Diagnostic Accuracy of Histopathologic and Cytopathologic Examination of *Aspergillus* Species

*Akeesha A. Shah, MD, and Kevin C. Hazen, PhD**

Key Words: *Aspergillus* species; Diagnostic accuracy; Histopathology; Cytology

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Upon completion of this activity you will be able to:
- list fungal species that can morphologically mimic *Aspergillus* species.
- discuss the limitations of histopathologic/cytopathologic examination in the diagnosis of *Aspergillus* species.
- state features of mimickers that may distinguish them from *Aspergillus* species.

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Questions appear on p 125. Exam is located at www.ascp.org/ajcpcme.

Abstract

To assess the diagnostic accuracy of histopathologic and cytopathologic examination (HCE) of Aspergillus *species (spp), we performed an 11-year retrospective review to correlate surgical/cytology cases with a diagnosis of* Aspergillus *spp with their concurrent fungal culture results. Diagnostic accuracy was defined as the percentage of cases with culture-proven* Aspergillus *spp divided by the number of cases diagnosed as* Aspergillus *spp on HCE that had growth on fungal culture. Ninety surgical/cytology cases with concurrent fungal culture were reviewed, 58 of which grew a fungal organism. Of these 58 cases, 45 grew an* Aspergillus *spp, whereas 13 grew an organism other than* Aspergillus *spp, including both common (*Scedosporium*,* Fusarium*, and* Paecilomyces *spp) and uncommon mimickers (*Trichosporon loubieri*), resulting in a diagnostic accuracy of 78%. The low diagnostic accuracy indicates that several fungal organisms can morphologically mimic* Aspergillus *spp and can only be distinguished by fungal culture and DNA sequencing.*

Aspergillus species (spp) exist as septate molds and are a common cause of opportunistic mycoses in the immunocompromised host. *Aspergillus* spp can cause a range of clinical infections in the skin, eyes, ears, lung, and other organs. Histopathologic and cytopathologic examination (HCE), one of the major tools used in the diagnosis of these infections, is considered one of the criteria for diagnosing invasive fungal infections, as proposed by 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.[1]

Early and accurate diagnosis of any fungal infection is critical. However, identification in histopathologic and cytopathologic specimens of *Aspergillus* spp can be challenging because a number of other fungal species are morphologically similar, such as *Scedosporium* spp, *Penicillium* spp, and *Fusarium* spp. Distinguishing these organisms from *Aspergillus* spp is essential in guiding treatment and patient outcomes.

To date, few studies have assessed the accuracy of HCE in the diagnosis of aspergillosis. One of the largest studies, published in 2003, was performed by Tarrand et al,[2] who examined the correlation of microbiology cultures with anatomic pathology diagnoses of septate molds. Tarrand et al had a 23% positive concordance rate between histopathologic and cytopathologic demonstration of septate molds in tissue and culture; however, they did not address the accuracy of the presumptive identification of the etiologic agent and culture results. In 2009, Sangoi et al[3] conducted a retrospective review examining the accuracy of HCE in identifying all types of fungal organisms. Their study had a diagnostic accuracy of

79% and addressed the different ways that pathologists report the presence of fungal organisms. In an attempt to standardize pathology reporting of fungal infections and deemphasize species identification, they constructed templates for reporting hyphal and yeast-like fungal organisms.[3] Both of these studies examined a variety of organisms and did not focus specifically on the *Aspergillus* spp, a fungal genus that is frequently and often confidently diagnosed by pathologists. To assess the accuracy of the histopathologic and cytopathologic diagnosis of *Aspergillus* spp, we performed an 11-year retrospective review of all cytology/surgical pathology cases that had a diagnosis indicating the presence of *Aspergillus* spp and their concurrent fungal culture results.

Materials and Methods

Following approval from the University of Virginia (UVA) Institutional Review Board, a natural language search was performed using the anatomic pathology laboratory information system, CoPath (Cerner DHT, Waltham, MA). Search terms included *aspergillus*, *aspergilloma*, and *aspergillosis* in the final diagnosis or diagnosis comment fields in all surgical specimens and cytology specimens between December 31, 2000, and December 31, 2011. Autopsy cases were excluded. Using the patient's medical record number, the accession date of the surgical/cytology specimen, and the specimen type, concurrent fungal culture data were retrieved from the UVA's Clinical Repository Data (CDR). The CDR is a data warehouse containing a variety of information regarding patients seen at the University of Virginia Health System that is managed by the Clinical Informatics Division of the Department of Public Health.

