

The Halo Sign in Computed Tomography Images: Differential Diagnosis and Correlation With Pathology Findings

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The halo sign is a circular area of ground-glass attenuation that is seen around pulmonary nodules at computed tomography (CT). Although the sign is most often an indication of pulmonary hemorrhage, it may also accompany other lesions associated with different disease processes. Examples are hemorrhagic nodules of infectious origin (mucormycosis, candidiasis, tuberculosis, viral pneumonia, and invasive aspergillosis—the last being the most common cause of the CT halo sign); hemorrhagic nodules of noninfectious origin (Wegener granulomatosis, Kaposi sarcoma, and hemorrhagic metastases); tumor cell infiltration (bronchioloalveolar carcinoma, lymphoma, and metastasis with intra-alveolar tumor growth); and nonhemorrhagic lesions (sarcoidosis and organizing pneumonia). Diagnosis must therefore be based on careful consideration of all the CT chest findings within the context of the patient's clinical state. The aim of this review was to describe and illustrate different disease processes that appear as a halo sign on CT scans, to analyze the value of this diagnostic tool, and to assess its correlation with pathology findings.

Key words: Lung. Computed tomography. CT. Lung Infection. Lung tumors. Pulmonary nodule. Aspergillosis. Image findings.

Introduction

The chest computed tomography (CT) halo sign is an area of ground-glass attenuation seen around a pulmonary nodule or mass with central soft-tissue attenuation. The sign was first described by Kuhlman et al¹ in patients with hemorrhagic nodules associated with invasive pulmonary aspergillosis. Following this description, it was initially believed that the halo sign always indicated the presence of hemorrhagic pulmonary nodules.² The pathophysiologic

Signo del halo en la tomografía computarizada de tórax: diagnóstico diferencial con correlación anatomopatológica

El signo del halo consiste en un área circular de atenuación en vidrio deslustrado que rodea un nódulo pulmonar. Aunque la causa más frecuente es la hemorragia pulmonar, dicho signo se asocia a numerosas entidades, que corresponden a diferentes procesos anatomopatológicos: nódulos hemorrágicos de etiología infecciosa (aspergilosis invasiva—la causa más frecuente de nódulos pulmonares con halo—, mucormicosis, candidiasis, tuberculosis, neumonías víricas), nódulos hemorrágicos de etiología no infecciosa (granulomatosis de Wegener, sarcoma de Kaposi, metástasis hemorrágicas), nódulos con halo debido a infiltración de células neoplásicas (carcinoma bronquioloalveolar, linfoma, metástasis con crecimiento tumoral intraalveolar) y nódulos con halo debido a lesiones inflamatorias no hemorrágicas (sarcoidosis, neumonía organizada). Por lo tanto, el diagnóstico debe realizarse integrando todos los hallazgos de la tomografía computarizada de tórax en el contexto clínico del paciente. El objetivo de la presente revisión es describir e ilustrar enfermedades que pueden manifestarse como nódulos pulmonares con el signo del halo, analizando su utilidad diagnóstica y discutiendo su correlación radiopatológica.

Palabras clave: Pulmón. Tomografía computarizada. Infección pulmonar. Neoplasia pulmonar. Nódulo pulmonar. Aspergilosis. Signos en imagen.

mechanisms that can cause a pulmonary nodule to hemorrhage vary according to the underlying disease process, but they are associated with vasculitis, neovascular tissue fragility, hemorrhagic pulmonary infarction, necrosis, bronchoarterial fistula, and even transbronchial biopsy injury.²⁻⁴ The halo sign has also been linked to a wide variety of other anatomical and disease processes, however, though such associations are less common. One example is nonhemorrhagic infiltration by tumor or inflammatory cells (Table).

The aim of this review was to describe and illustrate different disease processes that can manifest with a halo sign on chest CT scans, to analyze the diagnostic value of this sign, and to assess its correlation with pathology findings in order to further our understanding of this diagnostic tool.

