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A case series of intertriginous rashes in cancer patients

Alexandria Weygand, Pratiksha Patra, John Greene

ABSTRACT

Introduction: Immunocompromised patients, especially those with cancer, face an elevated risk of developing inflamed and painful rashes between the skinfolds. These intertriginous conditions are not always easy to identify.

Case Series: We report a case series of three neutropenic patients, two with acute myeloblastic leukemia (AML) and one with metastatic left invasive ductal carcinoma, presenting to the hospital dermatology consult team with intertriginous skin eruptions. The patients were diagnosed with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), ecthyma gangrenosum, and toxic erythema of chemotherapy. Treatment and management of these cases involved topical steroids, antibiotics, and chemotherapy dosing adjustment.

Conclusion: This paper explores the various infectious, inflammatory, and other etiologies of intertriginous rashes in immunocompromised and neutropenic patients.

Keywords: Acute myeloblastic leukemia, Intertrigo, Neutropenia, SDRIFE

How to cite this article

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Alexandria Weygand[1], Pratiksha Patra[2], John Greene[3]

Affiliations: [1]Researcher, University of South Florida, Tampa, FL, USA; [2]Student Researcher, Dermatology and Cutaneous Surgery, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [3]Professor, Infectious Diseases and Tropical Medicine, Moffitt Cancer Center & Research Institute, Tampa, FL, USA.

Corresponding Author: Alexandria Weygand, 31027 Endendale Drive, Wesley Chapel, FL 33543, USA; Email: alexandriaweygand@gmail.com

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INTRODUCTION

Intertrigo is a common inflammatory skin condition resulting from chronic friction of the body's intertriginous zones. The axillae, groin, and inframammary folds are most often implicated and present as mildly erythematous, symmetrical papules [1]. Intertrigo may become exacerbated due to secondary complications, such as bacterial or fungal infections, and lead to maceration, oozing, odor, and crusting. Common differential diagnoses of intertrigo include atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis, and psoriasis vulgaris inversa [1]. Intertrigo has several mimickers, especially in the immunocompromised population. Cancer patients particularly are at higher risks of developing certain intertriginous eruptions as a result of various drug reactions, cutaneous manifestation, and suppressed immune function. These eruptions include, but are not limited to, erythrasma, Sweet's syndrome, ecthyma gangrenosum, and leukemia cutis. The following case series discusses cases of cancer patients with intertriginous rashes and the steps taken to treat them. We aim to differentiate between the various causes of intertriginous rashes in cancer patients to explore the various presentations and treatment styles and bring awareness to the dermatology community on this unique yet treatable disease.

CASE SERIES

Case 1: Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

A 29-year-old female with acute myeloblastic leukemia (AML) presented with an erythematous, petechial rash involving her buttocks, groin, flank, and bilateral axillae (Figures 1 and 2). She denied pruritus or pain and was otherwise asymptomatic. Her past medical history was significant for refractory AML, being treated with azacitidine and investigational flotetuzumab. Additional

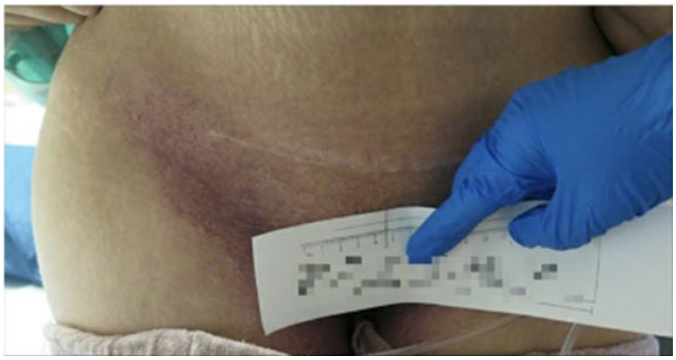

Figure 1: Sharply demarcated erythema of the right inguinal crease with reported symmetry.

