

Pictorial review

CT halo sign: the spectrum of pulmonary diseases

Y R LEE, MD, Y W CHOI, MD, K J LEE, MD, S C JEON, MD, C K PARK, MD and J-N HEO, MD

Department of Diagnostic Radiology, College of Medicine, Hanyang University, 17 Haengdang-dong, Sungdong-gu, Seoul 133-792, Korea

Abstract. The CT halo sign indicates ground glass attenuation surrounding a pulmonary nodule on CT. Although it was initially proposed as an early, specific finding of invasive pulmonary aspergillosis, it can be caused by many other pathological conditions such as infection, neoplastic and inflammatory diseases. The halo of ground glass attenuation pathologically represents pulmonary haemorrhage, tumour infiltration, or non-haemorrhagic inflammatory processes. Although non-specific, this sign is important because the clinical setting and associated radiological features may give a clue to the differential diagnosis. In this review, we demonstrate the spectrum of pulmonary diseases showing the “CT halo sign” on thin-section CT and discuss their radiological and clinical features.

The CT halo sign, also known as the halo sign, indicates ground glass attenuation surrounding a pulmonary nodule on thin-section CT. This appearance was first described in immunocompromised patients with invasive pulmonary aspergillosis [1]. Besides infectious conditions such as aspergillosis, many neoplastic and inflammatory processes may also cause the halo sign (Table 1) [1–7]. Thus, the sign itself is non-specific. However, in the appropriate clinical setting, the sign may be very helpful.

The presence of a halo of ground glass attenuation is usually associated with haemorrhagic nodules, and the mechanism of the haemorrhage may include haemorrhagic infarction, vasculitis, fragility of neovascular tissue, bronchoarterial fistula, or necrosis [3]. The halo may also be caused by neoplastic or inflammatory infiltration of the lung parenchyma. We demonstrate the spectrum of pulmonary diseases showing the CT halo sign and discuss their clinical and radiological features.

Infectious diseases

A number of infectious conditions produce pulmonary nodules surrounded by haemorrhage, infiltrations of inflammatory cells, or both, which may cause the CT halo sign (Table 1). Invasive pulmonary aspergillosis is the most common fungal infection showing the CT halo sign in immunocompromised patients. It is characterized pathologically by foci of infarction surrounded by alveolar haemorrhage. Haemorrhagic infarction is caused by vascular invasion of *Aspergillus* organisms and subsequent thrombosis of small- to medium-sized vessels and ischaemic necrosis of the lung parenchyma [1]. The central area of necrosis corresponds to the nodule, whereas surrounding haemorrhage due to haemorrhagic infarction corresponds to the halo of ground glass attenuation (Figure 1) [1, 3]. Early in the course of the disease, CT may reveal rims of ground glass attenuation surrounding multiple

1–3 cm nodules (the CT halo sign). Later, the nodules can enlarge and eventually may demonstrate cavitation with an air crescent sign, a finding that occurs during granulocyte recovery. The frequency of the halo sign in patients with invasive pulmonary aspergillosis is relatively high in the early stages of the disease, but becomes progressively less frequent. In a group of 25 patients with invasive aspergillosis studied by using serial CT scans, the frequency of this sign ranged from 96% at day 0 to 19% at day 14. Thus, in severely neutropenic patients with a fever that does not respond to antibiotics, the CT halo sign is an early indicator for diagnosing invasive aspergillosis

Table 1. List of diseases showing the CT halo sign

Infectious diseases
Fungus; aspergillosis ^a , mucormycosis, candidiasis, coccidioidomycosis, cryptococcosis
Septic embolism
Mycobacteria; tuberculosis, <i>Mycobacterium avium</i> complex
Rickettsia; <i>Coxiella burnetii</i>
Virus; herpes simplex virus, varicella-zoster virus, cytomegalovirus, myxovirus
Neoplastic diseases
Primary tumours; squamous cell carcinoma, Kaposi sarcoma, bronchioloalveolar carcinoma ^b , adenocarcinoma
Metastatic tumours; angiosarcoma, choriocarcinoma, osteosarcoma, melanoma, hydatidiform mole, metastatic tumours from gastrointestinal malignancies
Lymphoproliferative disorders
Non-neoplastic, non-infectious, inflammatory diseases
Wegener's granulomatosis
Eosinophilic lung disease; parasitic infestation (schistosomiasis), simple pulmonary eosinophilia, hypereosinophilic syndrome
Pulmonary endometriosis
Organizing pneumonia
Hypersensitivity pneumonitis
Iatrogenic injury; transbronchial lung biopsy, catheter-induced pulmonary pseudoaneurysm

^aThe most common condition showing the CT halo sign in immunocompromised patients.

^bThe most common condition showing the CT halo sign in immunocompetent patients.

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Address correspondence to Dr Yo Won Choi.



