Diagnostic Findings of Invasive Cutaneous Fungal Infections: A Retrospective Study

Kelsey B. Nusbaum, MD[1]; Zaynah Awethe, BS[1]; Mary McGrath, MD[1]; Benjamin H. Kaffenberger, MD, MS[1]; John Trinidad, MD, MPH[1]; Natalie Spaccarelli, MD[1]; Catherine G. Chung, MD[1,2]

[1]*Department of Dermatology, The Ohio State University College of Medicine, Columbus, OH, USA*

[2]*Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH, USA*

Abstract

INTRODUCTION The diagnosis of invasive cutaneous fungal infections is challenging, with delayed diagnosis potentially leading to worsened outcomes for patients. Current gold standard techniques of culture and histopathology are limited by poor sensitivity. **METHODS** We retrospectively reviewed all inpatient dermatology consultations from 2017-2020 with confirmed invasive fungal infections by histopathologic and/or tissue culture identification of fungal organisms. Tissue specimens were obtained via 4-millimeter punch biopsies of skin lesions. Microscopic examination of slides was performed by a board-certified dermatopathologist. **RESULTS** Twenty-three cases were identified, with 18 demonstrating classic histopathologic features of invasive fungal infection and five demonstrating atypical features or focal findings limited to the base of the biopsies. In two cases, features of leukemia/lymphoma cutis obscured findings of an infectious etiology. **CONCLUSIONS** Histopathologic evidence of invasive cutaneous fungal infections may be focal and limited to deeper sections of skin, as well as obscured by a separate processes. Performance of deeper biopsies may improve diagnostic yield and capture previously missed cases of invasive cutaneous fungal infection.

Keywords: inpatient dermatology, cutaneous infection, fungal, mycosis, immunocompromised.

Academic Dermatology (2026) 4(1):1-7 | https://doi.org/10.18061/ad.5820

Published: March 23, 2026.

Contact author: Catherine.Chung@osumc.edu

INTRODUCTION

Invasive cutaneous fungal infections (ICFIs) are a significant source of morbidity and mortality in immunocompromised patients, and their incidence is rising in the United States. The burden of opportunistic fungal infections is increasing in association with the number of solid organ and hematologic transplant recipients who require chronic immunosuppressive therapies.[1,2] Prompt diagnosis is critical to allow for the early initiation of antifungal therapy, which is known to improve patient outcomes.[3-5]

Early diagnosis of ICFIs requires the recognition of their clinical features and the performance of an appropriate diagnostic workup. The clinical presentation of ICFIs varies, and they can manifest as non-specific isolated or disseminated papules, nodules, necrotic patches, or cellulitis.[6,7] As a result, diagnosing ICFIs on clinical impression alone is challenging. Serologic and molecular tools offer rapid, point-of-care testing that can facilitate early diagnosis. However, these techniques are limited by variable sensitivity and specificity, poor standardization, and restricted availability.[8-10] While traditional techniques of culture and histopathology remain the gold standards for diagnosing ICFIs,[11] their sensitivity is relatively low, and there is the potential to miss a number of patients with invasive infections.[9,12,13] Missed or delayed diagnoses are associated with increased mortality in this immunocompromised population, and thus, techniques to improve sensitivity may translate to better outcomes. The current study aims to identify subtle histopathologic features associated with ICFIs to improve the diagnostic yield of skin biopsies.

METHODS

We retrospectively reviewed all inpatient dermatology consults where a skin biopsy was performed over a three-year period from June 2017 to May 2020 at The Ohio State University Wexner Medical Center in Columbus, Ohio, to identify all skin and soft tissue ICFIs evaluated by the dermatology consultation service. A confirmed ICFI was defined as the identification of fungal organisms by histopathologic evaluation and/or tissue culture. Twenty-three cases were identified. Tissue specimens were obtained via 4-millimeter punch biopsies of skin lesions. Histologic slides were stained with Grocott Methenamine Silver (GMS) in all cases and periodic acid Schiff (PAS) in all but one case. Microscopic examination of slides was performed by a board-certified dermatopathologist.