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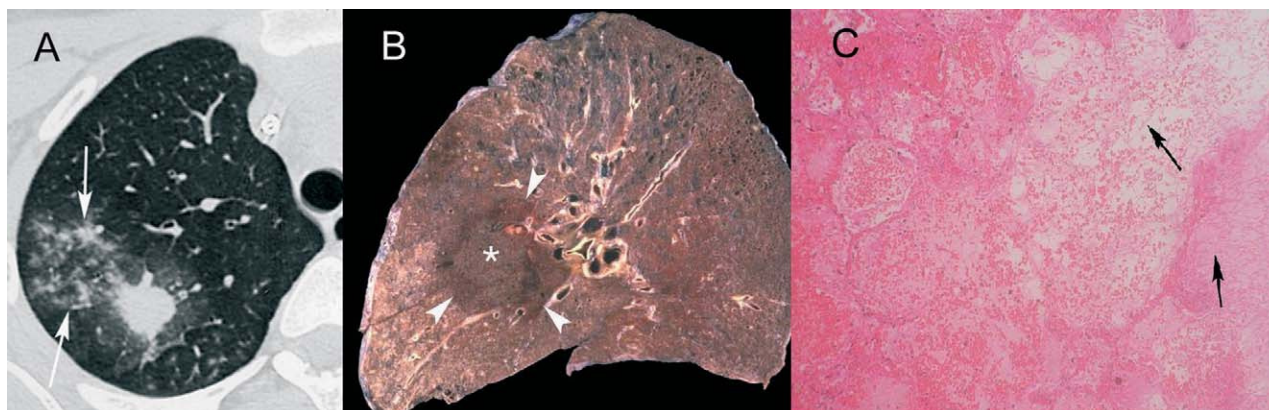


Figure 1. Invasive pulmonary aspergillosis. **A:** Computed tomography (CT) scan of a patient with acute lymphoid leukemia and neutropenia showing a nodule surrounded by a halo in the right upper lobe, with adjacent acinar involvement (arrows). In the follow-up CT scan (not shown) taken after 3 weeks of treatment with amphotericin B, the nodule had cavitated but the halo sign was no longer visible. **B:** Macroscopic sagittal slice of another patient's lung showing a round necrotic lesion (asterisk) surrounded by a hemorrhagic halo (arrowheads), corresponding to invasive pulmonary aspergillosis. **C:** Microscopic image of the margin of the lesion described in B, with visible pulmonary necrosis and hemorrhage. The image also shows the hyphae of *Aspergillus fumigatus* (arrows), which are of regular caliber, septate, and branching at acute angles (hematoxylin-eosin, magnification $\times 2$).

Infectious Diseases

When the halo sign is detected in immunocompromised patients, it is most often an indication of infectious disease and, in most cases, the sign corresponds to hemorrhagic nodules.

Fungi

Aspergillosis. The halo sign was first described in patients with acute leukemia and invasive pulmonary aspergillosis¹—the latter being the most common cause of the CT halo sign in immunocompromised patients.⁵ Pulmonary aspergillosis belongs to a clinical spectrum of diseases caused by the fungus *Aspergillus fumigatus*. It can take many forms, including aspergilloma, allergic bronchopulmonary aspergillosis, chronic necrotizing aspergillosis, airway-invasive aspergillosis, and invasive pulmonary aspergillosis. Invasive pulmonary aspergillosis affects immunosuppressed patients, and particularly those with marked neutropenia. Its clinical manifestations are quite nonspecific and include cough, chest pain, and hemoptysis. Fungal infections must therefore be considered in the differential diagnosis of a severely immunocompromised patient with fever, and because invasive pulmonary aspergillosis is associated with high mortality, it is very important to reach a quick diagnosis and initiate aggressive treatment immediately. Although invasive pulmonary aspergillosis has several characteristic CT findings, such as cavitation and the air crescent sign, these only become evident late in the course of infection.^{6,7} The halo sign, in contrast, appears in the early stages of disease, and in the right clinical setting, it can be useful in the early diagnosis of aspergillosis^{1,8} (Figure 1A).

The invasion of small and medium-sized lung vessels by *A. fumigatus* causes thrombosis and hemorrhagic infarction. In such cases, the central nodule on the CT scan corresponds to a central area of necrosis and the fungal hyphae—which are morphologically characteristic in that they are septate, and have a regular diameter and

distinctive acute-angle branching. The halo around the nodule corresponds to hemorrhagic necrosis^{2,9,10} (Figures 1B and C).

