REVIEW ARTICLE
J Mycol Infect 2024; 29(4): 175-180
pISSN:3058-423X, eISSN:3058-4302
https://dx.doi.org/10.17966/JMI.2024.29.4.175

JMI

Cutaneous Infections of the Patients with Malignancy

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Cutaneous infections are a significant concern in patients with malignancies, due to immunocompromised from both the underlying disease and its treatment. This review aims to explore the etiology, pathogenesis, and clinical management challenges of cutaneous infections in cancer patients, focusing on viral, bacterial, and fungal pathogens. Early recognition and accurate diagnosis are crucial in managing these infections. Treatment typically involves targeted antimicrobial therapies, with surgical intervention deemed necessary in severe cases.

Key Words: Chemotherapy, Cutaneous infection, Immunocompromised host, Malignancy

INTRODUCTION

Cancer continues to be a major global health challenge, with both its incidence rates and burden steadily increasing. In 2019 alone, an estimated 23.6 million new cancer cases and 10 million cancer-related deaths occurred worldwide[1], marking a substantial increase from 2010, with new cases rising by 26.3% and deaths by 20.9% over the decade. The global burden of cancer, measured in disability-adjusted life years, also reached 250 million in 2019, underscoring the need for enhanced prevention and treatment strategies. The impact of cancer varies across different sociodemographic regions, with the largest increases observed in lower and lower-middle-income countries.

Cytotoxic therapy for cancer can significantly impair host defense mechanisms, thereby increasing the risk of infections. Such defense mechanisms encompass humoral immunity, such as complement cascade and immunoglobulins, cell-mediated immunity, including thymus-derived T lymphocytes, bone marrow-derived phagocytes, such as monocytes/macrophages and neutrophils, and the integrity of the host's integument. The integrity of these defense mechanisms can be further compromised by factors such as the patient's pre-existing health conditions, the nature and characteristics of the underlying cancer, and the impact of anticancer treatments[2].

Cutaneous infections are prevalent among immunocompromised patients, particularly those with neutropenia, which increases susceptibility to fungal, bacterial, and viral infections. Consequently, prophylactic use of antibacterial, antifungal, and antiviral agents can significantly reduce the incidence of these infections. Cutaneous infections in this population can be categorized into two main types: primary cutaneous infections and infections occurring as part of a widespread systemic infection[3].

Breakthrough invasive fungal infections (IFIs) are defined as infections that occur despite the ongoing use of antifungal prophylaxis or therapy[4]. These infections can be caused

Received: August 27, 2024 Revised: October 14, 2024 Accepted: October 24, 2024
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by pathogens that fall outside the spectrum of activity of the antifungal agents used or by organisms that have developed resistance to the antifungal drugs[5]. The mechanisms underlying breakthrough IFIs include factors such as host immunosuppression, fungal resistance to antifungal agents, inadequate drug levels due to pharmacokinetic variability, and the presence of fungal biofilms on medical devices, which can protect pathogens from antifungal agents[6,7]. Additionally, certain antifungal drugs may induce changes in fungal virulence or promote the emergence of resistant strains, further complicating treatment.

In this manuscript, we explore the etiology and pathogenesis of cutaneous infections in malignancy, along with the associated challenges in clinical management.

VIRAL INFECTIONS

Herpes simplex infection

In 2016, an estimated 3.7 billion people, representing approximately 66.6% of the global population aged 0~49 years, were infected with Herpes simplex virus (HSV-1). Additionally, approximately 491.5 million people, or 13.2% of the world's population aged 15~49 years, were infected with HSV-2[8]. The prevalence of HSV infection or reactivation is notably higher among cancer patients[9]. HSV infections are a significant concern in cancer patients due to their compromised immune systems. Reactivation of HSV, particularly HSV-1, is common in this population and is often associated with chemotherapy-induced oral mucositis[10]. Although HSV is frequently isolated from tissue specimens in cancers such as oral squamous cell carcinoma, esophageal cancer, and cervical cancer, its role in carcinogenesis remains unproven[11]. However, cancer patients undergoing treatments that weaken their immune system, such as myelosuppressive chemotherapy or hematopoietic stem-cell transplantation (HSCT), are at higher risk for severe HSV complications, including visceral infections like esophagitis, pneumonitis, and encephalitis[12]. Treatment of HSV mucocutaneous infection or esophagitis can involve the intravenous administration of acyclovir at a dose of 250 mg /m^2 or 5 mg/kg every 8 hours. Alternatively, oral treatment options include acyclovir at 400 mg five times per day, valacyclovir at 500~1,000 mg every 12 hours, or famciclovir at 500 mg every 12 hours. For HSV visceral, disseminated, or central nervous system disease, the recommended treatment is acyclovir at 500 mg/m^2 or 10 mg/kg, given intravenously every 8 hours[9].

