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BRIEF REPORT

Limited Index of Clinical Suspicion and Underdiagnosis of Histopathologically Documented Invasive Mold Infections

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Invasive mold infections (IMIs) are difficult to diagnose. This analysis of histopathologically proven IMIs at our institution (2010–2019) showed that 11/41 (27%) of them were not suspected at the time of biopsy/autopsy (9/17, 53% among autopsies). The rate of missed diagnosis was particularly high (8/16, 50%) among nonhematologic cancer patients.

Keywords. aspergillosis; autopsy; biopsy; lymphoma; mucormycosis; mycelia; solid tumor.

Invasive mold infections (IMIs), such as invasive aspergillosis or mucormycosis, are life-threatening complications in severly immunocompromised individuals, such as hematologic cancer patients or transplant recipients, who represent the classical high-risk population [1–3]. However, the development of novel immunomodulatory drugs for the treatment of cancer or autoimmune disorders has expanded the spectrum of immunocompromised patients who are at risk of developing IMIs [4–8]. The diagnosis of IMI is challenging because of the nonspecificity of clinical signs and the low yield of conventional culture methods. Nonculture diagnostic tools, such as fungal biomarkers (eg, galactomannan or (1→3)-β-D-glucan) and polymerase chain reaction (PCR), are adjunctive tools for the diagnosis of invasive aspergillosis, but their sensitivity is not optimal and could be even lower among patients receiving prophylactic or empirical antifungals [9–11]. The diagnosis of mucormycosis and other rare mold infections is even more challenging because of the lack of specific fungal biomarkers [12–14]. The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) has established standard definitions to assess the presumption of IMIs with a scale of probability (possible, probable, or proven) on the basis of host, clinical, and mycological criteria [15, 16]. However, a substantial proportion of IMIs can still remain undiagnosed. The aim of this study was to assess the proportion of histopathologically proven IMIs that were not suspected by the clinicians and/or not retrospectively classified as at least possible IMI according to EORTC/MSGERC definitions at the time of biopsy/autopsy.

METHODS

This was a retrospective study conducted at Lausanne University Hospital (Switzerland), a 1500-bed hospital including an onco-hematology unit and a transplantation center. High-risk onco-hematology patients are managed according to a preemptive approach (bi-weekly serum galactomannan screening and computed tomography scan for persistent or relapsing neutropenic fever) without administration of antimold prophylaxis.

All deep tissue biopsy or autopsy reports mentioning the presence of mycelial elements were identified by keyword search (eg, "mycelia," "fungal," "*Aspergillus,*" "*Mucor,*" "hyphae") over a 10-year period (2010–2019). The biopsy/autopsy reports were checked for the presence of angio-invasion and/or tissue destruction/necrosis. Cases with histopathologic description consistent with chronic pulmonary aspergillosis or localized tracheobronchitis were excluded. The clinical history was obtained from the electronic medical records, including the following elements: underlying diseases and factors of immunosuppression, clinical signs/symptoms of infection, radiological and microbiological results, antifungal therapy, and outcome. IMIs were classified as proven, probable, possible, or "no IMI" according to the EORTC/MSGERC criteria of 2008 and the updated version of 2020 [16] by 2 investigators taking into account the clinical and microbiological data preceding the autopsy/biopsy results. Clinical suspicion of IMI according to the attending physician's appreciation was assessed at the time of histopathology sampling on the basis of the notes from the medical records and consultants' reports.

RESULTS

A total of 107 histopathology reports mentioning the presence of fungal elements were selected. Among them, 66 were

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identified (41 chronic pulmonary aspergillosis, 5 *Aspergillus* tracheobronchitis, 8 yeast infections, and 12 for lacking data or refusal of consent). Of the 41 histopathology reports of angioinvasive mold infection, 17 (41%) were autopsies, and the remaining cases were lung tissue samples obtained by open surgery (n = 14) or transbronchial/transparietal biopsy (n = 10). The characteristics of these 41 cases are described in Table 1. At the time of biopsy/autopsy, 7/41 (17%) patients had no host criteria, and 10/41 (24%) cases were not recognized as IMIs according to the updated EORTC/MSGERC definitions [16]. Using the older definitions [15] resulted in a slightly higher proportion of cases without host criteria and without IMI diagnosis (22% and 29%, respectively). All IMI cases who did not meet the EORTC/MSGERC criteria were non-neutropenic patients except 1 (ie, drug-induced neutropenia).