Other fungi. The lung may also become infected by other fungi, such as *Mucor* species, which cause often-fatal opportunistic infections in patients with diabetes or a compromised immune system. Characteristic radiologic findings include single or multiple nodules and areas of consolidation that may extend to more than a single lobe.

Causes of Pulmonary Nodules With a Halo Sign

Infections
Fungi: invasive aspergillosis; infection by <i>Mucor</i> , <i>Candida</i> , <i>Cryptococcus</i> , and <i>Coccidioides</i> species
Viruses: herpes simplex virus, cytomegalovirus, varicella-zoster virus, myxovirus
Bacteria: slow-resolving bacterial pneumonia, <i>Coxiella burnetii</i> , <i>Actinomyces</i> species
Mycobacteria: <i>Mycobacterium tuberculosis</i> , <i>Mycobacterium avium intracellulare</i>
Parasites: <i>Paragonimus</i> and <i>Schistosoma</i> species
Neoplasms
Bronchioloalveolar carcinoma
Lymphoproliferative disease
Hemorrhagic metastasis of angiosarcoma, choriocarcinoma, melanoma, osteosarcoma, and renal cell carcinoma
Nonhemorrhagic metastases of adenocarcinoma of the digestive tube, pancreas, and lung
Kaposi sarcoma
Primary angiosarcoma
Noninfectious inflammatory diseases
Wegener granulomatosis
Sarcoidosis
Organizing pneumonia
Eosinophilic diseases
Other
Endometriosis
Transbronchial biopsy injury (in lung transplant patients)
Amyloidosis
Amiodarone-induced toxicity

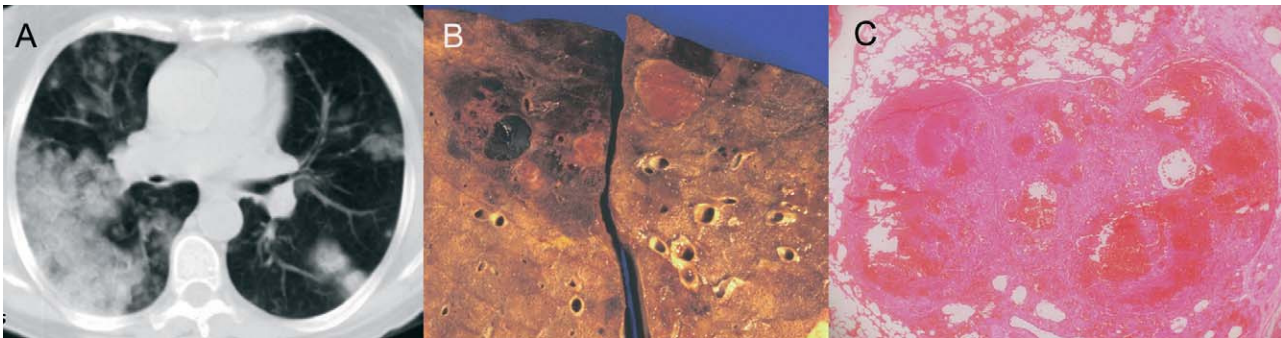


Figure 2. Hemorrhagic metastasis in a patient with choriocarcinoma who presented with massive hemoptysis. A: Computed tomography scan of the chest shows multiple hemorrhagic pulmonary nodules with a halo sign that have coalesced in the posterior segments of the right lung. B: Macroscopic lung slice showing several round hemorrhagic lesions. C: Macroscopic image of nodules containing hemorrhagic areas, fibrin, and tumor cells (hematoxylin-eosin, magnification 10).

