MAJOR ARTICLE

The Reversed Halo Sign: Pathognomonic Pattern of Pulmonary Mucormycosis in Leukemic Patients With Neutropenia?

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Background. Pulmonary mucormycosis (PM) is a life-threatening fungal infection with an increasing incidence among patients with acute leukemia. In some immunocompromised hosts, the reversed halo sign (RHS) has been described on the pulmonary computed tomographic (CT) scan of patients with mucormycosis.

Methods. This study reports a single-center experience with PM exclusively in patients with acute leukemia. Clinical records, laboratory results, and CT scans were retrospectively analyzed to evaluate the clinical usefulness of the RHS for the early identification and treatment of PM, with regard to outcomes in these patients.

Results. Between 2003 and 2012, 16 cases of proven PM were diagnosed among 752 consecutive patients receiving chemotherapy for acute myeloblastic or lymphoblastic leukemia. At the time PM was diagnosed, all patients but one were neutropenic. The study of sequential thoracic CT scans showed that during the first week of the disease, the RHS was observed in 15 of 16 patients (94%). Initially, other radiologic findings (multiple nodules and pleural effusion) were less frequent, but appeared later in the course of the disease (6% and 12% before vs 64% and 55% after the first week). After the diagnosis of PM, median overall survival was 25 weeks (range, 3–193 weeks), and 6 patients (38%) died before day 90.

Conclusions. In the particular setting of neutropenic leukemia patients with pulmonary infection, the presence of the RHS on CT was a strong indicator of PM. It could allow the early initiation of appropriate therapy and thus improve the outcome.

Keywords. reversed halo sign; computed tomography; mucormycosis; leukemia; neutropenia.

Mucormycosis is an emerging opportunistic infection caused by the Mucorales order of Zygomycetes fungi [1]. In a recent study, mucormycosis was the third most common invasive mycosis after candidiasis and aspergillosis among patients with hematologic diseases, and represented 8.3%–17% of all fungal infections [2]. In high-risk patients, pulmonary mucormycosis (PM) accounts for about two-thirds of all cases of mucormycosis, and 22%–44% occur in patients with hematologic malignancies [3–6]. Because the mortality rate is high in such patients (64%–76%), the early recognition of PM could improve the outcome [7, 8]. In hematologic patients with pulmonary invasive fungal disease (IFD), 40%–45% of the chest radiographs are falsely negative; high-resolution computed tomography (CT) has been a key advance for diagnosis [9, 10]. In invasive pulmonary aspergillosis (IPA), the CT halo sign (HS) has contributed to the early diagnosis and improved management of patients with hematologic diseases [11–13]. In 1996, Voloudaki et al described on CT images a focal ground-glass attenuation surrounded by a ring of consolidation in cryptogenic organizing pneumonia [14]. In 2000, Vogl et al identified the same morphologic criterion,

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named "bird's nest," as an early sign of PM [15]. Later on, other authors named this pattern the "atoll sign" [16] or "reversed halo sign" (RHS) [17], which is the preferred term according to the Fleischner Society [18].

Furthermore, the CT characteristics of pulmonary IFD were studied (Table 1). According to Chamilos et al, PM in patients with cancer could potentially be distinguished from IPA thanks to clinical and radiologic signs such as the presence of multiple (≥10) nodules and pleural effusions [19].

The RHS was described as an early sign of PM among 4% of the patients and was more specifically observed among 19% of patients with hematologic diseases [20]. Because the clinical features of PM are nonspecific and are not easily distinguishable from those of IPA, and given that the median time between first symptoms and diagnosis is about 2 weeks [21], optimal therapy is often delayed, which results in a 2-fold increase in 90-day mortality [19, 22]. The purpose of this report is to show that the RHS on early CT scans can have a significant impact on the diagnosis and management of PM and thus the outcome in specific population of patients with acute leukemia and neutropenia.

