Lethal Outbreak of Black Fungus Infection

To the Editor.—When the pandemic started in 2020, an article titled “Geospatial Spread of Antimicrobial Resistance, Bacterial and Fungal Threats to Coronavirus Infectious Disease 2019 (COVID-19) Survival, and Point-of-Care Solutions” by Kost1 in Archives of Pathology & Laboratory Medicine warned of the threat of fungal epidemics. The threat became a reality in India, where an outbreak of black fungus infection or mucormycosis recently killed more than 2100 COVID-19 patients.2 Molds called mucormycetes in the order Mucorales triggered the outbreak that damages the eyes, muscles, nerves, lungs, and brains of patients, with a mortality rate of 50%. India has recorded 29.7 million cases of COVID-19 infections and 382,000 deaths as of June 17, 2021. Major hospitals are facing chronic shortages of intensive care unit beds and oxygen. In this gloomy health crunch, the black fungus has infected more than 31,000 COVID-19 patients.2 The fungal outbreak has further amplified pressure on the already burdened health care system. In Bangalore, hospitals can no longer accommodate patients. The Delhi state government has ordered hospitals to set up emergency mucormycosis centers. Maharashtra state has recorded 7057 cases and 609 deaths, which is the highest in the country, followed by Gujarat with 5418 cases and 323 deaths.2 Unhygienic behavior can cause a flare-up of fungal infections, such as people in Gujarat state who cover their bodies with cow dung to evade COVID-19 infections, which should prompt a ban on superstitious endeavors regarding contagions.2 The lead scientific advisor to the government of India has recently warned about the upcoming third wave of COVID-19, so the health community must be well prepared to also tackle the black fungus recurrence.4

Mucormycosis is an emerging infectious disease in India and thus epidemiologic data are limited. A quick search of “mucormycosis India” in Web of Science from 1994 to 2021 resulted in only 79 hits with mere case studies and reviews. Long-term epidemiologic monitoring is therefore imperative. Hospitals are facing severe shortages of antifungal drugs and the treatment is expensive. A single antifungal intravenous shot costs about US $50, and a patient requires US $2800 for 8 weeks of therapy. But the poor cannot afford it, so subsidized treatment is required. What is worse is that India spends only 1.3% of its gross domestic product for health, which is one of the lowest percentages in the world. A 5-fold increase in health spending forthwith is essential, and only then can the crisis of COVID-19 allied black fungus be resourcefully tackled before it is too late.

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Importance of Commutability for Interoperability Within and Between Laboratories

To the Editor.—Lo and Alter1 have highlighted the importance of ensuring commutability of materials used for interinstrument comparisons. Laboratories that are College of American Pathologists (CAP) accredited will be familiar with the need to demonstrate comparability of instruments and methods described in the Common Checklist item COM.04250.2 This requirement states a preference to use patient specimens to avoid the matrix effects discussed by Lo and Alter1 but does allow quality control materials to be used for tests when the same instrument platform with both control material and reagents of the same manufacturer and lot number is in use. Such an approach would not necessarily detect all conceivable analytical differences between platforms, and patient samples would be the material of choice.

This checklist item is not applicable for laboratories with different CAP numbers and is relevant only to laboratories with multiple analytical platforms or whose satellite or “sister” laboratories share the same CAP number. The need to demonstrate similar comparability between independent laboratories displaying results in a common electronic medical record system is arguably outside the scope of this requirement. With the rise of regional and national electronic medical record systems, there is a pressing need for equivalent requirements on the agreement needed between institutions sharing a common electronic test repository and result interface to allow interoperability of numeric results. These should explicitly discuss the requirements that allow the use of common reference intervals and trending across institutions.3 For the CAP Accreditation Program, this could be covered within the computer section of the General Checklist or by revision and expansion of the existing Common Checklist item COM.04250 described above.4

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Traditionally, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with cytologic evaluation has been the method of choice for diagnosis of PCL. However, disappoimting results of its diagnostic yield have been reported, due to the lack of dispersed cells into the fluid. At the beginning of her article, Reid mentions that, to improve preoperative assessment of PCL, both the ancillary tests to be performed on cyst fluid (eg, molecular diagnostics) and new technologies for tissue collection have been developed. In particular, a microforceps (Moray Microforceps, US Endoscopy, Mentor, Ohio) able to perform a biopsy of the cyst wall passing through a 19G needle has been recently introduced. However, we believe that through-the-needle biopsy (TTNB) is not a simple implementation of EUS-FNA but a breakthrough in the field that deserves more comment. TTNB allows the acquisition of histologic specimens from the cyst wall, which include both stroma and epithelium, a possibility that had never been realizable in the past. The presence of stroma, as well as the maintained tissue architecture of the cystic wall detected on TTNB specimens, is crucial for the differential diagnosis in many cases.

