RESEARCH ARTICLE

# Risk Factors for Invasive Fungal Infection among Thai Oncologic Patients with Febrile Neutropenia and Cutaneous Presentation: A 5-Year Retrospective Study in Southern Thailand

**Kumpol Aiempanakit[1]*, Surarit Naorungroj[1], Kanokphorn Chiratikarnwong[1], Sauvarat Auepemkiate[2], Benjawan Apinantriyo[3]**

## Abstract

**Background:** Febrile neutropenia (FNP) is a condition defined by fever and neutropenia. There are current only limited data on related cutaneous manifestations. This study aimed to assess cutaneous lesions and their etiologies in a Thai group of FNP patients. **Methods:** A retrospective analysis was conducted on 43 non-transplant febrile neutropenic patients with concurrent cutaneous lesions, as determined by dermatopathologic studies at Songklanagarind Hospital in Thailand over a five-year period. **Results:** The mean age was 39 years (SD: 18.8). Approximately 60% were male. The most common underlying disease was a hematologic neoplasm. Twenty-one of the participants had developed FNP within 7.5±8.7 days after presenting with skin lesions. Twenty-two participants had skin lesions 9.0±11.1 days after FNP diagnosis. Cutaneous manifestations were mostly in the form of multiple lesions (67.4%), of which the most common were nodular skin lesions (37.2%) presenting on the lower extremities of the body (58.1%). The dermatopathologic diagnoses included infections which were almost all fungal and leukemia cutis. The development of skin lesions after FNP proved to be a statistically significant risk factor for fungal infection (OR 8.13, P = 0.009), whereas age (over 40 years) proved to be a statistically significant protective factor (OR 0.20, P = 0.04). **Conclusions:** There are a variety of cutaneous manifestations in FNP, of which the most common were cutaneous nodular skin lesions in the lower extremities. The most frequent infection was fungal in patients under 40 who had developed skin lesions after FNP.

**Keywords:** Febrile neutropenia- cutaneous- fungal infection- hematologic malignancy- Thailand

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## Introduction

Febrile neutropenia (FNP) is a common condition in cancer patients who have been treated with chemotherapy. Infections, particularly those caused by bacterial pathogens, are the major cause of FNP related deaths. During the chemotherapy treatment period, a diagnosis of infection is often hampered, as the immunologic response can retard and mask symptoms.

According to recent Asian study, FNP had an incident rate in 14.9% or 24.8 per 1,000 cycles of chemotherapy per year (Limvorapitak and Khawcharoenporn, 2015). Approximately 6-15 percent of infections are located in the skin and soft tissue (Jagarlamudi et al., 2000; Roongpoovapart and Suankratay, 2010; Karanwal et al., 2013). In addition to infection, cutaneous lesions which include leukemia cutis, Sweet's syndrome, cutaneous vasculitis, acute graft versus host disease and cutaneous drug eruptions, are symptoms during FNP (Bodey, 1994; Mays and Cohen, 2006; Farmakiotis et al., 2013; Llamas-Velasco et al., 2013). The purpose of this study was to describe the etiologies of dermatologic manifestations in febrile neutropenic patients and to assess factors associated with common causes of FNP. The final aim was to compare diagnostic yield between tissue biopsy for dermatopathologic and mycological studies.

## Materials and Methods

*Study Design*

A comprehensive review of the electronic medical records of all patients with FNP who were diagnosed at the Songklanagarind Hospital Medical School in Southern Thailand between November 2009 and October 2014 was completed. Inclusion criteria were patients who (1) were diagnosed FNP in accordance with the 2010 Guidelines

