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Clinical Manifestation and Diagnosis of Invasive Fungal Sinusitis in Patients with Hematological Malignancy

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Abstract

Background: Invasive fungal sinusitis (IFS) is a potentially deadly infection especially in patients with immunocompromising conditions.
Objectives: The current study aimed to evaluate the clinical manifestations, outcomes and factors that may affect survival of patients with IFS.
Methods: A cross sectional descriptive study was performed on hospitalized patients admitted to Taleghani hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, from October 2012 to October 2013. The clinical data of 24 patients with IFS were reviewed. All patients had hematologic malignancies, and received broad spectrum chemotherapy. Demographic data, clinical characteristics, presented symptoms and signs, underlying diseases and outcomes of the patients were studied.
Results: The age range of patients was 15 - 60 years. The IFS was proven, probable and possible in 25%, 66.7% and 8.3% of the cases, respectively. Serum galactomannan antigen was positive in 41.6% of the cases; 15 out of 24 cases with IFS had received antifungal chemoprophylaxis before diagnosis, 54% fluconazole and 8.3% itraconazole. *Aspergillus flavus* (33%), *Aspergillus fumigatus* (20.8%), *Aspergillus niger* (16.7%) and *Mucor* spp. (16.7%) were responsible for incidence of IFS; 54% of IFS cases occurred in summer and 91.6% of occurred during hospital construction; a risk factor in 91.6% of the cases.
Conclusions: Current study revealed that *A. flavus* was the most common isolated pathogen. Moreover, *A. fumigatus* was the second common isolated pathogen in patients with IFS. Additionally, the hospital construction was an important environmental risk factor for acquisition of infection in patients with hematological malignancy. The most common season for IFS incidence was summer. Additionally, the common causes of death in patients with IFS were primary disease and also resistance to chemotherapy (37.5%).

Keywords: Sinusitis, Hematologic Neoplasm, Mycoses, *Aspergillus* spp., *Mucor* spp

1. Background

Invasive fungal sinusitis (IFS) is an important cause of morbidity and mortality in patients with immunocompromising conditions (1, 2). Complications such as orbital and intracranial extensions with cavernous sinus thrombosis, parenchymal cerebritis or abscess, meningitis, osteomyelitis, mycotic aneurysm, stroke, and hematogenous dissemination are reported (3). However, there is controversy regarding the best methods for the prevention, diagnosis and treatment of IFS. Early diagnosis and intervention are critical and could be lifesaving (4). The identification of species of the fungi is a key to anti-fungal therapy and also surgical intervention. Studies reported that *Aspergillus* species are the most common cause of invasive infections in patients with immunocompromising conditions (5); although a growing number of other organisms such as *Mucor* and *Trichosporon* species are reported in patients with IFS (6, 7). The definite diagnosis of IFS is troublesome, since early physical findings of IFS and also radiologic results are non-specific (such as nasal obstruction, discharges and epistaxis) (8-10). Additionally, bone and tissue necrosis are often found only in the late stages of sinusitis (11). Moreover, diagnosis, prevention and effective treatment of IFS still remains a challenge in patients with hematological malignancies (12). It is well accepted that some patients with immunocompromising conditions are at greater risk of developing an IFS than others (13). However, it is troublesome to predict which populations of these patients are at greater risk of developing IFS. Additionally, some studies showed that the types of fungal infections in patients with cancer are different among the countries, creating uncertainty among clinicians about the appropriate prophylac-

tic strategies (14, 15). The incidence of IFS in patients with cancer depends on several factors including the prognosis of the underlying illness, treatment and environmental factors such as seasonal alteration (14). Since there is limited evidence of IFS in Asia and different risk factors of the disease were determined by various investigators, it is difficult to compare these studies.

2. Objectives

The current study aimed to review clinical data of patients with IFS to determine outcomes and related-factors that may affect patient survival. Therefore, a cross-sectional descriptive study on IFS was performed at the hematology unit of Taleghani hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3. Methods

3.1. Study Design and Patients

A cross-sectional descriptive study was performed to include all of the patients with IFS admitted to hematology unit of the single tertiary care at Taleghani hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, from October 2012 to October 2013. The data and statistical analysis was done by SPSS version 22 and Chi-square tests.

