Invasive Mucormycosis in Patients with Hematological Malignancies

Subjects: Infectious Diseases | Hematology

Contributor: Nuobing Yang , Lining Zhang , Sizhou Feng

The incidence rate of invasive mucormycosis (IM) in patients with hematological malignancies (HMs) is increasing year by year, ranging from 0.07% to 4.29%, and the mortality rate is mostly higher than 50%. With the ongoing pandemic of COVID-19, COVID-19-associated mucormycosis (CAM) also became a global health threat.

invasive mucormycosis | hematological malignancies | high risk factors

1. Introduction

In recent years, the incidence rate of invasive mucormycosis (IM) in patients with hematological malignancies (HMs) increased, making it the most common disease among non-*Aspergillus* invasive mold infections (NAIMIs) [1]. Acute leukemia, allogeneic hematopoietic stem cell transplantation (allo-HSCT), chronic severe neutropenia, use of immunosuppressants, complicated with diabetes mellitus, iron overload, and use of deferoxamine to reduce serum iron are all high risk factors for HMs patients to be infected by *Mucorales*. Although IM is relatively rare in patients with HMs, its mortality rate is over 50% [2][3], which deserves clinical attention. In addition, the ongoing COVID-19 pandemic leads to immune dysregulation and increased use of steroids, thus making COVID-19 patients more susceptible to *Mucorales* and contributing to the surge of COVID-19-associated mucormycosis (CAM) cases.

Epidemiology and Risk Factors

The incidence rate of IM in patients with HMs is increasing year by year. An autopsy-based study showed that the prevalence of IM in patients with HMs increased from 0.006 cases per 100 autopsies in 1989–1993 to 0.018 cases per 100 autopsies in 2004–2008 (p = 0.04) [4]. Another study collected data from autopsy reports published during 2008–2013, and found that the incidence rate of invasive fungal infections in patients with HMs was 25% (711/2804), of which IM accounted for 6%, as the third commonest invasive fungal infection after invasive aspergillosis (IA) (55.5%) and invasive candidiasis (IC) (28.5%) [5]. A Spanish study reported that the prevalence of IM increased from 1.2 per 100,000 inpatients between 1988 and 2006 to 3.3 per 100,000 inpatients between 2007 and 2015, of which 52.6% had HMs [6]. From 2001 to 2006, the Transplant-Associated Infection Surveillance Network (TRANSNET) in America reported 44 IM (0.3%) of 15,820 HSCT patients [7]. A multicenter, retrospective study conducted in America found that 1133 of 962,428 HMs patients suffered from IM (0.12%) between 2007 and 2019 [8]. From 2007 to 2017, a survey of the Children's Cancer Hospital in Egypt found 45 cases of proven IM among 13,735 hospitalized children (0.33%) who suffered from tumors [9].

There are apparent differences in the risk factors of IM among countries with geographical and economic differences. A prospective study in India between 2016 and 2017 on 465 patients diagnosed with proven IM showed that diabetes mellitus was the major risk factor associated with IM (*n* = 342, 73.5%), whereas epidemiological studies on patients with IM in Japan and North America showed that patients suffered from HMs accounted for 56.39% (75/133) and 61.2% (74/121) of the total number of patients with proven or probable IM, respectively, indicating that HMs were the most common underlying diseases in these countries [10][11][12]. Typically, those suffering from HMs have poorer prognosis than patients with other underlying diseases. An epidemiological study in France between 2005 and 2007 included 101 patients diagnosed with proven or probable IM, among whom 50 (50%) were complicated with HMs, 23 with diabetes (23%), and 18 with trauma (18%) [13]. The result showed that there was a significant difference in the mortality rate of these three types of patients infected with IM (60% vs. 32% vs. 11%, $p = 0.008$), and the mortality was higher for patients with HMs compared with patients with diabetes mellitus or with trauma.

Acute leukemia, neutropenia, steroid therapy, allo-HSCT, and graft-versus-host disease (GvHD) are factors contributing to high susceptibility to IM in patients with HMs. **Table 1** collects data of risk factors for IM in patients with HMs or those undergoing HSCT from 9 studies. In a retrospective study of 32,815 patients with HMs and 1765 patients undergoing HSCT, the incidence rate of IM was highest in allo-HSCT recipients (1.19%), followed by acute lymphoblastic leukemia (0.75%) patients and acute myeloid leukemia (0.45%) patients and IM was associated with the shortest median survival time compared with IA and IC (3 months vs. 7 months vs. 7 months) [14]. Riches et al. found 6.01 cases of IM per 1000 patients who received allo-HSCT, and the high-risk factors for IM included history of *Aspergillus* infection (relative risk (RR) 4.91, $p = 0.0007$), preceding acute GVHD (RR 1.78, $p = 0.027$), and age > 50 years (RR 2.28, $p = 0.0006$) [15].

