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MODESTUM

Case Report **OPEN ACCESS**

Balanitis with palmoplantar erythrodysesthesia: A case report and review of literature

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ABSTRACT

Capecitabine a pro-drug of 5-fluorouracil is a commonly used chemotherapeutic agent for the treatment of many cancers. A common side effect of this agent is palmar-plantar erythrodysesthesia. However, genital ulceration is an unusual side effect reported only a few times in the literature. Herein, we present a patient with unusual genital ulceration and palmoplantar erythrodysesthesia following capecitabine chemotherapy and review similar cases from the literature and review their pathophysiology and management strategies.

Keywords: capecitabine, palmar-plantar erythrodysesthesia, 5-fluorouracil, genital ulceration, chemotherapy, adverse reaction

INTRODUCTION

Cutaneous adverse events of systemic chemotherapeutic agents are common. Capecitabine is a commonly used chemotherapeutic agent for the treatment of colonic adenocarcinoma. It is a pro-drug of the chemotherapeutic agent 5-fluorouracil.

One of its most notable side effects is palmoplantar erythrodysesthesia which is characterized by painful erythema involving the hands and feet. The incidence of hand-foot syndrome (HFS) in patients receiving capecitabine varies across studies.

For instance, a study reported that 68.3% of patients experienced at least one episode of HFS during capecitabine therapy [1]. Another study indicated an incidence rate of 34% [2]. These variations may be attributed to differences in patient populations, cancer types, and treatment regimens.

However, concurrent acral and genital Involvement is an unusual side effect of its use, with only a handful of cases reported in the literature.

CASE PRESENTATION

We were consulted to evaluate a 58-year-old gentleman with a history of painful genital ulceration involving the glans penis for 1 week.

The patient is a known case of stage III colonic adenocarcinoma T3 N2 M0 receiving adjuvant chemotherapy oxaliplatin 109 mg given intravenously at a dose of 85 mg/m^2 and capecitabine 1,673 mg at a dose of 1,000 mg/kg. His latest dose of capecitabine was 1 week prior to the appearance of genital lesions.

On examination, there were multiple well-defined erythematous erosions and ulceration involving the glans penis and distal penile shaft (**Figure 1**).

There was also diffuse erythema with desquamation over the palms bilaterally in association with 3 small, rounded ulcers over the dorsal tongue (sub-figure A and sub-figure B in **Figure 2**).

Our differential diagnosis included: genital herpes, fixed drug eruption, genital ulceration with palmoplantar erythrodysesthesia, and chemotherapy-induced mucositis.

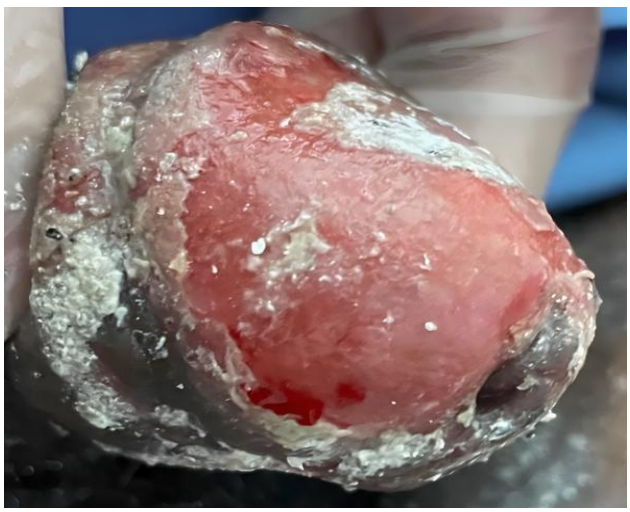

Figure 1. Genital involvement (Reprinted with permission of patient)

