

CASE REPORT

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# Reversed halo sign in pneumocystis pneumonia: a case report

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## Abstract

**Background:** The reversed halo sign may sometimes be seen in patients with cryptogenic organizing pneumonia, but is rarely associated with other diseases.

**Case presentation:** We present a case study of a 32-year-old male patient with acquired immunodeficiency syndrome, who had previously been treated with chemotherapy for non-Hodgkin's lymphoma. A chest X-ray showed bilateral patchy infiltrates. High-resolution computed tomography revealed the reversed halo sign in both upper lobes. The patient was diagnosed with pneumocystis pneumonia, which was successfully treated with sulfamethoxazole trimethoprim; the reversed halo sign disappeared, leaving cystic lesions. Cases such as this one are rare, but show that the reversed halo sign may occur in patients who do not have cryptogenic organizing pneumonia.

**Conclusion:** Physicians can avoid making an incorrect diagnosis and prescribing the wrong treatment by carefully evaluating all clinical criteria rather than assuming that the reversed halo sign only occurs with cryptogenic organizing pneumonia.

## Background

Pneumocystis pneumonia (PCP) is the most common serious respiratory complication found in patients with acquired immunodeficiency syndrome (AIDS) [1]. The typical radiographic features of PCP are bilateral perihilar distributions of ground-glass opacities (GGOs); however, a