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First Case of Symmetric Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) due to Rivastigmine?

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Abstract

The term 'baboon syndrome' was introduced in 1984 to describe a special form of systemic, contact-type dermatitis that occurs after ingestion or systemic absorption of a contact allergen in individuals previously sensitized by topical exposure to the same allergen in the same areas. Its clinical picture presents as an erythema of the buttocks and upper inner thighs resembling the red bottom of baboons. This reaction was originally observed with mercury, nickel, and ampicillin. In 2004, some authors proposed the acronym SDRIFE standing for 'symmetric drug-related intertriginous and flexural exanthema' specifically for cases elicited by systemically administered drugs. Since 1984, about 100 cases have been reported in the literature; for most of the concerned drugs, previous skin sensitization or possible cross-sensitization has not been shown.

We report the first case of SDRIFE due to rivastigmine, with the exception of an erythematous maculopapular eruption due to rivastigmine that was previously reported. Rivastigmine is a reversible and noncompetitive acetylcholinesterase inhibitor used for the treatment of Alzheimer disease.

SDRIFE is an important condition to keep in mind in order to avoid a misdiagnosis when dealing with other exanthematous disorders and to prevent re-exposure to the responsible allergen in the future.

Baboon syndrome, reminiscent of the red gluteal area of the baboon, is a relatively uncommon but distinct, cutaneous adverse drug reaction. In 1984, Andersen et al.[1] published three cases showing a sharply demarcated, gluteal and intertriginous erythema with positive patch tests to ampicillin, nickel, and mercury. Baboon syndrome originally occurs after the administration or absorption of contact allergens in individuals previously sensitized by topical exposure to the same allergen. Unlike the first cases, most of the subsequent cases have been described without known prior sensitization to the causative agent.

A large number of drugs such as ampicillin, amoxicillin, cephalosporins, erythromycin, roxithromycin, aminosalicylic acid, heparin, aminophylline, pseudoephedrine, terbinafine, immunoglobulins, radio contrast media, mitomycin, and others have been implicated, although inhalation of mercury vapor from a broken thermometer is a common cause.[2]

This syndrome presents as a systemic contact dermatitis with a pruritic and confluent maculopapular, light-red eruption localized in the gluteal area and the major flexures, provoked by allergens administered through a systemic route (oral, inhalation, or intravenous). In 2004, Häusermann et al.[3] proposed the acronym SDRIFE, standing for 'symmetric drug-related intertriginous and flexural exanthema,' specifically for cases elicited by systemically administered drugs.

Since the Andersen et al.[1] publication, there have been over 100 cases of baboon syndrome published but, to the best of our knowledge, there have been no cases of baboon syndrome due to rivastigmine described in the literature.[3-22]

1. Case Report

An 88-year-old man had a history of prostate cancer and arterial high blood pressure. His current medications included leuprorelin for the previous 7.5 years, nifedipine, allopurinol, alprazolam, lorazepam, zolpidem, PEG 4000 (macrogol 4000), and nicergoline, which he had taken for several years. For the treatment of dementia with mild cognitive impairment, the

cholinesterase inhibitor rivastigmine 1.5 mg twice daily was introduced on 15 December 2006.

On 10 March 2007, the patient developed a pruritic, symmetric, erythematous, purplish rash in the axillary and inguinal areas (figures 1 and 2). Examination revealed a light-red maculopapular rash symmetrically distributed. He was treated with loratadine and topical hydrocortisone butyrate from 13 to 24 March. At a consultation on 15 March, the pruritus was ameliorated but not the eruption affecting the groin and axillary areas. On 22 March, the lesions had worsened despite the continuation of symptomatic treatment. There were no systemic symptoms or signs. After withdrawal of rivastigmine on 23 March, the skin lesions completely resolved spontaneously in 2–3 days. The patient's other usual treatments were continued until October 2007, at which date alprazolam, lorazepam, and zolpidem were stopped.

There was no relapse of the eruption at the 1-year follow-up on 16 April 2008. Rivastigmine was not reintroduced. The dermatologist made a clinical diagnosis of baboon syndrome due to rivastigmine.

2. Discussion

With the acronym SDRIFE, the criteria proposed are: exposure to a systemically administered drug (classical contact allergens have to be excluded); sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; involvement of at least one other intertriginous/flexural fold; symmetry of affected areas; and absence of systemic symptoms and signs.[3] The two latter points are important to distinguish SDRIFE from other distinct, cutaneous drug eruptions such as drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or acute generalized exanthematous pustulosis (AGEP). There is a surprising predominance of affected male patients.[3,23,24]

Fig. 1. Sharply demarcated, V-shaped erythema in the inguinal/perigenital area.