A fungal culture was considered concurrent if it was obtained from a specimen that was divided into 2 parts, with one part sent for culture and the other sent to anatomic pathology, or if the specimen representing the same sampling area as that of the anatomic pathology specimen was obtained within 3 days of the anatomic pathology specimen. If a patient had multiple specimens submitted for HCE only, the first anatomic sample submitted that had a positive microbiology culture was included in our analysis. This was done to decrease the bias that would be incurred in cases that already had an established aspergillosis diagnosis.

Microbiology cultures performed on sterile body fluids/tissue involved plating the specimen on 3 media: inhibitory mold agar (IMA), IMA with gentamicin, and brain heart infusion agar (Remel, Lenexa, KS). Respiratory samples were plated on IMA and IMA with gentamicin. An initial gram stain was performed on all samples. All fungal cultures were incubated at 30°C for a total of 4 weeks. Cultures were inspected for growth once every 24 hours for the first 3 days, on day 7, and then once every week for the remaining 3 weeks. Fungal identification was based on macro- and microscopic characteristics. If identification of the fungal species was not possible with macro- and microscopic characteristics, then DNA sequencing of the D2 region of the 26S ribosomal DNA was performed using primers described by Kurtzman and Robnett.[4]

Patient age, sex, and clinical history were all obtained from the anatomic pathology final report. The surgical/cytologic diagnosis and diagnosis comment for each case were recorded. The final fungal culture results were obtained from the CDR. These results were compared with the anatomic pathology diagnoses to assess diagnostic accuracy.

Diagnostic accuracy was defined as the percentage of cases with culture-proven *Aspergillus* spp divided by the number of cases diagnosed as *Aspergillus* spp on HCE that had growth on fungal culture. In addition, antifungal medication data were retrieved from the CDR. Any patient on antifungal medications prior to submission of his or her anatomic specimen was recorded. When applicable, statistical analysis was performed using a 2-tailed Fisher exact test with significance set at a P value of less than or equal to .05 (GraphPad Software, La Jolla, CA).

Results

With use of the CoPath search terms described earlier, 112 surgical/cytology cases were identified. All cases indicated the presence of *Aspergillus* spp either in the final diagnosis or diagnosis comment section of the anatomic pathology report. Of these 112 cases, 90 were submitted for fungal culture (80%). The 90 cases represented 53 male and 37 female patients with an average age of 51 years (range, 5-81 years). These cases consisted predominantly of bronchoalveolar lavages (36 cases, 40%), followed by lung biopsies/resections (18 cases, 20%) and then nasal sinus biopsies (12 cases, 13%) Table 1.

Table 1
Distribution of Cases With and Without Positive Fungal Culture Results

Specimen Type	Site	No. of Culture-Negative Cases (n = 32)	No. of Culture-Positive Cases (n = 58)
Cytology	Bronchoalveolar lavage	3	33
	Bronchial washing	3	3
	Nasal sinus fluid	0	1
	Lung aspiration	3	3
	Pleural fluid	2	0
	Cerebrospinal fluid	1	0
	Total cytology cases, No. (%)	12 (37.5)	40 (69.0)
Surgical	Lung	9	9
	Nasal sinus	5	7
	Skin	3	1
	Brain	1	1
	Liver	1	0
	Eye	1	0
	Total surgical cases, No. (%)	20 (62.5)	18 (31.0)

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Overall, there were more cytology specimens (52 cases, 58%) than surgical biopsy/resection cases (38 cases, 42%). Thirty-two (36%) cases resulted in no fungal growth, whereas 58 (64%) cases demonstrated growth of a fungal organism.

The 32 cases with no fungal growth consisted of 12 (37.5%) cytology specimens and 20 (62.5%) surgical biopsy/resection specimens. The 58 cases with fungal growth consisted of 40 (69%) cytology specimens and 18 (31%) surgical biopsy/resection specimens. There was a significant difference in the percentage of cytology cases (77%) that had growth of a fungal organism compared with that of surgical biopsy/resection cases (47%) (P = .007). The clinical histories provided to the pathologists indicated that the patient population consisted predominantly of patients who were immunocompromised due to hematologic malignancy, solid malignancy, human immunodeficiency virus infection, or lung/solid organ transplant (31 patients, 53%). Sixteen (28%) patients presented with a mass-like lung lesion or pulmonary infiltrates. Two (3%) patients had a history of aspergillosis, and no clinical history was provided for 9 (16%) patients.

