First report of tamoxifen-induced baboon syndrome

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Abstract

Background: Baboon syndrome is a rare, type IV hypersensitivity reaction causing a maculopapular rash. Tamoxifen is an antineoplastic agent, working as an estrogen receptor antagonist, also called a selective estrogen receptor modulator. A variety of rashes were reported with Tamoxifen use to-date except baboon syndrome. The Tamoxifen-induced baboon syndrome seems to be reversible, as discontinuation of the drug improves clinical outcomes.

Aim: Herein, we present the first case of Tamoxifen-induced baboon syndrome which occurred 8 years after initiation of Tamoxifen use.

Patients: A 44-year-old woman presented with papulovesicular eruption on her body and erythema on her face for a duration of 6 months. There was no evidence of ocular or mucosal involvement. She was diagnosed with breast cancer and treated with tamoxifen 10 mg twice daily over the past 8 years. She was not taking other medications or over-the-counter supplements at the time of presentation. The patient underwent urgent skin biopsies of two lesions on her buttock and thigh. No organisms were seen on Gram stain. The patient’s skin biopsy revealed extensive hyperorthokeratosis, minimal parakeratosis, hypergranulosis, and lichenoid interface dermatitis in the irregularly acanthotic epidermis supporting diagnosis of fixed drug eruption. Following a multidisciplinary discussion, the patient was diagnosed with baboon syndrome or symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) associated with Tamoxifen.

Results: Hence, Tamoxifen was immediately discontinued and treated with oral steroid along with topical agents. She showed improvement of clinical abnormalities within days after discontinuation of Tamoxifen.

Conclusions: Given the widespread use of Tamoxifen in the management of patients with breast cancer, it is important that healthcare professionals monitor for rare, however clinically significant, and potentially life-threatening dermatological manifestations of Tamoxifen use, such as baboon syndrome.

KEYWORDS
Baboon syndrome, drug eruption, tamoxifen
1 | INTRODUCTION

Baboon syndrome, also named symmetrical drug-related intertrig-
inous and flexural exanthema (SDRIFE), is an uncommon type IV
hypersensitivity causing a distinct form of fixed drug eruption or
systemic contact dermatitis.1 The name Baboon syndrome stems
from the rashes on the patient’s buttocks resembling the red but-
tocks of baboons.2 Baboon syndrome is featured by erythematous
maculopapular rashes with a diffuse and symmetrical pattern on the
flexures, forming a V-shape on the medial thighs and scattered
erythema covering the buttocks. In addition to chronic dermatitis
with different etiologies, it can also appear in its acute form only
days after systemically administering substances, including contact
allergens such as mercury and nickel and certain drugs.4 In the last
few decades, hundreds of drugs have been introduced as the cause
of this disease. Amoxicillin, ceftriaxone, penicillin, and erythromycin
are among the most common drugs, but many other medications like
antihypertensive drugs and contrast agents may also cause Baboon
syndrome.5 Tamoxifen is a selective estrogen receptor modulator
that blocks the transcriptional activity of estrogen receptors by di-
rectly binding to them, creating a complex in the cell nucleus which
causes a decrease in estrogen transcription and functional activities.
Tamoxifen is widely used as adjuvant therapy in treating the early
stages of invasive breast cancer and ductal carcinoma in situ.6

We present the first case of Tamoxifen-induced baboon syn-
drome which occurred 8 years after initiation of Tamoxifen use. The
Tamoxifen-induced baboon syndrome seems to be reversible as dis-
continuation of the drug improves clinical outcomes. Given the wide-
spread use of Tamoxifen in the management of patients with breast
cancer, it is imperative that healthcare professionals recognize the
rare, however clinically significant, and potentially life-threatening
dermatological manifestations of Tamoxifen use such as baboon
syndrome.

2 | CASE PRESENTATION

A 44-year-old woman presented with papulovesicular eruption on
her body and erythema on her face for the duration of 6 months.
There was no evidence of ocular or mucosal involvement. The initial
skin manifestations were self-limited; however, the skin eruptions
progressively worsened about 1 month prior to her first clinic visit.
The rashes were associated with pruritus, but without burning sen-
sation. She denied history of similar skin manifestations in the past.

Her past medical history was significant for history of invasive
ductal carcinoma stage 2B breast cancer diagnosed 8 years prior pre-
sentation in our clinic. She underwent total mastectomy followed by
28 sessions of chemotherapy with Taxotere over a period of 4 years.
She was also treated with Microrelin 3.75 mg for the period of three
months and Tamoxifen 10 mg twice daily over the past 8 years. She
was not taking other medications or over-the-counter supplements
at the time of presentation. She denied history of other medical ill-
ness, family history, and exposure to radiation or chemical agents.

Physical examination was remarkable for papulovesicular rashes on
her arms, legs, back, chest, buttocks, axillary, and inguinal areas. In
addition, there was an erythema on her face (Figure 1). There was
no evidence of ocular or genital mucosal involvement. The patient
was conscious, well oriented, and afebrile. Vital signs were stable.
The patient underwent skin biopsies of two lesions on her buttock
and thigh. No organisms were seen on Gram stain. The patient’s skin
biopsy revealed extensive hyperorthokeratosis, minimal paraker-
tosis, hypergranulosis, and lichenoid interface dermatitis in the ir-
regularly acanthotic epidermis. Additionally, necrotic keratinocytes,
civatte bodies, melanin incontinence, mild perivascular lymphocytic
infiltration, a few eosinophils, and mast cells were also evident. The
clinical manifestations and the pathological findings of the skin le-
sions supported the diagnosis of baboon syndrome associated with
Tamoxifen (Figure 2).