Histopathologic features including specimen depth, characterization of the inflammatory infiltrate, presence or absence of an additional pathologic process, and results of special stains and immunohistochemistry were documented. Tissue cultures for fungal organisms were performed in all cases and held for 28 days. One result was canceled due to the death of the patient prior to a positive culture. Patient data were collected, including: age; sex; duration of condition prior to dermatology consultation; lesion morphology; comorbid conditions; immune status; blood, sputum, and tissue culture results; laboratory studies; and ancillary studies including (1-3)-β-d-Glucan Test (Fungitell® assay); Aspergillus, Blastomyces, Cryptococcus, and Histoplasma antigens; and tissue PCR.

RESULTS

Twenty-three ICFIs confirmed by identification of fungal organisms on histopathology and/or tissue culture were identified (Tables 1 and 2).

Table 1. *Summary of typical cases.*

Age, Sex	Underlying Conditions	Blood Cultures	Tissue Culture	Treatment	Outcome
44, M	IgA nephritis on prednisone	Neg.	Aspergillus	Debridement, posaconazole, below-knee amputation	Resolved s/p below-knee amputation
72, F	Cirrhosis, ESRD	Neg.	Cryptococcus neoformans	Fluconazole, amphotericin B, flucytosine	Deceased
18, M	Aplastic anemia	Neg.	Aspergillus spp.	Posaconazole	Resolved
70, M	AML s/p BMT	Neg.	Filamentous fungus, not otherwise specified	Posaconazole, isavuconazonium, amphotericin B	Deceased
52, F	T2DM, CAD, ESRD	Neg.	Neg.	Fluconazole	Resolved
27, M	Ulcerative colitis, autoimmune hepatitis	Neg.	Neg.	Amphotericin B, fluconazole	Resolved
33, M	Alcoholic cirrhosis, pancreatitis	Neg.	Rhizopus spp., Candida glabrata	Amphotericin B, voriconazole, fluconazole, caspofungin	Deceased
64, M	Mixed connective tissue disorder, CAD	Neg.	Histoplasma capsulatum	Itraconazole	Improved on therapy before lost to follow-up
60, F	ESRD on dialysis	Neg.	Rhizopus microsporus, Candida albicans	Debridement, amphotericin B, caspofungin	Deceased
49, F	Follicular lymphoma, s/p BMT	Neg.	Mucormycosis spp.	Debridement, amphotericin B	Deceased
56, F	Follicular lymphoma, s/p BMT	Neg.	Not performed	None	Deceased
56, M	T2DM, small cell lung carcinoma	Neg.	Trichosporon asahii	Voriconazole, amphotericin B	Deceased
58, M	Follicular lymphoma	Neg.	Neg.	Voriconazole	Resolved
66, M	AML	Neg.	Fusarium spp.	Debridement, amphotericin B, isavuconazonium	Deceased
70, F	T2DM, RA	Neg.	Neg.	Itraconazole, amphotericin B	Deceased

Age, Sex	Underlying Conditions	Blood Cultures	Tissue Culture	Treatment	Outcome
70, M	Metastatic RCC	Neg.	Neg.	None; patient rapidly decompensated	Deceased
36, F	SLE	Neg.	Mucor cicinelloides	Debridement, amphotericin B, caspofungin	Deceased
46, M	CML s/p BMT	Neg.	Neg.	Isavuconazonium	Resolved

Table 2. *Summary of atypical cases.*

Age, Sex	Underlying Conditions	Blood Cultures	Fungal Blood Culture	Tissue Cultures	Fungal Serology Studies	Treatment	Outcome
59, M	CLL	Neg.	Asper-gillus	Asper-gillus	Pos.	Voriconazole	Deceased
46, F	ALL	Staphylococcus lugdunesis, staphylococcus caprae	Neg.	Neg.	Neg.	Isavucona-zonium	Resolved
58, M	Follicular lymphoma	Staphylococcus aureus	Neg.	Neg.	Neg.	Voriconazole	Resolved
60, F	AML	Neg.	Neg.	Neg.	Neg.	Voriconazole, amphotericin B	Resolved
60, M	RCC, ESRD s/p renal transplant	Neg.	Neg.	Neg.	Neg.	None	Lost to follow-up

*Typical cases contained typical histopathologic features of invasive fungal infection, including: granulomatous and/or suppurative inflammation; necrosis; and readily identifiable organisms by special stains.

