

Reversed Halo Sign in Invasive Pulmonary Fungal Infections

Hisham Wahba,^{1,4} Mylene T. Truong,¹ Xiudong Lei,³ Dimitrios P. Kontoyiannis,² and Edith M. Marom¹

Departments of ¹Diagnostic Radiology and ²Infectious Diseases, Infection Control and Employee Health, and ³Department of Biostatistics of Quantitative Sciences, University of Texas M. D. Anderson Cancer Center, Houston, Texas; and ⁴Department of Diagnostic Radiology, National Cancer Institute, Cairo, Egypt

Computed tomography scans of documented pulmonary mold infections were reviewed for the presence of the reversed halo sign, a focus of ground-glass attenuation surrounded by a solid ring. The reversed halo sign was an early sign, seen in ~4% of patients with pulmonary mold infections, usually with zygomycosis.

Opportunistic fungal pneumonias are associated with high morbidity and mortality rates [1–3]. Although invasive pulmonary aspergillosis (IPA) is the most common type of fungal pneumonia, other angioinvasive molds, such as *Fusarium* and *Zygomycetes* species, are increasingly encountered in severely immunocompromised hosts. Because early institution of high-dose antifungal therapy is associated with improved outcomes [4, 5], early recognition of invasive fungal disease is important. However, cultures of respiratory secretions are neither sensitive nor specific, and lavage and invasive procedures often cannot be done for these patients because of coagulation abnormalities and thrombocytopenia [6, 7]. Thus, diagnosis of invasive pulmonary fungal disease relies heavily on imaging [8]. CT is often used in an attempt to identify fungal pneumonia in a timely fashion.

The reversed halo sign (RHS) is a CT finding, a focal round area of ground-glass attenuation surrounded by a ring of consolidation, which has been described in cryptogenic organizing pneumonia [9, 10].

The purpose of the present study was to evaluate whether

the RHS is evident on CT images of patients with invasive fungal pulmonary infections, the prevalence of RHS, and whether RHS can serve as an early sign of infection.

Materials and methods. We identified, through a computerized infectious diseases database, patients who were treated for pulmonary zygomycosis, pulmonary fusariosis, or IPA at the University of Texas M. D. Anderson Cancer Center from September 2002 through April 2007. We included patients with proven and probable pulmonary fungal infection, as defined by international consensus criteria [8], and excluded patients who had concomitant bacterial or viral respiratory pathogens. We retrospectively reviewed the patients' medical records for patient and infection characteristics, and we reviewed all chest CT images and chest radiographs obtained during the course of infection. This study was approved by our institutional review board, with a waiver of informed consent, and it was in compliance with Health Insurance Portability and Accounting Act regulations.

Chest CT images were obtained with use of a variety of scanners, with slice thicknesses of 2.5 mm or 3.75 mm. Each CT image was reviewed on a workstation by 2 experienced chest radiologists, and differences were resolved by reaching consensus. The RHS was considered to be present if the radiologists identified a focal round area of ground-glass attenuation surrounded by a crescent or ring of consolidation. The size of the RHS (the largest RHS if >1 was present), accompanying radiographic abnormalities, and evolution of the sign on follow-up chest CT images and chest radiographs were determined. The timing of the RHS relative to symptoms, other imaging findings, and death was also evaluated.

The χ^2 test was used to examine associations between types of infection and the RHS. A *P* value <.05 was considered to be significant. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute).

Results. One hundred eighty-nine patients were treated for proven and probable fungal pneumonia, as follows: 132 with IPA, 37 with zygomycosis, and 20 with fusariosis. Of the 189 patients, the RHS was seen in 8 patients (4%), as follows: 7 with pulmonary zygomycosis and 1 with IPA. Thus, the RHS was seen in 19% of patients with zygomycosis, in <1% of patients with IPA, and in no patients with fusariosis (*P* < .001) (table 1).

Seven of the 8 patients with RHS had leukemia; the other patient had diabetes. The patients' symptoms at presentation were fever (for 7 patients), cough (3), hemoptysis (2), and shortness of breath (1). Culture and/or histopathological proof

Received 16 December 2007; accepted 22 January 2008; electronically published 17 April 2008.