Most anatomic pathology cases were diagnosed as either fungal forms consistent with *Aspergillus* spp or fungal organisms identified with the diagnosis comment indicating the presence of *Aspergillus* spp **Table 2**. There were 3 cases with necrotizing invasive fungal infections. Of the 58 cases with positive fungal cultures, 38 cases grew a single *Aspergillus* species, 1 case grew 2 distinct *Aspergillus* species, 6 cases grew an *Aspergillus* species in addition to another fungal organism (most often of the *Candida* species), and 13 cases grew a fungal organism other than *Aspergillus* spp **Table 3**.

The diagnostic accuracy of HCE of *Aspergillus* was 78% (45 of 58). The 13 cases with discordant fungal culture results were predominantly pulmonary specimens (9 cases, 69%) followed by nasal sinus biopsy specimens (3 cases, 23%) and a single skin biopsy specimen (8%). Various organisms were grown in fungal culture, from the well-known mimickers *Scedosporium* and *Fusarium* species to the more distinct-appearing Zygomycetes **Table 4**. There was no difference in concordant results between cytology and surgical tissue specimens (P = 1.0).

Table 3
Fungal Culture Results From the 90 Surgical and Cytology Cases

Fungal Culture Results	Total (n = 90)
Aspergillus	
fumigatus	34
flavus	1
terreus	1
ustus	1
fischerianus	1
Total cases with *Aspergillus* spp only	38
More than 1 *Aspergillus* spp	
nidulans + *fumigatus*	1
Total cases with >1 *Aspergillus* spp	1
Aspergillus + other fungal organism	
fumigatus + Zygomycetes	1
flavus + *Candida* spp	2
fumigatus + *Candida* spp	1
fumigatus + *Paecilomyces* spp	1
fumigatus + *Penicillium* spp	1
Total cases with *Aspergillus* and another fungal spp	6
Not *Aspergillus* spp	
Zygomycetes	2
Alternaria + *Penicillium* spp	1
Trichosporon loubieri	1
Scopulariopsis spp	1
Curvularia spp	1
Fusarium spp	1
Paecilomyces lilacinus	1
Scedosporium apiospermum	1
Yeast not *Candida* spp	3
Yeast not *Candida* + *Penicillium* spp	1
Total cases with growth of non-*Aspergillus* spp	13
No growth	32

Table 2
Relationship of Histopathologic/Cytopathologic Diagnosis With Concordant Fungal Cultures

Anatomic Pathology Diagnoses	No. of Cases (n = 58)	No. of Cases With Fungal Cultures Positive for *Aspergillus* (n = 45)
Fungal forms consistent with *Aspergillus*	30	26
Fungal organisms identified; the diagnosis comment indicates the presence of *Aspergillus*	13	6
Fungal forms present favor *Aspergillus*	2	2
Aspergilloma	5	4
Necrotizing invasive fungal infection; the diagnosis comment states suggestive of *Aspergillus*	2	1
Fungal form suggestive of *Aspergillus*	1	1
Necrotizing invasive fungal infection consistent with *Aspergillus*	1	1
Chronic necrotizing aspergillosis	1	1
Microorganisms identified; the diagnosis comment states yeast and hyphae consistent with but not specific for *Aspergillus*	1	1
Organized *Aspergillus* abscess	1	1
Fungal forms consistent with *Aspergillus*	1	1

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Table 4
Clinicopathologic Features of Cases With Discordant Fungal Culture Results

Clinical History	Patient Age, y	Sex	Specimen	Anatomic Diagnosis	Fungal Culture Result
Possible aspergilloma	36	F	NSBx	Aspergilloma	*Scopulariopsis* spp
History of aspergillosis in past	51	M	BAL	Fungal forms consistent with *Aspergillus* spp	*Paecilomyces lilacinus*
I/C, possible fungal infection	59	M	BAL	Fungal forms consistent with *Aspergillus* spp	Yeast not *Candida albicans*
I/C, possible fungal infection	65	F	BAL	Fungal forms consistent with *Aspergillus* spp	Yeast not *C albicans*
Lung mass	50	F	BW	Fungal forms consistent with *Aspergillus* spp	Yeast not *C albicans*, *Penicillium* spp
I/C, possible fungal infection	9	M	NSBx	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	Zygomycetes
LTX with pulmonary infiltrates	64	M	BAL	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	*Fusarium* spp
LTX with pulmonary infiltrates	41	F	BAL	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	Zygomycetes
LTX, possible fungal infection	60	M	BAL	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	*Alternaria* spp, *Penicillium* spp
LTX, possible fungal infection	68	F	BW	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	*Scedosporium apiospermum*
LTX, possible fungal infection	73	M	BAL	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	Yeast not *C albicans*
LTX, possible fungal infection	20	F	Skin biopsy	Fungal organisms identified; comment indicates presence of *Aspergillus* spp	*Trichosporon loubieri*
I/C, possible fungal infection	51	F4	NSBx	Necrotizing invasive fungal infection; comment states suggestive of *Aspergillus* spp	*Curvularia* spp