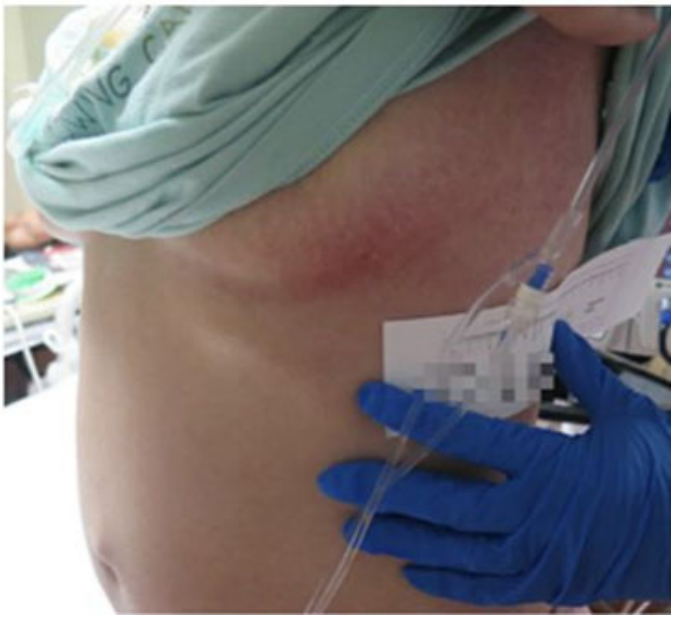

Figure 2: Non-blanching erythematous patch with mild petechiae in the left axillary region.

history included prolonged neutropenia, sinusitis, and recurrent right facial cellulitis. Her medications included lactulose and docusate-senna, dilaudid to manage breakthrough pain, allopurinol, meropenem, vancomycin and acyclovir, isavuconazole, and cefepime for neutropenia. On the day of presentation, the patient was febrile (Tmax 102.3°F), but her other vitals were within normal limits. Her physical examination was notable for a minimally blanched rash distributed within the intertriginous folds of the groin and perianal region, as well as symmetrical erythema of the inguinal/perianal region. A blood panel including a comprehensive metabolic panel (CMP), basic metabolic panel (BMP), complete blood count (CBC), and group A strep was unremarkable. Polymerase chain reaction (PCR) analysis for cytomegalovirus (CMV), Epstein–Barr virus, and herpes simplex virus (HSV) yielded negative results. Additionally, blood, urine, wound, and throat cultures were negative. However, a chest computed tomography (CT) showed new nodular densities in the left lower and right upper lobes, concerning for an infectious or inflammatory process. Given the risks and benefits, the patient declined a biopsy. The clinical picture was most consistent with symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) due to the intertriginous involvement, timely exposure to a systemic drug, and symmetrical erythema of the inguinal/perianal area. Vancomycin and allopurinol were identified as the suspected culprits and promptly discontinued. The patient was started on a five-day course of intravenous (IV) methylprednisolone, in addition to triamcinolone 0.1% topical ointment daily to the buttocks and flank and desonide 0.05% cream to the groin, inframammary region, and axillae. Complete resolution of the rash was noted at 1-week follow-up.