Reprints or correspondence: Dr. Edith M. Marom, Dept. of Diagnostic Radiology, Unit 371, University of Texas M. D. Anderson Cancer Ctr., 1515 Holcombe Blvd., Houston, TX 77030 (emarom@di.mdacc.tmc.edu).

Clinical Infectious Diseases 2008;46:1733–7

© 2008 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2008/4611-0014\$15.00

DOI: 10.1086/587991

Table 1. Disease and imaging findings in patients with the reversed halo sign (RHS) and invasive mold infection.

Patient	Sex	Age, years	No. of RHSs	RHS size, cm	Lobe	Additional parenchymal finding(s)	Primary diagnosis	Neutropenia	Steroid therapy	BMT	GVHD	Status	Fungus
1	M	66	1	8.8	RUL	None	AML	Yes	Yes	Yes	Yes	Deceased	<i>Zygomycetes</i>
2	M	61	1	6.2	LUL	GGO adjacent to RHS	CLL	Yes	No	No	No	Deceased	<i>Zygomycetes</i>
3	M	34	2	7.1	LUL	LLL consolidation, TNTC 1–2.5-cm solid nodules	CML	No	Yes	Yes	Yes	Deceased	<i>Zygomycetes</i>
4	M	42	1	5.8	RUL	GGO adjacent to the RHS	CLL	No	Yes	Yes	Yes	Deceased	<i>Aspergillus</i>
5	F	24	6	5.0	RUL	None	AML	Yes	Yes	Yes	Yes	Alive	<i>Zygomycetes</i>
6	M	60	1	3.7	LUL	None	CLL	Yes	Yes	Yes	Yes	Alive	<i>Zygomycetes</i>
7	F	70	1	4.1	RML	Two nodules	Diabetes	No	No	No	No	Unknown	<i>Zygomycetes</i>
8	F	49	1	5.0	Lingula	GGO adjacent to RHS and in the abutting LLL	AML	No	No	Yes	No	Deceased	<i>Zygomycetes</i>

NOTE. AML, acute myelogenous leukemia; BMT, bone marrow transplantation; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GGO, ground-glass opacities; GVHD, graft-versus-host disease; LLL, left lower lobe; LUL, left upper lobe; RHS, reversed halo sign; RML, right middle lobe; RUL, right upper lobe; TNTC, too numerous to count.

of the pulmonary fungal infection was obtained via bronchoalveolar lavage (for 4 patients), transthoracic needle biopsy (2), transbronchial biopsy (1), or lobectomy (1); additional sites of disease were confirmed via brain biopsy (1) and oral biopsy (1).

Chest CT images were obtained to investigate the symptomatology described above. In the 7 patients with leukemia, the initial CT study was performed 1–7 days (mean, 3.6 days) from presentation of initial symptoms and 0–30 days (mean, 10.9 days) from final histopathological and/or culture proof of diagnosis. The patient with diabetes was referred from abroad, after partial therapy; thus, data on initial imaging in relation to presenting symptoms were not available.

The RHS mean diameter was 5.7 cm (range, 3.7–8.8 cm). The RHS was usually solitary (for 5 patients), with an upper lobe predominance (table 1); it traversed a fissure in 3 patients and involved the chest wall in 1 patient. An ipsilateral small pleural effusion was seen in 5 patients, with no mediastinal or hilar adenopathy. Extrathoracic imaging findings included low-attenuation liver lesions (for 1 patient), confirmed at autopsy to represent fungal abscesses, and brain parenchymal hemorrhage (for 1 patient), confirmed by imaging follow-up and excisional biopsy to be the result of brain abscesses.

A histopathological assessment of the entire lesion that comprises the RHS was available for 3 patients via autopsy (for 2 patients) or lobectomy (1). The RHS was attributable to infarcted lung tissue, with a greater amount of hemorrhage at the periphery than in the center (figure 1).

The RHS preceded respiratory symptoms in 4 (57%) of 7 patients with presenting symptom information. Long-term follow-up was available for 7 patients; 5 (71%) had cavitation on subsequent CT studies that appeared 23–55 days (mean, 32.6 days) after initial presentation of the RHS (figure 2). At the time cavitation was observed, the patients had recovered from neutropenia.