3.2. Data Collection

The patients were identified through a tertiary hospital registry system from October 2012 to October 2013 in Iran; 1385 patients with hematological malignancies were admitted and among them 248 patients had neutropenic fever .Twenty-four patients with neutropenic fever developed IFS in the study period. Demographic data of patients were studied. All patients had immunocompromising conditions and hematological malignancies with possible, probable and proven IFS. Only patients with rejected IFS were excluded. Clinical information about age, gender, underlying hematological disease, presented symptoms, radiography evidence of sinuses and mortality rate was recorded.

3.3. Proven, Probable and Possible IFS

Based on the controversy concerning the diagnostic criteria of IFS, the European organization for research and treatment of cancer (EORTC) and the US mycoses study group (MSG) recently reported an international consensus for patients with cancer (16, 17) and suggested three degrees of probability: proven, probable and possible IFS. Proven IFS was identified by the presence of fungi related to tissue damage by examination of a biopsy specimen; or positive culture results from sterile sites. Probable IFS was defined by the presence of at least one microbiological criterion and one clinical criterion. Possible IFS was defined by the presence of at least one clinical criterion.

3.4. Antifungal Prophylaxis

Antifungal prophylaxis treatments such as fluconazole and itraconazole were prescribed in 15 patients with hematological malignancies that received standard chemotherapy. Fluconazole (100 mg twice daily) prophylaxis was administrated to 13 cases and itraconazole (200 mg twice daily) was administrated to two cases of 24 patients.

3.5. Mycological Culture Examination

Para-nasal sinuses secretions were collected under endoscopic view in patients for the presence of fungi. The specimens were fixed in formalin and embedded in paraffin. All specimens were examined by direct microscopy after preparatory treatments with potassium hydroxide (KOH), Gram and Giemsa staining techniques. Mycological analysis was examined via the culture of the mucus in three fungal culture mediums (sabouraud dextrose agar, brain heart infusion (BHI) agar and selective agar (Merck, Darmstadt, Germany). Incubation was at 25°C and 35°C and cultures were observed up to 20 days before release as negative for fungi. Hematoxylin and eosin (H and E) stained sections of the sinus material were evaluated for the presence of fungi. Periodic acid-Schiff (PAS) staining technique was also applied to the sections in order to confirm the diagnosis. The taxonomic identification of fungi was made from morphology, macroscopic features and microscopic structures.

3.6. Galactomannan EIA

Six milliliters of blood was collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and stored at -20°C.

The quantity of galactomannan (GM) antigen in each sample was measured using the Platelia®*Aspergillus* enzyme immunoassay (EIA) (Bio-Rad) by technicians unaware of the clinical manifestation of the patients. Measurements of optical density were performed by a semi-automatic analyzer (Behring ELISA processor III; Dade Behring), according to the manufacturer's instruction. Optical densities were read at 450 and 620 nm. Positive, negative and threshold control samples provided by the manufacturer were included in each run. An index value of $\geq$ 0.5 was considered a positive result if confirmed via subsequent sample.

4. Results

4.1. Clinical Characteristics of Patients with IFS

The demographical and clinical characteristics of the cases are shown in Table 1. Laboratory data, clinical manifestations and outcomes of the cases are shown in Tables 2 and 3. IFS was proven in 6 cases (25%), probable in 16 (66.7%) and possible in 2 (8.3%). Twenty-three cases with IFS (95.8%) daily received frequent transfusion. In addition to sinuses, fungal infection developed in lungs in 6 cases (25%) and brain in 1 case (4.2%). Generally, mortality was 12 cases (50%); five out of which did not receive any antifungal prophylaxis agents.

4.2. Diagnostic Procedure

The functional endoscopic sinus surgery (FESS) was performed in 18 cases with IFS. Results of computed tomography (CT) scan and findings of sinus endoscopy and FESS are shown in Table 4.

4.3. Fungal Spectrum

Twenty-four patients from October 2012 to October 2013 had serial follow-up of galactomannan antigen test. Serum galactomannan antigen was positive in 10 cases (41.6%) with IFS (Table 5). *Aspergillus* spp. were isolated from sinus culture of the 10 cases. Results of fungal culture are shown in Table 5. The most common isolated pathogen was *A. flavus*. Moreover, it was found that the types of the fungi in patients with IFS were not associated with underlying hematological disease status, number of chemotherapy, platelet count and environmental factors.