*[1]Division of Dermatology, Department of Internal Medicine, [2]Department of Pathology, Faculty of Medicine, Prince of Songkla University, [3]Hematology Unit, Bangkok Hospital Hatyai, Hatyai, Songkhla, Thailand. *For Correspondence: akumpol@medicine.psu.ac.th*

of the Infectious Diseases Society of America (IDSA) that specified that patients must have a fever and neutropenia; (2) had developed skin lesions and had undergone a histopathologic study during the FNP period. According to the IDSA, fever is defined as a single oral temperature of ≥38.3 ºC or a temperature of ≥38.0 ºC sustained over a one-hour period. Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/cu.mm or an ANC that is expected to decrease to <500 cells/cu.mm within 48 hours (Freifeld et al., 2011). Patients with transplants were excluded. Patient data including information on age, gender, underlying diseases, chemotherapy regimen, and prescribed antibiotics were collected. Additionally, data pertaining to FNP, skin lesions, dermatopathologic diagnoses, and skin culture reports were collected. The patients with anticipated prolonged (>7 days duration), profound neutropenia (ANC ≤100 cells/cu.mm) and/or significant medical co-morbid conditions, were categorized as high risk for FNP. Patients with few or no co-morbidities and brief neutropenic periods were categorized as low risk (Freifeld et al., 2011).

The study was approved by the Research Ethics Committee, Faculty of Medicine, Prince of Songkla University in accordance with the Declaration of Helsinki (REC 57-326-14-4). All patients were written inform consent before dermatopathologic studies.

*Statistical Analysis*

All statistical analyses were performed using the epicalc package (version 2.15.1.0) in R statistical software (version 3.2.2). Quantitative variables were described using mean and standard deviation (SD) for continuous variables and number and percentage for categorical variables. Comparisons between the two groups (fungal and non-fungal infection) were conducted using chi-squared test and Fisher's exact test. Univariate and multivariate analyses were conducted using linear regression analysis. Statistical significance was defined at $\alpha$=0.05.

## Results

*Demographics (Table 1)*

We found forty-three patients meeting the study criteria. The mean age was 39 ± 18.8 years and the study population was comprised of 24 males and 19 females. There were 41 cases of hematologic neoplasm.

*Characteristic cutaneous lesions*

The majority of patients had multiple skin lesions (67.4%). The most common morphology were nodular lesions (37.2%), and 58.1% was located on the lower extremities. Twenty-one (48.8%) of the patients had diagnosed FNP within 7.5±8.7 days after presenting with skin lesions. Whereas, 22 (51.2%) had skin lesions approximately 9.0±11.1 days after a diagnosis of FNP.

*Dermatopathologic diagnosis*

Fourteen (32.6%) of lesions were the result of infection, and 85.7% of these were fungal. Fourteen (32.6%) were the result of leukemia cutis.

Table 1. Basic Demographic, Clinical and Dermatopathologic Characteristics of the 43 Patients

| Characteristic | No. | (%) |
|---|---|---|
| Age, mean (SD), y | 39 | (18.8) |
| Sex | | |
| Male | 24 | 55.8 |
| Female | 19 | 44.2 |
| Underlying malignancy | | |
| AML | 21 | 48.8 |
| Lymphoma | 11 | 25.6 |
| ALL | 6 | 13.9 |
| MDS/other hematologic | 3 | 7 |
| Solid | 2 | 4.7 |
| Number of skin lesions | | |
| Single | 14 | 32.6 |
| Multiple | 29 | 67.4 |
| Morphology of skin lesions | | |
| Nodule | 16 | 37.2 |
| Papule | 12 | 27.9 |
| Plaque | 6 | 13.9 |
| Blister | 5 | 11.6 |
| Ulcer | 4 | 9.3 |
| Other | 8 | 18.6 |
| Location of skin lesions | | |
| Lower extremities | 25 | 58.1 |
| Upper extremities | 20 | 46.5 |
| Torso | 20 | 46.5 |
| Head and neck | 11 | 25.6 |
| Other | 3 | 7 |
| Dermatopathologic diagnosis | | |
| Infections | 14 | 32.6 |
| Fungus | 12 | |
| Leukemia cutis | 14 | 32.6 |
| Drug reactions | 6 | 13.9 |
| Other/non-diagnosis | 9 | 20.9 |

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome

*Predictive factors influencing common etiologies*
*Fungal infection*

Twelve patients were diagnosed with having a fungal infection. 58.3% were male, and 75% were under the age of 40. All patients were in the high-risk group. 58.3% had been using antibacterial agents for more than seven days. The onset of skin lesions in patients with fungal infection occurring after FNP was statistically significantly higher than in the non-fungal infection group (Table 2).

