Invasive Fungal Infections at Presentation of Untreated Hematologic Malignancies: Rare and Elusive

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Invasive fungal infections (IFIs) are a feared complication of hematologic malignancy (HM) treatment. Infrequently, the diagnosis of a new IFI contemporaneously with a new untreated HM has been sporadically described in case reports. We performed a comprehensive search of published literature and reviewed cases describing this synchronous disease phenomenon.

Keywords.   hematologic malignancy; invasive fungal infections; molds; yeasts.

Despite progress, invasive fungal infections (IFIs) are a feared complication of hematologic malignancy (HM) treatment [1–4]. Active HM, prolonged cytopenias after cytotoxic high-dose chemotherapy, medical comorbidities, corticosteroids, and other immunosuppressive agents are considered classic risk factors of IFIs [1, 5–7]. Although functional or numerical defects in innate and adaptive immune effector cells are not uncommon in the setting of a new HM, IFIs occurring at the time of HM diagnosis (synchronous IFI) are rare, at an incidence between 3% and 4%, compared with the relative incidence of bacterial infections [7]. We reviewed the scarce published literature on concomitant diagnoses of a new HM contemporaneously with an IFI to better describe the occurrence of this synchronous disease phenomenon.

METHODS

We queried Medline (Ovid), Embase (Ovid), Scopus, and Google Scholar using controlled vocabulary and natural language terms for fungi, fungal infections, leukemia, lymphoma,

and other HMs. Abstracts were manually screened to ensure concurrent diagnosis timelines, excluding IFIs that were diagnosed after chemotherapy. The IFIs were defined in accordance with the revised 2019 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [8]. We only included publications that provided substantial case information and illustrated synchronous IFI and HM diagnoses. We define synchronous diagnosis as a new HM occurring within 2 months of a new IFI. If the signs and symptoms of the new HM and IFI were discordant by more than 2 months, the diagnoses were not considered synchronous. We excluded patients with a history of other active non-HM undergoing treatment, human immunodeficiency virus, human T-lymphotropic virus, and other immunocompromising conditions (eg, hypogammaglobulinemia, chronic corticosteroid use, and transplantation). We only reviewed case reports published in English.

RESULTS

Patient Characteristics

We identified 21 cases (Supplementary Table 1) (ref. S1–S21) over 43 years. The average age was 46 years (range: 16 months to 82 years). The male to female ratio was 2:1. Non-Hodgkin lymphoma (NHL) (11 of 21, 52%) was the predominant HM diagnosed, followed by leukemia (7 of 21, 33%) and Hodgkin lymphoma (HL) (2 of 21, 10%) (Table 1). Limited information was available on patients' prediagnoses environmental exposures, comorbidities, and habits contributing to the risk of developing an IFI. The most common presenting symptoms included fever in 14 patients (67%), weight loss in 7 patients (33%), and cough or shortness of breath in 6 patients (29%) (Table 1). Gastrointestinal symptoms were common, including abdominal pain (n = 2), ascites (n = 1), hepatosplenomegaly (n = 2), and jaundice (n = 1). Three cases had prominent skin lesions (*Fusarium* = 2, *Sporothrix schenkii* = 1) (Supplementary Table 1).

Laboratory Values

Approximately half of the patients (7 of 15, 47%) with reported white blood cell counts (WBCs) had severe neutropenia with an absolute neutrophil count <500 cells/mm^3, and 3 patients (20%) were noted to have leukopenia (WBC <4000 cells/mm^3) (Supplementary Table 1). Five of the patients presenting with severe neutropenia (B-cell acute lymphocytic leukemia [ALL] = 2, hairy cell leukemia [HCL] = 2, and acute myeloid leukemia [AML] = 1) had mold pathogens (*Aspergillus* = 2, *Fusarium* = 2, *Mucor* = 1). Among 5 patients presenting with normal or high WBC, NHL was the most common malignancy (n = 4), and

Table 1.   Synchronous IFI and HM Case Characteristics

Case Characteristics	No. of Cases (%)
Gender	
Male/female	14/7
Age (Years)	
0–20	4 (19)
21–60	12 (57)
>60	5 (24)
Presenting Signs and Symptoms	
Fever	14 (67)
Weight loss/anorexia	7 (33.3)
Cough/shortness of breath	6 (28.5)
Lymphadenopathy	4 (19)
Gastrointestinal	4 (19)
Skin lesions[a]	3 (14.3)
Eye/vision changes	2 (9.5)
Laboratory	
Neutropenia (neutrophils <500 cells/mm^3)	7 (33.3)
Normal or high	5 (24)
Leukopenia (WBC <4000 cells/mm^3)	3 (14.3)
N/A	6 (28.6)
HM Diagnosed[b]	
Non-Hodgkin Lymphoma	11 (52.4)
Leukemia	7 (33.3)
Hodgkin Lymphoma	2 (9.5)
Other	1 (4.7)
Causative Fungal Pathogens	
Mold	
Aspergillus spp	8 (38)
Fusarium spp	3 (14.3)
Mucorales	2 (9.5)
Non-Molds	
Histoplasma spp	4 (19)
Pneumocystis carinii	1 (4.7)
Candida sp	1 (4.7)
Sporothrix schenkii	1 (4.7)
Cryptococcus neoformans	1 (4.7)
Reported Outcomes	
Died during hospitalization	9 (43)
Died before 12-month follow-up	2 (9.5)
Survived to end of HM treatment	3 (14.3)
Alive at 3-month follow-up	1 (4.7)
Alive at 6-month follow-up	1 (4.7)
Alive at 2-year follow-up	1 (4.7)
N/A	4 (19)