Pathology typically shows the characteristic angioinvasion by the variable-caliber, aseptate, and right-angle branching hyphae of these species. CT findings then show pulmonary nodules with a halo sign corresponding to thrombosis and hemorrhagic pulmonary infarction when the infection invades the lung.^{10,11}

Lung infection due to *Candida* species may also manifest with a halo sign on a CT scan.^{2,8} Pulmonary candidiasis acquired by hematogenous dissemination, for example, causes microabscesses, vasculitis, infected thrombi, and areas of hemorrhagic infarction.³

Infections due to *Cryptococcus* and *Coccidioides* species may also, exceptionally, manifest with a halo sign.^{2,8,12}

Viruses

Viral pneumonia occurs more frequently in immunocompromised patients, for whom prognosis is also poorer. CT findings are variable and include centrilobular nodules, segmental areas of consolidation, areas of ground-glass attenuation with or without interlobular septal thickening, and pulmonary nodules.¹³ Many viruses can cause lung infection but those that are most frequently associated with the CT halo sign are herpes simplex viruses, cytomegalovirus, varicella-zoster virus, and myxovirus.^{2,8,14} On histopathologic examination, the halo sign in viral pneumonia generally corresponds to intra-alveolar hemorrhage.¹³

Mycobacteria

Mycobacterium tuberculosis and *Mycobacterium avium intracellulare* infections have also been reported to cause an area of ground-glass attenuation around pulmonary nodules in CT images.¹⁴⁻¹⁷ The origin of the halo sign in this case is not clear as it may be due to either alveolar hemorrhage or a granulomatous reaction without hemorrhage.^{15,17}

Other infectious diseases that can exceptionally manifest with a CT halo sign are *Coxiella burnetii* infection, parasitic disease such as paragonimiasis and schistosomiasis, slow-resolution bacterial pneumonia, septic emboli, and actinomycosis.^{3,18,19} In such cases, the halo sign is caused by the infiltration of inflammatory cells and exudates into the lung.

Neoplastic Diseases

A halo around a tumor nodule in the lung may be due to hemorrhage from the nodule itself or to the infiltration of tumor cells into the adjacent lung parenchyma.

Hemorrhagic Tumor Nodules

A variety of lung tumor processes can cause hemorrhaging that appears as a halo around a pulmonary nodule on the CT chest scan. Such tumors are hypervascular, with fragile neovascular tissue whose rupture causes pulmonary bleeding.² Examples include metastatic tumors in angiosarcoma, choriocarcinoma, melanoma, osteosarcoma, and renal cell carcinoma.^{2,3,14,20,21} Choriocarcinoma tumor cells, for example, have a characteristic ability to erode blood vessels, causing bleeding³ (Figure 2).

Several primary lung tumors, including pulmonary angiosarcoma and Kaposi sarcoma, can also form hemorrhagic pulmonary nodules.^{2,22} Primary Kaposi sarcoma is most common in homosexual males with human immunodeficiency virus infection, and both immunologic and infectious factors (such as coinfection by herpes simplex virus type 8) are thought to be implicated in the mechanisms of disease. CT findings for such patients generally reveal poorly defined, predominantly peribronchovascular nodules that are occasionally surrounded by a halo.⁵ Histologic features include thin-walled vascular spaces and red blood cells extravasated due to wall rupture. These blood cells appear as a halo on the CT scan.²³

Tumor Cell Infiltration

A halo around a tumor nodule may also indicate tumor cell infiltration. There are 2 basic forms of tumor growth in the lung: the first, and most common, involves the proliferation of infiltrating tumor cells that destroy lung tissue (expansive growth), while the second respects the pulmonary architecture, as tumor cells spread by attaching to the alveolar walls (intra-alveolar or lepidic growth). This latter form of growth is mostly associated with bronchioloalveolar carcinoma and exceptionally with