Figure 1. Invasive pulmonary aspergillosis in a 39-year-old man with acute myelogenous leukaemia and neutropenia. Thin-section CT at the level of the lung apex shows multiple nodules surrounded by a halo of ground glass opacity in both upper lobes.

even before serological tests become positive, and it warrants administration of systemic antifungal therapy [7]. Haemorrhagic nodules showing the CT halo sign may also be caused by other angioinvasive fungal species such as mucormycosis [1, 3]. Mucormycosis is a serious, often fatal, opportunistic infection usually seen in immunocompromised patients or patients with diabetes mellitus or renal disease [5], and frequently shows the halo sign, which was reported to be seen in three of eight patients with *Mucor* infection [7]. Pulmonary candidiasis and coccidioidomycosis uncommonly show the sign [3]. Pulmonary candidiasis with haematogenous spread leads to diffuse microabscesses, infected thrombi, and areas of haemorrhagic infarction. This kind of candida infection may manifest as disseminated miliary nodules, each less than 1 cm in diameter, which is usually distinct from invasive pulmonary aspergillosis.

The CT halo sign may result from inflammatory infiltration of the lung in some infections, which include cryptococcosis, herpetic pneumonia and cytomegalovirus pneumonia (Figure 2) [2, 3]. Pulmonary cryptococcosis may display solitary or multiple pulmonary nodules with or without the CT halo sign, particularly in immunocompromised patients. Pulmonary nodules associated with the CT halo sign were reported in three of 11 patients with pulmonary cryptococcosis [2]. On histological examination, areas of ground glass attenuation represented granulomatous inflammation [2]. Herpes simplex virus and cytomegalovirus (Figure 2) are major causes of pulmonary morbidity and mortality in the immunocompromised host. These viruses may cause interstitial pneumonia, haemorrhagic nodules, and diffuse alveolar damage, and predominantly show areas of ground glass attenuation and/or focal areas of consolidation. Nodules with the CT halo sign are rarely present.

Some infectious diseases have been reported to show the halo sign of uncertain pathological causes. Those include *Mycobacterium avium* complex, *Coxiella burnetii*, myxovirus and septic embolism [3, 5, 7]. The cause of the halo sign in patients with a pulmonary tuberculoma was presumed inflammation or perilesional haemorrhage due to rupture of an arterial vessel [4, 7].



Figure 2. Cytomegalovirus pneumonia in a 45-year-old woman with rapidly progressive glomerulonephritis. Thin-section CT of the right lung base demonstrates multiple tiny nodules (arrows) with the CT halo sign in the right lower lobe.

Neoplastic diseases

Lung metastases from hypervascular tumours such as angiosarcoma, choriocarcinoma, osteosarcoma and melanoma can manifest with a halo of ground glass attenuation that most likely results from peritumoral haemorrhage secondary to the fragility of neovascular tissue [1, 3, 4]. Pulmonary Kaposi sarcoma typically manifests as ill-defined nodules predominantly seen in a peribronchovascular distribution. The disease may also show haemorrhagic nodules with the halo sign (Figure 3) [3].

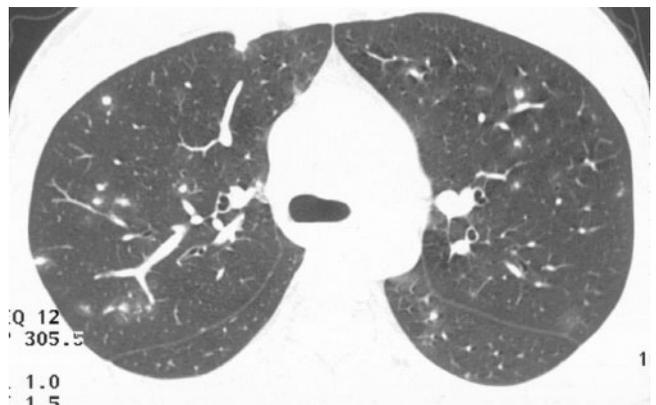


Figure 3. Kaposi sarcoma in a 29-year-old woman with a history of renal transplantation. Thin-section CT at the level of the carina shows multiple nodules with a surrounding halo of ground glass opacity in both lungs, which are dissimilar to flame-shaped lesions, the classic findings of Kaposi sarcoma.

Squamous cell carcinoma of the lung has also been reported to show a nodule surrounded by a haemorrhagic halo [4].