In the multivariable analysis, which was controlled for age, onset of skin lesions, FNP group, and prolonged antibiotic use, an 80% reduced likelihood of fungal infection with patients who were over 40 years of age (OR, 0.20; 95% CI, 0.04-1.03; P= 0.04) was found. Patients who developed skin lesions after developing FNP were 8.13 times more likely to have fungal infections (OR, 8.13; 95% CI 1.4-47.17; P= 0.009) (Table 3).

Table 2. Characteristics of the Study Participants with Skin Fungal Infection Versus Non-Fungal Infections

| Characteristic | No. (%) | | | | P Value |
|---|---|---|---|---|---|
| | Fungal infection | | Non-fungal infection | | |
| Age, y | | | | | |
| <40 | 9 | (75) | 12 | (38.7) | 0.07[a] |
| ≥40 | 3 | (25) | 19 | (61.3) | |
| Sex | | | | | |
| Male | 7 | (58.3) | 17 | (54.8) | 1.00[a] |
| Female | 5 | (41.7) | 14 | (45.2) | |
| Onset of skin lesions | | | | | |
| Before FNP | 2 | (16.7) | 19 | (61.3) | 0.02[a] |
| After FNP | 10 | (83.3) | 12 | (38.7) | |
| Number of skin lesions | | | | | |
| Single | 5 | (41.7) | 9 | (29) | 0.48[b] |
| Multiple | 7 | (58.3) | 22 | (71) | |
| Morphology of skin lesions | | | | | |
| Nodule | 5 | (41.7) | 11 | (64.5) | 0.74[b] |
| Location of skin lesions | | | | | |
| Lower extremities | 7 | (58.3) | 18 | (58.1) | 1.00[a] |
| Upper extremities | 7 | (58.3) | 13 | (41.9) | 0.53[a] |
| Torso | 6 | (50) | 14 | (45.2) | 1.00[a] |
| Head and neck | 4 | (33.3) | 7 | (22.6) | 0.47[b] |
| FNP group | | | | | |
| High-risk | 12 | (100) | 23 | (74.2) | 0.08[b] |
| Low-risk | 0 | 0 | 8 | (25.8) | |
| Antibiotics use >7 days | | | | | |
| No | 5 | (41.7) | 23 | (74.2) | 0.07[b] |
| Yes | 7 | (58.3) | 8 | (25.8) | |

FNP, febrile neutropenia; [a], chi-squared test; [b], Fisher's exact test.

*Leukemia cutis*

Fourteen patients were diagnosed with leukemia cutis. Fifty-seven percent were male and presented with skin lesions before the onset of FNP. No factors predictive of leukemia cutis were found.

*Dermatopathologic study and skin culture*

Skin cultures were performed on 29 patients, and six were found to be positive for fungal infection. *Aspergillus spp.* was identified in two patients, *Candida spp.* in two, *Fusarium spp.* in one, and *Cladosporium spp.* in the other. Four of the six patients also tested positive for fungus in the pathological sections. Of the 23 patients found to be negative, surprisingly, five were found to be positive in the pathological sections.

## Discussion

Typically, oncologic patients undergo multiple kinds of chemotherapy, and approximately 15% of patients developed FNP (Limvorapitak and Khawcharoenporn, 2015). These FNP patients must receive an empirical treatment with broad-spectrum antibiotics, antifungal drugs as well as leucocyte stimulating agents (Freifeld et al., 2011). When those of patients with FNP developed skin lesions, the differential diagnosis varies from patient's disease, a complication of the treatment, etc. The infection including bacteria, virus, and fungus, the most important one of complications from chemotherapy, should be first considered because of an immunosuppressed status. This infection could be localized on the skin or systematized from internal organs (Mays et al., 2006). Furthermore, receiving many medications; therefore skin reaction and cutaneous drug eruptions could be occurring in febrile neutropenic patients (Mays and Cohen, 2006; Farmakiotis et al., 2013; Llamas-Velasco et al., 2013).