Table 1. Risk factors for IM in patients with HMs or HSCT.

Characteristics of Studies				Risk Factors/Underlying Diseases, *n* (%)						
Reference	**Time Period**	**Countries of Origin of Cases**	**Total Number of Patients**	**AL**	**Hyperglycemia**	**Neutropenia**	**Steroids**	**HSCT**	**GvHD**	**Voriconazole**
Park et al., 2011 [7]	2001–2006	America	105	28 (26.7%)	46 (43.8%)	39 (37.1%)	59 (56.2%)	76 (72.4%)	61 (58.1%)	47 (44.8%)
Kontoyiannis et al., 2000 [16]	1989–1998	America	24	9 (37.5%)	6 (25.0%)	22 (91.7%)	20 (83.3%)	10 (41.7%)	2 (8.3%)	NA
Kontoyiannis et al., 2014 [10]	2004–2008	North America	74	NA	24 (32.4%)	45 (60.8%)	54 (73.0%)	32 (43.2%)	10 (13.5%)	40 (54.1%)
Lanternier et al., 2012 [13]	2005–2007	France	50	27 (54.0%)	9 (18.0%)	41 (82.0%)	13 (26.0%)	12 (24.0%)	5 (10.0%)	NA

Characteristics of Studies				Risk Factors/Underlying Diseases, *n* (%)						
Reference	Time Period	Countries of Origin of Cases	Total Number of Patients	AL	Hyperglycemia	Neutropenia	Steroids	HSCT	GvHD	Voriconazole
Xhaard et al., 2012 [17]	2003–2008	France	29	12 (41.4%)	14 (48.3%),	6 (20.7%)	26 (89.7%)	29 (100%)	22 (75.9%)	12 (41.3%)
Pagano et al., 1997 [2]	1987–1995	Italy	37	32 (86.5%)	NA	33 (89.2%)	37 (100.0%)	NA	NA	NA
Muggeo et al., 2019 [18]	2009–2016	Italy	15	11 (73.3%)	5 (33.3%)	10 (66.6%)	13 (86.6%)	5 (33.3%)	NA	3 (20.0%)
Pagano et al., 2004 [19]	1987–2001	Multi-center	59	46 (78.0%)	10 (16.9%)	47 (79.7%)	59 (100.0%)	5 (8.5%)	NA	NA
Madney et al., 2019 [9]	2007–2017	Egypt	45	39 (86.7%)	NA	41 (91.1%)	16 (35.6%)	1 (2.2%)	1 (2.2%)	13 (28.9%)

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breakthrough invasive mold infections that occurred during posaconazole (*n* = 8) or voriconazole (*n* = 16) prophylaxis among patients with HMs or undergoing transplantation (HSCT or lung transplantation) during 2009–2013 at Duke University, Lamoth et al. found that BT-MCR was one of the most common breakthrough invasive mold infections (9/24, 37.5%), of which seven cases received voriconazole and two cases received posaconazole for prophylaxis [20]. Another retrospective study of 145 HMs patients and HSCT recipients who received isavuconazole prophylaxis between 2016 and 2018 found that 12 patients (8.3%) had breakthrough invasive fungal infections including five cases of *Aspergillus fumigatus*, two cases of other *Aspergillus* species, two cases of *Mucorales*, two cases of *Fusarium* species, and one case of *Candida glabrata*, and all 12 patients had a median duration of neutropenia of 25.5 days and relapsed/refractory acute leukemia [21]. Between 2000 and 2020, 103 patients experienced BT-MCR in a single center, among whom 16 patients developed BT-MCR while on *Mucorales*-active antifungals (nine cases of isavuconazole, six cases of posaconazole, one case of AmB) and the other 87 patients developed BT-MCR while on antifungals without anti-*Mucorales* activity such as voriconazole, echinocandins, and itraconazole [22]. The 42-day mortality of patients developing BT-MCR while on *Mucorales*-active antifungals was higher than that of the remaining patients (63% vs. 25%, $p = 0.006$), and exposure to *Mucorales*-active antifungals was an independent predictor of death in patients with BT-MCR (hazard ratio (HR) 4.64, $p < 0.001$). **Table 2** summarized characteristics of patients with BT-MCR.

