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BRIEF REPORT

Insect Bite–Associated Invasive Fungal Infections

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Insect bites are rarely reported to result in myocutaneous mycoses. We reviewed the literature and report 22 cases. Molds were the most common pathogens (15), especially *Mucorales* (9). Infections were typically misdiagnosed, and 68% had necrotizing features, often requiring amputation or extensive surgery. Both immunocompetent and immunosuppressed patients were affected.

Keywords. insects; molds; yeast; cutaneous infections; mucormycosis.

Myocutaneous invasive fungal infections are typically the consequence of penetrating trauma [1–3]. The contribution of direct inoculation of a fungus to the skin through an insect bite is considered rare and has been the subject of sporadic case reports. For example, insect or spider bites have been implicated in only 3% of cases of cutaneous mucormycosis [4] and in only 2/31 cases of cutaneous sporotrichosis [5].

To that end, we performed a comprehensive search of the literature, carried out by a medical librarian (R.S.H.). Medline (Ovid), Embase (Ovid), and Google Scholar were queried, with no date restrictions, utilizing both controlled vocabulary and natural language terms for fungi (specifically *Mucorales* or zygomycosis or zygomycetes or mucormycosis or *Fusarium* or sporothrichosis or *Sporothrix* or *Coccidioides* or coccidioidomycosis or mycetoma or *Candida* or *Aspergillus* or aspergillosis or *Scedosporium* or *Alternaria* or *Acremonium* or phaeohyphomycosis or chromoblastomycosis), insects, spiders, scorpions, bites, stings, mosquitoes, midges, sandflies, bed bugs, head lice, fleas, and necrosis. We included only cases that gave information about patient demographics, clinical presentation, fungal pathogen, diagnosis, and treatment. We reviewed only reports in English. We excluded cases of fungal allergic dermatitis and cases of fungal colonization in skin lesions following an arthropod bite.

We identified only 22 insect bite–associated cutaneous invasive fungal infections (IBA-IFIs) (Table 1; Supplementary Data, refs. 1–22), all subjects of case reports. Twelve of 22 infections (55%) were in immunocompetent patients, whereas the remaining patients had various immunosuppressive conditions (cancer in 4, transplant in 3, and HIV, HTLV infection, and idiopathic thrombocytopenic purpura [ITP] on corticosteroids/azathioprine in 1 each). Four patients had underlying diabetes mellitus. IBA-IFI cases were reported in both temperate and tropical areas. In the 12 cases for whom such information was available, 11/12 were insects whose bite is associated with toxin release, specifically spiders (n = 8), scorpions (n = 2), and bees (n = 1). Molds (*Mucorales* in 8, *Aspergillus* in 4, and *Fusarium, Purpureocillium,* and *Exophiala* in 1 each) were the pathogens in the majority (15/22, 68%) of cases. Four of the 8 *Mucorales* were uncommon species (*Apophysomycetes elegans* and *Saksenae vasiformis*, 2 cases each). Two cases were mixed fungal infections (*Aspergillus flavus* and *Fusarium proliferatum*, *Aspergillus flavus* and *Candida* spp., 1 each). In the remaining IBA-IFI cases, a variety of yeasts and dimorphic fungi (*Sporothrix* in 2, agents of chromoblastomycosis in 2, *Coccidioides* and *Cryptococcus* in 1 each) were the culprits. Five of 22 (23%) infections were mixed bacterial and fungal infections. A variety of bacteria were seen in these mixed infections (*N. asteroides*, *S. epidermis*, *Klebsiella* spp., and *Bacillus* spp.). IBA-IFIs occurred in exposed areas of the body, typically the arms (n = 8), face (n = 3), eyes (n = 3), and legs (n = 3).

Misdiagnosis at presentation was universal (19/19 cases with information), as 12/22 (54%) patients were initially diagnosed with bacterial cellulitis and given antibacterials. Other initial diagnostic impressions were cutaneous leishmaniasis (n = 2), dermatophytosis (n = 2), necrosis from the spider bite, bee sting–induced keratouveitis, loxoscelism, necrotizing arachnidism, and allergic dermatitis (1 case each). A variety of clinical evolutions were seen, from chronic persisting plaques to fulminant fasciitis (cases 2, 13, 22 in Table 1). Causes of fasciitis were due to *Cryptococcus gattii*, a mixed infection by *Aspergillus flavus* and *Fusarium proliferatum*, and *Saksenea vasiformis* (1 case each). Fifteen of 22 (68%) of IBA-IFI cases had necrotic features. Particularly, 13 of the 15 (87%) IBA-IFIs due to molds had necrotizing features (eg, necrotic ulcers, fistulas, necrotic nodules, eschars). Despite the local destructive features of these infections, dissemination appeared to be a rare event (1

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Table 1. Clinical Features of 22 Patients With Insect-Associated Myocutaneous Invasive Fungal Infections