PATIENTS AND METHODS

Clinical Database

Between January 2003 and December 2012, we retrospectively identified patients with acute leukemia who were treated for PM at the Department of Clinical Hematology, University Hospital of Dijon, France. Among our leukemia patients with prolonged neutropenia (>10 days), most of whom received broad-spectrum antibiotics, the occurrence of fever, cough, chest pain, or hemoptysis triggered a CT scan. Day 0 of the disease was defined as the day with the first evidence of the RHS on a CT scan performed after the onset of clinical symptoms. The proof of the infection was based on mycologic data (direct examination or culture), pathologic examination, or molecular methods using polymerase chain reaction (PCR) and direct sequencing on tissue biopsy or culture [23]. We included patients with proven pulmonary mucormycosis as defined by the revised criteria of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) [24]. We retrospectively analyzed clinical data and the global response, assessed as the success or failure of antifungal therapy at 30, 60, and 90 days after the first CT scan showing the RHS as evidence of PM. The response to treatment was based on the international consensus criteria of EORTC/MSG, which incorporate clinical and radiologic features [25]. The local institutional review board approved the study.

Image Database

The image database included thoracic CT findings from 17 patients. These included 16 patients with proven PM and 1 patient with possible PM. Only the 16 patients with proven PM are reported in this paper. Images at presentation and their

Table 1. Retrospective Studies With Computed Tomographic Scan Findings in Hematologic Patients With Pulmonary Mucormycosis

Reference	Time Period	Patients With Proven/ Probable PM, No.	Presence of the RHS on First CT, No.	Patients With Acute Leukemia, No.	Acute Leukemia With Neutropenia, No.	Time to Perform First CT Scan After the Onset of Clinical Symptoms	Time to Achieve Mycologic Diagnosis of PM After First CT	Diameter of the Biggest Lesion on First CT	Pleural Effusion on First CT	Cavitation
Wahba et al, 2008 [20][a]	2002–2007	37	7/37	3/7[b] HM	2/3	1–7 d (mean, 3.6 d)	0–30 d (mean, 10.9 d)	3.7–8.8 cm (median, 5 cm)	5/7 RHS	5/7 available data at 23–55 d after initial RHS (mean, 32.6 d)
Chamilos et al, 2005 [19][a]	2002–2004	16	NA	9/15 HM	9/15	2–19 d (median, 5 d)	NA	5/16 patients with lesion >3 cm (range, 3.8–5.8 cm)	10/16	4/16 on first CT scan
Vogl et al, 2000 [15]	1997–1999	9	5/9 (including 3/7 acute leukemia)	7/9 HM	NA	NA	NA	2–5 cm (median, 4 cm)	3/9	NA

Abbreviations: CT, computed tomography; HM, hematologic malignancies; NA, not available; PM, pulmonary mucormycosis; RHS, reversed halo sign.

[a] An overlap may be possible between the 2 publications.

[b] Only cases with reversed halo sign.

evolution during the course of the disease were screened to evaluate the clinical usefulness of the RHS for the early diagnosis of PM. The RHS was considered to be present on the CT if a focal ground-glass opacity surrounded by a solid ring of consolidation was observed. Other CT findings of the lesions such as location, diameter, ground-glass aspect, presence of cavitation (or air-crescent sign), pleural effusion, or multiple micronodules (>10 nodules <1 cm) were noted. All the CT scans were reviewed by clinical hematologists (D.C. and C.L.) and by a radiologist (L.E.).

RESULTS

Clinical Characteristics

During the studied period, 752 patients with acute leukemia received 1258 courses of intensive chemotherapy, which induced prolonged neutropenia. Among these patients, there were 16 cases of proven PM, meaning an incidence of 2.2% of the patients and 1.3% of the neutropenia episodes. This study population included 10 men and 6 women ranging in age from 32 to 74 years (median, 60 years). Eleven patients had acute myeloblastic leukemia and 5 had acute lymphoblastic leukemia. Nine patients were currently receiving induction or consolidation chemotherapy whereas 7 patients were in progressive disease or relapse. At the time PM was diagnosed, all of the patients but one were neutropenic (white blood cell count <500 cells/μL). The median duration of neutropenia before the first clinical signs was 14 days (range, 5–98 days; Table 2).