Table 1. Demographic and Clinical Characteristics of Patients with Invasive Fungal Infections

Procedures	No. (%) of Patient, n = 24
Gender	
Male	13 (54.2)
Female	11 (45.8)
Age group	
15-19 years	4 (16.6)
20-24 years	4 (16.6)
25-29 years	5 (20.8)
30-34 years	4 (16.6)
35-39 years	3 (12.5)
40-49 years	3 (12.5)
50-60 years	1 (4.2)
Blood group	
A	7 (29.2)
B	2 (8.3)
AB	3 (12.5)
O	10 (41.7)
Missing data	2 (8.3)
Environmental factors:	
Construction sector	
yes	22 (91.6)
no	2 (8.3)
Season	
spring	2 (8.3)
summer	13 (54.2)
fall	7 (29.2)
winter	2 (8.3)
Underlying hematological disease	
Acute lymphoblastic leukemia	1 (4.2)
Acute lymphoblastic leukemia-pre βcell	8 (33.3)
Acute lymphoblastic leukemia-pre Tcell	2 (8.3)
Acute lymphoblastic leukemia-non M3	11 (45.8)
Myelodysplastic syndrome	1 (4.2)
Aplastic anemia	1 (4.2)
Antifungal prophylaxis	
Fluconazole	13 (54.2)
Itraconazole	2 (8.3)
No prophylaxis	9 (37.5)

5. Discussion

Invasive fungal sinusitis (IFS) is an important complication in patients with hematological malignancy, and causes high mortality and morbidity rate in such patients (1, 2, 18). In patients with IFS, without early treatment, the different types of fungi may rapidly spread by the blood, causing death within days (19). Since, rare IFS evidence is reported in Asia, further epidemiological studies should investigate this area. Here, 24 cases of IFS were reported; these patients were identified in hospitalized patients from October 2012 to October 2013. It seems that there were more patients in the current study compared with some other studies; Foshee et al., identified twenty-seven patients in departmental records from 1998 to 2014 in a single center in Philadelphia (19), and Pagella et al., reported 18 cases of IFS among patients with hematological malignancy and diabetes from 2002 to 2013 in a hospital in Italy (20). IFS is developed more frequently in patients with acute myeloid leukemia (AML) non-M3 (45.8%). The current study showed that high incidence of IFS was

Table 2. Laboratory Data of Patients with Invasive Fungal Infections

Procedures	No. (%) of Patient, n = 24
Platelet count, cell/μL	
100000 - 150000	3 (12.5)
50000 - 100000	1 (4.2)
10000 - 50000	17 (70.8)
< 10000	3 (12.5)
Glomerular filtration rate	
< 60 mL/min	2 (8.3)
$\leq$ 60 mL/min	22 (91.6)
Neutrophil count, cell/μL	
> 2000	3 (12.5)
1000 - 2000	4 (16.7)
500 - 1000	3 (12.5)
200 - 500	6 (25)
100 - 200	6 (25)
< 100	2 (8.3)

in summer. Some evidence showed that summer months are associated with the highest risk of IFS (21-23). Moreover, in the present study patients with positive culture results were in an older section of the hospital adjacent to a building construction site that created great amounts of dust in the hospital vicinity. It is likely that this factor increased the risk of IFS in patients with cancer. Several studies indicated that building construction can lead to outbreak of invasive fungal infections. Additionally, fluconazole prophylaxis was prescribed to 13 patients. Since fluconazole has no therapeutic effects on *Aspergillus* spp. and *Mucor* spp. infections, prophylaxis with that was not effective in prevention of these mold infections. In the current study, only two patients received itraconazole (200 mg twice daily) and this agent was not effective in prevention of IFS. It is likely that the current dosage of itraconazole might not induce effective blood concentration to prevent IFS. In the current study, type of the fungal agents in patients with IFS was not associated with the underlying hematological disease status, number of chemotherapy, platelet count and environmental factors. Moreover, *A. flavus* was the most common etiology of fungal sinusitis in patients of the study (33.3%). *Aspergillus flavus* was also reported by Iwen et al. (24), as the most common cause of infection in patients admitted to the University of Nebraska Medical Center (Omaha, USA). In contrast, Wald et al. (25), showed that *A. niger* was the dominant isolate from the rectum of patients colonized with a known species of *Aspergillus*. Moreover, in the current study, the second common cause of infection was *A. fumigatus* (20.8%). In contrast, Teh et al. (26), in a study on *Aspergillus sinusitis*, showed that *A. fumigatus* was the most common cause in patients with AIDS. It seems that the difference between fungi species in patients with IFS is associated with host defense impairment and environmental factors. Moreover, *A. fumigatus* was also reported by both Drakos et al. (27), and Talbot et al. (28), as the most common cause of invasive mold sinusitis. In the current study, the common causes of death in patients with IFS were the primary disease and little response to chemotherapy (37.5%) (In In the current study, results of CT scan showed that 37.5% of the patients with IFS had pan sinusitis. The endoscopy findings of the study also showed that corneal necrosis (54.2%) was most common in the patients with IFS. Serum galactomannan antigen was positive in 10 cases (41.6%) with IFS; however negative in 13 patients (54.1%). This test is still an excellent diagnostic method in patients with cancer with a high pretest probability (29, 30). Since in the current study, fungal sinusitis was local, galactomannan test was disappointing. However, early diagnosis by serial *Aspergillus* galactomannan antigen test to detect IFS may lead to early antifungal therapy, and also decrease mortality rate in patients (31). The study had some limitations: it was a one-year study in a single university in Iran (Tehran). Some of the clinical and diagnostic findings of the patients with IFS were missing; therefore, the obtained results are limited. Additionally, the common causes of death in patients with IFS were the primary disease and also resistance to chemotherapy (37.5%). The advantage of the study compared to other studies was that it could find a large number of patients with IFS (24 patients) in one year; while in other studies this issue was considered as an important problem (6, 8, 11).