Case 2: Ecthyma Gangrenosum

A 37-year-old man with a history of acute myeloid leukemia and pseudomonas bacteremia presented to the dermatology consult team with a right groin lesion. Of note, the patient has a history of buttock abscesses in the past treated with ertapenem. He is status post attempted ultrasound guided drainage of the area with finding of no drainable collection. He was recently seen to have purulent fluid from the groin and swelling. It had taken several weeks for the lesion to develop from scrotal cellulitis and yeast intertrigo. The patient reported no other associated symptoms besides chills. His notable medications included diphenhydramine for sleep, hydromorphone for pain, metronidazole, and cefepime for toxic shock syndrome prophylaxis. He had also recently been treated with micafungin prophylaxis and piperacillin-tazobactam in the weeks prior, and had been switched to cefepime and metronidazole from piperacillin-tazobactam due to worsening hyperbilirubinemia. On the day of consultation, the patient's vitals were stable, and he was afebrile. On skin examination, he was found to have an erythematous, well-defined subcutaneous mass in the right groin with induration of the right scrotum (Figure 3). There was active drainage of mostly bloody, serous material at the time. Daily complete blood count (CBC) reports were unremarkable for any recent changes, though significant for prolonged anemia and neutropenia. Wound culture swabs taken around the time of consult showed 3+ *Enterococcus faecalis*, 2+ *Staphylococcus haemolyticus*, and 2+ mixed gram-positive flora. The dermatology consultation team recommended additional swabs and imaging to evaluate for anaerobic and fungal organisms. Computed tomography of the thorax, abdomen, and pelvis with contrast revealed a "relatively stable appearing right groin/peroneal complex collection/phlegmon with internal gas bubbles, suspicious for infectious etiology." Several days later, 3+ *Klebseilla pneumoniae* with highest susceptibility to piperacillin/tazobactam was also isolated from skin wound culture. Initially, the dermatologic differential diagnoses included abscess versus hidradenitis suppurativa versus less likely

a lymph node or tumor. Vancomycin had been initiated for methicillin-resistant *Staphylococcus aureus* as a possible contributor for abscess. The patient had been off of piperacillin-tazobactam for several weeks due to hyperbilirubinemia, which caused the infection to worsen as evidenced by a repeat right groin ultrasound one week later. After reviewing the latest microbiology and imaging results, a diagnosis of ecthyma gangrenosum from *Klebseilla* and *Staphlycoccus haemolyticus* was made. Piperacillin-tazobactam was re-initiated, and three weeks later, repeat CT showed that the right groin/perineal gas-containing collection had decreased in size. The patient was ultimately discharged with four more weeks of piperacillin-tazobactam to be administered through home health care. This led to resolution of the infection completely, proven by CT imaging done two months post-initial consult which showed no mass or infectious fluid collection at all.

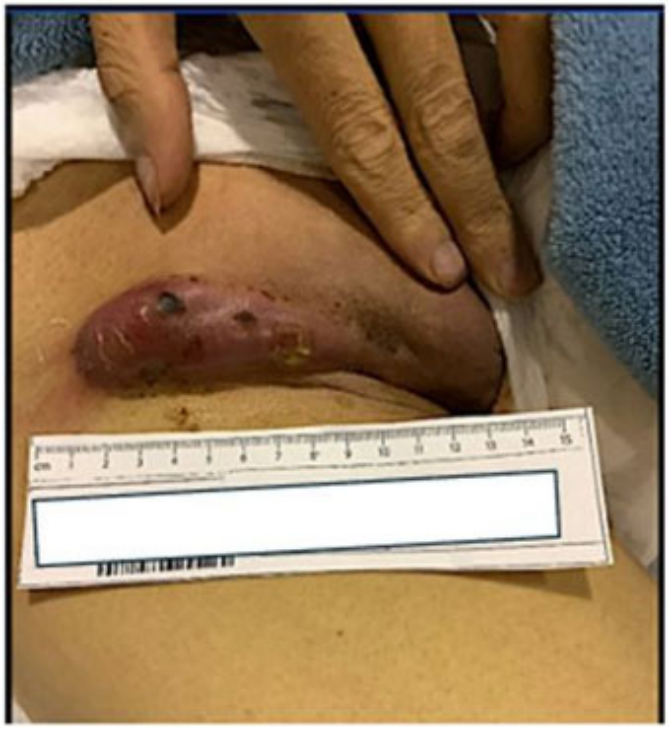

Figure 3: Erythematous, well-defined subcutaneous mass in the right groin with induration of the right scrotum.