BAL, bronchoalveolar lavage; BW, bronchial washing; I/C, immunocompromised; LTX, lung transplant; NSBx, nasal sinus biopsy.

Fourteen of the 58 patients (23%) were treated with antifungal agents prior to submission of their fungal cultures. These agents included intravenous or oral azoles (voriconazole, itraconazole, and fluconazole), amphotericin B, and anidulafungin. The number of days that patients received antifungal treatment prior to fungal culture ranged from 1 to 14. Four of these patients with prior antifungal treatment had discordant fungal culture results, whereas 10 of these patients had concordant fungal culture. Antifungal use prior to specimen submission did not affect the rate of the concordant fungal culture results ($P = .71$).

Discussion

Aspergillosis refers to the wide variety of diseases in humans that are caused by *Aspergillus* spp, and HCE is one way of diagnosing these infections. This study attempts to analyze the accuracy of HCE of *Aspergillus* spp by correlating surgical/cytology cases diagnosed as *Aspergillus* spp with concurrent fungal culture results. Our diagnostic accuracy rate was 78%, with 13 of 58 cases growing organisms other than *Aspergillus* spp in fungal culture. Although we limited our examination to *Aspergillus* spp, our diagnostic rate was essentially identical to that of Sangoi et al[3] (79%), who examined all fungal organisms (ie, yeasts and molds). There are limitations to using culture as the gold standard for detecting fungal organisms, as the recovery rate is not 100%. However, fungal culture is considered the gold standard for speciation, especially when combined with modern DNA sequencing techniques.

The vast majority of our cases were respiratory samples from immunocompromised hosts. In this setting, a variety of traditionally nonpathogenic fungi have the potential to cause serious disease. In the past decade, it has been increasingly recognized that hyaline molds and dematiaceous fungi are a growing group of important invasive fungal organisms.[5] However, there is sparse literature detailing the histopathology of these organisms. It is known that many of these organisms can mimic the more common *Aspergillus* spp, and thus culture is of paramount importance, especially since some of these organisms demonstrate resistance to a variety of antifungal agents.[5] In our study, 4 cases grew organisms that are known to mimic *Aspergillus* spp infection both clinically and morphologically. These included *Scedosporium*, *Paecilomyces*, *Scopulariopsis*, and *Fusarium* spp. A detailed description of each of these fungal organisms is beyond the scope of this article. However, some key points regarding the morphology of each of these organisms will be discussed to bring some attention to these less well-known organisms in the pathology literature.

In acute infections, *Aspergillus* spp have septate hyphae with dichotomous branching. The hyphal walls are often parallel and display a uniform width (3-6 μm)[6] **Image 1**. In chronic infections, the hyphae can become larger (up to 12 μm), distorted, and more tortuous.[6] In our experience, dichotomous or Y-shaped branching is a helpful means to distinguish *Aspergillus* spp from Zygomycetes and other fungal organisms. The hyphae of Zygomycetes are broader in width (6-16 μm), are ribbon-like with nonparallel walls, and can appear twisted **Image 2**.[6,7] They often stain less