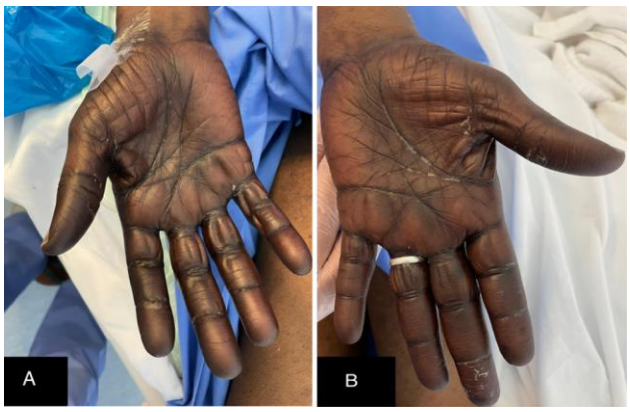

Figure 2. Erythema and desquamation over (A) the right & (B) the left palm (Reprinted with permission of patient)

Figure 3. Palms and genitalia after treatment (Reprinted with permission of patient)

Laboratory investigations including complete blood count, renal function test, and liver function test were all within normal limits.

Treatment with topical acyclovir cream was prescribed for the genital ulcerations and showed little to no efficacy. Instead, emollients and potassium permanganate alongside zinc oxide cream were offered to the patient to facilitate healing. We have also added short courses of topical hydrocortisone cream to alleviate any associated burning sensation.

After approximately 3 months of therapy, the patient's condition improved. His palmar lesions disappeared, and his genital ulceration has improved significantly (**Figure 3**). Given the clinical presentation and close temporal association of capecitabine dose and lesion emergence, we diagnosed the patient with balanitis and palmoplantar erythrodysesthesia.

DISCUSSION

Several chemotherapy drugs, such as 5- fluorouracil [3], cytarabine [4], docetaxel [5], and doxorubicin [4] have been linked to the development of PPE [6]. But they rarely present with penile and scrotal involvement. Few cases have been reported in the literature that associated this presentation with the chemotherapeutic agent capecitabine (**Table 1**) [6-11].

Table 1. Reported cases of capecitabine induced palmoplantar erythrodysesthesia with genital involvement

R	Year	Age	Race	Diagnosis & stage	Cancer treatment regimen	Onset of symptoms	Reported symptoms	PPE grade	How symptoms were treated & when symptoms resolved?	Other drugs used with capecitabine	Recurrence with capecitabine resumption
[6]	2007	67	White	T3 N1 M0 colon cancer	**Capecitabine** 1 g orally BID for 14 days followed by 2 weeks of rest	3rd cycle	• Swelling of his penis and a pruritic scrotal erythema with 2 areas of ulceration • Early ulcer on thumb • Diarrhea, fever, and chills	Grade 3	**Capecitabine cessation** • Diarrhea resolved within 2 days • penile and scrotal symptoms resolved within 2 weeks	Clonidine, iron-polysaccharide, terazosin, nisoldipine, HCTZ, & minoxidil	-
[6]	2007	63	White	T4 N1 M0 colon cancer & T1 N0 M0 gastric cancer	**Capecitabine** 1 g orally BID for 14 days followed by 1 week of rest **Oxaliplatin** 100 mg	Day 12 of 1st cycle	• Palmoplantar erythema • Painful erythema of scrotum and penis with moist ulcers	Grade 3	**Capecitabine cessation** • scrotal and penile symptoms clearance within 2 weeks	Multivitamins	-
[7]	2011	84	?	Metastatic sigmoid cancer	**Capecitabine**	After 1 month	Painful erythema and erosions in the scrotum	-	**Oral steroids, topical antibiotics, steroids, and antifungal agents** ineffective **Capecitabine cessation** Clearance after 10 days	-	Yes
[7]	2011	78	?	Metastatic colon cancer	**Capecitabine**	After 1st cycle	Asymptomatic palmoplantar erythema and painful erythema and erosions in the scrotum		**Topical steroids, antibiotics, and oral pyridoxine** ineffective **Capecitabine cessation** Clearance after 2 to 3 weeks	-	Yes, drug introduction was at a lower dose
[7]	2011	73	?	Rectosigmoid cancer	**Pelvic radiotherapy & capecitabine**	After 1 week	Painful erythema and erosions in the scrotum and penis	-	**Topical corticosteroid** clearance in 2 weeks	-	-
[8]	2017	63	?	Metastatic colon cancer	**XELIRI (irinotecan and capecitabine) + bevacizumab**	• During 2nd cycle > PPE • During 4th cycle > genital involvement	• Painful redness of his feet and palms • Painful penile and scrotal ulcerations		**Skin barrier cream, moisturized ointments, and potent topical corticosteroids** Ineffective **Capecitabine cessation** Clearance within 3 weeks	-	Yes, after 3 months of drug resumption

