattern-based approach coupled with knowledge of the distribution of the abnormalities in the lung parenchyma. Some findings and distributions of small nodules are specific for certain diseases, but atypical patterns have been described, especially for granulomatous diseases such as sarcoidosis and tuberculosis. Unusual HRCT aspects that involve the coalescence of small nodules have been termed the “sarcoid galaxy sign” and the “sarcoid cluster sign.” Other imaging findings such as the “reversed halo sign” and the “fairy ring sign” can also be composed of small nodules. The aim of this review was to describe and illustrate a range of conditions that manifest with atypical distribution of small nodules on HRCT. We discuss the various aspects, associated findings, and differential diagnosis particularly in sarcoidosis and tuberculosis.

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Introduction

Small lung nodules are recognized as belonging to one of three distribution patterns: perilymphatic, random, or centrilobular. Although there may be some overlap between these classifications, in most cases, a distinguishing distribution of small nodules is evident on high resolution computed tomography (HRCT). However, some atypical patterns of nodules distribution have been seen in HRCT, mainly in granulomatous diseases. Recently, some CT signs have been described, improving the characterization of these less common nodules distributions. In this study we will discuss three new atypical patterns of small nodules distribution: the sarcoid galaxy sign (SGS); the sarcoid cluster sign (SCS) and the reversed halo sign (RHS).

The SGS is a large parenchymal nodule arising from coalescent small nodules, and surrounded by many tiny satellite nodules. The SCS is also characterized by clusters of multiple small nodules in the pulmonary parenchyma but, in contrast to the SGS, the nodules do not tend to coalesce. These two signs were initially described in sarcoidosis, but were subsequently also identified in tuberculosis. The RHS is defined as a focal, rounded ground-glass area surrounded by a nearly complete ring of consolidation. This sign is also non-specific but when observed in sarcoidosis or tuberculosis, the peripheral ring is frequently composed of multiple small nodules, indicating another atypical pattern of nodular distribution.

The aim of this work was to review the atypical patterns of nodular distribution in granulomatous diseases, and discuss other associated imaging findings that can help in the differential diagnosis of these diseases.

Sarcoïd galaxy sign

Nakatsu et al. described the SGS as a tomographic aspect in sarcoidosis corresponding to large parenchymal nodules arising from a coalescence of small nodules. At the periphery of the large nodules, each constituent small nodule had a relatively distinct margin. The appearance of the large parenchymal nodules was considered similar to the appearance of a galaxy composed of a vast collection of stars. Pathologically, the SGS represents numerous coalescent granulomas. The granulomas were described as much more concentrated toward the center of the sarcoïd galaxy, than at the periphery. When granulomas were not as densely assembled, individual macroscopic granulomas could be identified. Peripheral low-attenuation spots corresponded to the spaces between partially coalescent small nodules. Most cases were associated with mediastinal and hilar lymphadenopathy.

Heo et al. described a similar aspect in active tuberculosis, and suggested the term "clusters of small nodules" instead of SGS as a better description of the pathological morphology. However, the new term, although more precise, could be confusing, because of the SCS in sarcoidosis that was recently described by Ortega et al.

Sarcoïd cluster sign

Ortega et al. described the SCS as a new HRCT sign, observed in cases of sarcoidosis. It correspond to rounded or long clusters of multiple small nodules in the pulmonary parenchyma that are close to each other but not confluent. These tiny nodules represent noncaseating granulomas without coalescence. Perilymphatic nodules and lymph node enlargement were also observed as associated findings in most of the described cases.

Marchiori et al. described similar findings in a patient with proven pulmonary tuberculosis. Unlike the cases described by Ortega et al., this patient did not show perilymphatic nodules or lymph node enlargement. The authors concluded that the SCS may be seen in both pulmonary sarcoidosis and pulmonary tuberculosis. The absence of perilymphatic nodules and lymph node enlargement was also an associated finding.
nodules and/or lymph node enlargement should favor the diagnosis of tuberculosis rather than sarcoidosis.5

Reversed halo sign

The RHS is defined as a focal, rounded area of ground-glass opacity, surrounded by an almost complete ring of consolidation. This finding was first described by Voloudaki et al.7 as a crescent or ring-shaped opacity that surrounds areas of ground-glass attenuation, in patients with cryptogenic organizing pneumonia (COP). Zompatori et al.8 described the same findings as the “atoll sign”, because it resembles ring-shaped coral reefs of the tropics that enclose a lagoon with shallow waters. The sign was named the RHS by Kim et al.,4 as a finding specific to COP. Subsequently, various authors demonstrated the presence of this sign in a wide spectrum of diseases, including infectious and non-infectious conditions.9,10

Marlow et al.11 reported a peculiar CT finding in a patient with pulmonary sarcoidosis that was a ring of granulomatous tissue extending concentrically from a specific point in the lung. The central area of the lesion was composed of normal lung tissue, and the halo had a nodular border. The authors named these lesions the “fairy ring” sign, after rings from Celtic mythology. According to legend, fairies come out at night and dance in small circles in the grass, and tiny feet beat a bare circular path at the edge of a ring.11