5.1. Conclusion

The current study revealed that *A. flavus* was the first common isolated pathogen followed by *A. fumigatus* in patients with IFS. The most common season for the incidence of IFS was summer and hospital construction was an important environmental risk factor for acquisition of the infection. Furthermore, it was found that the type of the fungi in patients with IFS was not associated with the underlying hematological disease status, number of chemotherapy, platelet count and environmental factors.

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Table 3. Clinical Manifestation and the outcome of Patients with Invasive Fungal Infections

Procedures	No. (%) of Patient, n = 24
Diagnosis of IFS after chemotherapy	
After the first time	8 (33.3)
After the third time	3 (12.5)
Refractory time	12 (50.0)
After the third time and refractory	1 (4.2)
The time between diagnosis of primary malignancy and IFS	
2 months	10 (41.7)
2 - 4 months	2 (8.3)
6-12 months	5 (20.8)
> 12 months	7 (29.2)
Major signs of IFS	
Fever	4 (16.7)
Fever + headache	2 (8.3)
Fever +swelling of face	3 (12.5)
Fever +rhinorrhea + swelling of face	2 (8.3)
Fever +headache +nasal obstruction	1 (4.2)
Fever +headache +swelling of face	3 (12.5)
Fever +headache +swelling of face +nasal obstruction	4 (16.7)
Fever +rhinorrhea	1 (4.2)
Swelling of face +eye ptosis	1 (4.2)
Fever +nasal obstruction+ swelling of face	1 (4.2)
Fever +headache +nasal obstruction	2 (8.3)
Obstruction +rhinorrhea + swelling of face	0 (0.0)
Involvement	
Lung	6 (25)
Brain + lung	1 (4.2)
No involvement	17 (70.8)
Outcome	
Survival	9 (37.5)
Survival with bone marrow transplantation	3 (12.5)
Death	12 (50)
The causes of death	
Primary malignancy + low response to chemotherapy	9 (37.5)
Progressive infection	1 (4.2)
Low response to chemotherapy + progressive infection	1 (4.2)
other	-

Abbreviation: IFS, invasive fungal sinusitis.

Table 4. Diagnostic Procedures

Procedures	No. (%) of Patient, n = 24
Results of FESS functional endoscopic sinus surgery	
Necrosis of the mucosa of the septum	3 (12.5)
A middle corneal involvement with necrosis	7 (29.2)
The lower corneal involvement	2 (8.3)
Nasopharyngeal mass	1 (4.2)
Necrosis of the corneal middle and septum	1 (4.2)
Necrosis of the left and right corneal lower + septum	3 (12.5)
Necrosis of the corneal middle and lower	1 (4.2)
Do not have FESS	6 (25)
Results of endoscopy	
Normal	3 (12.5)
Corneal necrosis	13 (54.2)
Septum necrosis	2 (8.3)
Corneal and septum necrosis	2 (8.3)
Missing data	4 (16.7)
Results of CT scan	
Maxilla involvement	5 (20.8)
Maxilla and ethmoid involvement	8 (33.3)
Ethmoid involvement	2 (8.3)
Pan-sinusitis	9 (37.5)

Abbreviations: CT scan, computed tomography; FESS, functional endoscopic sinus surgery.