Fig. 2. Sharply demarcated erythema in the axillary fold.

Rivastigmine, an acetylcholinesterase inhibitor, degrades acetylcholinesterase, allowing levels of acetylcholine (a neurotransmitter critical to the neurons involved in cognition) to increase. Adverse effects including nausea, vomiting, diarrhea, abdominal pain, and anorexia are generally transient and of mild to moderate intensity. Rivastigmine has not been associated with adverse skin reactions, although an erythematous maculopapular eruption and a purpuric rash in a patient receiving donepezil have been described.[25] No cases of baboon syndrome with other acetylcholinesterase inhibitors have been reported.

Monastero et al.[9] reported a case of an erythematous maculopapular eruption in a 73-year-old woman with a 2-year history of memory loss treated with rivastigmine 1.5 mg twice daily. After 5 days of treatment, she developed diarrhea, vomiting, and a rash symmetrically distributed on her wrists and lower trunk and concentrated on her legs and buttocks. Blood chemistry and hematology were normal. Rivastigmine treatment was discontinued and the gastrointestinal symptoms resolved, and her rash disappeared completely in about 2 weeks following treatment with mizolastine and oral corticosteroids. The patient was again treated with rivastigmine and 4 days later the skin eruption recurred but not the gastrointestinal symptoms. Rivastigmine therapy was immediately stopped and the rash resolved after 2 weeks.

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The two cases, our case and the case reported by Monastero et al.,[9] are similar concerning the area of the eruptions, the absence of systemic symptoms such as fever, and the favorable outcome after stopping the drug. We believe that they are also similar to those reported as baboon syndrome.[9]

Regrettably, in these two cases, neither biopsies nor skin tests were performed. Drug-related baboon syndrome shows homogeneity for clinical distribution, range of primary cutaneous lesions, and course. In contrast, heterogeneity is observed histologically and in the results of skin tests and *in vitro* investigations. In most cases, histopathology of the skin lesions reveals a superficial, perivascular, mononuclear cell infiltrate with some neutrophils and eosinophils.[3,6,14] Patch tests are positive in some cases of baboon syndrome although not in all of them. A positive test indicates a T-cell-mediated pathomechanism and may suggest that the eruption is a cutaneous, contact sensitization dermatitis.[15] Immuno-allergologic investigations (e.g. patch tests, prick tests, and intradermal tests), human basophil degranulation tests, and lymphocyte activation tests provided negative results in other cases.[4,5,14,26,27] Oral provocation tests, when they were possible, provided more positive results.[3,4] Furthermore, in spite of the absence of skin tests in the two rivastigmine-related cases, the complete and spontaneous regression after drug withdrawal suggests that rivastigmine was responsible.[9] Assessment of causality using the Naranjo algorithm[28] established a 'probable' relationship with rivastigmine in the case by Monastero et al.[9] and a 'possible' relationship in our case.

The pathogenesis of baboon syndrome remains unknown. The reason for the flexural predilection of the lesions is unclear and could be only partially explained by local occlusion and sweating.[1] Delayed T-cell-type hypersensitivity mechanisms play a key role in the evolution of characteristic flexural eruptions.[17] The time pattern of the reaction, skin tests, and the histology indicate that the pathomechanisms of these reactions are likely a cell-mediated, type IV allergy.[20] These drug eruptions with very specific involvement sites are presumably elicited by an immunologic type IV mechanism but it is difficult at present to propose additional predisposing factors such as the density of apocrine or exocrine glands, humidity, or the recall phenomenon as suggested by Wolf et al.[15] Further investigations are needed to elucidate if a genetic predisposition exists for this rare syndrome, since two simultaneous cases have been described in the same family.[21] The precise immunologic and pathogenetic mechanisms of baboon syndrome have not yet been elucidated, nor why some patients develop this particular pattern while others develop disseminated exanthemas (e.g. DRESS, anaphylaxis, and fixed drug eruptions) following exposure to the same drug.

3. Conclusions

We present a case of SDRIFE or baboon syndrome possibly elicited by rivastigmine. Baboon syndrome is a rare and often under-diagnosed drug eruption with distinct clinical features. Because of possible misdiagnosis and its rare incidence, no estimate of the prevalence of this syndrome can been made. Therefore, it is essential to communicate with health professionals about this phenomenon, first, so that the patient can avoid the allergen in the future and therefore prevent accidental re-exposure and, second, to enable recognition and diagnosis of the baboon syndrome, a relatively benign condition, in contrast to bullous eruptions or DRESS.[3,17]

[See also the review article by Winnicki and Shear on pages 171-180.]

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