wide variety of radiographic findings have been observed [2-4]. The reversed halo sign is reported to be specifically associated with cryptogenic organizing pneumonia (COP) [5], but here we present the first case, to our knowledge, of PCP with a reversed halo sign.

## Case presentation

A 32-year-old man was admitted to our hospital with an eight-week history of fever and productive cough. Approximately two years prior to presentation, extranodal B-cell non-Hodgkin's lymphoma (NHL) had been diagnosed, for which the patient had undergone chemotherapy. On admission, the patient's body temperature was 38.8°C, blood pressure was 124/72 mm Hg, pulse

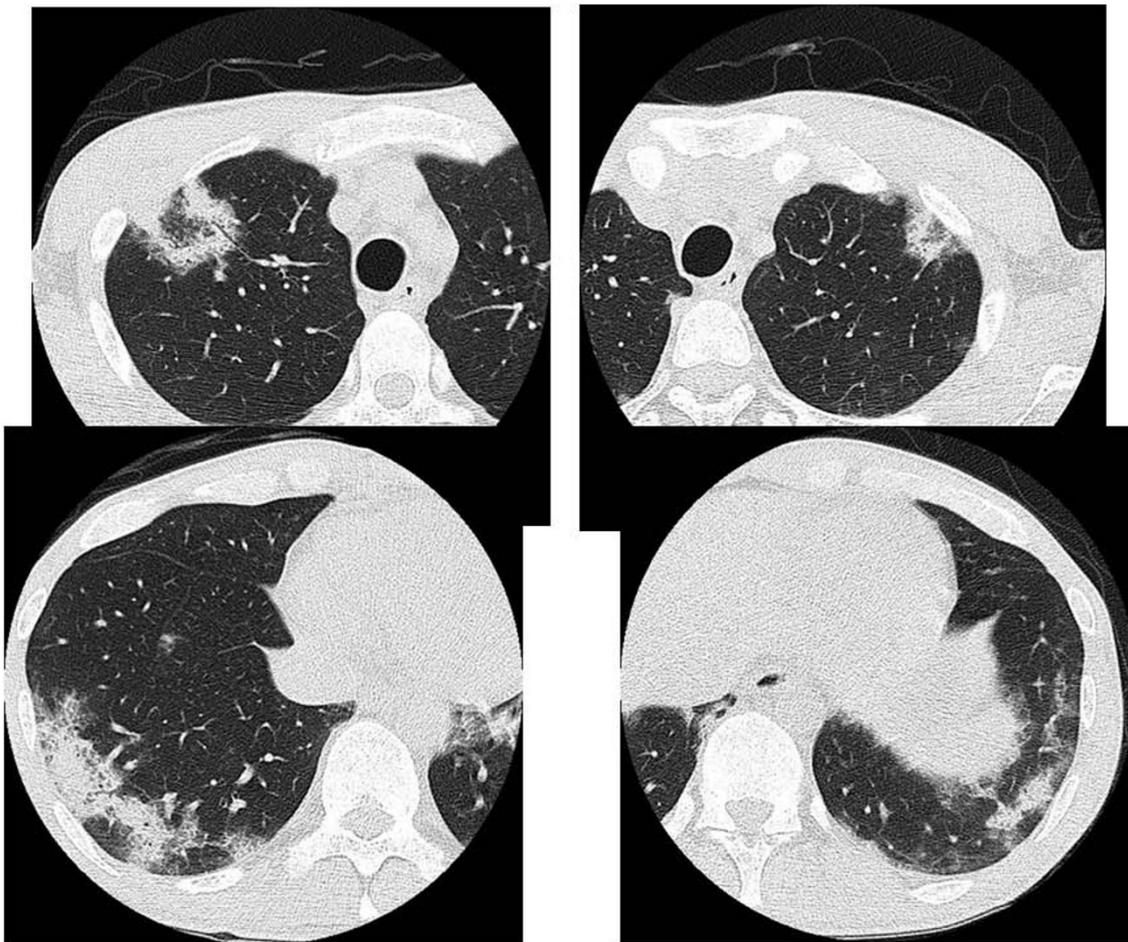
rate was 106 beats/min, and percutaneous oxygen saturation was 96% in room air. Physical examination revealed coarse crackles over the posterior right lung. The patient's white blood count was 5,500 cells/mm<sup>3</sup> (lymphocytes = 25%, neutrophils = 55%, and atypical = 8%). CD4 cell count was 53 cells/ $\mu$ l and HIV-1 RNA count was  $2.5 \times 10^4$  copies/ml. Chest radiography showed bilateral patchy infiltrates. A high-resolution computed tomography (HRCT) scan showed the reversed halo sign in the upper lobes and patchy parenchymal infiltrates in the lower lobes (Figure 1). A transbronchial lung biopsy was performed from the upper segmental bronchus. Histologically, the Grocott stain showed characteristic staining of many round structures surrounded by foamy, intra-alveolar exudate and unaccompanied by interstitial pneumonitis (Figure 2).