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Footnotes

Authors' Contribution: Study concept and design, Sara abolghasemi, Yazdanali Faghani; acquisition of data, Mahdi Tabarraee; analysis and interpretation of data, Sara Abolghasemi,Yazdanali Faghani; drafting of the manuscript, Sara Abolghasemi, Yazdanali Faghani; critical revision of the manuscript for important intellectual content, Masoud Mardani; statistical analysis, Yazdanali Faghani, Sara Abolghasemi; administrative, technical and material support, Masoud Mardani, Mahdi Tbarraee; study supervision, Masoud Mardani.

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Table 5. Type of Fungal Infection

Procedures	No. (%) of Patient, n = 24
Galactomannan test	
Positive test	10 (41.6)
Negative test	13 (54.1)
Missing data	1 (4.2)
Number of Galactomannan samples	
Do not have	1 (4.16)
Once	6 (25)
Twice	3 (12.5)
A few times	14 (58.3)
Culture of fungus	
Aspergillus flavus	8 (33.3)
Aspergillus fumigatus	5 (20.8)
Aspegillus niger	4 (16.7)
Mucor spp.	4 (16.7)
Aspergillus spp. + *Mucor* spp.	1 (4.2)
No detection	2 (8.3)

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References

1. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis.* 1996;**23**(3):608–15. [PubMed: 8879787].
2. Mousset S, Buchheidt D, Heinz W, Ruhnke M, Cornely OA, Egerer G, et al. Treatment of invasive fungal infections in cancer patients-updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol.* 2014;**93**(1):13–32. doi: 10.1007/s00277-013-1867-1. [PubMed: 24026426].
3. Gavito-Higuera J, Mullins CB, Ramos-Duran L, Sandoval H, Akle N, Figueroa R. Sinonasal Fungal Infections and Complications: A Pictorial Review. *J Clin Imaging Sci.* 2016;**6**:23. doi: 10.4103/2156-7514.184010. [PubMed: 27403401].
4. Dwyhalo KM, Donald C, Mendez A, Hoxworth J. Managing acute invasive fungal sinusitis. *JAAPA.* 2016;**29**(1):48–53. doi: 10.1097/01.JAA.0000473374.55372.8f. [PubMed: 26704655].
5. Nazeri M, Hashemi SJ, Ardehali M, Rezaei S, Seyedmousavi S, Zareei M, et al. Fungal rhino sinusitisin in tehran, iran. *Iran J Public Health.* 2015;**44**(3):374–9. [PubMed: 25905081].
6. Anselmo-Lima WT, Lopes RP, Valera FC, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. *Rhinology.* 2004;**42**(3):141–4. [PubMed: 15521667].
7. Ruhnke M, Bohme A, Buchheidt D, Donhuijsen K, Einsele H, Enzensberger R, et al. Diagnosis of invasive fungal infections in hematology and oncology–guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol.* 2003;**82 Suppl 2**:S141–8. doi: 10.1007/s00277-003-0768-0. [PubMed: 13680169].
8. Almyroudis NG, Segal BH. Prevention and treatment of invasive fungal diseases in neutropenic patients. *Curr Opin Infect Dis.* 2009;**22**(4):385–93. doi: 10.1097/QCO.0b013e32832e074d. [PubMed: 19506476].
9. Denning DW, Evans EG, Kibbler CC, Richardson MD, Roberts MM, Rogers TR, et al. Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. British Society for Medical Mycology. *Eur J Clin Microbiol Infect Dis.* 1997;**16**(6):424–36. [PubMed: 9248745].
10. Kordbacheh P, Badiee P, Alborzi A, Zaini F, Mirhendi H, Mahmoudi M, et al. Acute Fulminant Fungal Sinusitis in Patients with Acute Leukemia. *Iranian J Pub Health.* 2008;**37**(4):46–51.
11. Howells RC, Ramadan HH. Usefulness of computed tomography and magnetic resonance in fulminant invasive fungal rhinosinusitis. *Am J Rhinol.* 2001;**15**(4):255–61. [PubMed: 11554658].
12. Moghadami M, Ruzbahani H, Badiee P, Faramarzi A, Peymani P, Bagheri Lankarani K. Invasive fungal sinusitis in immunocompromised patients: a multicenter, university hospital experience in Shiraz. *Adv Infect Dis.* 2013;**3**(4):263–8.
13. Suslu AE, Ogretmenoglu O, Suslu N, Yucel OT, Onerci TM. Acute invasive fungal rhinosinusitis: our experience with 19 patients. *Eur Arch Otorhinolaryngol.* 2009;**266**(1):77–82. doi: 10.1007/s00405-008-0694-9. [PubMed: 18470528].
14. Warnock DW. Fungal infections in neutropenia: current problems and chemotherapeutic control. *J Antimicrob Chemother.* 1998;**41 Suppl D**:95–105. [PubMed: 9688455].
15. Martino R, Subira M. Invasive fungal infections in hematology: new trends. *Ann Hematol.* 2002;**81**(5):233–43. doi: 10.1007/s00277-002-0466-3. [PubMed: 12029531].
16. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, 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**(1):7–14. doi: 10.1086/323335. [PubMed: 11731939].
17. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008;**46**(12):1813–21. doi: 10.1086/588660. [PubMed: 18462102].
18. Rinaldi MG. Problems in the diagnosis of invasive fungal diseases. *Rev Infect Dis.* 1991;**13**(3):493–5. [PubMed: 1866555].
19. Foshee J, Luminais C, Casey J, Farag A, Prestipino A, Iloreta AM, et al. An evaluation of invasive fungal sinusitis outcomes with subsite analysis and use of frozen section analysis. *Int Forum Allergy Rhinol.* 2016;**6**(8):807–11. doi: 10.1002/alr.21714. [PubMed: 27272979].
20. Pagella F, De Bernardi F, Dalla Gasperina D, Pusateri A, Matti E, Avato I, et al. Invasive fungal rhinosinusitis in adult patients: Our experience in diagnosis and management. *J Craniomaxillofac Surg.* 2016;**44**(4):512–20. doi: 10.1016/j.jcms.2015.12.016. [PubMed: 26857760].
21. deShazo RD, Chapin K, Swain RE. Fungal sinusitis. *N Engl J Med.* 1997;**337**(4):254–9. doi: 10.1056/NEJM199707243370407. [PubMed: 9227932].
22. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8 ed. New York: Livingston; 2015. pp. 3425–39.
23. Panackal AA, Li H, Kontoyiannis DP, Mori M, Perego CA, Boeckh M, et al. Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. *Clin Infect Dis.* 2010;**50**(12):1588–97. doi: 10.1086/652761. [PubMed: 20450414].
24. Iwen PC, Rupp ME, Hinrichs SH. Invasive mold sinusitis: 17 cases in immunocompromised patients and review of the literature. *Clin Infect Dis.* 1997;**24**(6):1178–84. [PubMed: 9195079].
25. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone