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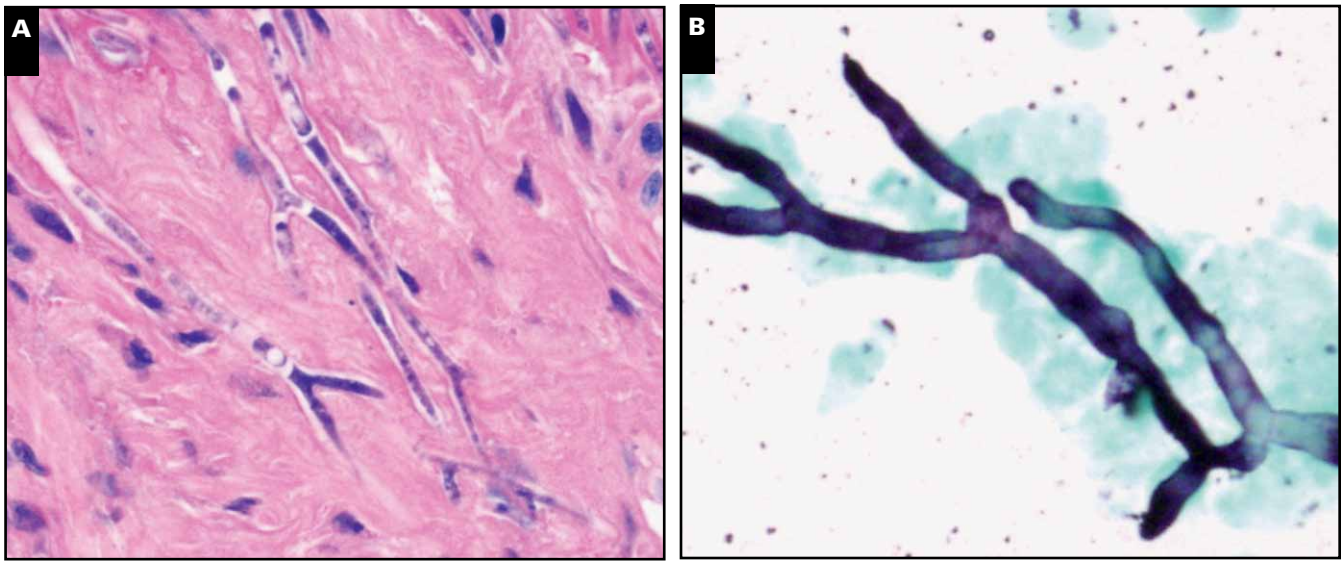

Image 1 The classic dichotomous branching of *Aspergillus* spp. **A**, *Aspergillus* spp in a sinus biopsy (H&E, ×40). **B**, *Aspergillus* spp in a bronchoalveolar cytology specimen (Grocott methenamine silver, ×40).

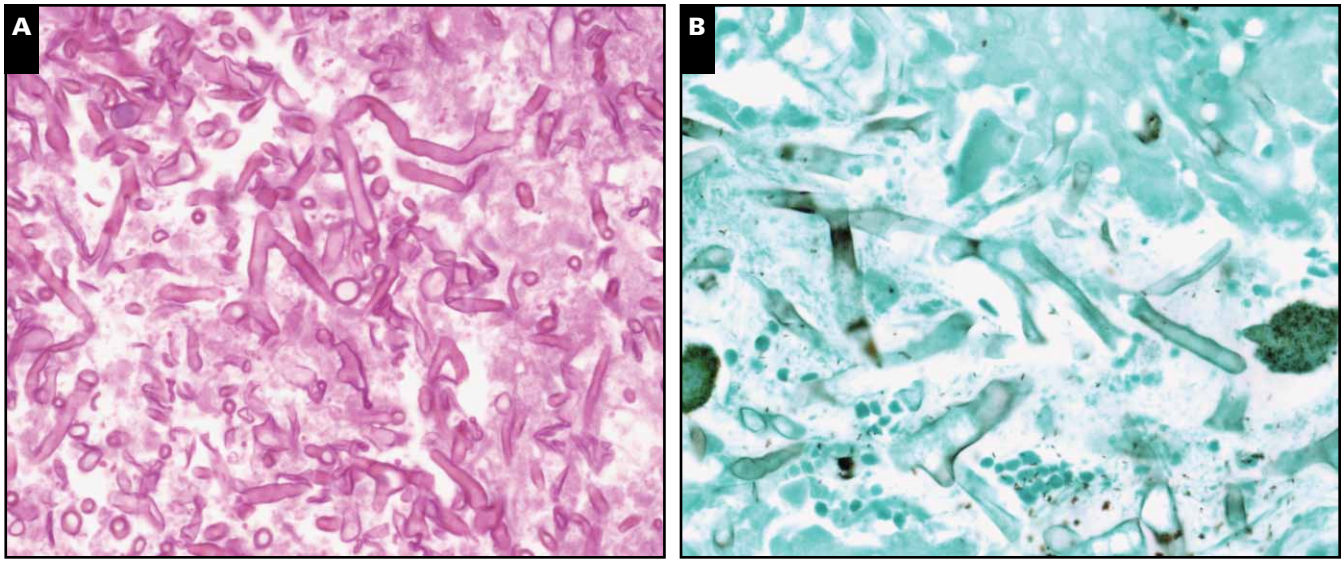

Image 2 A case of Zygomycetes that was diagnosed as *Aspergillus* spp. **A**, Zygomycetes in a sinus biopsy. Note the twisting of the hyphae, broad hyphal width, and less frequent septations compared with *Aspergillus* spp. There are some areas suggestive of dichotomous branching, but the hyphal walls are more tortuous and variable (H&E, ×400). **B**, Zygomycetes in a sinus biopsy. Note the relatively faint and nonuniform staining (Grocott methenamine silver, ×40).