The patient was diagnosed with PCP and AIDS. He was treated with sulfamethoxazole trimethoprim. The symptoms improved within 20 days, and chest radiography showed normal and chest CT showed remarkable improvements; the reversed halo sign disappeared, leaving cystic lesions (Figure 3).

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**Figure 1** High-resolution computed tomography images of the lung before sulfamethoxazole trimethoprim treatment. The reversed halo signs and consolidations are shown.

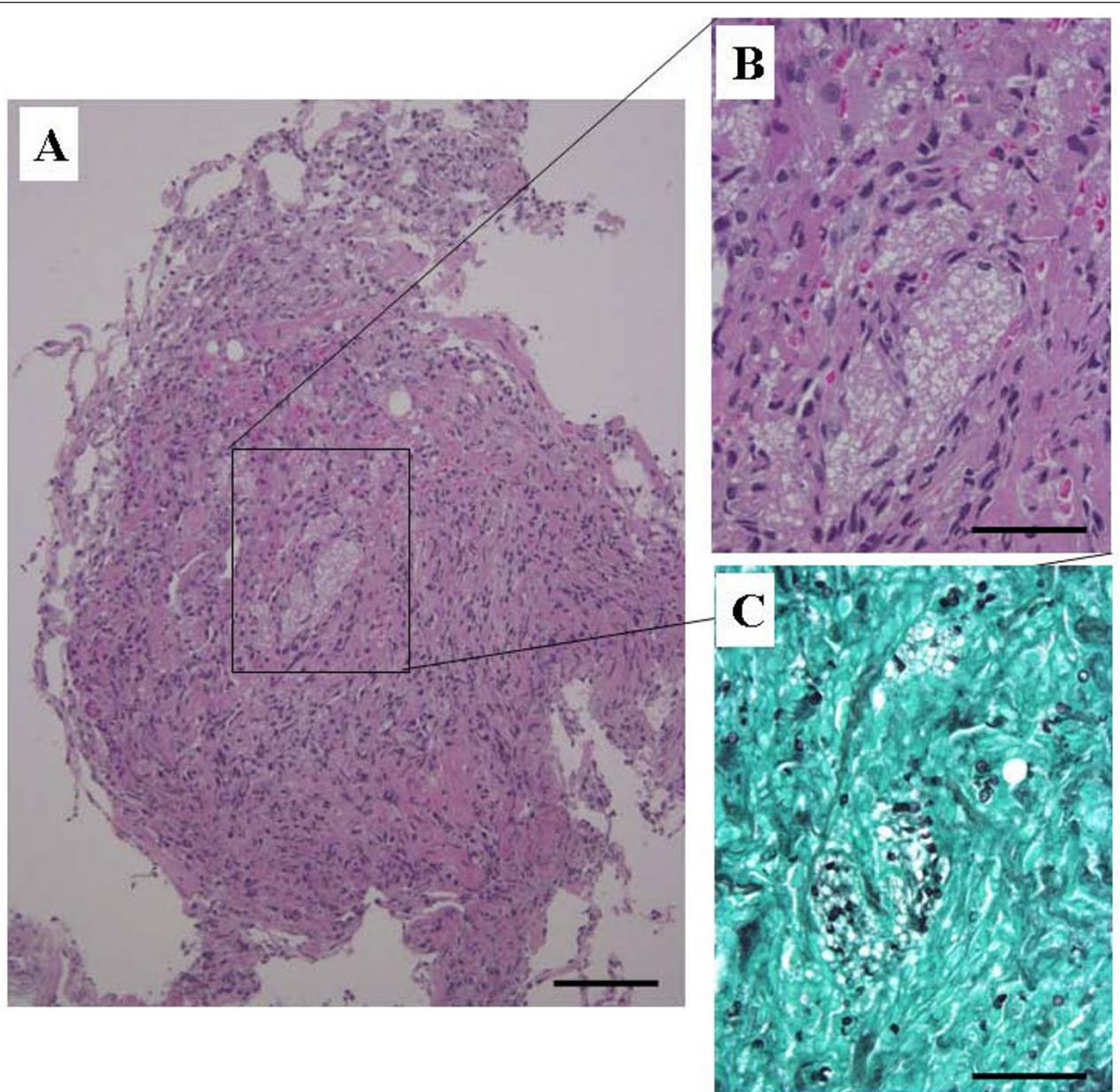
## Discussion

In 1996, Voloudaki et al. [6] reported two cases of COP that appeared on HRCT scans as central GGO surrounded by a denser air-space consolidation of crescent and ring shapes. This appearance was later named the “reversed halo sign” and defined as central GGO surrounded by a denser consolidation of crescentic (forming more than three-fourths of a circle) or ring (forming a complete circle) shapes that are at least 2 mm in thickness [5]. In studies of patients with COP, the reverse halo sign has been found in 12-19% of patients [5,7] (Table 1). In fact, the reversed halo sign is so closely associated with COP that its presence is commonly used to make a diagnosis.

In Voloudaki’s study of COP [6], the central GGO corresponded histopathologically to the area of alveolar septal inflammation and cellular debris; the ring-shaped or crescentic peripheral air-space consolidation corresponded to the area of organizing pneumonia within the alveolar ducts. The mechanism behind the reversed halo

sign, in association with non-infectious diseases, has been likened to dropping a pebble into a pond: Inflammation occurs in the middle and spreads outward, while simultaneously improving at the site of occurrence. The changes in the center of the “pond” result in the GGO appearance [8].