marrow transplantation. *J Infect Dis.* 1997;**175**(6):1459–66. [PubMed: 9180187].
26. Teh W, Matti BS, Marisiddaiah H, Minamoto GY. Aspergillus sinusitis in patients with AIDS: report of three cases and review. *Clin Infect Dis.* 1995;**21**(3):529–35. [PubMed: 8527538].
27. Drakos PE, Nagler A, Or R, Naparstek E, Kapelushnik J, Engelhard D, et al. Invasive fungal sinusitis in patients undergoing bone marrow transplantation. *Bone Marrow Transplant.* 1993;**12**(3):203–8. [PubMed: 8241977].
28. Talbot GH, Huang A, Provencher M. Invasive aspergillus rhinosinusitis in patients with acute leukemia. *Rev Infect Dis.* 1991;**13**(2):219–32. [PubMed: 1904160].
29. Kawazu M, Kanda Y, Nannya Y, Aoki K, Kurokawa M, Chiba S, et al. Prospective comparison of the diagnostic potential of real-time PCR, double-sandwich enzyme-linked immunosorbent assay for galactomannan, and a (1–>3)-beta-D-glucan test in weekly screening for invasive aspergillosis in patients with hematological disorders. *J Clin Microbiol.* 2004;**42**(6):2733–41. doi: 10.1128/JCM.42.6.2733-2741.2004. [PubMed: 15184460].
30. Sulahian A, Boutboul F, Ribaud P, Leblanc T, Lacroix C, Derouin F. Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. *Cancer.* 2001;**91**(2):311–8. [PubMed: 11180076].
31. Herbrecht R, Letscher-Bru V, Oprea C, Lioure B, Waller J, Campos F, et al. Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. *J Clin Oncol.* 2002;**20**(7):1898–906. [PubMed: 11919250].