Five (71%) of the 7 patients with presenting symptom information died with the pulmonary infection 18–64 days

(mean, 43 days) after diagnosis or a range of 38–105 days after the initial CT study showing the RHS. Three of these patients had relapse of their leukemia, and 2 were in remission but had severe graft-versus-host disease. Follow-up CT images were available for 4 of these patients and showed cavitation of the RHS for 3 patients. Follow-up chest radiography showed progressive bilateral airspace disease in 4 of 5 patients.

Two patients are alive >3 years after diagnosis of fungal pneumonia. Both achieved remission of their leukemia, although both have graft-versus-host disease that is being treated with steroids. Both patients developed cavitation after initial demonstration of the RHS but never developed bilateral airspace disease.

Discussion. To our knowledge, ours is the first systematic study of the RHS in patients with invasive fungal pneumonia. We found that this sign is present early in the disease course and that it is more common among patients with zygomycosis than among patients with other forms of invasive fungal pneumonia.

The RHS was once thought to be pathognomonic of cryptogenic organizing pneumonia [9] but later was found among immunocompetent patients with paracoccidioidomycosis [11] and tuberculosis [12]. Histologically, the RHS in cryptogenic organizing pneumonia and paracoccidioidomycosis is attributable to a greater amount of inflammatory cells in the periphery of the lesion than in the center. The histology of the RHS in invasive fungal pneumonia, obtained at least 7 weeks after appearance of the sign, represents infarcted lung with a greater amount of hemorrhage in the peripheral solid ring than in the center ground-glass region. It is unknown whether early pathology of the RHS from fungal disease represents inflammatory cell infiltration, similar to that found in cryptogenic organizing pneumonia.

The importance of our study lies in its potential clinical applications. Of the known CT signs for pulmonary fungal infections, the halo sign is an early sign seen in 60% of patients [4, 5]. Other signs that have been described with invasive pul-