The reversed halo sign has also been observed in association with other diseases, including the infectious diseases paracoccidioidomycosis (PCM), tuberculosis (TB), pulmonary zygomycosis, and pulmonary aspergillosis. In fungal infections, histology revealed that the lung was infarcted and had more hemorrhaging in the periphery than in the center [9]. However, in patients with PCM who underwent surgical lung biopsy, the central area of the lesions consisted of an inflammatory infiltrate in the alveolar septa, composed of macrophages, lymphocytes, plasma cells, and some giant cells, with relative preservation of the alveolar spaces [10]. The peripheries of the lesions consisted of dense and homogeneous intra-alveolar cellular infiltrates. There was no evidence of organizing

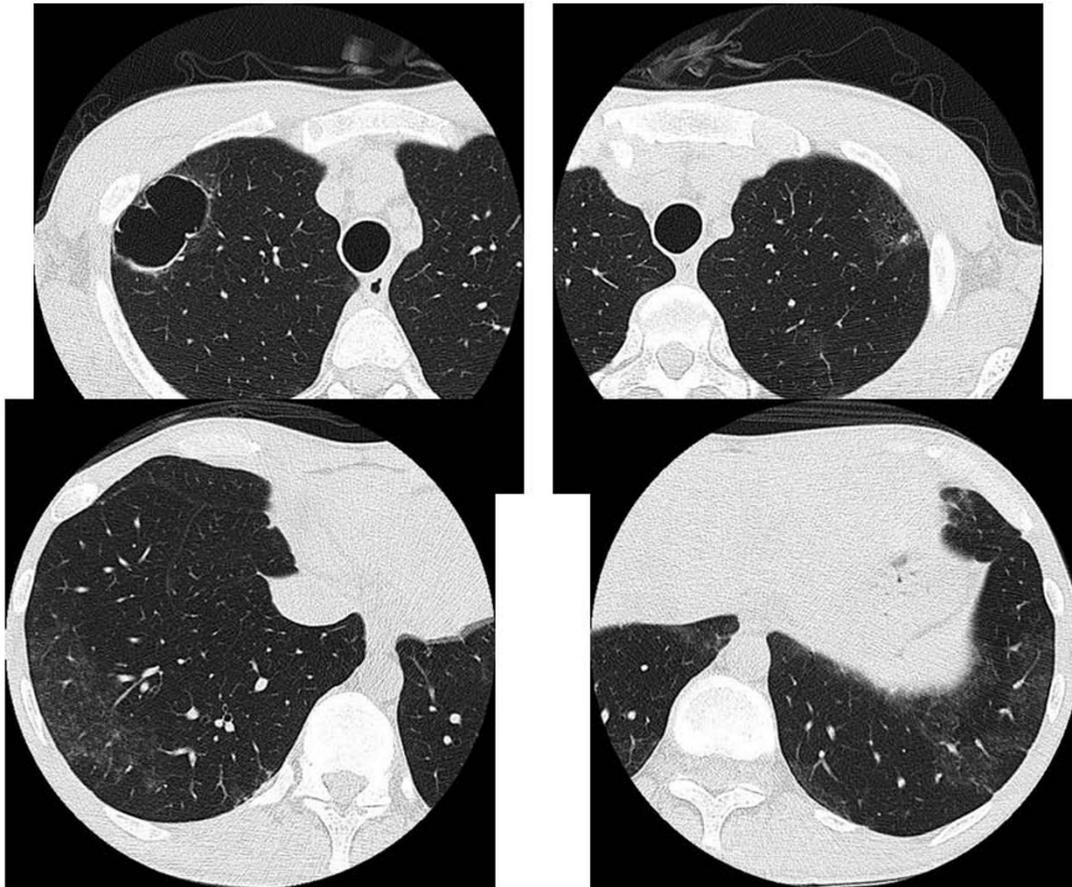


**Figure 2 Lung specimen obtained by transbronchial lung biopsy.** Pathological findings of the specimen show many cysts and intra-alveolar exudates. (A, internal scale bar = 100  $\mu$ m hematoxylin and eosin stain. B, internal scale bar = 50  $\mu$ m hematoxylin and eosin stain. C, internal scale bar = 50  $\mu$ m Grocott stain.)

pneumonia or large hemorrhage. Grocott-Gomori methenamine-silver stain confirmed the presence of fungus (*P. brasiliensis*) in the alveolar septa and in the air spaces. In TB cases, pathology revealed the presence of caseating granulomas. The pathological findings for each infectious disease are distinct, greatly diminishing the chance of a misdiagnosis.