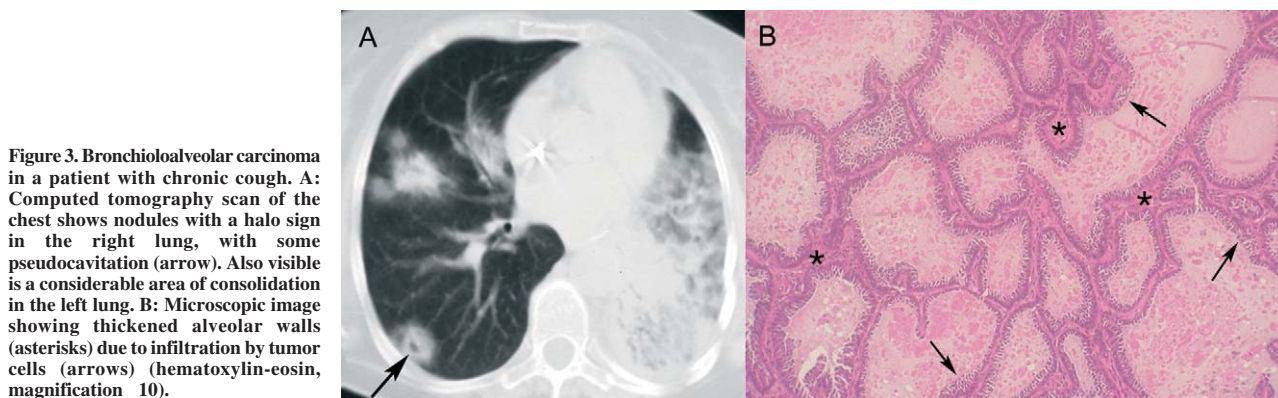


Figure 3. Bronchioloalveolar carcinoma in a patient with chronic cough. **A:** Computed tomography scan of the chest shows nodules with a halo sign in the right lung, with some pseudocavitation (arrow). Also visible is a considerable area of consolidation in the left lung. **B:** Microscopic image showing thickened alveolar walls (asterisks) due to infiltration by tumor cells (arrows) (hematoxylin-eosin, magnification 10).

metastatic adenocarcinoma of the digestive tube, pancreas, or lung.²⁴⁻²⁶ The halo sign in these cases corresponds to alveolar wall thickening due to the spread of tumor cells, with partial occupation of the alveolar air space.^{2,23} Quantifying the size of the halo sign in small peripheral lung adenocarcinomas may be of prognostic value as several authors have reported that the larger the halo sign, the greater the bronchioloalveolar carcinoma component and, consequently, the better the prognosis.²⁷⁻²⁹ Bronchioloalveolar carcinoma, for its part, is the most common reason for the halo sign in immunocompetent patients¹⁴ (Figure 3).

The halo sign has also been associated with other histologic variants of primary lung tumors such as squamous cell carcinoma and mucinous cystadenocarcinoma.^{14,30}

Pulmonary lymphomas can also manifest with areas of consolidation or as single or multiple pulmonary nodules on CT scans.³¹ These nodules may be surrounded by a halo in primary lymphomas (such as mucosa-associated

lymphoid tissue lymphomas), secondary lymphomas, and posttransplant lymphoproliferative disease.³²⁻³⁴ The nodule seen in such cases corresponds to the dense central tumor infiltration area while the halo corresponds to the less dense interstitial tumor cells around the nodule^{14,33} (Figure 4).

Noninfectious and Nontumoral Diseases

The diseases described in this section can also manifest with hemorrhagic or nonhemorrhagic nodules. In the case of nonhemorrhagic nodules, the halo sign corresponds to the presence of an inflammatory infiltrate, which normally affects the alveolar interstitium.

Hemorrhagic Nodules

Wegener granulomatosis is a form of granulomatous vasculitis that manifests with the classic triad of lung disease, sinusitis accompanied by fever, and necrotizing