The clinical features were nonspecific. Fever (87%) and chest pain (81%) were the most common symptoms. Cough and hemoptysis (most often minor) were noted in 37% and 31% of patients, respectively. The detection of *Aspergillus* antigenemia was performed in all of the patients (Platelia Aspergillus, Bio-Rad Laboratories, Marne la Coquette, France), and 191 assays were done during the hospitalizations (median number of tests per patient, 13; range, 6–17). Only 1 patient (6%) had positive tests (6 positive tests of a total of 12) with no evidence of concomitant aspergillosis.

During the 6 months before the diagnosis of PM, 9 patients had received systemic antifungal agents for >15 days (fluconazole, voriconazole, and itraconazole in 5, 3, and 1 cases, respectively). PM was confirmed in 16 cases (CT-guided transthoracic needle biopsy in 8 patients, pulmonary surgical resection in 6, cutaneous biopsy in 2, and pleural puncture in 1). No significant adverse events were noted after the surgical procedures or transthoracic CT biopsies. Three patients also had mucormycosis in extrapulmonary locations (2 cutaneous ulcers and 1 endocarditis). For the 16 proven cases, the median time between the onset of the first symptoms and diagnosis was 11 days (range, 1–35 days). Culture or PCR analysis showed *Rhizomucor*, *Rhizopus*, *Lichtheimia*, and *Mucor* in 8, 3, 3, and 2 patients, respectively (Table 2).

Value of Initial Thoracic CT Scan for the Diagnosis of Mucormycosis

The median time between the first clinical signs of PM and the initial CT scan was 1 day (range, 0–6 days). In 14 cases (88%), this first CT showed a solitary macronodule located in the upper or middle lobe (56% and 12%, respectively). The median diameter of the lesion was 4.55 cm (range, 1.7–9.9 cm). Among the 16 patients, 15 had a main lesion that consisted of a focal ground-glass opacity surrounded by a ring of consolidation, defining the RHS (Figure 1). All of the patients with the RHS had neutropenia (Supplementary data). Interestingly, ground-glass opacity, but not the RHS, was seen in the patient who did not have neutropenia.

Evolution of Thoracic CT Scans in Mucormycosis

The CT scans evolved quickly during the first week of the disease (Table 3). Overall, 50 thoracic CT scans were performed between day 0 and day 26 after the onset of PM.

Between day 0 and day 5, all of the patients underwent at least 1 thoracic CT scan, and a typical RHS was seen on 15 of them (94%); micronodules or pleural effusions were noted in 6% and 12% of patients, respectively.

From day 6 to day 14 and beyond, other signs appeared. In parallel with an increase in the diameter of the lesion, micronodules and pleural effusion were frequently observed (up to 91% and 64%, respectively). The RHS, which was present in 64% of the cases between day 6 and day 14, was no longer observed after day 14. The air-crescent sign (meaning a cavitation) appeared later in the course of the disease (Figure 2).

Management and Outcome of Patients With PM

When the RHS was observed, the diagnosis of mucormycosis was raised and antifungal treatment was started. All of the patients received amphotericin B (liposomal amphotericin B in 12 cases, amphotericin B colloidal dispersion in 1 case, and amphotericin B deoxycholate in 3 cases). Posaconazole was associated in 14 cases. Ten patients were treated with antifungal agents alone, whereas 6 patients underwent pulmonary resection (Table 2). On day 90, the CT scan was evaluated and complete response, partial response, stable disease, and failure or progression was found in 37.5%, 19%, 12.5%, and 31% of patients, respectively.

To date, the median overall survival is 25 weeks (range, 3–193 weeks) after the diagnosis of PM. Survival at 30, 60, and 90 days was 94%, 75%, and 62%, respectively. Mortality directly attributed to PM was 31%. Interestingly, the 6 patients treated with a medicosurgical approach were alive at day 90 whereas 6 of the 10 patients (60%) treated with antifungal therapy alone died before this date.