intensely and nonuniformly with special stains. The Zygomycetes are considered pauciseptate, and when septations are seen, they are infrequent, thin, and irregularly spaced.[6]

The *Scedosporium* as well as *Fusarium* spp are emerging opportunistic pathogens in both immunocompromised and immunocompetent hosts that can cause a wide range of infections, including invasive pulmonary infections.[5,8] These organisms, like *Aspergillus* spp, produce hyaline (nonpigmented) hyphae with regular septations.[9] They display acute angle branching as well as dichotomous branching and may show angioinvasion.[6] The hyphae of *Scedosporium* spp often have an irregular branching pattern, unlike the regular dichotomous branching of *Aspergillus* spp.[8,9] *Scedosporium* spp, unlike *Aspergillus* spp, can produce terminal and intercalary chlamydospores as well as ovoid conidia, both of which can be confused with yeast. These structures can be useful features in its identification.[8,9] Distinguishing *Scedosporium* spp from *Aspergillus* spp cannot be reliably achieved with HCE and requires definitive identification with culture.[5,8] Accurate identification of these organisms is critical, as both species are resistant to many antifungal agents.[10]

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One of our cases represented a sinus infection with *Scopulariopsis* spp that was thought clinically and histologically to be consistent with an aspergilloma. Like *Scedosporium* and *Fusarium* spp, culture is needed for definitive identification.[5,8,11,12] In our case, the H&E-stained sections of the nasal biopsy specimen demonstrated necrotic tissue with masses of mycelial forms. The morphology of the individual hyphae was difficult to appreciate on H&E and was better seen on a silver stain, which revealed areas of branching with septations **Image 3**. However, the hyphal forms are more tortuous and less parallel than what is classically seen with *Aspergillus* and are somewhat reminiscent of Zygomycetes.

In one of our cases with discordant results, a yeast, *Trichosporon loubieri*, was isolated from a skin biopsy specimen of a lung transplant patient. This organism is of particular interest, as only 3 case reports in the literature have documented this organism as a human pathogen.[13-15] In infections with other *Trichosporon* spp, histology often demonstrates a mixture of hyphae, pseudohyphae, and budding yeasts that resemble *Candida* spp.[5,6] In our case, definitive angioinvasion with masses of hyphal elements filling and invading the vessel wall was seen. The hyphae were of variable length, had thick walls, but were overall very long with rare branching **Image 4**. Definitive arthroconidia was not seen.