Case 3: Toxic Erythema of Chemotherapy

A 53-year-old female with metastatic left invasive ductal carcinoma developed erythema on her left inner thigh. It spread and continued to ulcerate until it covered both of her upper thighs by three months. She reported bleeding with wiping when toileting and burning discomfort. She was being treated with Enhertu, or Famtrastuzumab deruxtecan-nxki for the past five months, and she noticed the rash began after her first dose and worsened after each subsequent dose. The ulcerations were severely painful, but she denied any other systemic signs and symptoms. She had been instructed to use Vashe to keep the growing wound clean. Her past medical history included chemotherapy-induced dermatitis at her intertrigo areas (underarms and under the breasts) which was managed without medical intervention. Her other chronic issues included type 2 diabetes mellitus, anemia due to chemotherapy, and chemotherapy-induced peripheral neuropathy. Her vitals were stable, and her physical examination findings were significant for ill-defined dusky erythema on the bilateral inframammary and axillary folds as well as red-purple edematous plaques on the bilateral inner thigh with multi-focal shallow yellow-white based ulcers (Figure 4). Computed tomography of the pelvis with intravenous contrast revealed only mild skin thickening in the bilateral inner thighs with no significant underlying drainable fluid collections. Herpes simplex virus (HSV) and cytomegalovirus (CMV) testing were negative by PCR. Cultures of the erythema and ulceration were positive for pseudomonas confirming a secondary infection to toxic erythema of chemotherapy. Antimicrobial management was deferred to infectious disease, and dermatology consult recommended gentle saline/Vashe rinses followed by liberal application of zinc oxide to protect open wounds wrapped in loose gauze. Levofloxacin was initiated for streptococcal coverage along with ongoing piperacillin/tazobactam (Zosyn) and doxycycline. Toxic erythema of chemotherapy is not a hypersensitivity reaction and should improve with adjusted frequency of chemotherapy; topical steroids were considered for non-ulcerated areas. Ultimately, chemotherapy was held due to rash progression to both thighs and recommendations of adjusting future doses were followed.

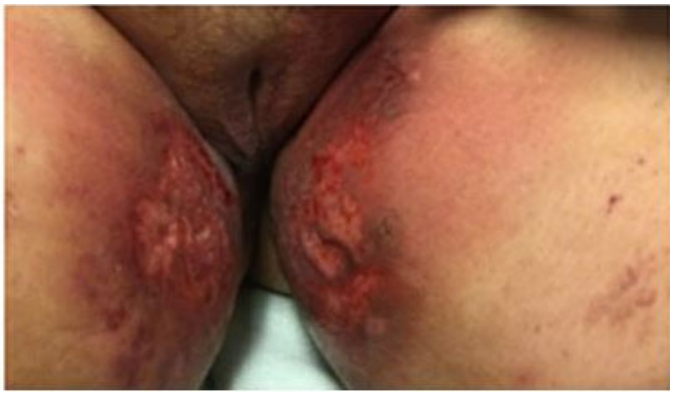

Figure 4: Erythema with ulceration on the bilateral inguinal folds and upper inner thighs.

DISCUSSION

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) is a rare cutaneous drug eruption clinically characterized by symmetrically distributed, V-shaped erythema of the inguinal, genital, gluteal, and perianal areas [2]. Diagnostic criteria of SDRIFE include

erythema of the gluteal/perianal area, flexural eruptions appearing in at least one other intertriginous region, exposure to a systemically administered drug, symmetry of the affected areas, and lack of systemic involvement [3].

Clinical features of SDRIFE involve the appearance of vesicles, purpura, pustules, and less commonly bullae, which are restricted to intertriginous regions. Symmetrical drug-related intertriginous and flexural exanthema is most commonly induced by beta-lactam antibiotics, such as amoxicillin, and chemotherapeutic agents like mitomycin and cetuximab [3]. Other implicated causative agents include allopurinol, iodinated radio contrast media, cimetidine, deflazacort, intravenous heparin, oxycodone, and risperidone [3].

Furthermore, SDRIFE has also been documented upon the administration of experimental monoclonal antibody treatment, such as Auristatin E conjugate (CR011-vcMMAE), in the treatment of metastatic melanoma [4]. This is important to note in the context of dermatology as SDRIFE is an intertriginous rash to look out for while treating metastatic melanoma cancer patients.