Table 2. Characteristics of the 16 Leukemia Patients With Proven Pulmonary Mucormycosis

Characteristic	No. (%)
Age, y, median (range)	60 (32–74)
Male sex	10 (62)
Hematologic diagnosis	
Acute myeloblastic leukemia	11 (69)
Acute lymphoblastic leukemia	5 (31)
Stage of leukemia	
Induction/consolidation	9 (56)
Progressive disease/relapse	7 (44)
Clinical features before diagnosis	
Fever, temperature >38.5°C	14 (87)
Cough	6 (37)
Thoracic pain	13 (81)
Hemoptysis (including hemoptoic sputum)	5 (31)
Patients with extrapulmonary location of PM	3 (19)
Patients with neutropenia (PNN <500 cells/μL) before first symptoms	15 (94)
Duration of neutropenia before first symptoms, d, median (range)	14 (5–98)
Patients treated for >15 d with systemic antifungal agents within 6 mo	9 (56)
Voriconazole	3 (19)
Itraconazole	1 (6)
Fluconazole	5 (31)
Time between first clinical signs and first CT scan, d, median (range)	1 (0–6)
Initial thoracic CT scan findings	
Mass >3 cm	14 (88)
Diameter of the biggest lesion, cm, median (range)	4.55 (1.7–9.9)
Solitary lesion	15 (94)
Presence of RHS	15 (94)
Air-crescent sign	0
Pleural effusion	2 (12)
Cluster of small nodules <1 cm	1 (6)
Time between first clinical signs and confirmation of diagnosis, d, median (range)	11 (1–35)
Methods used for diagnosis	
CT-guided transthoracic needle biopsy	8 (50)
Surgical pulmonary resection	5 (31)
Other[a]	3 (19)
Mucorales species	
Rhizomucor (*Rhizomucor pusillus* = 6, *Rhizomucor* spp = 2)	8 (50)
Rhizopus (*Rhizopus oryzae* = 1, *Rhizopus microsporus* = 1, *Rhizopus* sp = 1)	3 (19)
Mucor spp	2 (12)
Lichtheimia (*Lichtheimia corymbifera* = 1, *Lichtheimia* spp = 2)	3 (19)
90-day CT response (EORTC-MSG criteria)	
Complete response	6 (37)
Partial response	3 (19)
Stable disease	2 (12)
Progression	5 (31)
Outcome	
Overall survival, wk, median (range)	25 (3–193)
Death directly attributed to PM	5 (31)
90-day survival in patients undergoing surgery and medical antifungal therapy	6/6 (100)
90-day survival in patients undergoing medical antifungal therapy alone	4/10 (40)

Abbreviations: CT, computed tomography; EORTC-MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; PM, pulmonary mucormycosis; PNN, polynuclear neutrophils; RHS, reversed halo sign.

[a] Other methods used for diagnosis were 2 cutaneous biopsies and 1 culture of pleural puncture.

DISCUSSION

Mucormycosis is a rare and life-threatening infection. In our institution, over a 10-year period, the incidence of PM was approximately 2% in the particular setting of hospitalized patients with acute leukemia receiving intensive chemotherapy. This rate is in keeping with the 1%–1.9% described in the literature [26].

This fungal infection most frequently arises in patients with hematologic malignancies and particularly in neutropenic patients with acute leukemia [3]. However, making the diagnosis in this population is still a great challenge. According to our

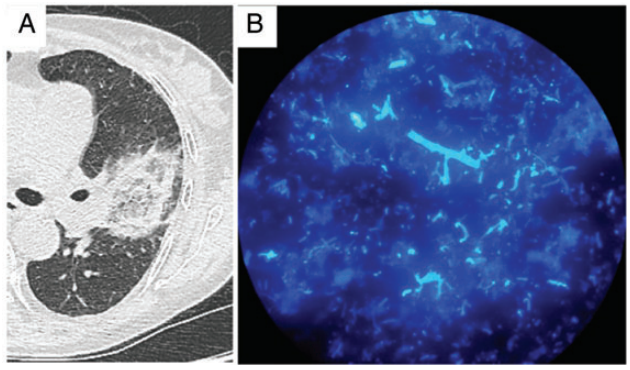

Figure 1. Computed tomographic (CT) image and microscopic examination of mucormycosis in a febrile 71-year-old woman with neutropenia who had received chemotherapy for relapsed acute myeloblastic leukemia. *A*, Thin-section chest CT scan performed 6 days after initial symptoms showed a ring of consolidation surrounding a center of ground-glass opacity, the reversed halo sign. *B*, Microscopic examination of pulmonary biopsy showing fungal hyphae with 90° branching suggesting Zygomycetes. Polymerase chain reaction sequencing identified *Rhizomucor pusillus*.