In humans, PCP is caused by infection with *Pneumocystis jirovecii*. This pathogen exists in two dominant forms: a cyst and a trophozoite. In humans, the trophozoite attaches

itself to type 1 alveolar epithelial pneumocytes by way of interdigitation with the host cell membrane. This causes proteinaceous fluid to leak into the alveolar spaces. These spaces become filled with a characteristic “foamy” eosinophilic exudate that contains trophozoites, cysts, fibrin, and dead cells. Type 2 pneumocytes replicate in order to replace the damaged type 1 pneumocytes. This leads to mobilization of lung macrophages and plasma cells within the interstitium, causing a mild interstitial pneumonitis. Eventually, interstitial fibrosis develops as the lung tries to



**Figure 3** High-resolution computed tomography images of the lung 20 days after sulfamethoxazole trimethoprim treatment. Various sizes of cystic lesions are seen in the bilateral upper lobes and small nodules are seen in the bilateral lower lobes.

**Table 1** Summary of reported cases of Reversed Halo Sign

Diagnosis	Number of patients (%)	[Ref.]
Bronchiolitis obliterans organizing pneumonia	2	[6]
Sarcoidosis	1	[8]
Cryptogenic organizing pneumonia	6/31 (19%)	[5]
Paracoccidioidomycosis	15/148 (10%)	[10]
Cryptogenic organizing pneumonia	2/34 (5.9%)	[7]
Secondary organizing pneumonia (of 1 breast cancer and 1 rheumatoid arthritis patient)	2/34 (5.9%)	[7]
Paracoccidioidomycosis	15/77 (19%)	[13]
Lymphomatoid granulomatosis	1	[14]
Tuberculosis	1	[15]
Lipoid pneumonia	1	[16]
Wegener's granulomatosis	1	[17]
Zygomycosis	7/37 (19%)	[9]
Invasive pulmonary aspergillosis	1/132 (<0.7%)	[9]
Sarcoidosis	1	[18]
Sarcoidosis	1	[19]
Tuberculosis	1	[20]
Cryptogenic organizing pneumonia	1	[21]
Pneumocystis pneumonia	1	present

repair itself [2]. This process produces the GGO and consolidation findings that can be observed with HRCT.

In the case presented here, pathological findings showed an inflammatory infiltrate in the alveolar space, without a great amount of hemorrhage, and unassociated with organizing pneumonia. PCP and PCM have many pathological and biological similarities. Thus, the mechanism causing the reversed halo sign in the two diseases may be the same, possibly stemming from the host's immune response or the biological features of mycosis.

To our knowledge, PCP has never been reported in connection with the reversed halo sign. PCP occurs not only in patients with AIDS, but also in individuals with other malignant diseases; the radiological features of PCP differ depending on patients' exact medical histories [11]. For instance, patients with AIDS presented GGO without consolidation on CT [11]. However, patients with malignancy were likely to experience PCP with diffuse GGO with inhomogeneous distribution unrelated to secondary lobes, and consolidation with GGO [11]. Additionally, PCP with malignancy has been observed in conjunction with nodular infiltration [12]. Consolidation in HIV-negative patients may be associated with severe inflammation of the lung. In the case study presented here, the reversed halo sign with HIV-PCP is induced by the special condition of the host's immune system; his underlying diseases, including NHL and HIV, are likely to have influenced the development of the disease. The HIV infection is also likely to have been responsible for the cystic lesions that remained after the reversed halo sign disappeared, though this characteristic is much more commonly observed in PCP patients with AIDS [2].

## Conclusions

The reversed halo sign does not appear to be specific for COP, and may be seen in patients with any active infection. This is likely because there are a number of different mechanisms that can cause this characteristic pattern. In this case, the reversed halo sign is likely to have been found in association with PCP because of the patient's infection with HIV. Because the reversed halo sign can indicate different diseases that require very different treatments, physicians should not assume a diagnosis of COP whenever patients present with this trait.

## Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying imagings. A copy of the written consent is available for review by the Editor-in-chief of this journal.

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## Authors' contributions

HO was in charge of the overall care of the patient, performed the literature search, compiled data and drafted the manuscript. KT, TS and AI provided intellectual input and revised the manuscript. KH has participated in the histological diagnosis of the case. All authors have read and approved the final manuscript.

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## Competing interests

The authors declare that they have no competing interests.

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