The exact pathogenic mechanism of SDRIFE is currently unknown. It is hypothesized to be a type IV delayed hypersensitivity immune response, as evidenced by significant cellular infiltration of CD4+ T cells and an increase in the expression of a type 1 helper T cell recruiter, CD26P-selectin [5].

The mainstay of treatment is discontinuation of the suspected offending agent resulting in the resolution of the rash. Other treatments include supportive therapy with mild-to-moderate strength topical steroids to manage symptoms of pruritus, and/or systemic corticosteroids for more severe cases.

Immunosuppressed and neutropenic patients, such as in the three cases described above, often have increased susceptibility to cutaneous drug eruptions. Low-intensity therapeutic regimens, with chemotherapeutic agents like azacitidine, are commonly initiated with prophylactic antimicrobial treatments to decrease the incidence of infections [6]. Thus, when evaluating intertriginous rashes, it is important to consider systemic antibiotics and chemotherapy as potential causes of SDRIFE in otherwise asymptomatic cancer patients.

Leukemia cutis is defined as the infiltration of neoplastic leukocytes or their precursors into the skin tissue resulting in recognizable cutaneous lesions. The presence of rash is related to the diagnosis of leukemia, and may present before, after, or during diagnosis and treatment. Treatment of the lesion involves chemotherapy targeting the specific leukemia [7].

The following sections will explore other causes of intertriginous rashes in both immunocompromised and immunocompetent patients (Table 1).

A common cause of intertriginous eruptions is candidal infections. Candidal intertrigo is distinguished by areas of maceration, erythema, and crusting presenting with satellite pustules or papules [8]. Affected regions include the axilla, genitocrural folds, cervical creases, finger or toe webs, intergluteal areas, and infra-mammary folds [8]. Increased inflammation in these warm, occlusive skinfolds are associated with intense pruritus, burning, and foul odor. Although diagnosis is often based on clinical appearance alone, the presence of pseudo-hyphae on microscopic potassium hydroxide preparation is diagnostic.

Erythrasma is a bacterial infection caused by gram-positive *Corynebacterium minutissimum* which can involve intertriginous zones, such as the axillae, inguinal folds, and interdigital regions [9]. Erythrasma presents as well-demarcated, reddish-brown plaques that are often peripherally hyperpigmented, finely scaled, and otherwise asymptomatic [9]. Wood lamp examination can aid in the proper diagnosis with its characteristic bright coral-pink fluorescence.

Scabies may also present as a symmetrical rash in intertriginous zones. Common scabies, caused by an infestation of the *Sarcoptes scabiei* varietas hominis mite, is clinically observed on the volar surfaces of the wrist, medial thighs, waistline, umbilicus, axillae, interdigital spaces, the areolae in women, and the penis or scrotum in men [10]. Scabies manifests as an erythematous, pruritic rash with burrows, typically white in color and adjacent to a small, scaled pustule [10].

Although rare, disseminated HSV has been known to cause linear, intertriginous ulcerations ("knife-cut" sign) in individuals lacking personal or family history of Crohn disease [11]. These unusual presentations of HSV may be observed in immunocompromised patients, such as cancer patients. Yacoub et al. [12] describe two cases of disseminated HSV in immunocompromised