Abbreviations used: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplant; CAD, coronary artery disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ESRD, end-stage renal disease; Neg., negative; Pos., positive; RA, rheumatoid arthritis; RCC, renal cell carcinoma; SLE, systemic lupus erythematosus; T2D, type 2 diabetes

Eighteen out of twenty-three cases (78%) demonstrated classic histopathologic features of ICFIs, including granulomatous and/or suppurative inflammation, necrosis, and readily identifiable organisms by special stains. In five cases (22%), diagnostic features were extremely focal; in each of these cases, fungal organisms were rare and identified only along the base and/or tissue edges of the biopsies (Figures 1 and 2).

Figure 1. *Punch biopsy demonstrating non-specific papillary dermal edema and perivascular lymphohistiocytic infiltrate with numerous eosinophils (A, H&E 20x; B, H&E 200x). There is focal deep necrosis within subcutaneous septa (C, H&E 100x). In the area of necrosis, an aggregate of branching fungal hyphae is identified on fungal stains (D, GMS 200x; E, PAS 200x).*

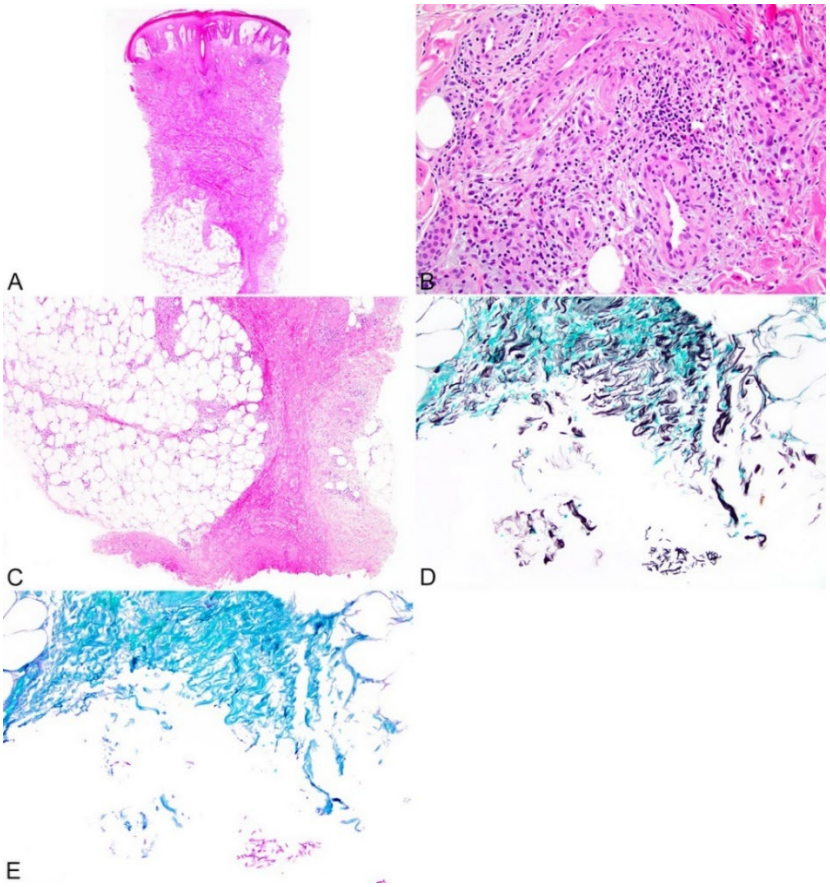
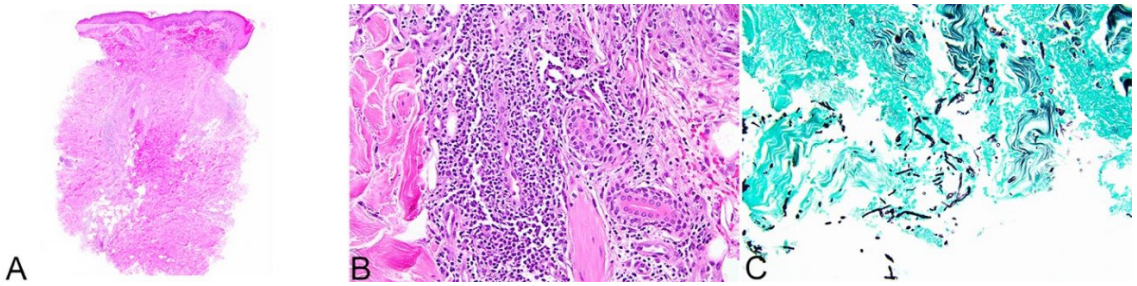
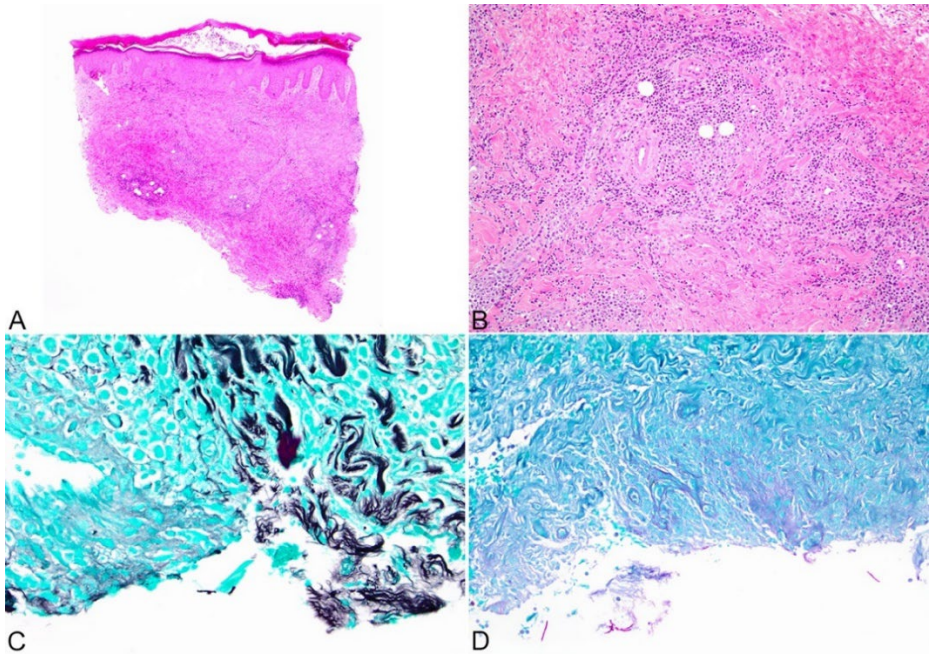