Table 3. Evolution of Computed Tomographic Scans of 16 Patients With Proven Pulmonary Mucormycosis

CT characteristics	Days 0–5	Days 6–14	Days 15–26
No. of patients with CT performed	16/16 (100)	11/16 (69)	11/16 (69)
No. of CTs performed	25	14	11
No. of patients with CT during neutropenia	15/16 (94)	9/11 (82)	4/11 (36)
Typical RHS	15/16 (94)	7/11 (64)	0/11 (0)
Diameter of lesion ≤3 cm	2/16 (12)	0/11 (0)	1/11 (9)
Diameter of lesion >5 cm	7/16 (44)	8/11 (73)	9/11 (82)
Micronodules	1/16 (6)	7/11 (64)	10/11 (91)
Pleural effusion	2/16 (12)	6/11 (55)	7/11 (64)
Air-crescent sign or cavitation	0/16 (0)	1/11 (9)	4/11 (36)

Data are presented as No. of scans with characteristic/No. of scans with available data (%). Day 0 corresponds to the day of the first CT scan. Micronodules are defined by diameter <1 cm.

Abbreviations: CT, computed tomography; RHS, reversed halo sign.

results and those of the literature, the clinical signs are not specific, and the time between the first symptoms and microbiology and/or histopathology assessment is frustratingly long. Therefore, for patients with acute leukemia and prolonged neutropenia, the contribution of CT to the early diagnosis of PM appears to be very useful. Indeed, some case reports [24, 27] underlined the interest of the RHS in this disease, but to our knowledge, no study has assessed the impact of the early diagnosis of PM in these patients.

In patients with neutropenia, the HS and RHS seem to be 2 interesting signs to help to differentiate between IPA and PM. The difference between these 2 radiologic patterns is probably due to their different physiological and pathological aspects. Indeed, Mucorales infections generally occur earlier and are more angioinvasive (as observed in the rhino-orbito-cerebral lesions where necrosis is usually more extensive and more rapid) than *Aspergillus* infections. As suggested by Wahba et al [20], the extent of necrosis and peripheral hemorrhage is probably greater in PM than in IPA.

Up to now, no blood test or imaging examination has proved to be superior in the early diagnosis of invasive fungal pneumonia in immunocompromised patients. Magnetic resonance imaging is no better than CT [28]. Fluorodeoxyglucose positron emission tomography is not very useful for the diagnostic strategy for pulmonary fungal infection but has its place in detecting extrapulmonary lesions or guiding therapy duration [29, 30]. Conventional laboratory assessments for mucormycosis lack sensitivity and take a long time. New molecular, proteomic, or metabolite detection assays could improve the rate of early diagnosis for invasive mucormycosis [31]. Detection of *Mucorales*-specific T cells seems to be promising when used as a surrogate diagnostic marker for patients with hematologic diseases, but is unavailable in current practice [32]. To date, CT is the most effective tool for diagnosing invasive fungal pneumonia in immunocompromised patients [33].

About two-thirds of our patients were still alive 3 months after the diagnosis of PM. In these leukemia patients with neutropenia, these encouraging results were probably due in most of the cases to the early detection of signs of possible PM with evidence of the RHS on the first CT. The timing of CT scans once the first clinical symptoms of PM have appeared is important because it significantly influences the findings. Indeed, in our institution, the median time between the first clinical symptoms and first CT scan was short (median, 1 day), and a typical CT RHS was present in 94% of cases. It is particularly interesting to note that the RHS (which was present in 64% of our