A comprehensive example of the diagnostic yield of TTNB is seen with mucinous cyst lesions in which the capability of the microforceps to sample the ovarian-like stroma beneath the mucinous epithelium allows the conclusive diagnosis of mucinous cystic neoplasms, a cyst histotype requiring specific management. Available literature speaks in favor of TTNB compared with cytology. A meta-analysis including 454 patients demonstrated a technical success rate of 98.5%, a histologic rate of 86.7%, and a diagnostic yield of approximately 70%, significantly higher than that of cytology (approximately 29%). Importantly, in an interobserver agreement study among expert pathologists, a specific diagnosis of cyst histotype was reported in 84.7% of cases, with a substantial agreement between the raters (Gwet AC1, 0.62; 95% CI, 0.57–0.67), suggesting that TTNB samples are not misleading and are easily evaluable. Also, TTNB findings seem reliable when compared with surgical specimens, with a correspondence rate with surgical pathology of 93%. Finally, TTNB is feasible even when fluid aspiration is not possible owing to thick cyst content. Recently, a helpful algorithm has been proposed by Rift et al in which, in the presence of epithelium and/or stroma on initial evaluation of the biopsy sample, different immunohistochemical stains can be added to establish a diagnosis. Of course, clinical suspicion based on patient demographics and lesion imaging features should be also considered. A similar policy is applied at our institution. We commend Dr Reid for her wonderful article, which is complete and comprehensive, and serves as a guide for pathologists for such a difficult evaluation as PCL cytology. However, even if cytology still represents a widespread method for PCL evaluation, we believe that TTNB should be performed in select cases, especially when a specific diagnosis of cyst histotype is required for proper patient management.

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1. Reid MD. Cytologic assessment of cystic/intraductal lesions of the pancreatobiliary tract [published online April 9, 2021]. Arch Pathol Lab Med. doi:10.5858/arpa.2020-0553-RA

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Through-The-Needle Biopsy: Shifting From Cytology to Histology for Preoperative Assessment of Pancreatic Cystic Lesions

To the Editor.—We congratulate Michelle Reid, MD, on her exhaustive and comprehensive review on fluid cytology for assessment of pancreatic cystic lesions (PCLs).

Traditionally, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with cytologic evaluation has been the method of choice for diagnosis of PCL. However, disappointing results of its diagnostic yield have been reported, due to the lack of dispersed cells into the fluid. At the beginning of her article, Reid mentions that, to improve preoperative assessment of PCL, both the ancillary tests to be performed on cyst fluid (eg, molecular diagnostics) and new technologies for tissue collection have been developed. In particular, a microforceps (Moray Microforceps, US Endoscopy, Mentor, Ohio) able to perform a biopsy of the cyst wall passing through a 19G needle has been recently introduced. However, we believe that through-the-needle biopsy (TTNB) is not a simple implementation of EUS-FNA but a breakthrough in the field that deserves more comment. TTNB allows the acquisition of histologic specimens from the cyst wall, which include both stroma and epithelium, a possibility that had never been realizable in the past. The presence of stroma, as well as the maintained tissue architecture of the cystic wall detected on TTNB specimens, is crucial for the differential diagnosis in many cases.

A comprehensive example of the diagnostic yield of TTNB is seen with mucinous cyst lesions in which the capability of the microforceps to sample the ovarian-like stroma beneath the mucinous epithelium allows the conclusive diagnosis of mucinous cystic neoplasms, a cyst histotype requiring specific management. Available literature speaks in favor of TTNB compared with cytology. A meta-analysis including 454 patients demonstrated a technical success rate of 98.5%, a histologic rate of 86.7%, and a diagnostic yield of approximately 70%, significantly higher than that of cytology (approximately 29%). Importantly, in an interobserver agreement study among expert pathologists, a specific diagnosis of cyst histotype was reported in 84.7% of cases, with a substantial agreement between the raters (Gwet AC1, 0.62; 95% CI, 0.57–0.67), suggesting that TTNB samples are not misleading and are easily evaluable. Also, TTNB findings seem reliable when compared with surgical specimens, with a correspondence rate with surgical pathology of 93%. Finally, TTNB is feasible even when fluid aspiration is not possible owing to thick cyst content. Recently, a helpful algorithm has been proposed by Rift et al in which, in the presence of epithelium and/or stroma on initial evaluation of the biopsy sample, different immunohistochemical stains can be added to establish a diagnosis. Of course, clinical suspicion based on patient demographics and lesion imaging features should be also considered. A similar policy is applied at our institution. We commend Dr Reid for her wonderful article, which is complete and comprehensive, and serves as a guide for pathologists for such a difficult evaluation as PCL cytology. However, even if cytology still represents a widespread method for PCL evaluation, we believe that TTNB should be performed in select cases, especially when a specific diagnosis of cyst histotype is required for proper patient management.

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In Reply.—We appreciate the comments by Dr Hawkins and want to emphasize that the key to all of them is the need to use appropriately commutable material for comparison across platforms, especially in this era of nonstandardized hospital systems, where there is an urgent need to have some form of comparability across said systems. We stand by the facts that the best material for this project is ultimately patient samples and that proficiency testing material shouldn’t be used for this exercise.

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Through-The-Needle Biopsy: Shifting From Cytology to Histology for Preoperative Assessment of Pancreatic Cystic Lesions

To the Editor.—We congratulate Michelle Reid, MD, on her exhaustive and comprehensive review on fluid cytology for assessment of pancreatic cystic lesions (PCLs).