Figure 2. *Punch biopsy demonstrating superficial and deep perivascular and periadnexal atypical lymphocytic infiltrate, consistent with cutaneous involvement by chronic lymphocytic leukemia (A, H&E 20x; B, H&E 200x). There is a focus of deep necrosis where broad, septate branching hyphae are identified (C, GMS 200x).*



The depth of tissue specimens ranged from four to eight millimeters, with extension at least to the lower dermis. Four out of five patients (80%) with atypical histopathological features had hematologic malignancies compared to six out of eighteen (33%) in the readily diagnostic group. In two out of five cases, features of leukemia/lymphoma cutis obscured findings of an infectious etiology (Figure 3).

Figure 3. *Punch biopsy demonstrating a superficial and deep perivascular and interstitial atypical myeloid infiltrate, consistent with leukemia cutis (A, H&E 20x; B, H&E 100x). Along the deep edge of the biopsy, rare fungal hyphae are identified (C, GMS 200x; D, PAS 200x).*



Blood cultures were negative in all patients. Fungal tissue cultures were only positive in one patient in the atypical group (20%), which identified Aspergillus, compared to eleven out of seventeen (64.7%) specimens in which histopathologic findings of ICFI were conspicuous and tissue culture was performed.

CONCLUSIONS

The diagnosis of ICFIs remains a challenge given the non-specific clinical presentation and current diagnostic studies limited by low sensitivity.[8,9,12] To improve the means of obtaining an early diagnosis of ICFI, efforts to develop molecular-based testing as well as refine existing modalities continue to be needed. Our study retrospectively reviewed cases of ICFI to further evaluate key features of histopathology to facilitate the diagnosis.

