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ORIGINAL RESEARCH

Risk of Superficial Fungal Infections in WHIM Syndrome

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ABSTRACT

Introduction: WHIM syndrome is a rare autosomal dominant inborn error of immunity caused by gain-of-function mutations in the chemokine receptor *CXCR4*. Patients with WHIM syndrome frequently suffer from an increased risk for bacterial and viral infections, especially warts due to human papillomavirus. Associations between WHIM syndrome and fungal infections have not been previously identified. The objective of this study was to estimate the prevalence of superficial fungal infections in patients with WHIM syndrome.

Methods: This retrospective single-institution cohort study assessed patients with genotype-confirmed WHIM syndrome evaluated between March 2007 and March 2024.

Results: Of 45 patients with WHIM syndrome, 18 (40%) were diagnosed with at least one superficial fungal infection. These infections included dermatophytosis ($n=14$, 78%), pityriasis versicolor ($n=6$, 33%), and pityrosporum folliculitis ($n=1$, 6%). No correlation was detected between superficial fungal infection risk and the degree of peripheral neutropenia, lymphopenia, or hypogammaglobulinemia. The median time to resolution of the longest episode of superficial dermatophytosis (skin or hair) was 171.5 (range 53–3650) days, and several patients experienced prolonged courses requiring serial retreatments.

Conclusions: These findings suggest that frequent or prolonged superficial fungal infections may be a useful clinical sign to prompt consideration of a WHIM syndrome diagnosis, especially in patients with numerous cutaneous warts or other history to suggest immunodeficiency.

Trial Registration: Participants were enrolled in a natural history trial registered with ClinicalTrials.gov (NCT00128973).

Keywords: WHIM syndrome; Superficial fungal infections; Dermatophyte; Tinea

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Key Summary Points
Why carry out the study?
WHIM syndrome is a rare immunodeficiency with diverse clinical findings, making early diagnosis difficult.
WHIM syndrome has not previously been associated with superficial fungal infections.
This single-institution cohort study sought to estimate the prevalence of superficial fungal infections in patients with WHIM syndrome.
What was learned from the study?
A high prevalence of superficial fungal infections was identified among patients with WHIM syndrome.
The presence of frequent or prolonged superficial fungal infections may be a useful clinical indicator to prompt consideration of a WHIM syndrome diagnosis.

INTRODUCTION

WHIM syndrome is a rare autosomal dominant primary immunodeficiency caused by gain-of-function mutations in the chemokine receptor *CXCR4* [1]. WHIM is an acronym referring to the four cardinal manifestations of the syndrome: warts, hypogammaglobulinemia, infections, and myelokathexis [2]. WHIM-associated myelokathexis is thought to arise from hyperactive CXCR4 signaling impeding neutrophil migration out of the bone marrow, resulting in myeloid hyperplasia, dysmorphic bone marrow neutrophils, and circulating neutropenia. Current treatments include granulocyte colony-stimulating factor, intravenous immunoglobulin, and the CXCR4 antagonists plerixafor and mavorixafor [3, 4]. In addition to neutropenia, most individuals with WHIM syndrome have monocytopenia, lymphopenia (involving both B cells and T cells), hypogammaglobulinemia, and an increased susceptibility to recurrent oto-sino-pulmonary infections [5, 6]. Cutaneous manifestations of WHIM syndrome include bacterial and viral skin infections, particularly persistent HPV-driven warts, which can be severe [6]. However, to our knowledge, an increased susceptibility to superficial fungal infections (those involving the outer layers of the skin, hair, or nails) has not been associated with WHIM syndrome. After recently reporting a case of severe recalcitrant tinea capitis in a patient with WHIM syndrome [7], we sought to investigate superficial fungal infections among patients with WHIM syndrome at the National Institutes of Health (NIH) Clinical Center. The aim of our study was to estimate the prevalence of superficial fungal infections in this patient cohort.