Table 3. Multivariable Analysis of Factors Influencing Fungal Infection

| Factor | OR (95% CI) | | P Value | P Value |
|---|---|---|---|---|
| | Crude | Adjusted[a] | (Wald's test) | (LR-test) |
| Age, y | | | | |
| <40 | 1 [Reference] | 1 [Reference] | | |
| ≥40 | 0.21 (0.05-0.94) | 0.2 (0.04-1.03) | 0.05 | 0.04 |
| Onset of skin lesions | | | | |
| Before FNP | 1 [Reference] | 1 [Reference] | | |
| After FNP | 7.92 (1.47-42.53) | 8.13 (1.4-47.17) | 0.02 | 0.009 |

FNP, febrile neutropenia; OR, odds ratio; [a], model adjusted for age; the onset of skin lesions, FNP group, and antibiotic use.

Proper diagnosis of cutaneous lesions in FNP is important. In our study, the most common etiologies of skin lesions were a fungal infection and leukemia cutis. These results align with a previous study which found the first three common causes of cutaneous lesions in FNP were an infection, leukemia cutis, and drug reactions, respectively (Farmakiotis et al., 2013).

Previous studies reported that an absolute neutrophil count of fewer than 100 cells/cu.mm, and greater than seven days of antibiotic use were risk factors for a fungal infection (Freifeld et al., 2011; Farmakiotis et al., 2013). The aforementioned factors were not found in this study possibly due to the small sample size; however, we found an analogous result with those who were diagnosed with fungal infections and with an absolute neutrophil count of fewer than 100 cells/cu.mm.

Additionally, we found two new predictors of a fungal infection. First, patients under the age of 40 had approximately a five times higher risk of fungal infection. In the past, advanced age patients with FNP receiving standard regimen were associated with increased mortality (Chindaprasirt et al., 2013). It was later almost always recommended a reduced- or palliative-dose chemotherapy in those with FNP who had significant co-morbidity (Brandwein et al., 2017; Iioka et al., 2016), thereby, theorettically developed less toxicity from the treatment, i.e., fewer FNP episodes and severity of neutropenia (Shayne et al., 2007; Xie et al., 2017). These possibly could result in decreasing risk of fungal infection in an older patient (Freifeld et al., 2011; Farmakiotis et al., 2013). Second, patients with skin lesions which occurred after diagnosed FNP had approximately an eight times higher risk of fungal infection. Patients who have had a neutropenic status might be at risk of fungal infection due to contracted circulating neutrophils and a lack of adequate

myeloid marrow reserve (West et al., 2017).

In contrast, leukemia cutis could have occurred any time before, during or after FNP and there were no predictive factors. To our knowledge, there were no studies on the correlation between onset to diagnosis of FNP and leukemia cutis. The large study from Korea reported 75 patients with leukemia cutis commonly presented with cutaneous nodules on the extremities, and the disease was associated with high mortality within a year (Kang et al., 2013). There was a difficulty in separating two significant conditions between leukemia cutis and fungal infection because the characteristic skin lesions of both entities were similar. Then, the skin biopsy must benefit tool for diagnosis in these patient setting.

The authors found the most common fungal organisms were *Aspergillus spp., Candida spp.* and *Fusarium spp.* which was similar to findings in previous studies (Mays et al., 2006; Farmakiotis et al., 2013). Only 4 of 11 cases had concordant results between the pathologic diagnosis and tissue culture. A possible explanation for the discordance between the two test results might be that the tissue contained heterogeneity or nonviable fungi (Tarrand et al., 2003; Sangoi et al., 2009; Guarner and Brandt, 2011; Gonzalez Santiago et al., 2014). These discordant results lead to a recommendation that both a tissue biopsy for pathologic study and a skin culture be conducted to reach more definitive conclusions.

This study had some limitations. This was a retrospective of a small case from a single university hospital. Patients in the study were all non-transplant and had undergone histopathology during the FNP period.

In conclusion, cutaneous manifestations in patients with FNP were common in the multiple cutaneous nodules of the lower extremities. Fungal infection was a significant consideration, especially in patients who were young (under 40) and who had developed skin lesions after FNP. The authors recommend both a tissue biopsy for dermatopathologic study and culture to ensure a more efficient plan of treatment.

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*Conflicts of interest*

The authors have no conflicts of interest to declare.

*Previous Presentation*

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