Table 2. Characteristics of patients with BT-MCR.

Reference	Number of Patients	Underlying Disease	BT-MCR Patients	Prophylactic Drugs	Characteristics of BT-MCR Patients
Rothe et al. (2021) [23]	15	AML, ALL, MDS, MM	6	Posaconazole (*n* = 5), isavuconazole (*n* = 1).	All patients required invasive mechanical ventilation and were treated with broad-spectrum antibiotics.
Lerolle et al. (2014) [24]	270	AML, GvHD	2	Posaconazole oral suspension.	Patients received broad spectrum antibiotics the month before BT-MCR

Reference	Number of Patients	Underlying Disease	BT-MCR Patients	Prophylactic Drugs	Characteristics of BT-MCR Patients
					onset, and were neutropenic at the time of BT-MCR onset.
Fontana et al. (2020) [21]	145	AML, MDS, HSCT	2	Isavuconazole.	Patients had a median duration of neutropenia of 25.5 days and relapsed/refractory acute leukemia.
Rausch et al. (2018) [25]	100	AML, ALL	4	Isavuconazole.	Patients were with prolonged neutropenia and relapsed/refractory leukemia at the time of BT-MCR.
Axell-House et al. (2021) [22]	103	Leukemia, MDS	103	*Mucorales*-active antifungals (9 cases of isavuconazole, 6 cases of posaconazole, 1 case of AmB); antifungals without anti-*Mucorales* activity (52 voriconazole, 22 echinocandins, 8 itraconazole, 5 echinocandin + voriconazole).	Patients developing BT-MCR while on *Mucorales*-active antifungals had a higher 42-day mortality (63% vs. 25%, $p = 0.006$).

OVID-19) made it a global health threat. As of 7 June 2021, India recorded 28,252 cases of IM, among whom 24,370 cases with a history of COVID-19 [26]. Moreover, CAM cases were also reported worldwide including in Turkey, Egypt, China, America, Iran, Spain, and so on [27][28]. Most of these patients were complicated with poorly controlled blood glucose and were treated with heavy steroids and broad-spectrum antibiotics for SARS-CoV-2 infection, which resulted in weakened immune system and highly susceptibility to *Mucorales* [28][29]. Arora et al. conducted a case–control study comparing cases diagnosed with CAM with controls who recovered from COVID-19 without developing CAM [30]. A total of 152 patients of CAM (cases), including 120 proven and 32 probable, and 200 controls were included in the study. The result showed that diabetes (92.1% vs. 28%, $p < 0.001$), poor glycemic control (90.6% vs. 51.5%, $p < 0.001$), severe COVID-19 (21% vs. 9.9%, $p < 0.001$), systemic use of steroids (65.8% vs. 48%, $p = 0.001$) were more frequently observed in cases than controls.

A study in Australia on 74 patients diagnosed with proven or probable IM, among whom 36 (48.6%) were complicated with HMs, and found that *Rhizopus* spp. (20/36, 55.6%) was the most common genus of *Mucorales* organisms, followed by *Mucor* spp. (6/36, 16.7%) and *Rhizomucor* spp. (4/36, 11.1%) [31]. Another meta-analysis reported 851 patients with proven or probable IM, of which 275 (33%) were complicated with HMs, and it documented that *Rhizopus* spp. was the major pathogen of IM, followed by *Mucor* spp. (14%) and *Lichtheimia* spp. (13%) [32]. Other pathogenic genera included *Apophysomyces* spp., *Cunninghamella* spp., *Rhizomucor* spp., *Saksenaea* spp., and *Synchephalastrum* spp., but they were relatively rare. Of note, the mortality associated with *Cunninghamella* infections was remarkably higher than that caused by other genera of *Mucorales* organisms (71% vs. 44%, $p < 0.001$). The author of this research summarized the clinical data of 1568 patients with IM (whose

underlying diseases included HMs, diabetes mellitus, trauma, etc.) from nine studies (which included more than 50 cases) [7][10][11][13][31][32][33][34][35], and found that the three major pathogenic genera were *Rhizopus* spp. (*n* = 778, 53.8%), *Mucor* spp. (*n* = 199, 13.8%), and *Lichtheimia* spp. (*n* = 152, 10.5%). **Figure 1** illustrates the general distribution of common pathogenic genera of *Mucorales* organisms.