Abbreviations: HM, hematologic malignancy; IFI, invasive fungal infection; mm^3, cubic millimeter; N/A, not available; spp, species; WBC, white blood cells.

[a]Skin lesions described included a nodular plaque that evolved into a painful crusted lesion of right leg, ulcerated lesion with black eschar of left elbow with multiple erythematous nodular lesions over body, and multiple purulent eruptions of left thigh and calf.

[b]Hematologic malignancies were categorized broadly as either HL, NLH, or leukemia based on case diagnoses.

80% (4 of 5) of IFIs were caused by molds (*Aspergillus* = 3, Zygomycetes = 1), suggesting a state of functional neutropenia.

Synchronous Invasive Fungal Infections

Molds represented the majority (n = 13) of IFIs diagnosed concomitantly with an HM (Table 1). *Aspergillus* spp were the most common IFI (n = 8), followed by *Fusarium* spp (n = 3), and Mucorales (n = 2). Of the non-mold IFIs, more than half (5 of 8, 63%) were dimorphic fungi (*Histoplasma* = 4, *Sporothrix schenkii* = 1). We identified 1 case each of *Candida* sp (case 10), *Cryptococcus* (case 19), and *Pneumocystis* (case 8) IFI (Supplementary Table 1). Mold IFIs coupled with NHL were the most commonly reported (10 of 21, 47.6%) synchronous diagnoses, followed by HCL and HL diagnosed with dimorphic fungi (5 of 21, 23.8%). The majority (3 of 4) of AML and B-cell ALL patients were also diagnosed contemporaneously with mold IFIs (*Mucor* = 1, *Aspergillus flavus* = 1, *Fusarium solani* = 1). One report of extensive esophageal candidiasis was diagnosed concomitantly with AML (case 10) (Supplementary Table 1).

Time to Diagnosis

Fourteen case reports included sufficient information on the time between the first diagnosis of either IFI or HM and the second diagnosis (Table 2). Seven patients in this group had the diagnosis of both a new HM and IFI made simultaneously on the same biopsy specimen. Excluding the 7 simultaneous cases, IFIs were more likely to be diagnosed first (5 of 7, 71.4%) followed by the HMs after an average of 19.3 days (range, 7–42 days) (Table 2). Molds were the most common initial IFI diagnosed (*Aspergillus* = 2, *Fusarium* = 1).

Invasive Fungal Infections Mimicking Malignancy

Eight patients (38%) featured signs and symptoms from their IFI that mimicked the presentation of malignancy (pulmonary nodules = 3, mass = 3, persistent fevers = 2), and *Histoplasma* (n = 3) and *Aspergillus* (n = 3) were the most common IFIs mimicking a HM. A patient diagnosed with NHL underwent biopsy of pulmonary nodules for staging purposes and was found to have synchronous *Cryptococcus*, delaying induction chemotherapy to address the IFI (case 19) (Supplementary Table 1) [S19]. Weeks et al [S21] described a patient who underwent a bone marrow biopsy for persistent fevers and was discovered to have HCL; however, the fevers continued despite receiving chemotherapy (case 21) (Supplementary Table 1). Eventually, the bone marrow fungal culture grew *Histoplasma capsulatum*, and fevers abated with antifungals [S21]. Mandegari et al [S13] described a febrile adolescent who was diagnosed with central nervous system ALL. Three days after starting chemotherapy and steroids, he developed an obstructive nasal mass from invasive *Mucor* sinusitis (case 13) (Supplementary Table 1). All 3 patients who presented initially with a mass lesion (lung, eye, nasal; 1 each) were presumed to have malignant processes, but histopathology revealed synchronous IFIs (*Histoplasma* = 1, *Aspergillus* = 1, Zygomycetes = 1) along with the HMs on histopathology. In each of these cases, a combination of antifungals and chemotherapy or radiation was started (cases 5, 6, and 9) (Supplementary Table 1) [S5, S6, S9].