METHODS

This is a retrospective cohort study of patients with genotype-confirmed WHIM syndrome evaluated at the NIH Clinical Center between March 2007 and March 2024. All patients received care at NIH as part of participation in a natural history study (NCT00128973). Patient demographics, CXCR4 genotype, medical history, medications, and laboratory tests were extracted from the medical record. Patients whose medical history included at least one diagnosis of a superficial fungal infection were identified. Statistical comparisons between quantitative variables were performed using the Mann-Whitney *U* test, while categorical variables were analyzed with the Fisher's exact test. NIH IRB approval (05-I-0213) and written informed consent were required for participation in the natural history study (NCT00128973). No additional informed consent or IRB approval was required for patient data inclusion in this study. This study was performed in accordance with the Helsinki Declaration.

RESULTS

A total of 45 patients with WHIM syndrome were evaluated at the NIH between March 2007 and March 2024. A diagnosis of WHIM syndrome was based on characteristic laboratory findings, past medical history, and pathogenic

CXCR4 variants on genetic testing (See Table S1 in the electronic supplementary material). The median age of WHIM syndrome diagnosis was 17 (range 0–59) years. Twenty-nine patients were women (64%).

Among the 45 patients with WHIM syndrome, 18 (40%) had been diagnosed with at least 1 superficial fungal infection. Nine of these patients (50%) were women. There was no significant difference in the age of WHIM syndrome diagnosis or the degree of neutropenia, lymphocytopenia, or gammaglobulinemia between those with versus without a history of superficial fungal infections (Table 1). Patients presented with their first superficial fungal infection at a median age of 17.4 (range 4–57) years. Superficial fungal diagnoses included dermatophyte infections ($n=14$, 78%), pityriasis versicolor ($n=6$, 33%), and pityrosporum folliculitis ($n=1$, 6%) (Fig. 1). Three patients had superficial fungal infections from multiple categories (see Table S1 in the electronic supplementary material). Three patients had a history of dermatophyte infections that resolved prior to NIH evaluation.

Of the 14 patients with dermatophyte infections, the median age of first diagnosis was 10 (range 4–57) years. Seven patients (50%) were women. Diagnoses included tinea corporis ($n=5$, 36%), tinea capitis ($n=5$ 36%), tinea pedis ($n=3$, 21%), and onychomycosis ($n=3$, 21%). The median age of onychomycosis presentation was 36 (range 17–54) years. A diagnosis of dermatophyte infection was made via characteristic findings on clinical examination ($n=6$, 33%), skin scraping with visualization of fungal hyphae after potassium hydroxide (KOH) preparation ($n=7$, 39%), or fungal culture ($n=3$, 17%). Fungal culture identified *Microsporum canis* in two patients and *Trichophyton tonsurans* in one patient. Cutaneous dermatophyte infections were treated with topical antifungals. Tinea capitis was managed with a minimum of 2 months of oral antifungal therapies in combination with antifungal shampoos. Patients with onychomycosis did not receive treatment. Of eight patients with documented resolution of their dermatophyte infections, two experienced recurrences. The median time to resolution of the longest episode of superficial dermatophytosis (skin or hair) was 171.5 (range 53–3650) days. Four patients (29%, 3 tinea capitis, 1 tinea corporis) had prolonged courses requiring serial retreatments without resolution between treatments.

Table 1 Characteristics of 45 patients with WHIM syndrome with or without a history of superficial fungal infections

Characteristic	Superficial fungal infection	No superficial fungal infection	*P* value
N (%)	18 (40%)	27 (60%)	
Median age of Dx, years (range)	13 (1.5–54)	19.5 (0–59)	0.65
Female, *n* (%)	9 (50%)	19 (70%)	0.22
Median ANC, K/μl (range)	0.72 (0.08–4.88)	0.44 (0.01–16.26)	0.79
Median ALC, K/μl (range)	0.93 (0.4–13.5)	0.72 (0.33–1.98)	0.39
Median IgG, mg/dl (range)	809 (423–1415)	803 (528–1107)	0.58
Type of fungal infection, *n* (%)			
Dermatophyte	14 (78%)	N/A	
Pityriasis versicolor	6 (33%)	N/A	
Pityrosporum folliculitis	1 (6%)	N/A	