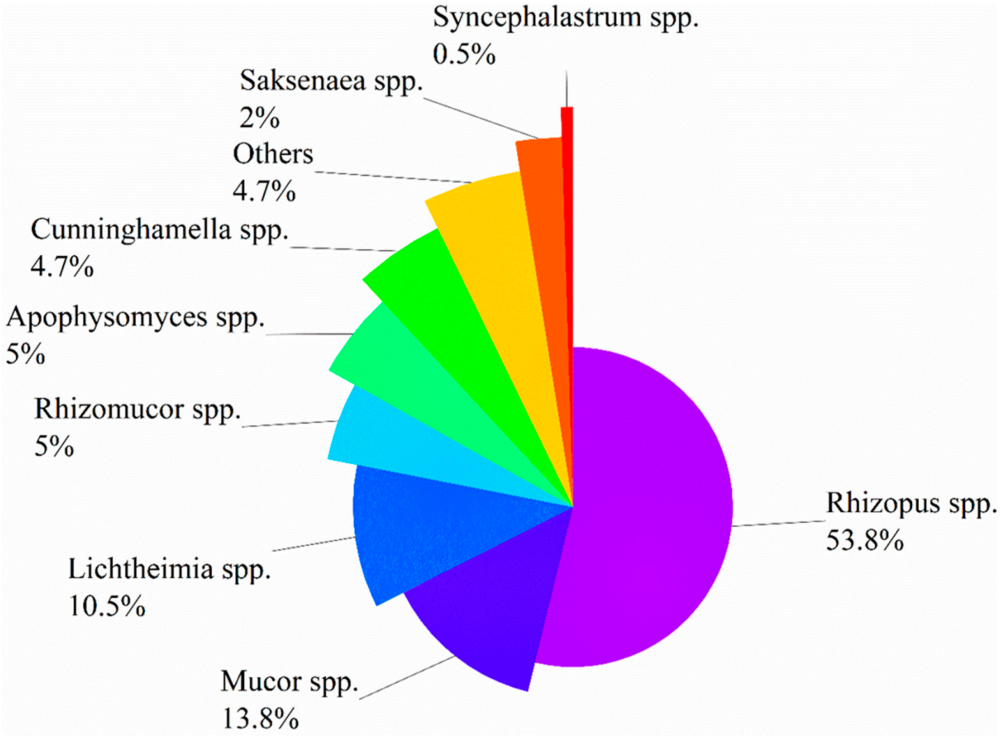


Figure 1. Distribution of *Mucorales* organisms causing infection.

To sum up, HMs are the most common risk factors associated with IM in developed countries, contrasting to diabetes mellitus in developing countries. Factors such as acute leukemia, neutropenia, allo-HSCT, and steroid therapy make patients with HMs highly susceptible to IM. BT-MCR still occurs in patients with active HMs, recurrent/refractory leukemia, and prolonged neutropenia under the prophylaxis of *Mucorales*-active antifungals, and such patients often have relatively high mortality and poor prognosis. *Rhizopus* spp. is the most common pathogen of IM, followed by *Mucor* spp. and *Lichtheimia* spp.

2. Clinical Manifestations

According to anatomic localizations and clinical manifestations, IM is divided into the following six clinical types: pulmonary mucormycosis (PM), rhino-orbital-cerebral mucormycosis (ROCM), disseminated mucormycosis, cutaneous/soft tissue mucormycosis, gastrointestinal mucormycosis and other rare forms, such as renal infection, endocarditis, osteomyelitis, peritonitis, and so on. CAM and IM in patients with diabetes mellitus usually manifest as ROCM. In contrast, most scholars believe that PM and disseminated mucormycosis occurs most often in patients with HMs. By analyzing cases of proven or probable IM in pediatric (≤19 years) patients, Pana et al. found that among 29 patients with PM, 22 had HMs, which were independently correlated with PM (odds ratio (OR) 4.4, *p*