Ground glass attenuation surrounding a nodule may represent tumour cell infiltration in several neoplasms including bronchioloalveolar carcinoma (Figure 4), other primary lung cancers, lymphoma and metastatic pulmonary neoplasms [4, 5]. Bronchioloalveolar carcinoma commonly appears as a solitary peripheral nodule associated with ground glass attenuation (Figure 4). In a series of 22 patients with bronchioloalveolar carcinoma, the halo sign was identified on CT images in two patients [7]. In addition, bronchioloalveolar carcinoma was reported to be the most common condition showing the CT halo sign in immunocompetent patients [4]. The ground glass attenuation in bronchioloalveolar carcinoma, reflects histopathologically, a unique lepidic growth pattern in which tumour spreads into distal air spaces by using the alveolar septa as a stroma with relative lack of acinar filling. Bronchioloalveolar carcinoma may also show pseudocavitation that represents focal areas of air within a nodule. In the presence of pseudocavitation, the CT halo sign is characteristic enough to suggest bronchioloalveolar carcinoma [4, 5].

In pulmonary lymphoproliferative disorders such as lymphoma or post-transplantation lymphoproliferative disorders, solitary or multiple pulmonary nodules are the most common radiographic findings. The lesion is often associated with a surrounding halo of ground glass opacity which represents an infiltration of the surrounding interstitium by less densely arranged tumour cells [4, 5]. In a series, which comprised 65 patients with lung metastases from extrapulmonary adenocarcinoma, the

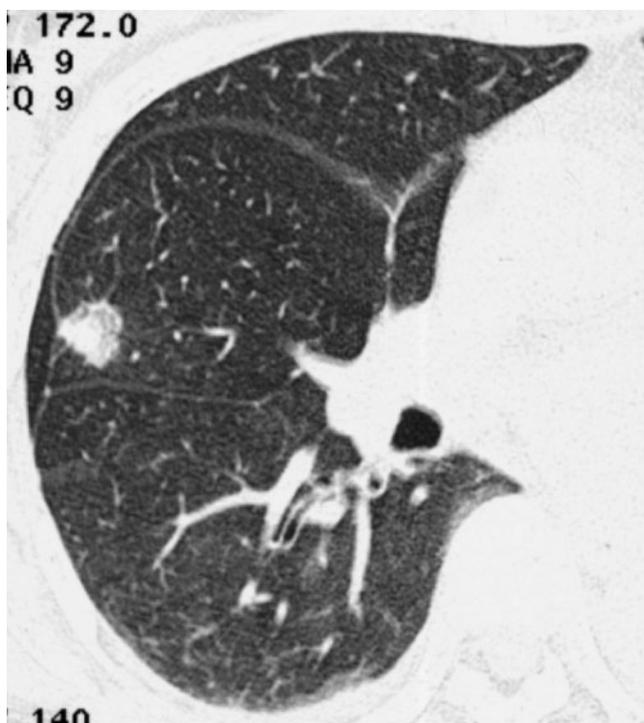


Figure 4. Bronchioloalveolar carcinoma in a 60-year-old woman. Thin-section CT obtained at the level of the bronchus intermedius shows a peripheral pulmonary nodule with the CT halo sign.

halo sign was present in two patients with gastrointestinal adenocarcinoma [8]. In these patients, tumour cell infiltration surrounding the main lesion appeared as the area of ground glass opacity [4, 5, 8].

Non-neoplastic, non-infectious diseases

The CT halo sign caused by pulmonary haemorrhage may also be seen in non-infectious, non-neoplastic, inflammatory conditions such as Wegener's granulomatosis (Figure 5), pulmonary endometriosis with catamenial haemorrhage and hydatidiform mole [5]. Wegener's granulomatosis is a condition characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, glomerulonephritis, and small-vessel vasculitis. Patients with Wegener's granulomatosis may have localized areas of haemorrhage related to pulmonary nodules (Figure 5) or may develop diffuse pulmonary haemorrhage [3].

Eosinophilic lung diseases including parasitic infestation such as schistosomiasis, simple pulmonary eosinophilia (Loeffler syndrome) (Figure 6), or idiopathic hypereosinophilic syndrome have been reported to show the CT halo sign on thin-section CT [4, 5]. In these conditions, ground glass attenuation of the CT halo sign is caused by pulmonary infiltrations of eosinophils and other inflammatory cells pathologically. The CT halo sign can also be seen in organizing pneumonia. In this process, the nodule corresponds histologically to a central area of neutrophilic abscess, whereas the surrounding ground glass attenuation to areas of intra-alveolar inflammatory exudates and fibrotic change and chronic inflammatory cell infiltration in the alveolar septa and peribronchiolar interstitium [5]. A case of hypersensitivity pneumonitis has been reported to show large and sharply defined nodular opacities, many of which were surrounded by a halo of ground glass attenuation. The nodules corresponded to areas with intraluminal granulation tissue polyps and organizing pneumonia, and the ground glass attenuation corresponded to