Herpes zoster infection

Herpes zoster (HZ), caused by the varicella-zoster virus, is a common complication following HSCT, with incidence rates ranging of 17~50% in allogeneic and 14~28% in autologous transplant recipients[13]. Most HZ cases occur within the first year posttransplant, typically around 5~6 months[14]. The risk of HZ significantly increases in patients with various immunocompromizing conditions, with the highest incidence observed among HSCT recipients, where rates vary depending on the type of transplant and the prophylaxis regimen used. Patients with hematologic malignancies are also a high-risk group for HZ, particularly those undergoing chemotherapy. Solid organ transplant recipients experience varying levels of HZ risk, with the highest rates noted in heart and lung transplant patients[15]. In contrast, individuals with solid tumors generally have a lower risk for opportunistic infections due to less significant compromise of the cellular immune system, though their HZ risk remains elevated compared to the general population[16]. Treatment of HZ can involve the intravenous administration of acyclovir at a dose of 500 mg/m^2 or 10 mg/kg every 8 hours. Alternatively, depending on the patient's clinical presentation and immune status[9], oral treatment options include acyclovir at 800 mg five times per day, valacyclovir at 1,000 mg every 8 hours, or famciclovir at 500 mg every 8 hours.

Cytomegalovirus

Human Cytomegalovirus (CMV) is a widespread virus with seroprevalence increasing with age: 10~20% of children are infected before puberty, rising to 40~100% by adulthood. Immunocompromised patients, particularly those undergoing chemotherapy for lymphoma, are at significant risk for both primary CMV infection and reactivation[17]. This can lead to persistent viremia and disseminated systemic disease, with CMV end-organ disease affecting organs such as the lungs, gastrointestinal tract, liver, eyes, and central nervous system. In patients with aggressive lymphoma, especially those treated with rituximab and HyperCVAD regimens (a chemotherapy regimen consisting of hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone), the risk of CMV reactivation is notably high[18]. Severe complications, including CMV retinitis, pneumonia, and myelitis, are common and require close monitoring and prompt antiviral treatment.

BACTERIAL INFECTIONS

Skin and soft tissue infection

Cellulitis and erysipelas are most commonly caused by Group A β-hemolytic streptococci (*Streptococcus pyogenes*) and *Staphylococcus aureus*, including Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection. However, identifying the causative organism is often challenging, with success achieved in fewer than one-third of all cases. While erysipelas was historically attributed solely to streptococci, recent studies indicate a microbial profile similar to that of classic cellulitis[19]. Other less common pathogens include Group B, C, and G streptococci and coagulase-negative staphylococci, which are more relevant in hospitalized patients. These patients are more susceptible to infections from a broader range of pathogens, including gram-negative bacteria and unusual organisms such as *Cryptococcus neoformans*, *Serratia marcescens*, and *Campylobacter fetus*[20-23]. The presence of systemic immunosuppression, whether due to conditions like HIV/AIDS, chemotherapy, or organ transplantation, further increases the risk of severe and recurrent cellulitis. In these cases, prompt identification and treatment with appropriate broad-spectrum antibiotics are crucial to managing the infection and preventing further complications. Early biopsy or aspiration for histologic and microbiological review is often recommended to ensure accurate diagnosis and effective treatment in these vulnerable patients[24]. While outpatient therapy with oral antibiotics is suitable for stable patients without systemic infection, hospitalization is often necessary for immunocompromised patients or those experiencing treatment failure. For nonpurulent cellulitis, antistreptococcal agents like cephalexin, dicloxacillin, or penicillin are recommended. In patients with penicillin allergy, clindamycin or macrolides can serve as alternative options. For severe or systemic infections, intravenous antibiotics such as cefazolin or ceftriaxone are used, while vancomycin is added if MRSA is suspected. For purulent cellulitis, incision and drainage are essential, and empiric therapy should cover Methicillin-Sensitive *Staphylococcus aureus* (MSSA) or MRSA. Cephalexin or dicloxacillin is first-line therapy for MSSA, while clindamycin or trimethoprim-sulfamethoxazole is used for MRSA. Severe infections in cancer patients require broad-spectrum antibiotics, often including MRSA coverage, with therapy adjustments based on culture results[24,25].