Table 1: Differential diagnoses of intertriginous rashes

Differential diagnoses of intertriginous rash		
Infections	**Inflammatory dermatosis**	**Other**
Candida intertrigo	Atopic dermatitis	Leukemia cutis
Tinea cruris	Allergic contact dermatitis	Hailey–Hailey disease
Erythrasma	Seborrheic dermatitis	Acquired acrodermatitis
Ecthyma gangrenosum	Inverse psoriasis	Enteropathica
Scabies	Hidradenitis suppurativa	Acanthosis nigricans
Atypical herpes	Sweet's syndrome	

hosts: a 40-year-old man with a history of human T-cell lymphotropic virus type 1-positive associated adult T-cell leukemia and a 66-year-old man with a history of metastatic adenocarcinoma, both exhibiting painful, ulcerated lesions with serpiginous borders. The first case involved the scrotum and gluteal cleft and the latter involved the right thigh and hip. Polymerase chain reaction results confirmed positive HSV and lesions resolved with topical trifluridine and oral famciclovir. Interestingly, Millian et al. [11] reports three cases of patients without active malignancy, autoimmune disease, or immunosuppressive therapy presenting with sharp, linear erosions in the abdominal folds. In each instance, the presence of HSV (type 1 or 2) was confirmed by PCR testing and the patient was started on antiviral therapy.

Ecthyma gangrenosum (EG) is an important diagnosis to consider in immunocompromised, neutropenic patients. Up to 62–75% of EG cases are associated with immunosuppression [13]. This entity, caused by gram-negative *Pseudomonas aeruginosa*, initially presents with red papules and plaques evolving into painful ulcers and eschars [13]. Lesions commonly involve the extremities, axillae, and gluteal/perianal area [13]. Treatment involves initiation with broad-spectrum antibiotics; however, more extensive gangrenous lesions may require debridement.

Hidradenitis suppurativa (HS) is frequently encountered on the major skinfolds, such as the axillae, groin, perianal/perineal regions, and inframammary area. Lesions often begin as tender, deep-rooted nodules with sinus tracts and painful abscesses [14].

Inverse psoriasis (IP) warrants particular consideration as a differential diagnosis of SDRIFE, due to its exclusive involvement of the intertriginous regions and flexural surfaces. This form of plaque psoriasis is most commonly observed on the inguinal folds, inframammary folds, axillae, perianal region, and umbilicus [15]. Less frequently, IP can involve the interdigital space, as well as the antecubital and popliteal fossae [15]. Resembling SDRIFE in its symmetrical, erythematous presentation, inverse psoriasis is clinically distinguished by its sharply defined borders, minimal scaling, and shiny, wet appearance. “Bushy” capillaries may also be seen on dermatoscopy [15]. Certain medications have been identified as triggering factors, including lithium, hydrochlorothiazide, tetracyclines, and beta blockers [16].

Hailey–Hailey disease is a rare hereditary skin condition commonly found in intertriginous zones. This chronic condition results in a symmetrical, bilateral distribution of painful, pruritic lesions often accompanied by blisters [17]. Rupture of these blisters results in foul-smelling crusting and erythematous, macerated plaques [17]. Affected areas include the cervical skin crease, axillae, infra-mammary folds, inguinal and perineal regions. Haley et al. [18] describes a case of a 58-year-old African American man with an unremarkable medical history presenting with a painful, hyperkeratotic, and malodorous rash on his right axilla and right lateral neck. A diagnosis of Hailey–Hailey disease was confirmed and the eruption improved upon topical treatment with both corticosteroids and antimicrobials.

Acanthosis nigricans (AN) is characterized by hyperpigmented, warty, thickened, and velvety plaques localized in intertriginous zones [19]. This condition most often involves the neck, but can be observed on the axillae, groin, umbilicus, ante-cubital and popliteal regions, inner thighs, and dorsal side of the hand joints [19]. Lesions are typically asymptomatic. However, highly pruritic lesions involving atypical sites such as the mucosa of the mouth may be indicative of an underlying malignancy. Acanthosis nigricans is a cutaneous sign often associated with other systemic conditions, including obesity, hyperinsulinemia, diabetes mellitus, Cushing syndrome, and polycystic ovarian disease [20].