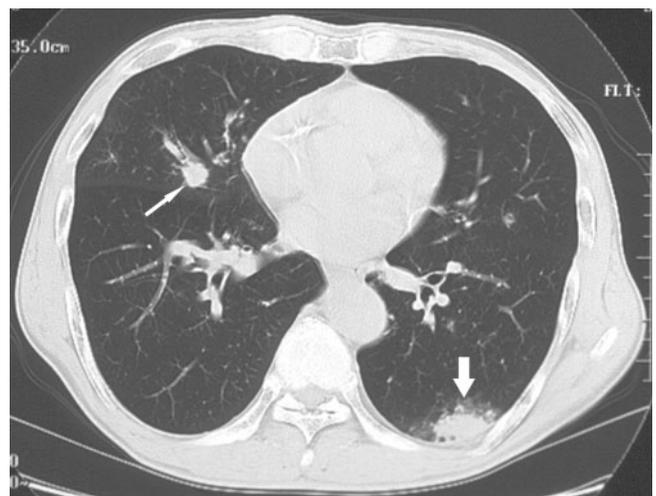


Figure 5. Wegener's granulomatosis in a 70-year-old woman. Thin-section CT shows a pulmonary nodule with the CT halo sign in the left lower lobe (thick arrow). Note another nodule in the right middle lobe but without surrounding ground glass opacity (thin arrow) (Courtesy of Kyung Soo Lee, MD, Samsung Medical Center, Seoul, Korea).

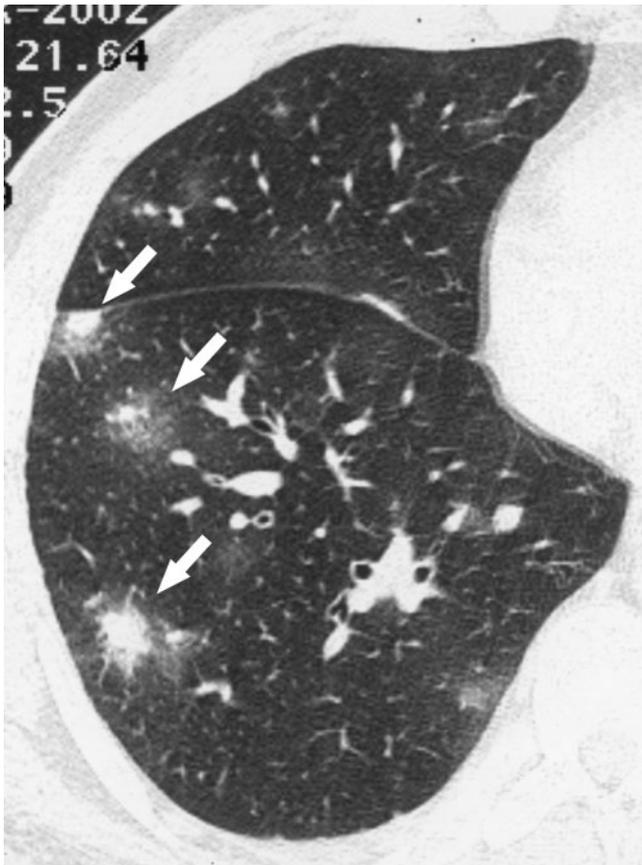


Figure 6. Simple pulmonary eosinophilia (Loeffler syndrome) in a 42-year-old man with peripheral eosinophilia (53.5% of eosinophils in the peripheral blood). Thin-section CT shows multiple small nodules (arrows) with a surrounding halo of ground glass opacity in the right lower lobe.

slight thickening of the alveolar walls caused by infiltrates of lymphocytes and non-caseating granulomas [6].

Iatrogenic injuries such as pulmonary artery catheterization or transbronchial biopsy may produce pulmonary nodules with the halo sign. Pulmonary artery pseudoaneurysms, which developed as a complication of pulmonary artery catheterization, have been reported to show the halo sign. In these cases, the halo around the nodule was considered to represent an intermediate stage of clearance of extravasated blood. Some patients who have undergone transbronchial biopsy can develop lung nodules associated with a halo sign. The halo was related to haemorrhage secondary to the lung injury [7].

Conclusion

The presence of a halo of ground glass attenuation surrounding a pulmonary nodule on CT has been named the CT halo sign. The sign itself is known to be non-specific because it can be seen in various pulmonary pathological processes such as infectious, neoplastic, and inflammatory conditions. Nonetheless, radiologists should be familiar with this sign because clinical settings and associated radiological features help to narrow the differential diagnosis. For example, in immunocompromised patients the presence of multiple nodules associated with the CT halo sign should suggest infectious diseases, Kaposi's sarcoma, and lymphoproliferative pulmonary disorders. Particularly in patients with acute leukaemia and bone marrow transplant recipients with fever, the presence of the CT halo sign strongly suggests invasive pulmonary aspergillosis. However, in immunocompetent patients, a solitary nodule with the CT halo sign and pseudocavitation has a high likelihood of being a bronchioloalveolar carcinoma. The CT halo sign suggests that the disease may be pathologically active with haemorrhage, inflammation, or tumour spread.

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