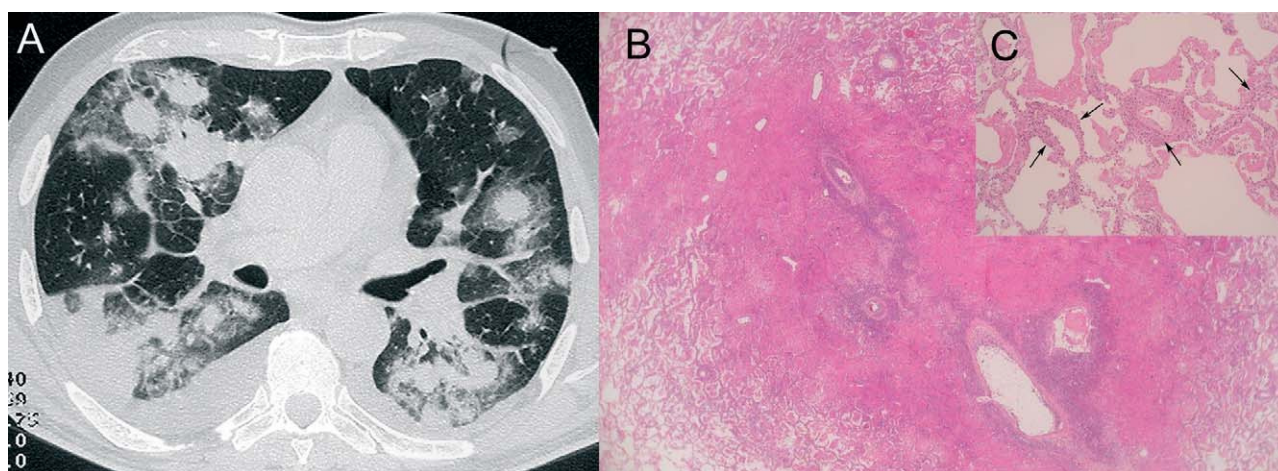


Figure 4. Pulmonary lymphoma in a 73-year-old patient who visited the emergency service with dyspnea. **A:** An axial scan of the lower pulmonary lobes shows multiple pulmonary nodules with a halo sign and a tendency to coalesce in the posterior segments. There is also bilateral pleural effusion, somewhat greater on the right side. The patient died 3 weeks after admission. Autopsy revealed lymphoma cells lysed by natural killer cells in several organs. **B:** Low-magnification image of pulmonary nodule showing mainly peribronchovascular tumor cell infiltration and marked necrosis (hematoxylin-eosin, magnification 4). **C:** A higher-magnification image of the periphery of the nodule shows the infiltration of tumor cells along the alveolar walls (arrows) (hematoxylin-eosin, magnification 10).

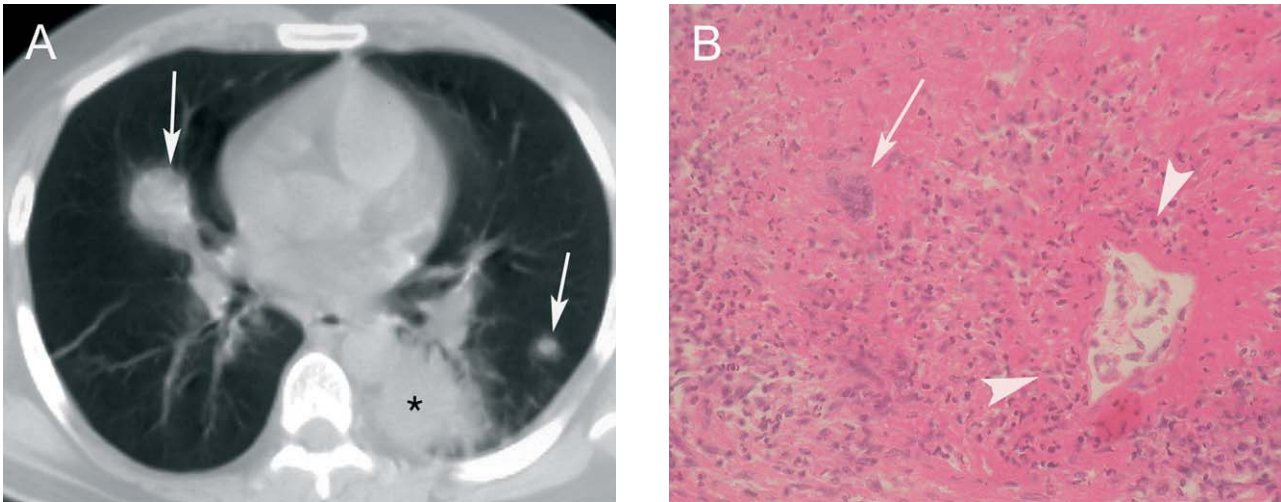


Figure 5. Wegener granulomatosis. **A:** Computed tomography scan showing 2 pulmonary nodules surrounded by a halo (arrows) and an area of consolidation in the left lower lobe (asterisk), also with a halo sign. The patient, whose first symptom was hemoptysis, also had rapidly progressing glomerulonephritis. **B:** Microscopic image showing inflammatory infiltration of the arterial wall with a multinucleated giant cell (arrow) and endothelial destruction (arrowheads) (hematoxylin-eosin, magnification 20).