Table 1 (Continued). Reported cases of capecitabine induced palmoplantar erythrodysesthesia with genital involvement

R	Year	Age	Race	Diagnosis & stage	Cancer treatment regimen	Onset of symptoms	Reported symptoms	PPE grade	How symptoms were treated & when symptoms resolved?	Other drugs used with capecitabine	Recurrence with capecitabine resumption
[9]	2018	43	White	T3c N2b M0 rectal cancer	**Capecitabine** 825 mg/m^2 orally BID, seven days a week **Radiotherapy** 5040 cGy delivered in 28 sessions	4th week	• Painful erythema involving hands, feet, penis, and scrotum • White exudate at the urethral opening causing urinary symptoms • Cramping pains in the mid-abdomen	Grade 2	**Capecitabine cessation** Hand and foot improved after 5 days Penis, scrotum and urinary symptoms improved after 11 days	-	-
[10]	2020	87	?	T3N0 rectal cancer	**Capecitabine** 1500 mg BID, Monday through Friday, skipping non-radiation days, for six weeks **Radiotherapy** 5040 cGy delivered in 28 sessions	3rd week of therapy	• Numbness of the hands and feet without erythema or skin changes • Scrotal discomfort		**Capecitabine and radiotherapy cessation, silver sulfadiazine cream, and antifungal cream** Significant improvement after 30 days	-	-
[11]	2024	38	?	cT3dN3 rectal cancer	**Capecitabine and oxaliplatin**	1st to 2nd cycle	• Dysuria, painful penile erythema and ulcerations • Erythema and pain in the hands and feet	Grade 2	**Topical antifungal cream and topical steroids** Worsening of symptoms **Dose reduction in cycle 3 Worsening of symptoms Delaying cycle 4 for weeks** improvement of palmoplantar symptoms, but a progression of balanitis **Topical tacrolimus with mupirocin** prompt improvement of balanitis	-	Patient resumed with full-dose capecitabine without recurrence of penile symptoms, and with mild PPE symptoms
PC	2024	58	?	T3 N2 M0 colon cancer	**Capecitabine and oxaliplatin**	After 1 week	• Painful erythematous erosions and ulceration involving penis • Ulceration in the tongue		**Topical acyclovir** Not effective **Emollients and potassium permanganate, zinc oxide cream and short courses of topical hydrocortisone** Significant improvement after 3 months	-	-

Note. R: Reference & PC: Present case

While palmar-plantar erythrodysesthesia (PPE) is a well-known adverse effect of capecitabine, this case represents a unique presentation with concomitant mucositis and genital involvement. In all reported cases, the onset of penile and scrotal involvement is during the first three cycles of capecitabine (**Table 1**) [6-11].

This is similar to the time when usually PPE appears [12]. In many of these cases, palmoplantar manifestations exhibit a concurrent onset with genital symptoms, although the severity and time of symptoms' clearance often vary independently. The majority of documented cases, including our own, involved chemotherapy as the sole treatment modality (**Table 1**) [6-11].

In contrast, three cases received chemoradiation. While this initially suggested radiation-induced dermatitis, this possibility was ruled out in all instances. Several studies indicate that the incidence and severity of PPE associated with capecitabine are dose-dependent. It was reported that PPE symptoms were more frequent at higher cumulative doses, with a significant increase in incidence during the first three cycles of treatment [12]. Among reported cases of PPE with genital involvement, most patients developed symptoms within the initial treatment cycles, suggesting a cumulative toxicity effect [6-11]. This pattern aligns with findings from [12], where PPE symptoms were most commonly observed during the early phases of chemotherapy.

Pathophysiology

Pathophysiology is less well defined. However, there are several proposed theories. One theory is that repetitive pressure and trauma to palmoplantar skin may rupture the tiny capillaries and release the drug into surrounding tissue, which in turn causes inflammation [13]. While the penis and scrotum can experience some physical friction during normal daily life, it is significantly less compared to the constant pressure endured by the palms and soles [10].