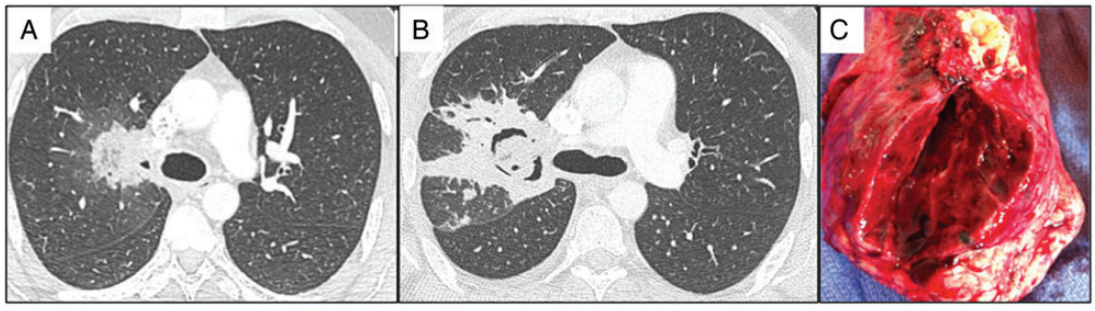

Figure 2. Evolution of computed tomographic (CT) images and macroscopic aspect of mucormycosis in a 32-year-old man with acute myeloblastic leukemia and fever during bone marrow aplasia. *A*, Thin-section CT scan performed 2 days after initial symptoms demonstrated a focal round area of ground-glass attenuation surrounded by a ring of consolidation, consistent with the reversed halo sign through contact with pulmonary artery. *B*, Evolution of CT 17 days after initial symptoms and recovery of neutropenia showing the appearance of cavitation. *C*, Macroscopic exam of upper right lobectomy realized 21 days after initial symptoms correlated with CT findings. Macroscopic lung section shows nodules with cavitation surrounded by a rim of hemorrhaging. Culture of pulmonary sample and polymerase chain reaction sequencing identified *Rhizomucor pusillus*.

cases between day 6 and day 14) was no longer observed after the fourteenth day. According to the literature, the frequency of the CT RHS is markedly lower (19% in the study of Wahba et al [20]) even in patients with hematologic diseases. The very short delay between the onset of symptoms and the CT examination in our study probably explains this difference. Moreover, other radiologic patterns, micronodules, and pleural effusion previously described in cases of PM were less frequent or appeared later in the course of the infection [19]. To demonstrate the value of the RHS in diagnosing PM in leukemia patients, we reviewed other pathologies associated with RHS. This particular CT feature was reported for the first time to be a relatively specific sign of cryptogenic organizing pneumonia in immunocompetent patients [16, 34]. Later, case reports described the presence of this sign in patients with bacterial infections (*Chlamydia psittaci*, *Legionella pneumophila*), mycobacterial infections, systemic inflammatory diseases, and neoplastic diseases [35–38]. The incidence of this sign in the above pathologies is not well known. Among patients with hematologic malignancies, the filamentous fungi most frequently found in cases of pulmonary mycosis are, in order of frequency, *Aspergillus*, Zygomycetes, and *Fusarium* [39]. According to Wahba et al, in immunocompromised patients, despite the lower prevalence of the RHS, it could be more predictive of PM. In addition, the same group identified the RHS in <1% of patients with IPA, and in no patients with fusariosis [20]. In our experience, the study of sequential thoracic CT scans, performed very early in the course of 25 proven cases of IPA occurring in neutropenic patients, showed that a typical CT halo sign was observed in 24 cases (96%) between day 0 and day 5, whereas no RHS was noted [13]. Nevertheless, further studies are needed to confirm the specificity of the HS and RHS in IPA and PM, respectively.

As leukemia patients who develop mucormycosis probably have a worse prognosis than those with IPA, it is important to distinguish between the 2 diseases [40]. Because the incidence of IPA is higher than that of PM and because the antifungal therapy for the 2 infections is different, the appropriate management of PM is often delayed. In such a setting, a CT scan could be very helpful to discriminate between these 2 opportunistic fungal infections.

CONCLUSIONS

In the particular setting of neutropenic patients with leukemia, the RHS appears to be a very interesting pattern, especially when thoracic CT is performed early in the course of the disease. The discovery of the RHS should lead to further examinations, such as CT-guided transthoracic needle biopsy and PCR analysis, to confirm or rule out PM. The CT scan therefore seems to be a major tool for the early diagnosis of PM and could improve outcomes in leukemia patients with PM.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. D. C. has served on the board and received consultancy support from Pfizer and Merck Sharp & Dohme. F. D. has received consultancy support from Merck Sharp & Dohme. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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