The notes in the medical records showed that an antimold active drug has been initiated for IMI suspicion in 21/41 (51%) cases before histopathology sampling. In 9/41 (22%) cases, IMI has been suspected by the clinicians, but antifungal therapy was not initiated because suspicion was low (n = 2), the therapeutic project was palliative (n = 2) or it was decided to perform the diagnostic biopsy before starting antifungals (n = 5). In 11/41 (27%) cases, there was no antifungal treatment and no suspicion of IMI preceding the biopsy/autopsy. The rate of unsuspected IMI was significantly higher in nonhematologic cancer patients (50% vs 12% in hematologic cancer patients; $P = .01$) and in non-neutropenic patients (45% vs 5% in neutropenic patients; $P = .005$). The analysis restricted to autopsy results showed that 9/17 (53%) IMI cases were not suspected ante mortem.

The overall characteristics of these 11 unsuspected IMI cases are shown in Table 2, and an individual description is provided in Supplementary Table 1. In 9 cases, IMI was a casual finding at autopsy. Solid tumor was the most frequent underlying condition (n = 4), followed by nonactive or occult lymphoma (n = 2) and auto-immune disorders (n = 2). Notably, 5 patients had no EORTC/MSGERC host criteria [16]. Three cases could be retrospectively classified as possible IMI, while 8 cases were considered "no IMI" according to EORTC/MSGERC criteria at the time of autopsy/biopsy. In most of these unsuspected IMI cases (7/11), the pathogenic mold could not be specified (ie, histopathological finding only).

The mortality rate was 68% (22 of 38 evaluable cases) and tended to be higher among patients for whom IMI diagnosis was not suspected (82% vs 48%; $P = .08$).

DISCUSSION

Diagnosis of IMI remains difficult. While clinicians are aware of this complication in classical high-risk populations, such as hematologic cancer patients and transplant recipients, IMI can be underdiagnosed among patients who are supposed to be at lower risk. Our analysis of 41 histopathologically proven IMI patients shows that 27% of cases were not suspected by

Table 1. Characteristics of Patients and Invasive Mold Infections

	n = 41
Demographic characteristics	
Male/female	27 (66)/14 (34)
Age, y	61 (8–83)
Main underlying diseases	
Acute leukemia[a]	16 (39)
Other hematologic cancer[b]	5 (12)
Allogeneic HSCT	4 (10)
Solid organ transplantation[c]	3 (7)
Auto-immune disorders[d]	6 (15)
Solid tumors[e]	5 (12)
Other[f]	2 (5)
Immunosuppressive conditions[g]	
Neutropenia[h]	19 (46)
Corticosteroid treatment[i]	11 (27)
Calcineurin inhibitors	6 (15)
Other immunosuppressive drugs[j]	7 (17)
Recent anticancer chemotherapy	22 (54)
Documented site of infection	
Lung only/disseminated (lung + other)[k]	32 (78)/9 (22)
Type of IMI	
Invasive aspergillosis[l]	21 (51)
Invasive mucormycosis[m]	10 (24)
Mixed invasive aspergillosis/mucormycosis[n]	2 (5)
Other invasive mold infection[o]	2 (5)
Unspecified mold infection[p]	6 (15)
EORTC/MSGERC criteria (before histopathology)[q]	
Host criteria 2008/2020	32 (78)/34 (83)
Clinical and radiological criteria 2008/2020	33 (80)/33 (80)
Mycological criteria 2008/2020	17 (41)/16 (39)
IMI 2008: probable/possible/no criteria	14 (34)/15 (37)/12 (29)
IMI 2020: probable/possible/no criteria	14 (34)/17 (41)/10 (24)
Clinical appreciation (before histopathology)	
Clinical suspicion of IMI	30 (73)
Mold-active antifungal therapy initiated[r]	21 (51)

Numbers are total No. (%) or median (range).