Hence, after consulting with her oncologist, Tamoxifen was
immediately discontinued. The patient was also treated with both
oral steroid, prednisolone 50 mg once daily for 3 days and tapering
doses thereafter, and topical corticosteroid initially with Clobetasol
propionate twice a day for 2 weeks and Mometasone once daily for
1 week. She showed a remarkable improvement of skin eruptions
within days after discontinuation of Tamoxifen and steroid therapies
(Figure 3).

3 | DISCUSSION

Herein, we report the first case of Tamoxifen-induced baboon syn-
drome which occurred 8 years after initiation of Tamoxifen use. The
Tamoxifen-induced baboon syndrome seems to be reversible, as dis-
continuation of the drug improved the clinical outcomes. This diag-
nosis was strongly supported by clinical presentations, pathological
studies of the skin biopsy specimens, and favorable clinical response
to the discontinuation of Tamoxifen.

There are several reports of baboon syndrome associated with
the systemic exposure to medications such as ampicillin, dapto-
mycin, penicillin, cephalosporins, hydroxyzine, paracetamol, ome-
prazole, clozapine, ranitidine, infliximab, chemotherapeutic agents,
pseudoephedrine, codeine, allopurinol, cimetidine, and nystatin.7 To
our knowledge, this is the first report of Tamoxifen-induced baboon
syndrome. The term baboon syndrome or SDRIFE is described as
an erythema affecting the gluteal and intertriginous surfaces with a
symmetrical pattern.1 The diagnosis of SDRIFE encompasses five
criteria: (a) first time administration of a systemic drug or exposure to
repeated doses (excluding contact allergens); (b) sharply demarcated
erythema of the gluteal/perianal area and/or V-shaped erythema
of the inguinal/perigenital area; (c) presence of at least another af-
fected intertriginous/flexural site; (d) symmetrical localization; and
(e) absence of systemic involvement.

The reason of the involvement of flexural areas is not known.
There are theories that describe it as a type of recall phenomenon
from an unlinked dermatitis in the past or because of excretion of the
causative drug metabolites from eccrine glands present in flexural
areas.  

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areas. Although the typical histological picture of SDRIFE is characterized by a superficial mononuclear perivascular neutrophilic and eosinophilic infiltration, and CD4 and CD3 T lymphocytes in the dermis, other features including subcorneal pustules, vacuolar degeneration and hydropic change in the basal cells with bullae in the subepidermal area, and necrosis of keratinocytes can be observed. In our case, the diagnosis of Tamoxifen-induced baboon syndrome was made according to a typical clinical course and the histopathology. The differential diagnoses of SDRIFE include fixed drug eruption (FDE), acute generalized exanthematous pustulosis (AGEP), and drug rash with eosinophilia (DRESS). AGEP and DRESS cause a widespread rash with accompanying systemic changes, while clinically, FDE can be easily differentiated from SDRIFE by round-oval patches or plaques that are most commonly pigmented and located on acral, genital (penis, vulva, glans penis), mucosal (like vulva mucosa), extremities (50% upper and 50% lower), lips, and face. These can be with or without bullous lesions. Also some cases are reported to have extreme FDE reactions known as baboon syndrome.\textsuperscript{3,5,8,9} The most important treatment in SDRIFE is to identify and stop the causative agent. The patient should be advised to avoid the causative medication lifelong. Topical steroids may reduce the redness while the reaction resolves. Recovery may take up to 3 weeks.

In summary, baboon syndrome is a relatively common drug hypersensitivity eruption. Here, we report the first case of Tamoxifen-induced baboon syndrome which occurred several years after initiation of Tamoxifen administration. The resolution of symptoms occurred after cessation of the offending drug, Tamoxifen; thus, early diagnosis is crucial for treatment strategy and improvement of prognosis. The best approach for the diagnosis of drug-induced adverse effects in clinical practice mostly relied on the physician to quickly evaluate suspicious cases and reach a conclusive diagnosis. This is at present best achieved by the combination of clinical judgment with and without pathological evaluation of skin biopsy specimens. In cases of skin manifestation injury after Tamoxifen administration, Tamoxifen should
either be discontinued or attenuated depending on the degree and extent of manifestations. Skin biopsy is useful in establishing a diagnosis and guiding management. Steroids should be considered if dermatological manifestations persist or worsen despite discontinuation of Tamoxifen. Given the widespread use of Tamoxifen in the management of patients with breast cancer, it is important that healthcare professionals monitor for rare, however clinically significant, and potentially life-threatening dermatological manifestations of Tamoxifen use.

**AUTHORS CONTRIBUTION**

Ramin Mofarrah has contributed to the conception and design of this paper as well as analysis and interpretation of data and revision of the drafted manuscript. Ramina Mofarrah, Kousar Jahani Amiri, Naghmeh Jallab, and Sueshianth Gobadiaski have each made substantial contributions to drafting the manuscript. Birger Kraenke, Maziar Rahmani, Narges Hashemi, Maryam Ghasemi, and Nazgol Rahmani have made critical revisions on this manuscript. All authors have given their approval of the version to be submitted for publication and have participated sufficiently in the work to take public responsibility for appropriate portions of the content and have agreed 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.

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