Patients received concurrent neutrophil mobilizing therapies

Abbreviations: *Dx* WHIM syndrome diagnosis, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *IgG* immunoglobulin G, *N/A* not applicable

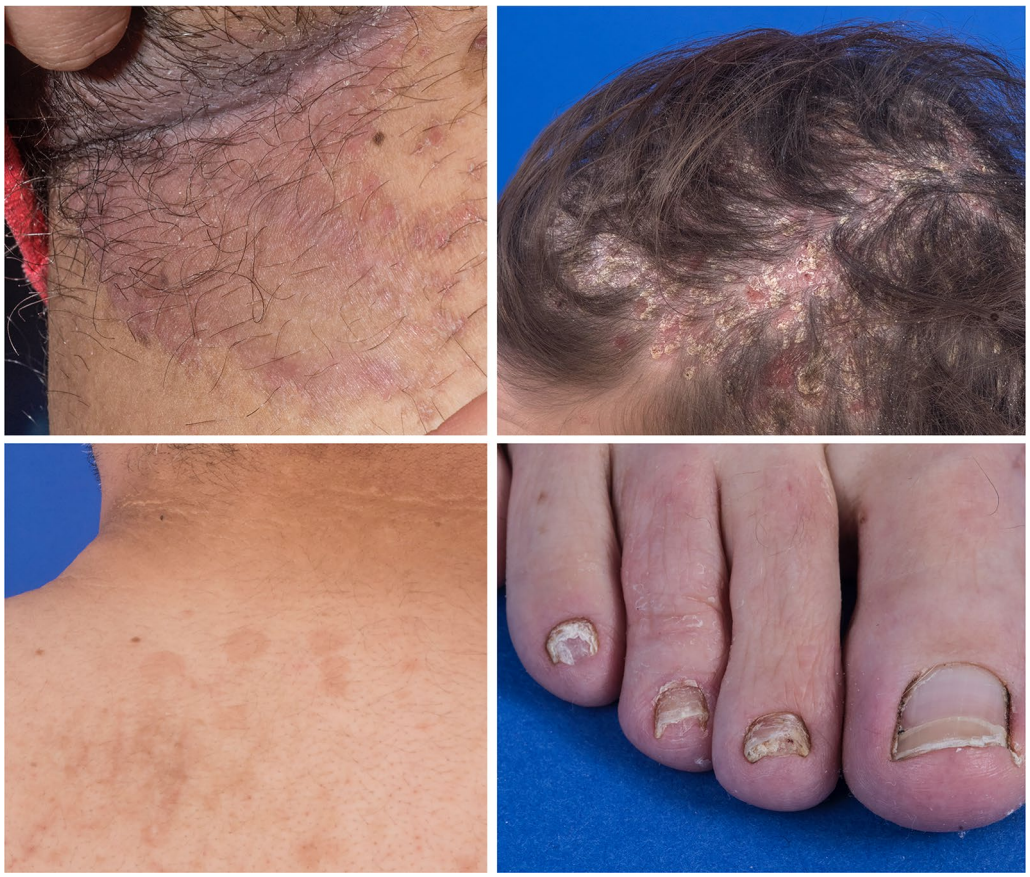

Fig. 1 Examples of superficial fungal infections in patients with WHIM syndrome. **A** Tinea corporis involving the upper thigh and crural fold, **B** tinea capitis (same patient reported here [7]), **C** pityriasis versicolor on the upper back, and **D** onychomycosis

Of patients with pityriasis versicolor and pityrosporum folliculitis, the median age of presentation was 23 (range 10–44) years. Diagnosis of pityriasis versicolor was made by clinical findings ($n=4$, 67%) and the presence of yeast and hyphae on KOH preparation ($n=2$, 33%). Treatment of pityriasis versicolor was with selenium sulfide shampoo and ketoconazole 2% shampoo and cream. Pityrosporum folliculitis was diagnosed via a skin biopsy demonstrating yeast colonies within the hair follicle. It resolved after management with ketoconazole 2% cream.