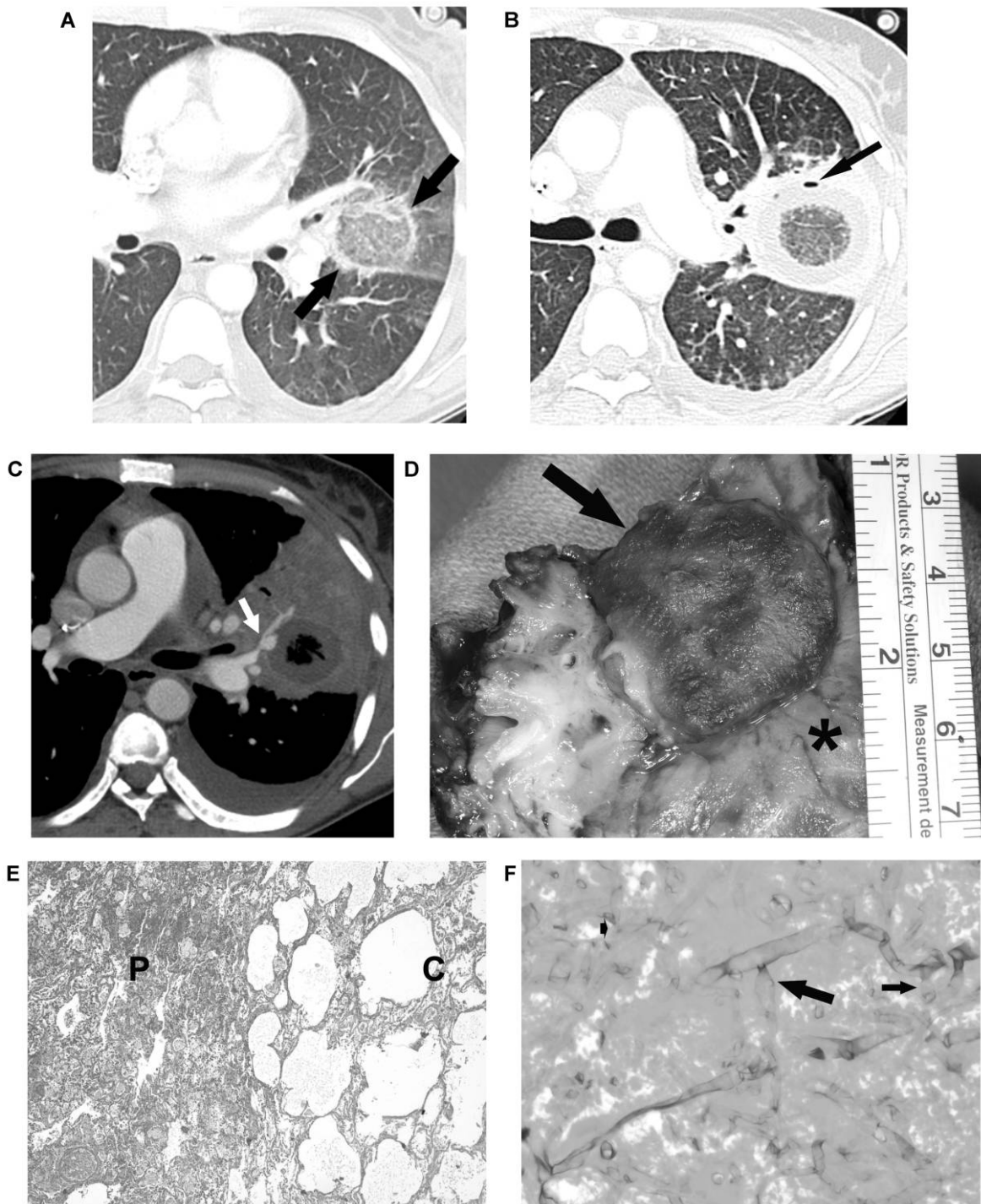


Figure 1. Images from a 49-year-old woman who presented with febrile neutropenia during treatment for recurrent acute myelogenous leukemia. *A*, Contrast-enhanced chest CT image at presentation, showing the reversed halo sign, a solid ring (arrows) with central ground-glass opacities. *B*, Contrast-enhanced chest CT image, which was obtained 4 weeks later because of some chest tightness and persistent fever, showing a better formed peripheral soft tissue ring with interval development of lingular consolidation. The arrow points to an air bubble that separates the infarcted reversed halo from the still viable consolidated lung peripheral to it. *C*, The patient developed a pseudoaneurysm (arrow) and underwent lobectomy. *D*, Lobectomy specimen, 7 weeks after presentation, showing that the reversed halo sign (arrow) was attributable to infarcted lung. The tissue surrounding the reversed halo (*) is lingular consolidation. *E*, Photomicrograph of the lobectomy specimen showing that the reversed halo sign was attributable to infarcted lung, with a greater amount of hemorrhage at the periphery (P) than in the center (C) (hematoxylin-eosin stain, $\times 10$). *F*, Photomicrograph showing fungal hyphae with 90° branching, consistent with *Zygomycetes hyphae* (arrows). (GMS staining, $\times 40$). A color version of the figure is available in the online edition of *Clinical Infectious Diseases*.