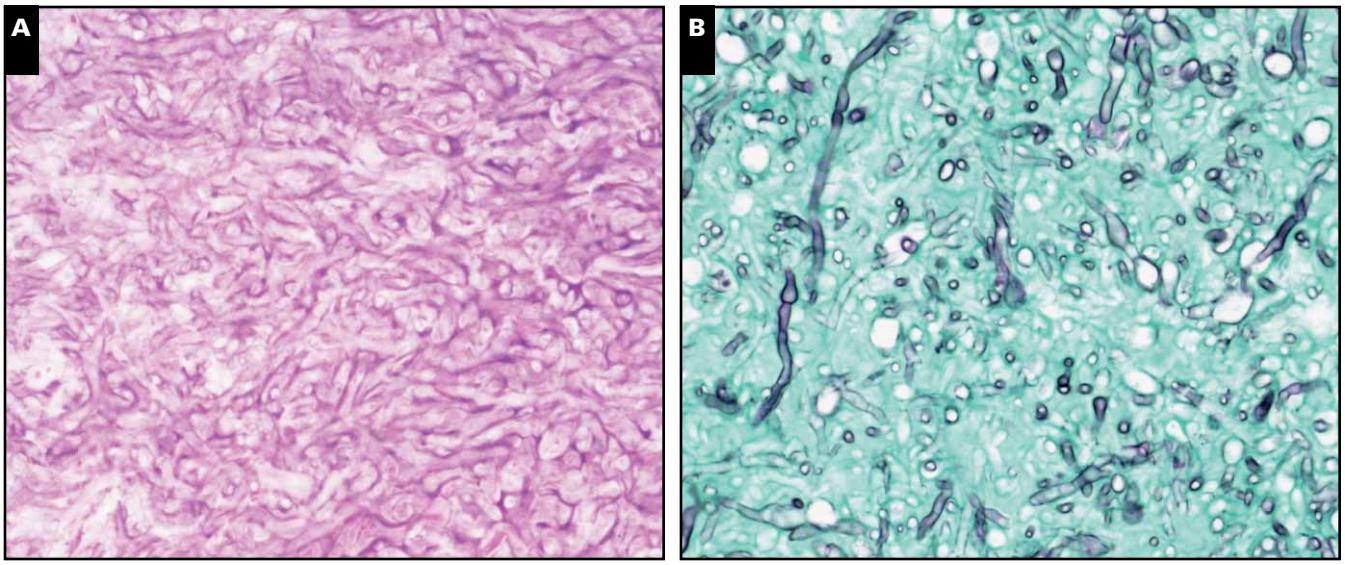

Image 3 *Scopulariopsis* spp in a nasal sinus biopsy specimen in a patient clinically suspected as having an aspergilloma. **A**, Numerous hyphal elements that vary in size and are tortuous (H&E, ×40). **B**, The hyphal walls are not parallel, as usually seen with *Aspergillus* spp, and appear more tortuous (Grocott methenamine silver, ×40).

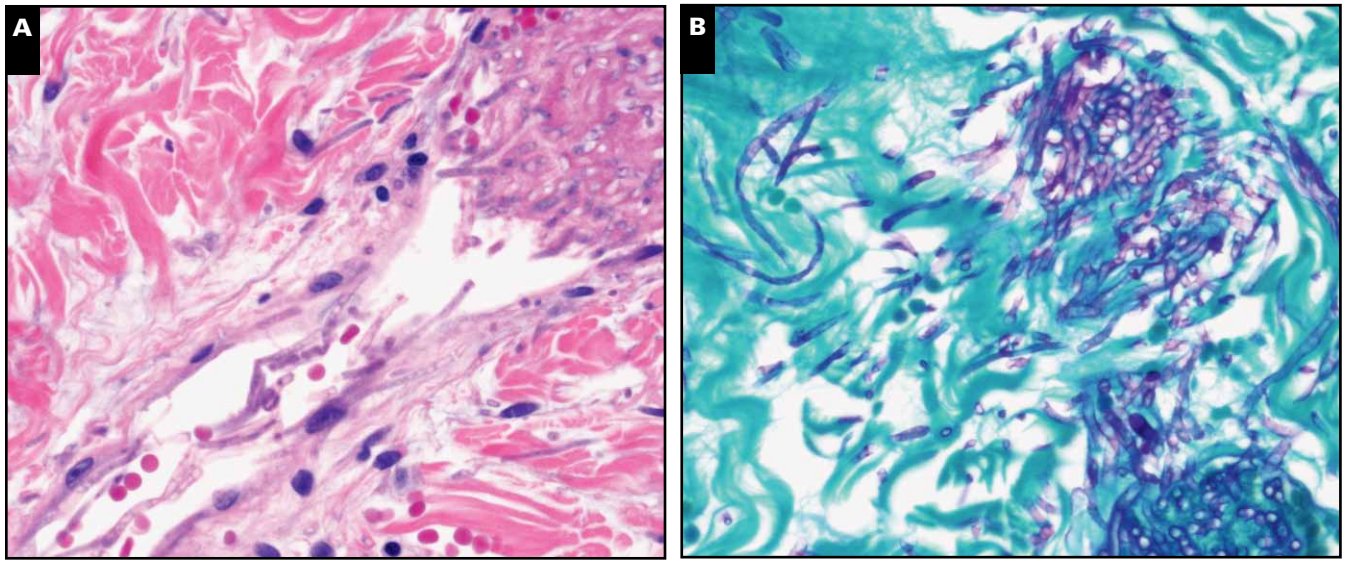

Image 4 *Trichosporon loubieri* from a skin biopsy specimen. **A**, Angioinvasion is shown with a mass of hyphal elements filling the vessel (H&E, ×40). **B**, Hyphal elements are of various lengths with rare branching (periodic acid–Schiff, ×40).