Another explanation is that the temperature gradient and abundance of sweat glands in certain areas could facilitate the accumulation of chemotherapy medications, resulting in skin toxicity by extravasation [6]. The body's highest concentration of sweat glands is found on the palms, soles, scalp, and genitals [10]. An alternative theory suggests that chemotherapy may directly induce eccrine sweat gland injury through a non-inflammatory process known as eccrine squamous syringometaplasia (ESS). This typically appears within a month of starting chemotherapy and usually clears up on its own within a week or two [10]. It's believed that histopathology can confirm ESS and rule out other potential causes [14].

The role of the immune system in the development of capecitabine-induced PPE and genital ulceration remains incompletely understood.

Table 2. NCI grading system for palmar-plantar erythrodysesthesia

Grade	Symptoms	Impact on daily activities
1	Minimal skin changes or dermatitis (erythema, edema, or hyperkeratosis) without pain	No impact on daily activities
2	Skin changes (peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain	Limits instrumental daily living activities
3	Severe skin changes (peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain	Limits self-care of daily living activities

However, several mechanisms suggest that immune status may influence susceptibility and severity. Capecitabine itself induces T cell apoptosis, selectively reducing the proportion of CD3+ T cells while increasing levels of anti-inflammatory cytokines such as IL-4 and IL-10 [15]. This suppression of immune responses may contribute to delayed healing of capecitabine-induced PPE and genital ulceration, as an impaired immune system is less effective at tissue repair and defense against secondary infections. An alternative hypothesis posits that cyclooxygenase-2 (COX-2) mediates the inflammatory response associated with this condition. Retrospective analysis of patients administered capecitabine concurrently with celecoxib, a COX-2 inhibitor, demonstrated a reduced incidence of PPE. Specifically, the incidence of grade 1 and grade 2 PPE decreased from 34.5% to 12.5% and from 17% to 3.1%, respectively [6].

The conversion of capecitabine to its active form, 5-FU, requires a sequence of enzymatic reactions. The enzyme dihydropyridine dehydrogenase (DPD) primarily breaks down 80-90% of the 5-FU drug into an inactive form [6]. Individuals with less than 70% normal DPD enzyme activity are considered at high risk for severe side effects from this medication [16].

It's estimated that 3 to 5 percent of Caucasians have a partial deficiency in the DPD enzyme, while a much smaller percentage, around 0.2%, have complete absence of this enzyme [10]. The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group have issued guidelines for the recommended dosing of fluoropyrimidines (capecitabine or 5-fluorouracil) based on DPD phenotype [16]. DPD deficiency might be a possible explanation for why some individuals would develop adverse effects of using capecitabine. But it's certainly not the only possible cause. One of the reported cases that had capecitabine-associated PPE with penile and scrotal involvement did a DPD genotype testing and had no mutation [9].

There's a grading system for capecitabine-associated PPE made by the National Cancer Institute (NCI) (**Table 2**). This system, however, does not describe genital involvement. According to the NCI grading system for HFS toxicity, higher grade levels, such as grade 3, correlate with more severe cutaneous manifestations and associated symptoms [11]. It has been suggested that genital involvement should be classified as grade 4 [6]. Nevertheless, two cases of the literature had grade 2 with scrotal and penile involvement, which may necessitate further subclassifications [9].

Painful ulcers in the genital area can significantly reduce a patient's quality of life and hope for recovery. These symptoms often force patients to temporarily or permanently stop cancer treatment, which can jeopardize the overall treatment plan. These can also be complicated by secondary infection and lead to illness exacerbation, requiring bed rest or even hospital admission. This highlights the importance of patient education and early detection to facilitate early intervention and provide timely management to avoid complications.