Although rare, acquired acrodermatitis enteropathica (AE), can also result in intertriginous dermatitis. Acrodermatitis enteropathica arises from a significant plasma zinc deficiency and most commonly in weaning infants [21]. This condition, with a prevalence of 1–9: 1,000,000, is clinically distinguished by the presence of a periorificial and acral cutaneous rash, diarrhea, and alopecia [21]. Baden [22] reports a case of a 54-year-old woman, having undergone gastric bypass eight years prior, presenting with an erythematous, crusting rash and excoriations on the lumbosacral, inguinal, and perioral region. This eruption was later diagnosed as acquired acrodermatitis and complete resolution was noted with adequate zinc supplementation.

In adults, seborrheic dermatitis, a common inflammatory skin condition, most frequently involves the scalp, retro-auricular areas, face, and chest. These lesions typically present as oily, honey-crusted scales with associated pruritus [23]. However, the axillae, umbilicus, breast folds, and inguinal area may also be affected and exhibit macerated, symmetrical erythema susceptible to secondary infection [23]. Of note, seborrheic dermatitis has a higher prevalence in the immunocompromised patient population, such as those with HIV/AIDS and lymphoma [23].

Intensely pruritic, erythematous patches on the anterior or lateral neck and flexural surfaces of the antecubital and popliteal fossa may indicate a form of eczema known as atopic dermatitis (AD). Morphology varies based on clinical phase, acute AD presenting as blistering, oozing vesicles, and chronic AD as visible lichenification and hyperpigmentation [24]. Uniquely, 90% of reported cases have an onset before the age of 5 years old [24]. A greater clinical picture is necessary to distinguish AD from other intertriginous disorders, notably a family history of atopy, a personal history of asthma or allergic rhinitis, and the presence of general xerosis [24].

Allergic contact dermatitis (ACD) may closely resemble SDRIFE. It is caused by a type IV delayed hypersensitivity reaction triggered by contact with

specific allergens. Unlike SDRIFE, ACD requires previous sensitization to an allergen to occur [25]. Mimicking SDRIFE in its erythematous and edematous presentation, ACD is not limited to intertriginous zones [3]. Common allergens include nickel, textile chemicals, fragrances, and preservatives [25]. As histopathology often reveals unspecific spongiosis, patch testing is the gold standard for diagnosis of ACD [25].

Tinea cruris, often caused by the dermatophyte *Trichophyton rubrum*, also involves the intertriginous folds, specifically the groin, perineum, upper thigh, and perianal skin [26]. This condition predominantly affects athletes and adult males, presenting as bilateral, erythematous, and scaly ring-shaped lesions that are highly pruritic in nature [26]. Borders of this annular eruption may feature vesiculopustules, generally sparing the penis and scrotum [27]. Tinea cruris should be ruled out in susceptible patient populations, including those with diabetes, renal disease, or impaired liver function [26].

Sweet's syndrome, otherwise known as acute febrile neutrophilic dermatitis, may rarely present in the skinfolds. Sweet's syndrome is more prevalent among females and has a predilection for the upper extremities, head, and neck [28]. Thebo et al. [29] describe a case of a 46-year-old man recently diagnosed with myelofibrosis presenting with febrile neutropenia and multiple, painful erythematous nodules on the umbilicus, left thigh, and left groin. A punch biopsy confirmed a diagnosis of Sweet's syndrome and the lesions resolved after treatment with glucocorticoids.

CONCLUSION

Cancer patients are more susceptible to developing intertriginous rashes due to immunosuppression, chemotherapy treatments, and increased hospitalization. The causes of these dermatoses range from common inflammatory conditions to complex infectious processes. Despite their varied etiologies, these conditions often have favorable prognoses, as demonstrated by our cases of SDRIFE, ecthyma gangrenosum, and toxic erythema.

This study highlights the significance of investigating underlying conditions, such as AML, diabetes mellitus, and HSV, in intertriginous presentations. Clinicians should consider the diagnoses discussed in this paper during examinations. Comprehensive patient histories and necessary microbiological testing are crucial for accurate diagnosis and effective treatment, particularly for the immunosuppressed patient population.

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Author Contributions

Alexandria Weygand – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Pratiksha Patra – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

John Greene – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.