Kumazoe et al.12 reported the RHS in a case of sarcoidosis in which the HRCT images showed multiple, central ground-glass opacities surrounded by crescent or ring-shaped areas of consolidation in both lungs. Moreover, the authors observed military nodules in the central ground-glass opacities, and around the outer areas of consolidation. The patient also presented with bilateral hilar and mediastinal nodules and/or lymph node enlargement should favor the diagnosis of tuberculosis rather than sarcoidosis.5

Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Main common associated findings for the differential diagnosis</th>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>Epidemiological history</td>
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<tr>
<td></td>
<td>CT findings are more common in the upper lobes and superior segment of the lower lobes and uncommon in the middle lobes;</td>
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<tr>
<td></td>
<td>Tree-in-bud opacities and cavitation are frequent findings</td>
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<td></td>
<td>Lymphadenopathy is rare (almost exclusive in patients with immunosuppression)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>CT findings are more common in the upper and middle lobes and uncommon in the lower lobes;</td>
</tr>
<tr>
<td></td>
<td>Ground-glass opacities are common</td>
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<td></td>
<td>Hilar and paratracheal lymphadenopathy;</td>
</tr>
<tr>
<td></td>
<td>Small nodules have perilymphatic distribution;</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Occupational history;</td>
</tr>
<tr>
<td></td>
<td>CT findings are more common in the upper lobes, with a predominant posterior lung distribution;</td>
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<td></td>
<td>Masses frequently show air bronchograms, punctiform calcifications and adjacent paracicatricial emphysema;</td>
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<tr>
<td></td>
<td>Hilar or mediastinal calcified lymph nodes</td>
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</table>

Figure 2 29-year-old woman with pulmonary tuberculosis. Axial HRCT scan obtained at the level of carina (A) and coronal reformatted image (B) shows a confluence of numerous poorly defined nodules resulting in three adjacent irregular large nodules in the right upper lobe. Small nodular opacities are seen around the large nodules (galaxy sign).

Figure 3 36-year-old man with pulmonary tuberculosis. HRCT demonstrates clusters of micronodules without confluence in both lower lobes (sarcoid cluster sign).
lymphadenopathy. In this case, instead of normal lung tissue, small nodules were observed inside the halo.

**Differential diagnosis**

The most important differential diagnosis for SGS (Figs. 1 and 2) and SCS (Fig. 3) are tuberculosis and sarcoidosis. Occasionally, clusters of coalescent small nodules can have an appearance that resembles progressive massive fibrosis associated with coal worker’s disease or silicosis. Although these aspects may not be distinguishable on HRCT, certain associated features might be helpful for differentiating these diseases (Table 1). Cluster of small nodules can also occur in other granulomatous diseases, such as criptococosis (Fig. 4), but it is a less common feature.

A wide spectrum of diseases can manifest with RHS, including infectious conditions such as paracoccidioido-mycosis, tuberculosis, zygomycosis, and aspergillosis, and non-infectious conditions including COP, Wegener’s granulomatosis, lymphomatoid granulomatosis, bronchioloalveolar carcinoma, and others. RHS is a recognized manifestation of COP, but in many diseases, including sarcoidosis and some granulomatous infections, it may also result from secondary organizing pneumonia, as a response to the primary disease. Consequently, the RHS is a relatively non-specific sign, that should include a broader differential diagnosis.

Many aspects of the halo contour and its central area are described in RHS cases reported in the literature, but lacking organization or classification. The halo rim may be smooth (Fig. 5) or nodular (Fig. 6), and the inner area may contain ground-glass attenuation (Fig. 7), small nodules or normal parenchyma. When granulomatous diseases presenting with the RHS are active, the ring or the inner area of the reversed halo may be nodular in appearance. Most RHS cases that were associated with proven active granulomatous disease exhibited nodular rings. Histopathological study of these specimens revealed granulomas within the ring portion of the reversed halo, whereas the same pattern was not seen in cases diagnosed as organizing pneumonia. Thus, the nodular appearance of the RHS ring is a useful finding, since it indicates the presence of active granulomatous disease, probably from infection or sarcoidosis, rather than organizing pneumonia.
Conclusion

SGS and SCS are HRCT findings observed in atypical distribution patterns of small nodules. They were initially described as a specific manifestation of sarcoidosis, however, they may occur in other granulomatous diseases. Since these signs are non-specific for sarcoidosis they require appropriate radiological characterization that better correlates to the pathological morphology. The association of these signs with other imaging findings may help in differential diagnosis, especially between granulomatous diseases. The RHS is also non-specific, occurring in granulomatous and non-granulomatous diseases, especially in organizing pneumonia. However, the presence of nodules in the peripheral ring can be helpful to differential diagnosis. A halo with a nodular border may indicate granulomatous disease, while a halo with a smooth contour suggests organizing pneumonia.

Conflict of interest

All authors inform that there are none conflicts of interest. We inform also that there are not financial or personal relationships that may inappropriately influence our actions.

References