Treatment

A variety of treatment options have been proposed, with varying degrees of efficacy. Modification or discontinuation of the causative agent remains the most efficient and rapid method for symptom relief. Seven out of all the ten reported cases of PPE with genital involvement necessitated the cessation of chemotherapy treatment (**Table 1**) [6-11]. Upon the emergence of any toxicity-related signs or symptoms, dose reduction may be a prudent course of action. Extending the dosing interval, either independently or in conjunction with dose reduction, may be efficacious [10]. The decision to discontinue capecitabine therapy involves a balance between reducing adverse effects and maintaining clinical benefits. Studies suggest that capecitabine maintenance therapy offers significant clinical advantages, particularly in terms of survival benefits and disease control. A cost-effectiveness analysis of capecitabine maintenance therapy in metastatic nasopharyngeal carcinoma found that one-year capecitabine treatment, compared to routine follow-up, was highly cost-effective and provided promising clinical benefits with acceptable increased costs [17]. Thus, cessation of capecitabine therapy may reduce these clinical benefits and cost-effectiveness, potentially leading to disease progression or recurrence. However, dose modifications or intermittent therapy may serve as an alternative strategy to balance toxicity management with continued therapeutic efficacy.

Supportive care including cooling the affected area can induce vasoconstriction, thereby reducing drug extravasation into the surrounding tissue and mitigating cutaneous toxicity. Topical moisturizers are recommended to maintain skin integrity [9]. For ulcerated areas, application of petroleum jelly is advised to retain moisture and improve healing [6]. Preventive measures include avoidance of sun exposure, hot water immersion, and tight-fitting garments [6]. Additionally, patients should be instructed to avoid repetitive friction on pressure-sensitive areas to minimize capillary dilation and subsequent drug extravasation. Both systemic and topical steroids have been employed in the management and prevention of PPE with varying degrees of efficacy.

One of the oral medications that has been used empirically to prevent chemotherapy-induced HFS is oral pyridoxine (vitamin B6). The idea to use pyridoxine for PPE came from observing similarities between PPE and acrodynia in rats caused by vitamin B6 deficiency [10]. However, the efficacy of pyridoxine in preventing or treating PPE is unsupported by substantial evidence. Three independent studies consistently found no evidence supporting the use of pyridoxine in preventing PPE [18-20]. Another oral medication that has been strongly suggested to prevent PPE is celecoxib. Celecoxib works by blocking COX-2, an enzyme believed to be implicated in the inflammatory processes associated with PPE. A systematic review and meta-analysis revealed that celecoxib significantly prevented moderate to severe PPE [21]. However, its use has been restricted due to its potential systemic adverse effects.

Topical voltaren (diclofenac) on the other hand, exerts a localized inhibitory effect on COX-2, thereby avoiding the risk of systemic side effects of celecoxib. A double-blinded randomized controlled trial found that topical Diclofenac gel dramatically reduced the risk of severe HFS by approximately 75% compared to placebo [22]. Topical Tacrolimus had been used in a reported case of capecitabine-Induced PPE with genital involvement and it showed significant improvement [11]. Further research is warranted to investigate the efficacy and safety of topical tacrolimus in treating such conditions. Topical sildenafil has been proposed as a potential treatment for alleviating PPE symptoms [23, 24]. It has been suggested that 12.5% urea cream can be efficacious in treating and preventing capecitabine-induced PPE [25]. However, a meta-analysis concluded that urea cream is not effective [21]. In addition, topical antiperspirants could potentially prevent PPE based on the hypothesis that these agents may inhibit the cutaneous accumulation of capecitabine via eccrine sweat glands [10]. antioxidant ointments are also thought to be beneficial. A randomized clinical trial compares mapisal, an antioxidant-containing ointment, with 10% urea. Topical urea was found to be more effective [26]. Silymarin gel 1%, a polyphenolic flavonoid extracted from silybum marianum (milk thistle) which has antioxidant and anti-inflammatory properties, is believed to be a good treatment option as well as in reducing the severity and delaying the onset of capecitabine-induced HFS [27].

CONCLUSION

Clinical significance of presentation lies in recognizing the association of palmoplantar and genital lesions with systemic administration of capecitabine. This will aid in rapid diagnosis, avoidance of unnecessary investigations, and providing timely symptomatic treatment to patients.

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Ethical statement: The authors stated that the study was approved Institutional Review Board (IRB) at King Fahad Specialist Hospital-Dammam under approval code IRB- Pub-024-032, dated 13 November 2024. Written informed consent was obtained from the patient for publication of this case report and images. All patient data were anonymized, and no personally identifiable information is disclosed. all patient data were kept secured on a password protected computer accessible only to the authors.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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