Article[a] Author, Year/Country	Patient Age and Sex, Underlying Disease(s)	Location of Insect Bite	Insect	Fungus	Clinical Manifestation	Initial Diagnosis/ Delayed Diagnosis	Medical Treatment	Surgical Treatment	Outcome
1. Lober, 1980 USA	44 M, immunocompetent	Central abdomen	NS	*Sporothrix schenckii*	Multiple nodular ulcerative lesions, cutaneous fistulas	Leishmaniasis	Oral potassium iodide	None	Resolved
2. Barrios, 1990 USA	5 F, ALL, neutropenia	Thenar eminence	Brown recluse spider	*Aspergillus flavus, Fusarium proliferatum*	Gangrenous changes, progressive nodules	Bacterial cellulitis	AMB, 5-FC, rifampin, WBC transfusions	Thumb and arm amputation	Survived, WBC recovery
3. Clark, 1990 USA	31 M, HTLV, DKA	Arm	Spider	*Rhizopus arrhizus*	Necrotic pustules, culture also grew *Klebsiella* and *Bacillus* spp.	Bacterial cellulitis	AMB, cefuroxime	Repeated debridements	Survived, WBC recovery
4.Prevoo, 1991 Netherlands	10 F, immunocompetent	Lateral eyebrow	NS	*Mucor* spp.	Slowly expanding plaque	Dermatophytosis	AMB, potassium iodide	None	Resolved
5.Weinberg, 1993 USA	59 M, immunocompetent	Prescapular area	Brown recluse spider	*Apophysomyces elegans*	Tender eschar	Brown recluse spider bite, bacterial cellulitis	AMB	Resection, skin graft	Flail shoulder, resolved
6.Adam, 1994 USA	43 M, cardiac transplant recipient on azathiprine + prednisone	Calf	Spider	*Rhizopus* spp.	Slowly progressing chronic ulcer	N/R	AMB,ketoconazole	None	Died within 7 d
7.Hicks, 1995 USA	31 M, Hodgkin's disease, s/p transplant, pancytopenia	Lateral neck	NS	*Rhizopus* spp.	Necrotizing neck cellulitis	Bacterial cellulitis	AMB, rifampin	Wide debridement	Resolved
8.Sauterteig, 1998 Venezuela	59 F, breast cancer	Upper arm	NS	Chromoblastomycosis	Nodular dark pink lesion, fistula	Cutaneous leishmaniasis	Not stated	Extirpation of lesion	Resolved
9.Moaven, 1999 Australia	31 F, immunocompetent	Wrist	Large hairy spider	*Sporothrix schenckii*	Rapidly evolving nodular ulcer, lymphangitis	Necrotizing arachnidism	Itraconazole	None	Resolved
10.Bauza, 2005 Spain	73 M, liver transplant recipient, DM	Arm	NS	*Cryptococcus neoformans* serotype D	Edema/suppuration	Bacterial cellulitis	AMB, fluconazole	Debridement, reconstruction, skin graft	Resolved
11.Takahara, 2005 Japan	85 F, ITP on azathioprine + prednisone	Middle finger, hand, arm	NS	*Exophiala spinifera*	Multiple nodules/ abscesses, lymphocutaneous nocardiosis	N/R	Itraconazole	None	Resolved
12.Lechevalier, 2008 France	14 M, immunocompetent	Calf	Scorpion	*Saksenaea vasiformis*	Cellulitis with necrotic eschar, fever	Bacterial cellulitis	AMB	Wide debridement, skin graft	Resolved
13.Rath, 2009 India	55 M, immunocompetent	N/R	NS	*Candida* spp., *Aspergillus flavus*	Periorbital necrotizing fasciitis	Bacterial orbital cellulitis	Fluconazole	Debridement, skin graft	Resolved
14.Saravia-Flores, 2009 Guatemala	30 F, immunocompetent	Medial thigh	Loxosceles spider	*Apophysomyces elegans*	Cellulitis with blisters, necrosis, disseminated sepsis	Bacterial cellulitis	AMB	Repeated debridements, limb amputation	Died after surgery

Table 1. Continued

Article[a] Author, Year/Country	Patient Age and Sex, Underlying Disease(s)	Location of Insect Bite	Insect	Fungus	Clinical Manifestation	Initial Diagnosis/ Delayed Diagnosis	Medical Treatment	Surgical Treatment	Outcome
15. Pourahmad, 2012 Iran	55 F, immunocompetent	Flank	Scorpion	Mucorales (NS)	Progressive extensive cellulitis, necrotic eschar	Bacterial cellulitis	AMB	Wide excision, reconstruction	Resolved
16. Ho, 2015 Singapore	73 M, DM	Hand	NS	*Cryptococcus gattii*	Necrotizing fasciitis	Bacterial cellulitis	AMB, 5-FC	Wide debridement, skin graft	Resolved
17. Thompson, 2015 Australia	72 W, immunocompetent	Hand	Spider	*Purpureocillium lilacinum*	Tender erythematous plaque	Allergic dermatitis	No	Repeated debridements	Resolved
18. Lee, 2016 Taiwan	61 M, immunocompetent	Eye	NS	*Aspergillus flavus*	Progressive keratitis, blepharitis	Bacterial keratitis	Topical natamycin	None	Resolved
19. Chen, 2016 China	42 M, immunocompetent	Ear	Dog flea	*Fonsecaea nubica*	Slowly progessing plaque	Bacterial cellulitis, dermatophytic infection	Itraconazole, terbinafine	None	Resolved
20. Fernandez, 2017 Mexico	47 M, HIV	Cheek	NS	*Cocciodioides posadasii*	Pruritic nodule, fever, malaise	N/R	AMB, itraconazole	None	Resolved
21. Dogra, 2018 India	25 M, immunocompetent	Eye	Honey bee	*Aspergillus fumigatus*	Necrotizing scleritis	Bee-sting induced toxic keratosclerouveitis	Itraconazole, topical AMB, intravitreal AMB + dexamethasone	Pars plana lensectomy and vitrectomy	Poor visual outcome
22. Tormos, 2018 Spain	71 M, colon adenocarcinoma, DM	Forearm	Loxosceles laeta spider	*Saksenaea vasiformis*	Rapidly evolving necrotic eschar, compartment syndrome	Cutaneous loxoscelism	AMB, anidulafungin	Fasciotomy, amputation of right arm	Resolved