= 0.01) [36]. However, Slavin et al. analyzed 162 patients with NAIMIs (145 proven and 17 probable), of whom 74 (45.7%) were IM, and found HMs independently predicted disseminated infections (OR 2.7, p = 0.03) [35]. A study in Europe between 2005 and 2007 on 102 patients with HMs who were complicated with proven or probable IM indicated that the major sites of IM in these patients were pulmonary (n = 35, 34%) and disseminated (n = 28, 27%) [33]. On the other hand, in a retrospective study that included 20 patients with HMs who were diagnosed with proven IM, the most frequently involved site of IM was paranasal sinuses (n = 19, 95%) and PM only occurred in one patient (5%) [37]. Researchers collected and analyzed infection sites of 604 cases of IM in HMs patients and HSCT patients from 11 studies [2][3][7][9][10][11][13][17][19][33][36] which included more than 25 cases and had detailed records of involved sites of IM (some patients have two or more infection sites). The result showed that the most common form of IM in patients with HMs or patients undergoing HSCT is PM (44.4%), followed by ROCM (27.6%) and disseminated mucormycosis (16%), which is shown in **Figure 2** and **Figure 3**.

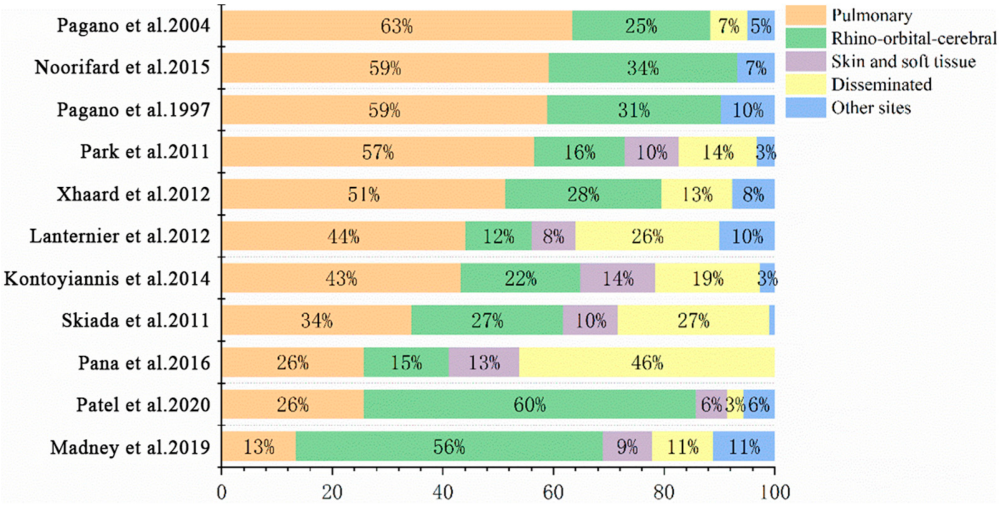


Figure 2. Sites of IM in patients with HMs.