Table 2. Intervals From First Diagnosis to Second Diagnosis

Case No.	First Diagnosis[a,b]	Interval Days From First Diagnosis to Second Diagnosis[c]	Second Diagnosis[a,b]
1	Sclerosing HL	N/A[d]	*Histoplasma*
2	HCL	Sync	*Histoplasma capsulatum*
3	*Aspergillus fumigatus*	N/A[d]	Peripheral T-cell NHL
4	AML due to MDS	N/A[d]	*Fusarium solani*
5	Primary pulmonary HL	Sync	*Histoplasma*
6	Low-grade B-cell lymphoma	Sync	*Aspergillus*
7	Small and large-cell NHL	Sync	*Aspergillus*
8	*Pneumocystis carinii*	7[d]	Histiocytic medullary reticulosis
9	T-cell NHL, large cell type	Sync	Zygomycetes
10	Esophageal Candidiasis	21	AML
11	*Sporothrix schenkii*	Sync[d]	HCL
12	High-grade T-cell lymphoma	N/A[d]	*A fumigatus*
13	B-cell ALL	11[d]	*Mucor* sp
14	Bone primary DLBCL	N/A	*F solani*
15	*Aspergillus flavus*	N/A[d]	Immunoblastic NHL
16	DLBCL	Sync	*Aspergillus* sp
17	*A flavus*	42	B-cell ALL
18	*Fusarium* sp	7[d]	T-cell lymphoma
19	Lymphocytic NHL	N/A[d]	*Cryptococcus neoformans*
20	*A fumigatus*	17[d]	DLBCL
21	HCL	30	*H capsulatum*

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; HCL, hairy cell leukemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndromes; N/A, duration between first and second diagnoses was not available in the case report; NHL, non-Hodgkin's lymphoma; sp, species; Sync, both IFI and hematologic malignancy diagnoses made simultaneously on same biopsy specimen.

[a]Hematologic malignancy classification/diagnosis as documented in case report.

[b]Taxonomic rank as documented (may include outdated names) or extrapolated from disease reported in case (eg, histoplasmosis = *Histoplasma*) and Latin genus and species names appear italicized.

[c]Time reported in days unless otherwise specified.

[d]Diagnosis 1 and 2 presumably made during same hospitalization based on available information in case report.

Outcomes

Outcomes were available for 17 patients. More than half (9 of 17, 53%) of the patients died during that initial hospitalization for their IFI and HM, and 3 of these patients died during the first week. Six patients survived to follow-up, half of whom survived to the end of chemotherapy (Table 1). Sufficient data were not available to assess the impact of IFI diagnoses on subsequent chemotherapy treatment and patient outcomes.

DISCUSSION

We review, for the first time, reported synchronous IFIs and newly diagnosed untreated HM, a rare co-occurrence, although underdiagnosis and underreporting are likely. An impaired macrophage-monocyte axis and neutropenia are the primary immune system defects that predispose patients to IFIs [9]. Neutrophil function, as a principal controller of fungal infections, is essential for provoking an acute inflammatory response and subsequent removal of fungal pathogens [9]. Patients with HMs can have neutropenia at presentation as a consequence of bone marrow infiltration by malignant cells and qualitative dysfunction of the remaining neutrophils causing reduced fungicidal activity [9, 10]. Consequently, a significant number of patients may present with a synchronous IFI at the time of their HM diagnosis but are underdiagnosed and underreported. No baseline study has been performed to assess the incidence of this synchronous process fully. In a single-center study, Bitterman et al [11] found that 5% (15 of 295) of high-risk HM patients were diagnosed with invasive pulmonary aspergillosis (IPA) on admission baseline chest computed tomography (CT), with an additional 9.8% diagnosed later during hospitalization. These 15 patients were older and more likely to have a new HM (11 of 15) compared with those who developed IPA at a later point [11]. In a subgroup analysis of newly diagnosed HM (AML) patients, 10% (11 of 107) had IPA identified on baseline chest CT and positive *Aspergillus* galactomannan (GM) in bronchoalveolar lavage (BAL) fluid [11, 12]. Most of these patients (8 of 11) were not neutropenic and (6 of 11) lacked symptoms [13]. Due to a lack of patient-level information, these 11 patients were not included in our review. In a web-based survey study, authors found a 9% IPA rate detected by baseline chest CT in high-risk HM patients compared with a 7% median IPA rate detected in high-risk HM patients at centers that did not use baseline chest CT [13]. Data for rates of IPA on baseline CT for newly diagnosed AML were not available.

CONCLUSIONS

Our review was limited by small numbers and case reports and subject to publication bias based on the severity of cases, diagnostic challenges, uncommon clinical circumstances, and unusual fungal pathogens. In addition, all reports were based on either direct observation of fungal elements in tissue or positive culture, a less common scenario of diagnosing some IFI, especially invasive aspergillosis in contemporary cohorts. It is unclear whether the routine use of baseline chest CT, coupled with serum or BAL GM, would demonstrate more synchronous IFIs, at least in patients with AML [11]. Multicenter studies are needed to validate the findings of Bitterman et al [11], to assess the true incidence of synchronous IFIs with new HM diagnoses, and to determine the impact on HM treatment outcomes. Our review highlights the need for clinicians to have a high index of suspicion for concomitant IFI at the time of a new, untreated HM diagnosis. Decisions regarding the timing of HM and IFI treatments and long-term management should be made in a multidisciplinary fashion between Hematologists and Infectious Diseases specialists.

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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