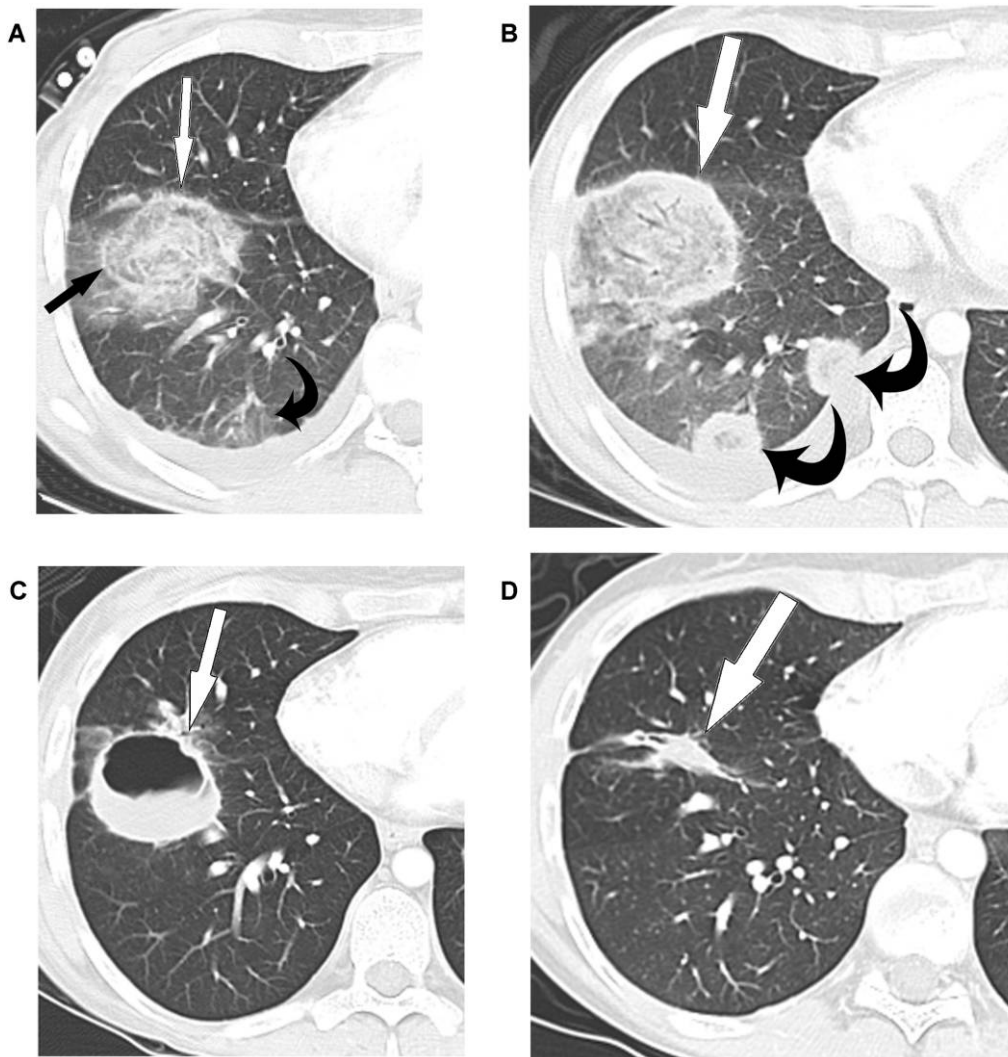


Figure 2. Images from a 24-year-old woman who presented with febrile neutropenia, with recurrence of acute myelogenous leukemia, and graft-versus-host disease 1 year after bone marrow transplantation. *A*, Contrast enhanced chest CT image obtained 7 days after patient presented with fever and chills, showing focal ground-glass opacity mass surrounded by soft tissue ring (*straight arrows*), the reversed halo sign. Curved arrow points to nodular ground glass opacity before formation of the sign. Dry cough developed 7 days after this CT image was obtained. *B*, CT image obtained 10 days after image in panel *A*, showing better delineation of the reversed halo sign, with increasing wall thickness (*straight arrow*) and interval formation of the sign around previously seen poorly marginated nodular ground-glass opacities (*curved arrows*). Results of transthoracic needle biopsy showed numerous fungal hyphae, which, on culture, were confirmed to represent *Zygomycetes* species. *C*, CT image obtained 2 months after image in panel *A*, showing interval cavitation of the reversed halo sign mass (*arrow*) and nodules (not shown). *D*, Follow-up chest CT image, obtained 2 years after that shown in panel *A*, showing residual scar in the right lower lobe (*arrow*).

monary fungal infection are the hypodense sign and crescent sign; however, these are considered to be late signs, because they appear 1–2 weeks after initial CT signs of fungal infection [13] and thus are not useful for early diagnosis and early treatment of fungal infection. Our study shows that the RHS in severely immunocompromised patients may indicate invasive pulmonary fungal infection, and early antifungal treatment of that infection should be initiated in a timely fashion.