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It is important to note that 6 cases in this study grew an additional fungal organism other than *Aspergillus* spp. One of these cases also grew a zygomycete and another *Paecilomyces* spp; growth of these additional organisms could potentially alter patient management. In addition, 1 case grew 2 species of *Aspergillus*: *Aspergillus nidulans* and *Aspergillus fumigatus*. These findings substantiate the need for culture, as identification of multiple organisms can be very difficult on histology. Antifungal therapy has been thought to affect morphology, but there was no difference in prior antifungal therapy in cases with concordant fungal culture results as compared with those with discordant results ($P = .71$).

In our experience, the classic defining features used to identify fungal organisms that most pathologists are taught are mostly applicable to the organism growing in an unimpeded state and not within the confines of an inflammatory tissue reaction. In addition, the fungal hyphae of *Aspergillus* spp can assume a different morphology in a chronic infection as opposed to an acute infectious state.[6] Upon reviewing the anatomic pathologic reports, it was interesting that only 5 of the 58 cases provided a differential diagnosis for the fungal organism seen, and only 11 of the 58 cases recommended correlation with microbiology. Given that the diagnostic accuracy of identifying *Aspergillus* spp was only 78%, we believe it is important that pathologists recommend correlation with microbiology or provide a cautionary statement to advise clinicians of the limitations of identifying organisms with histopathologic/cytopathologic examination. This may be especially true in the setting of an immunocompromised patient, because several traditionally nonpathogenic organisms can cause severe infections and morphologically mimic *Aspergillus* spp.

In conclusion, pathologists need to be aware of the many organisms that can histologically mimic *Aspergillus* spp. Microbiology cultures still remain the gold standard for species identification and are increasingly important with newly emerging fungal pathogens, given their resistance to antifungal agents and high mortality in immunocompromised patients.

From the Department of Pathology, University of Virginia Health System, Charlottesville, VA.

[*]Dr Hazen is currently at Duke University Medical Center, Durham, NC.

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Address reprint requests to Dr Shah: Dept of Pathology, University of Virginia Health System, PO Box 800214, 1215 Lee St, Charlottesville, VA 22908; aas7t@virginia.edu.

References

1. 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;46:1813-1821.
2. Tarrand JJ, Lichterfeld M, Warraich I, et al. Diagnosis of invasive septate mold infections: a correlation of microbiological culture and histologic or cytologic examination. *Am J Clin Pathol*. 2003;119:854-858.
3. Sangoi AR, Rogers WM, Longacre TA, et al. Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens. *Am J Clin Pathol*. 2009;131:364-375.
4. Kurtzman CP, Robnett CJ. Identification of clinically important ascomycetous yeasts based on nucleotide divergence in the 5' end of the large-subunit (26S) ribosomal DNA gene. *J Clin Microbiol*. 1997;35:1216-1223.
5. Varkey JB, Perfect JR. Rare and emerging fungal pulmonary infections. *Semin Respir Crit Care Med*. 2008;29:121-131.
6. Chandler FW, Kaplan W, Libero A. *Color Atlas and Text of the Histopathology of Mycotic Diseases*. Chicago, IL: Year Book Medical Publishers; 1980.
7. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev*. 2000;13:236-301.
8. Walts AE. Pseudallescheria: an underdiagnosed fungus. *Diagn Cytopathol*. 2001;25:153-157.
9. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev*. 2008;21:157-197.
10. Smith JA, Kauffman CA. Pulmonary fungal infections. *Respirology*. 2012;17:913-926.
11. Swick BL, Reddy SC, Friedrichs A, et al. Disseminated *Scopulariopsis*: culture is required to distinguish from other disseminated mould infections. *J Cutan Pathol*. 2010;37:687-691.
12. Endo S, Hironaka M, Murayama F, et al. *Scopulariopsis* fungus ball. *Ann Thorac Surg*. 2002;74:926-927.
13. Marty FM, Barouch DH, Coakley EP, et al. Disseminated trichosporonosis caused by *Trichosporon loubieri*. *J Clin Microbiol*. 2003;41:5317-5320.
14. Padhye AA, Verghese S, Ravichandran P, et al. *Trichosporon loubieri* infection in a patient with adult polycystic kidney disease. *J Clin Microbiol*. 2003;41:479-482.
15. Gabriel F, Noel T, Accoceberry I. A fatal invasive trichosporonosis due to *Trichosporon loubieri* in a patient with T-lymphoblastic leukemia. *Med Mycol*. 2011;49:306-310.

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