Gram-negative infections

Cutaneous lesions occur in approximately 30% of *Pseudomonas* bacteremia cases, with the respiratory or genitourinary tracts being the most common sites of origin[26]. *Pseudomonas aeruginosa* infections can also be acquired from humid environments, such as showers, sinks, and flower vases[3]. The dermatologic manifestations of *Pseudomonas* sepsis include ecthyma gangrenosum, hemorrhagic bullae, necrotizing or bullous cellulitis, painful vesicular lesions, small papules on the trunk resembling rose spots of typhoid fever, grouped petechiae, erysipelas-like lesions with hyperesthesia, erythematous or violaceous subcutaneous painful nodules, and necrotizing or malignant external otitis[27]. Ecthyma gangrenosum is traditionally considered a pathognomonic sign of *Pseudomonas aeruginosa* septicemia, though it can also occur as a result of other gram-negative bacterial, fungal, and viral infections, particularly in immunocompromised individuals[3].

FUNGAL INFECTIONS

Cutaneous candidiasis

Candida yeasts are ubiquitous in the environment and are common commensals of human skin, as well as oropharyngeal, respiratory, gastrointestinal, and genital mucosa. Candidal colonization has been reported in the oral mucosa of over 40% of healthy adults, with higher carriage rates among women and smokers[28]. Of over than 200 *Candida* species, at least 15 have been implicated in human disease. While *Candida albicans* is the most commonly implicated species in localized mucocutaneous candidiasis, an increasing number of other species, including *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis*, and *Candida dubliniensis*, are also associated with mucocutaneous disease. Additionally, although *C. albicans* remains the single most common species, non*albicans* species collectively now account for the majority of cases with invasive candidiasis and candidemia[29]. In immunocompromised patients, cutaneous candidiasis often presents similarly to cases in immunocompetent individuals, with conditions like intertrigo and vaginitis common observed. However, these infections may occur more frequently in patients undergoing systemic antibiotic or steroid treatments during oncologic care. While most superficial infections can be managed with topical antifungal treatments, disseminated candidiasis is a significant concern in these patients, particularly in those with hematologic malignancies or those who have undergone stem-cell transplantation. In these cases, non*albicans* species, such as *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*, are increasingly implicated[30]. The cutaneous manifestations of disseminated candidiasis include

pink papules, which may lead to eschar formation or skin necrosis, and are often accompanied by a high mortality rate, underscoring the need for prompt recognition and treatment[3]. Treatment of cutaneous candidiasis typically involves topical antifungal agents such as clotrimazole, nystatin, and miconazole, which are highly effective, achieving cure rates of 73~100%. In more severe or resistant cases, systemic antifungal therapy may be required, with oral fluconazole being a common choice due to its superior efficacy, comparable to that of topical treatments[31].

Fusariosis

Skin manifestations occur in up to 70% of patients with fusariosis, presenting as either localized or disseminated infections. Neutropenic patients with hematologic malignancies are particularly at high risk for this mold infection. Fungal paronychia is a key clinical presentation of localized fusarium infection in this population[3,32]. Histological findings typically reveal narrow, septated hyphae with 45° branching, along with club-shaped pseudohyphae. Triazoles, such as voriconazole, are the preferred antifungal treatment, with liposomal amphotericin B recommended if triazoles are contraindicated[33].

Mucormycosis

Mucormycosis is a serious but rare fungal infection caused by molds known as *mucormycetes*, which are prevalent in environments such as soil and decaying organic matter. This infection is particularly aggressive in immunocompromised individuals, including those with hematological malignancies, recipients of HSCT, and patients with extensive burns, where the all-cause mortality rates range from 40% to 80%[34]. The infection is difficult to diagnose and progresses rapidly, making early intervention critical[35]. The standard treatment involves high-dose liposomal amphotericin B, with surgical debridement often necessary to manage the infection effectively. In cases where triazoles like voriconazole are contraindicated, liposomal amphotericin B is recommended as an alternative treatment[36].

INFECTION RISKS FOR IMMUNOCOMPROMISED PATIENTS AFTER TRANSPLANTATION

Following organ transplantation, the risk and type of infections change over time. Within the first four weeks post-transplant, bacterial infections from surgical complications and hospital-acquired pathogens are most common, along with early viral infections such as herpesviruses. Between 1 and 12 months post-transplant, the risk shifts toward viral infections like *cytomegalovirus* (CMV) and *Epstein-Barr virus* (EBV), along with fungal infections such as *Aspergillus* and *Candida*, and bacterial infections, particularly from opportunistic pathogens. After 12 months, the focus centers on community-acquired infections including viruses, bacteria, and fungi, as well as late-occurring parasitic infections like *Toxoplasma gondii*[37].

CONCLUSION

In summary, the present review highlights the significant association between malignancy and the increased risk of cutaneous infections. Patients with malignancies are vulnerable to these infections, which are often exacerbated by the immunosuppressive effects of both the malignancy itself and its treatment. These infections present unique diagnostic and therapeutic challenges, making prompt and accurate diagnosis, as well as early and aggressive treatment with antibiotics, antivirals, and antifungals, crucial for managing these potentially life-threatening conditions.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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