For the diagnosis of ICFI, the interpretation of histopathology can be difficult, as our study found that diagnostic features of ICFIs may be present but subtle. In eighteen of the cases, typical features of fungal infection, including granulomatous and/or suppurative inflammation, necrosis, and readily identifiable organisms by special stain were detected. However, in the five atypical cases, fungal elements were extremely focal and difficult to identify even after staining with PAS and GMS. Further, the epidermis and much of the dermis were largely devoid of clues for fungal infection with hyphae sometimes restricted to the deep edge of the biopsies. These findings suggest that the depth of biopsy might contribute to the low sensitivity of histopathology and tissue culture testing for ICFIs.

Further complicating the ability to make an accurate diagnosis of ICFIs, discordant findings between histopathology and tissue culture are not uncommon. Results are potentially impacted by antifungal therapy, specimen damage during processing, tissue sampling from different areas, non-viable fungal organisms, and use of preservative-containing local anesthesia.[16,17] Although both gold standard tests are critical for the workup of ICFIs, accurate histopathologic analysis becomes especially important in the setting of false negative tissue culture

results in order to expedite appropriate treatment.[18] In our study, 80% of cases with focal histopathology and 33% with typical histopathology had negative cultures. In situations with high clinical suspicion of fungal infection but sterile cultures, sampling deeper tissues or reassessing slides at the base for fungal organisms could be a judicious course of action. Additionally, cultures can take weeks to yield results, while histopathology can reveal the diagnosis of ICFI much more quickly. While some fungal species share similar morphologic features, despite the inability to definitively identify the species, a diagnosis of ICFI can be made prompting the initiation of antifungal therapy while awaiting other testing.

As ICFIs are more common among the immunocompromised population, an increased index of suspicion is needed when these patients present with nonspecific systemic and cutaneous features.[1-3,6] Our study reiterated this predisposition, as all of our patients diagnosed with ICFIs were found to have underlying conditions with varying impairments of the immune system. In our study, the most common underlying comorbid conditions included hematologic malignancies, autoimmune diseases, diabetes mellitus, renal failure, and solid organ malignancies. The infectious etiology on biopsies was obscured in two of twenty-three (8.7%) cases by the underlying comorbid disease process, emphasizing the importance of a high degree of suspicion and careful evaluation of histopathologic sections, which may include multiple levels of sectioning. The landscape of available diagnostic tests for ICFIs has evolved over the last several years, with newer molecular methods now available. These include PCR-based assays; DNA sequencing; and proteomic approaches to detect fungal antigens, host antibodies to fungal antigens, fungal nucleic acids, and metabolite products. While these newer tests have the benefit of earlier detection of fungal infections, the sensitivity and specificity of most of these methods continue to be limited.[9,14,15] As such, a positive or negative result is often not enough to guide management. Further enhancement of these diagnostic techniques has the potential to have a greater impact on diagnosis in the future. However, this change could be accompanied by added time and costs. At the current time, traditional methods of culture and histopathology continue to be essential.

The current study is limited by the small sample size, inclusion of a single institution, and retrospective design. As the cases were identified for inclusion retrospectively based on final diagnosis, prospective research comparing the diagnostic yield of different techniques of skin biopsies and correlation with tissue culture and serologic fungal studies is ultimately needed. Additionally, multi-institutional studies involving several dermatopathologists and a greater number of included patients have the potential to further delineate the histopathologic features associated with ICFIs and identify techniques that may impact the ability to adequately detect these diagnostic features. An improved understanding of the impact of histopathologic techniques on diagnostic yield could thus lead to improved detection of ICFIs, facilitating better patient outcomes.

Despite the limitations of the current study, our findings show that histopathological evidence of ICFIs may be focal and limited to deeper sections of skin and/or obscured by a separate process. As the use of other diagnostic tests for ICFIs continues to be restricted by poor accuracy and inconsistent performance, refinement of a gold standard test may provide an alternative option for improving diagnosis. Although further prospective studies are needed, we suggest doing deeper biopsies, such as a tunneled punch or wedge biopsies; having a low threshold to perform fungal stains; and additional levels of sectioning in immunocompromised individuals, along with a meticulous search for organisms even in the absence of histologic findings suggestive of an infectious process to improve diagnostic yield and better identify ICFIs. Future studies with a larger number of patients and dermatopathologists from multiple institutions may further clarify methods associated with improved diagnostic yield.