glomerulonephritis, although the lung is the most commonly affected organ. The main histology findings are necrotizing granulomas accompanied by a mixed-cell infiltrate of neutrophils, histiocytes, and eosinophils, and focal necrotizing vasculitis of small and medium-sized vessels. Lung hemorrhage in this case is caused by necrotizing vasculitis,³⁵ and the CT halo sign corresponds to localized bleeding around the central nodule^{2,3} (Figure 5).

Pulmonary endometriosis can also manifest as hemorrhagic pulmonary nodules because even ectopic endometrial tissue can bleed during menstruation.³

Finally, there have been reports of lung transplant patients presenting nodules surrounded by a CT halo following a transbronchial biopsy; the halo sign in these cases was probably caused by bleeding due to biopsy injury.⁴

Nonhemorrhagic Nodules

Approximately 90% of patients with sarcoidosis develop lung disease. Histology findings typically include sarcoid granulomas, while CT findings include multiple small nodules (corresponding to sarcoid granulomas) with predominant perivascular and subpleural distribution and peribronchovascular interstitial and interlobular septal thickening. Coalescing granulomas may also form irregular pseudonodules, an image referred to as the sarcoid galaxy sign. There may also occasionally be areas of ground-glass attenuation, sometimes surrounding the nodules. Such areas are usually reversible and are believed to indicate alveolitis.³⁶

CT findings for organizing pneumonia include areas of consolidation or ground-glass attenuation, typically in subpleural or peribronchial areas, predominantly in the lower lobes. Some patients with organizing pneumonia develop multiple nodules with an irregular margin and, occasionally, a surrounding halo.^{13,37} There is also a report

of a patient with pneumonitis due to subacute hypersensitivity who developed bronchiolitis obliterans with organizing pneumonia, which manifested with nodular opacities corresponding to intraluminal polyps of granulation tissue caused by the organizing pneumonia.³⁸ The halo was an indication of alveolar wall thickening due to lymphocytic infiltration.

Eosinophilic pneumonia can also manifest with pulmonary nodules surrounded by ground-glass attenuation, and in this case the halo is probably due to infiltration by eosinophils and other inflammatory cells.^{3,14,39}

Nodules associated with pulmonary amyloidosis can also sometimes be surrounded by a halo, possibly reflecting the presence of nonspecific inflammatory cells, amyloid deposits on the peripheral alveolar walls, or both. Moreover, the halo sign is a useful prognostic factor in nodular pulmonary amyloidosis, as it is associated with faster disease progression and better response to treatment.⁴⁰

Several lung disorders caused by amiodarone pulmonary toxicity also manifest with nodules surrounded by a CT halo. Amiodarone can cause pneumonitis because its main metabolite, desethylamiodarone, interferes with lipid catabolism and induces generalized phospholipidosis, a iatrogenic cause of endogenous lipoid pneumonia. The halo seen on the CT scan may be due to the thickening of the alveolar walls caused by a mixed inflammatory cell infiltrate around a nodule of fibroblastic intraluminal polyps, which may mimic organizing pneumonia in sites other than the bronchioles.⁴¹

Conclusions

A wide spectrum of diseases can manifest with a halo on the CT chest scan. Although the halo sign is most often an indication of a hemorrhagic nodule, it may also

accompany other lesions such as inflammatory or tumor cell infiltrates. Consequently, while the halo sign is relatively nonspecific, it can be of great value for differential diagnosis. Such diagnosis, however, must be based on careful consideration of all the chest CT findings within the context of the patient's clinical state. Other CT findings, such as the number of nodules, the presence of diseased lymph nodes, or the discovery of pleural involvement can all help to narrow the diagnosis. The most likely diagnoses that should be considered in immunosuppressed patients are invasive pulmonary aspergillosis, viral pneumonia, Kaposi sarcoma, and lymphoma. In immunocompetent patients, particular attention should be paid to viral infections and bronchioloalveolar carcinoma and other neoplasms.

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