It is unknown why the RHS is significantly more common in pulmonary zygomycosis than in IPA ($P < .001$). It may be

related to the greater aggressiveness of *Zygomycetes* species, which have greater angioinvasion capacity compared with *Aspergillus* species.

Therapy for presumed fungal pneumonia is often aimed at the much more common fungus, IPA. Even though >10 pulmonary nodules and a pleural effusion are more commonly seen with zygomycosis [14], the imaging features of IPA, zygomycosis, and fusariosis are, in general, quite similar. Having an imaging feature that can differentiate zygomycosis from aspergillosis could have important therapeutic implications, be-

cause voriconazole, the preferred antifungal agent for IPA [15], has no activity against zygomycosis [6]. In contrast, only amphotericin B–based therapy [16] and possibly posaconazole [17] have been shown to have activity against *Zygomycetes* species. The presence of the RHS, in the appropriate context, should prompt consideration of pulmonary zygomycosis and selection of an antifungal therapy with coverage against *Zygomycetes* species.

Our study is somewhat limited by its retrospective design, and it is too small for us to draw firm conclusions about the prognostic value of the RHS. However, within our relatively homogeneous group of patients with underlying hematological malignancies or history of bone marrow transplantation, the development of bilateral airspace disease after the appearance of the RHS was seen only in patients who died with infection.

In conclusion, the RHS was seen in 4% of our immunocompromised patients with invasive pulmonary fungal infections—in particular, in patients with pulmonary zygomycosis—early in the disease course. Whether the use of the RHS as a criterion for improved selection of appropriate antifungal agents will translate to improved outcome is unknown and will need to be studied in a larger, prospective trial.

Acknowledgments

Potential conflicts of interest. D.P.K.: research support and honoraria from Merck, Fujisawa, Enzon, Pfizer, and Schering-Plough. All other authors: no conflicts.

References

1. Dasbach EJ, Davies GM, Teutsch SM. Burden of aspergillosis-related hospitalizations in the United States. *Clin Infect Dis* **2000**; 31:1524–8.
2. Lionakis MS, Kontoyiannis DP. *Fusarium* infections in critically ill patients. *Semin Respir Crit Care Med* **2004**; 25:159–69.
3. McAdams HP, Rosado de Christenson M, Strollo DC, Patz EF Jr. Pulmonary mucormycosis: radiologic findings in 32 cases. *AJR Am J Roentgenol* **1997**; 168:1541–8.
4. Caillot D, Casanovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* **1997**; 15:139–47.
5. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis* **2007**; 44:373–9.
6. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis* **2005**; 191:1350–60.
7. Tarrand JJ, Lichtenfeld M, Warraich I, et al. Diagnosis of invasive septate mold infections: a correlation of microbiological culture and histologic or cytologic examination. *Am J Clin Pathol* **2003**; 119:854–8.
8. Ascigliu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* **2002**; 34:7–14.
9. Kim SJ, Lee KS, Ryu YH, et al. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. *AJR Am J Roentgenol* **2003**; 180:1251–4.
10. Voloudaki AE, Bouros DE, Froudarakis ME, Datsis GE, Apostolaki EG, Gourtsoyiannis NC. Crescentic and ring-shaped opacities: CT features in two cases of bronchiolitis obliterans organizing pneumonia (BOOP). *Acta Radiol* **1996**; 37:889–92.
11. Gasparetto EL, Escuissato DL, Davaus T, et al. Reversed halo sign in pulmonary paracoccidioidomycosis. *AJR Am J Roentgenol* **2005**; 184:1932–4.
12. Ahuja A, Gothi D, Joshi JM. A 15-year-old boy with “reversed halo.” *Indian J Chest Dis Allied Sci* **2007**; 49:99–101.
13. Horgner M, Einsele H, Schumacher U, et al. Invasive pulmonary aspergillosis: frequency and meaning of the “hypodense sign” on unenhanced CT. *Br J Radiol* **2005**; 78:697–703.
14. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis* **2005**; 41:60–6.
15. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* **2002**; 347:408–15.
16. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* **1998**; 26:1383–96.
17. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. *Antimicrob Agents Chemother* **2006**; 50:126–33.