Abbreviations: EORTC/MSGERC, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; HSCT, hematopoietic stem cell transplantation; IMI, invasive mold infection.

[a]Acute myeloid leukemia (12), acute lymphoid leukemia (4).

[b]Lymphoma (2), chronic myeloid leukemia (1), multiple myeloma (1), myelodysplastic syndrome (1).

[c]Lung transplantation (2), heart transplantation (1).

[d]Hemophagocytic syndrome (2), disseminated lupus (1), rheumatoid arthritis (1), myasthenia gravis (1), idiopathic pulmonary fibrosis (1).

[e]Primary tumor site: cerebral (2), lung (1), thyroid (1), multimetastatic cancer of unknown origin (1).

[f]Multiple pulmonary infarcts (1), drug-induced neutropenia (1).

[g]More than 1 possible.

[h]Neutrophils <500/mm^3 for >10 days in the past 60 days.

[i]≥0.3 mg/kg prednisone-equivalent for ≥3 weeks in the past 60 days.

[j]Mycophenolate mofetil (3), tyrosine kinase inhibitors (2), anti–tumor necrosis factor (TNF) alpha (1), pomalidomide (1).

[k]More than 1 possible: brain (3), heart (3), thyroid (3), spleen (2), liver (2), intestine (1), kidney (1), skin (1).

[l]*A. fumigatus* (18), *A. flavus* (2), mixed *A. fumigatus* and *A. flavus* (1).

[m]*Rhizomucor* spp. (5), *Rhizopus* spp. (1), *Lichtheimia* spp. (1), mixed *Rhizomucor* spp. and *Rhizopus* spp. (1), unspecified "*Mucorales*" (large nonseptate hyphae at histopathology without microbiological documentation) (2).

[n]*A. fumigatus* and *Lichtheimia* spp., presumed *Aspergillus* spp. (positive GM only), and *Rhizomucor* spp.

[o]*Conidiobolus* spp., *Hormographiella aspergillata*.

[p]Septate branched hyphae at histopathology without microbiological documentation.

[q]According to EORTC/MSGERC criteria of 2008 and 2020 [15, 16].

[r]Amphotericin B formulations or mold-active triazoles (voriconazole, posaconazole, isavuconazole).

Table 2. Characteristics of the Histopathologically Proven IMI Cases That Were not Suspected Before Biopsy/Autopsy

	n = 11
Underlying conditions	
Solid-tumor[a]	4 (36)
Hematologic cancer	3 (27)
Lymphoma[b]	2
Allogeneic HSCT	1
Auto-immune disorders[c]	2 (18)
Solid-organ transplantation (heart)	1 (9)
Drug-induced neutropenia	1 (9)
Immunosuppressive conditions[d]	
Neutropenia > 10 days[e]	1 (9)
Neutropenia < 10 days[e]	1 (9)
Long-course corticosteroid treatment[f]	2 (18)
Short-course corticosteroid treatment[g]	2 (18)
Other immunosuppressive drugs[h]	3 (27)
Recent anti-cancer chemotherapy	2 (18)
None	3 (27)
EORTC/MSGERC criteria (before histopathology)[i]	
Host criteria	6 (55)
Clinical and radiological criteria	4 (36)
Mycological criteria	1 (9)[j]
IMI: possible/no criteria	3 (27) / 8 (73)
Mold pathogen identified on histopathology sample	
Aspergillus fumigatus	3 (27)
Rhizopus spp.	1 (9)
"*Aspergillus*-like" hyphae[k]	6 (55)
"*Mucorales*-like" hyphae[l]	1 (9)
Causes of death	**n = 9**
Attributed to IMI[m]	8 (89)
Other cause[n]	1 (11)

Numbers are N total (percentage).

IMI: invasive mold infections, HSCT: hematopoietic stem cell transplantation, EORTC/MSGERC: European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium.

[a]Primary tumor site: cerebral (2), lung (1), multimetastatic cancer of unknown origin discovered at autopsy (1).

[b]Lymphoma in remission (1), casual autopsy finding of low-grade lymphoma (1).

[c]Rheumatoid arthritis (1), idiopathic pulmonary fibrosis (1).

[d]More than one possible.