REFERENCES

1. Low C-Y, Rotstein C. Emerging fungal infections in immunocompromised patients. *F1000 Med Rep*. 2011;3. https://doi.org/10.3410/M3-14
2. Enoch DA, Yang H, Aliyu SH, et al. The changing epidemiology of invasive fungal infections. *Human Fungal Pathogen Identification.* Springer; 2017:17-65. https://doi.org/10.1007/978-1-4939-6515-1_2
3. Hahn-Ast C, Glasmacher A, Mückter S, et al. Overall survival and fungal infection-related mortality in patients with invasive fungal infection and neutropenia after myelosuppressive chemotherapy in a tertiary care centre from 1995 to 2006. *J Antimicrob Chemother*. 2010;65(4):761-768. https://doi.org/10.1093/jac/dkp507
4. Von Eiff M, Roos N, Schulten R, et al. Pulmonary aspergillosis: Early diagnosis improves survival. *Respiration*. 1995;62(6):341-347. https://doi.org/10.1159/000196477
5. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. *Clin Infect Dis*. 2006;43(1):25-31. https://doi.org/10.1086/504810

6. Mays SR, Bogle MA, Bodey GP. Cutaneous fungal infections in the oncology patient. *Am J Clin Dermatol*. 2006;7(1):31-43. https://doi.org/10.2165/00128071-200607010-00004
7. Maddy AJ, Sanchez N, Shukla BS, et al. Dermatological manifestations of fungal infection in patients with febrile neutropaenia: A review of the literature. *Mycoses*. 2019;62(9):826-834. https://doi.org/10.1111/myc.12928
8. Terrero-Salcedo D, Powers-Fletcher MV. Updates in laboratory diagnostics for invasive fungal infections. *J Clin Microbiol*. 2020;58(6):e01487-19. https://doi.org/10.1128/JCM.01487-19
9. Arvanitis M, Anagnostou T, Fuchs BB, et al. Molecular and nonmolecular diagnostic methods for invasive fungal infections. *Clin Microbiol Rev*. 2014;27(3):490-526. https://doi.org/10.1128/CMR.00091-13
10. Klutts JS, Robinson-Dunn B. A critical appraisal of the role of the clinical microbiology laboratory in diagnosis of invasive fungal infections. *J Clin Microbiol*. 2011;49(9, supplement):S39-S42. https://doi.org/10.1128/JCM.00468-11
11. De Pauw B, Walsh TJ, Donnelly JP, 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):1813-1821. https://doi.org/10.1086/588660
12. Chandrasekar P. Diagnostic challenges and recent advances in the early management of invasive fungal infections. *Eur J Haematol*. 2010;84(4):281-290. https://doi.org/10.1111/j.1600-0609.2009.01391.x
13. Perfect JR. Fungal diagnosis: How do we do it and can we do better?. *Curr Med Res Opin*. 2013;29(4, supplement):3-11. https://doi.org/10.1185/03007995.2012.761134
14. Yeo SF, Wong B. Current status of nonculture methods for diagnosis of invasive fungal infections. *Clin Microbiol Rev*. 2002;15(3):465-484. https://doi.org/10.1128/CMR.15.3.465-484.2002
15. Halliday C, Kidd S, Sorrell T, et al. Molecular diagnostic methods for invasive fungal disease: The horizon draws nearer?. *Pathology*. 2015;47(3):257-269. https://doi.org/10.1097/PAT.0000000000000234
16. Santiago TMG, Pritt B, Gibson LE, et al. Diagnosis of deep cutaneous fungal infections: Correlation between skin tissue culture and histopathology. *J Am Acad Dermatol*. 2014;71(2):293-301. https://doi.org/10.1016/j.jaad.2014.03.042
17. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev*. 2011;24(2):247-280. https://doi.org/10.1128/CMR.00053-10
18. Jensen HE. Histopathology in the diagnosis of invasive fungal diseases. *Current Fungal Infection Reports*. 2021;15(1):23-31. https://doi.org/10.1007/s12281-021-00412-y