DISCUSSION

We observed a high prevalence of superficial fungal infections among patients with WHIM syndrome. Superficial dermatophyte infections were most common, which is consistent with fungal infection trends in the US [8]. The prevalence of superficial dermatophyte infections in our cohort was 31%, in contrast to a worldwide prevalence of 10–25% [9]. This worldwide estimate likely overestimates the prevalence in

the US, which has a lower burden of cutaneous fungal disease [10]. Although difficult to estimate, the prevalence of pityriasis versicolor in the US has been estimated to be < 4%, notably lower than the prevalence of 13% observed in our cohort [11].

Dermatophytosis associated with WHIM syndrome can be severe and have a prolonged course, with a median time to resolution of 5 months. Patients with tinea capitis often required multiple oral therapies with treatment courses lasting > 8 weeks [7], while standard regimens start at 4 weeks duration [12]. Consistent with WHIM syndrome conferring increased susceptibility to onychomycosis, the median age of diagnosis was younger than expected—36 years compared to 56 years in the general population [13].

Traditionally, invasive rather than superficial fungal infections have been associated with inborn errors of neutrophil immunity [14]. In contrast, patients with WHIM syndrome rarely experience invasive fungal infections [15]. Moreover, some patients in our cohort developed superficial fungal infections with normal neutrophil counts. Susceptibility to superficial fungal infections in WHIM syndrome may be due to impaired skin immunity resulting from Langerhans cell dysfunction. In a mouse model of WHIM syndrome, CXCR4 activation impaired the lymph node migration of cutaneous dendritic cells and Langerhans cells [16]. This may increase superficial fungal infection risk as epidermal dendritic cells and Langerhans cells are central to initiating immune responses against dermatophytes [17]. Further research is needed to improve our understanding of CXCR4 in the function of Langerhans cells controlling superficial fungal infections.

Early diagnosis and treatment of WHIM syndrome is associated with improved disease outcomes [18]. However, diverse clinical manifestations and lack of awareness are barriers to early diagnosis [5, 18]. Currently, difficult to treat and extensive childhood warts are the cutaneous hallmark of WHIM syndrome. Our study suggests that frequent or prolonged superficial fungal infections may be another early cutaneous manifestation of WHIM syndrome.

Our study is limited by a small sample size and its retrospective nature. As these patients were primarily seen for a natural history cohort study, details of their fungal infections, laboratory values, and medical histories were sometimes limited. Moreover, although we were able to estimate the prevalence of superficial fungal infections in this WHIM syndrome cohort, we lacked a clinically matched control cohort for statistical comparisons. We also excluded suspected superficial candidal infections from our analysis because of the low specificity of clinical diagnoses. Further work will be needed to investigate any associations between cutaneous candidiasis and WHIM syndrome.

CONCLUSIONS

In summary, patients with WHIM syndrome may experience an increased risk of superficial fungal infections with prolonged courses. The presence of recalcitrant superficial fungal infections should prompt consideration of WHIM syndrome as an underlying diagnosis, especially in patients with numerous cutaneous warts or other history to suggest immunodeficiency.

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Sophia Martinez and Abigail Salancy contributed to data curation. Heidi H. Kong contributed to data curation, supervision and manuscript reviewing and editing. Edward W. Cowen, Leslie Castelo-Soccio, Philip M. Murphy, and David H. McDermott contributed to conceptualization, supervision and manuscript reviewing and editing. Isaac Brownell contributed to conceptualization, supervision, original draft preparation and manuscript reviewing and editing.

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Data Availability. The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Conflicts of Interest. Authors Jennifer Strong, Rutha Adhanom, Caleb S. Kim, Yoshine Saito, Jasmine C. Meltzer, Patrick Hallaert, Sophia Martinez, Abigail Salancy, Heidi H. Kong, Edward W. Cowen, Leslie Castelo-Soccio, Philip M. Murphy, David H. McDermott, and Isaac Brownell have no conflicts of interest to report.

Ethical Approval. National Institutes of Health IRB approval (05-I-0213) and written informed consent was required for the natural history study (NCT00128973). No additional IRB approval or informed consent was required for patient data inclusion in this study. This study was performed in accordance with the Helsinki Declaration.

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