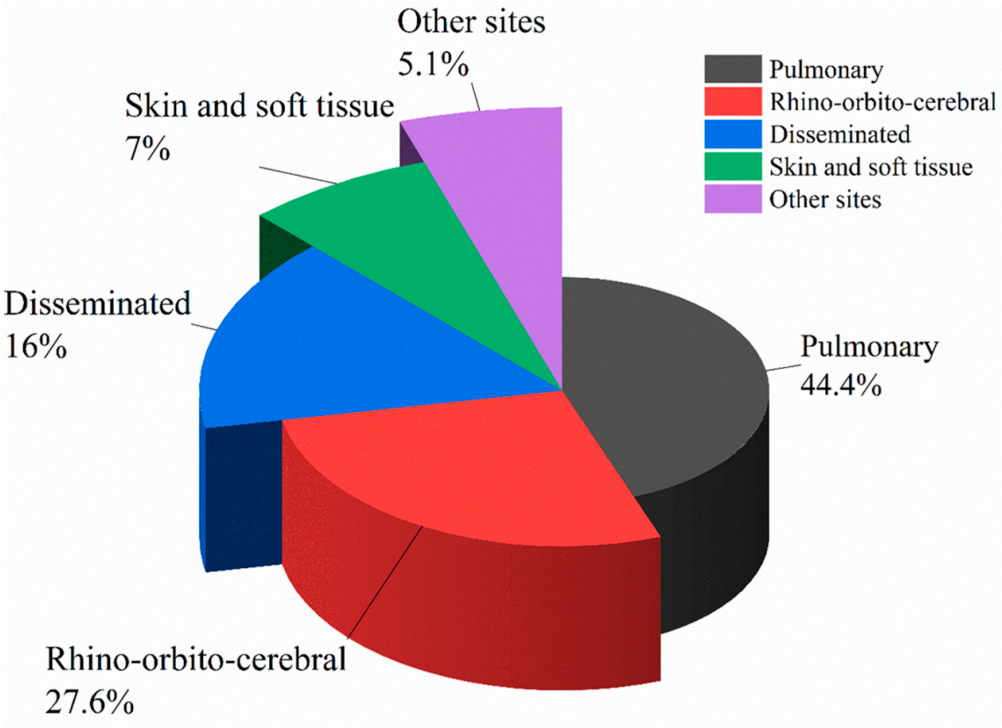


Figure 3. Proportion of various types of IM differentiated by sites in patients with HMs.

Fever is the most common clinical manifestation of IM, and almost all patients with IM have varying degrees of fever. **Table 3** summarized clinical and imaging manifestations of PM, rhino-orbital mucormycosis, and central nervous system (CNS) mucormycosis. The triad of “cough, dyspnea, and chest pain” is a relatively specific sign of PM. Imaging manifestations of PM include exudation, cavity, ground-glass lesion, consolidation, pleural effusion, atelectasis, halo sign, reverse halo sign, air-crescent sign, etc. A retrospective study on HMs patients with IM or IA, including 59 proven IM patients and 541 proven IA patients showed that, compared with patients with IA, patients with IM had a significantly higher frequency of local pain syndrome (53% vs. 5%, $p = 0.0001$), hemoptysis (32% vs. 6%, $p = 0.001$), pleural effusion (53% vs. 7%, $p = 0.003$), destructive lesions (38% vs. 8%, $p = 0.0001$), and “reverse halo” sign (17% vs. 3%) [38]. In addition, although neutropenia and lymphocytopenia represented the major risk factors in both groups, patients with IM had a longer duration of severe neutropenia (30 vs. 14 days, $p = 0.0001$) and lymphocytopenia (25 vs. 14 days, $p = 0.001$) [38]. Both Jung et al. and Chamilos et al. compared the CT findings of PM and IA in patients with HMs, and they found the frequency of “reverse halo” sign (54% vs. 6% $p < 0.001$), multiple (≥10) nodules (64% vs. 18%, $p = 0.02$) and pleural effusion (63% vs. 33%, $p = 0.1$) in patients with PM were significantly higher than those in patients with IA [39][40]. The CT findings of patients with rhino-orbital mucormycosis include thickened oedematous mucosa, opacification or obliteration of paranasal sinuses and bony destruction, while MRI shows non-enhancing mucosal tissue within the involved sinuses and turbinates, also known as “black turbinate sign” [41][42]. CNS mucormycosis can be isolated, but it can also occur due to contiguous spread from the paranasal sinuses and orbits or hematogenous spread [43]. Compared with CT, MRI can identify intracranial infections, such as intraventricular “fungus balls”, thrombosis of intracranial arteries, the inflammatory alterations of the cavernous sinus and the involvement of adjacent structures (such as meninges), more sensitively and accurately [44].

Table 3. Clinical and imaging characteristics of IM.

	Clinical Manifestations	Imaging Manifestations
Pulmonary mucormycosis	The triad of “cough, dyspnea, chest pain”, hemoptysis.	Exudation, cavity, ground-glass lesion, consolidation, pleural effusion, atelectasis, halo sign, reverse halo sign, air-crescent sign.
Rhino-orbital mucormycosis	Facial edema, pain, nasal congestion, rhinorrhea, eye pain, chemosis, proptosis, epiphora, and palatal ulcer destruction.	Thickened oedematous mucosa, opacification or obliteration of paranasal sinuses and bony destruction in CT, “black turbinate sign” in MRI.
Central nervous system mucormycosis	Headache, facial nerve palsy, ptosis, diplopia, hemiplegia, epilepsy.	Intraventricular “fungus balls”, thrombosis of intracranial arteries, the inflammatory alterations of the cavernous sinus and the involvement of adjacent structures (such as meninges).

In conclusion, the most common form of IM in patients with HMs is PM, followed by ROCM and disseminated mucormycosis. “Reverse halo” sign, multiple (≥10) nodules, and pleural effusion are relatively specific imaging manifestations of patients with PM, while the imaging manifestations of ROCM patients are not very specific. MRI can better reflect the intracranial infections than CT.

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