[e]Neutropenia defined as neutrophil count < 500/mm^3 in the past 60 days.

[f]≥0.3 mg/kg prednisone-equivalent for ≥3 weeks in the past 60 days.

[g]Any corticosteroid therapy during the past 10 days not fulfilling the definitions of long-course corticosteroid therapy (above).

[h]Calcineurin inhibitor (1), mycophenolate mofetil (1), anti-tumor necrosis factor alpha (1).

[i]According to EORTC/MSGERC criteria of 2008 and 2020 [15, 16]. Of note, assessment according to the 2008 and 2020 criteria was concordant in all cases.

[j]One positive culture for a single colony of "not yet identified" mold in a bronchial aspirate at day -2 before death (considered as contaminant or ignored by the clinician).

[k]thin septate hyphae evoking *Aspergillus*.

[l]large non-septate hyphae evoking *Mucorales*.

[m]At least partially considered as a cause of death based on autopsy report.

[n]Suicide (IMI was a casual finding at autopsy).

clinicians, and this proportion was as high as 50% among nonhematologic cancer patients. The mortality rate was higher among these unsuspected IMI cases. Indeed, most of them were casual autopsy findings. Interestingly, solid tumors and lymphoma were the predominant underlying conditions, including cancers that were occult or considered in remission before autopsy. Treatment with corticosteroids (including short-course treatments) or other immunomodulators was also relatively frequent among these missed cases.

Studies comparing clinical diagnosis with the gold standard of histopathologically proven IMI are scarce. Some studies have assessed the prevalence of IMI in autopsy reports [17–20]. Analyses limited to onco-hematological patients showed a decreased incidence of IMI autopsy findings over the last decades, which suggests a better recognition of the disease in this population [17, 20]. However, other studies emphasized the substantial proportion of IMI autopsy findings among nonhematologic cancer patients [19, 21]. Tejerina et al. observed that 60% of invasive aspergillosis at intensive care units (ICUs) was not identified ante mortem [21]. The ICU population represents a particular setting for which the EORTC/MSGERC criteria are not appropriate because host criteria are often absent. Other adapted criteria, such as those of Blot et al. or those specific to influenza or coronavirus disease 2019 should be applied in this setting [22–24]. Of note, only 1 ICU patient in our cohort did not match EORTC/MSGERC criteria but fulfilled the Blot criteria of putative IA ante mortem.

IMI definitions have been proposed by the EORTC/MSGERC experts panel and have been updated over time [15, 16, 25]. These criteria were initially intended for clinical trials but could serve as an adjunctive tool in clinical practice. In the present case series, we found that the criteria of probable/possible IMI had a similar sensitivity compared with clinical appreciation for the early identification of subsequently histopathologically proven IMI (71%, 76%, and 73% for the 2008 and 2020 definitions and the clinical assessment, respectively), which may suggest that clinicians use these definitions in routine practice, in particular among high-risk neutropenic and/or hematologic cancer patients. Indeed, most of the misclassified IMI cases were non-neutropenic patients. The performance of the EORTC/MSGERC criteria is notoriously lower in this population, as radiological signs are less specific and serum galactomannan is less sensitive [14, 26, 27].

The most important updates of the 2020 definitions consist of the expanded spectrum of host criteria and the inclusion of PCR as a mycological criterion [16]. Indeed, 83% of the patients in our study met the 2020 host criteria, compared with 78% for the 2008 criteria. However, the more stringent 2020 criteria about the galactomannan cutoffs may have counterbalanced the gain of PCR with a similar proportion of probable IMI cases (34%) using both definitions.

Besides the inherent limitations related to the small sample size and monocentric design, it should be mentioned that retrospective interpretation of pathology reports may be hampered by incomplete description. Moreover, different histologic patterns of IMI without clear evidence of angio-invasion may be observed in non-neutropenic patients [28]. Doubtful IMI cases were excluded from our analysis, which may suggest that the proportion of missed IMI cases could even be higher.

In conclusion, this study shows that up to one-quarter of histopathologically documented IMIs are missed by clinicians. Particular attention should be paid to patients usually classified as low risk (eg, solid tumors or lymphomas) or those on immunosuppressive therapies for auto-immune disorders.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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