Abbreviations: 5-FC, 5-flucytosine; ALL, acute lymphocytic leukemia; AMB, amphotericin B; DKA, diabetic ketoacidosis; DM, diabetes mellitus; F, female; HTLV, human lymphotropic virus; ITP, idiopathic thrombocytopenic purpura; M, male; N/R, not reported; NS, nonspecified; WBC, white blood cell.

[a]Arranged chronologically.

case). Diagnosis was difficult and was based on histopathology (n = 2), culture (n = 2), or both (n = 18). The typical delay from the onset of infection to diagnosis was 12 days (median). Although the fatality rate was only 9% (2/22 patients), morbidity was high. Fourteen patients had extensive debridement (often repeated debridements), and 3 had amputations. A variety of antifungals were used in conjunction with surgery. The 2 cases of eye IBA-IFIs had poor visual outcomes. The heterogeneity of treatment scenarios precluded conclusions regarding optimal strategies for management.

The exact incidence, prevalence, and epidemiology of IBA-IFIs are unknown, as the reports in the literature are subject to reporting biases of severe or recalcitrant cases, and these infections are in all likelihood under-reported. Specifically, it is unclear how many patients with an IBA-IFI had a self-limiting presentation and never sought medical attention. In addition, it is possible that most published information described in this review is biased toward case reports detailing atypical fungal organisms.

The pathogenesis of insect-associated infections, either bacterial or fungal, is unclear, as these infections are considered rare [6]. Most of the sparse literature describes bacterial superinfections, and there is no dedicated study of IBA-IFIs. The sequence of events leading to a cutaneous fungal infection following an insect bite is unknown. The common denominator for most of the cases where information about the offending insect was provided was that invasive fungal infections followed an insect whose bite is associated with toxin release. It is conceivable that the local effect of the toxin contained in the insect bites could play a role by promoting tissue necrosis and allowing fungi inoculated to the skin and/or subcutaneous tissues to invade. Tissue necrosis and myoglobulin access following muscle lysis serving as growth medium for fungi has been implicated in severe necrotizing cutaneous mucormycosis after severe trauma [7]. The local edema in the insect bite site could impair local lymphatic drainage and the access of immune cells to the site of fungal inoculation. However, other mechanisms could be operative. Specifically, most bites by arthropods such as mosquitoes, sandflies, bed bugs, head lice, midges, or fleas induce pruritic hypersensitive skin reactions. Excoriation or erosion of the skin following scratching could lead to superinfections, mostly bacterial. However, fungal skin superinfection by ubiquitously environmentally present fungi, with or without a bacterial coinfection (of note, 23 of the cases in our series were mixed bacterial and fungal infections), could also theoretically occur. Thus, as the inciting insect was not tested for the causative pathogen in all of these reports, the exact mechanism of IBA-IFIs remains speculative.

Various fungi are part of the insect mycobiome [8] and bodies of insects [9], although there are no systematic field studies. As insects are occasionally attracted by organic waste [10], contamination of insects by a variety of fungi is possible, and this could explain the frequent coinfection with bacteria. Interestingly, in 4 of the 8 reported *Mucorales* infections for which speciation was available, unusual *Mucoromycetes* such as non-*Rhizopus, -Mucor,* and *-Lichtheimia* species were the causes of infection (Table 1). These unusual *Mucorales* account for fewer than 1%–5% of reported cases of mucormycosis [11], and our data add to the emerging concept that there are distinct ecological niches for these rare human fungal pathogens.

In conclusion, in the present review, we aimed to comprehensively describe the range of IBA-IFIs, a subject of isolated case reports so far. Our data point to the need for an increased index of suspicion for these uncommon but potentially devastating infections. The clinician should elicit a careful history of prior insect bites in the affected patient, whether immunocompetent or immunocompromised, and needs to suspect fungal etiology in cases of recalcitrant cellulitis, especially if clinical features of necrosis and fistulization are seen. Aggressive efforts to establish a concrete diagnosis in cases of progressive cellulitis/fasciitis are paramount in an effort to decrease disfigurement and long-term morbidity.

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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