A new proposal for a clinical-oriented subclassification of baboon syndrome and a review of baboon syndrome

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Summary

Objective: **To review baboon syndrome (BS). Data Sources: Date sources were obtained from PubMed and Google Scholar: Photographs of baboon syndrome were obtained from our patient.**

Study Selections: **PubMed and Google Scholar were searched up to June 30, 2010. The search terms were "baboon syndrome", "SDRIFE" and "thimerosal allergy". Reverse references from relevant articles and Google Scholar were also used. As BS is a classical disease and cases of offending agents were relatively old, some references were more than five years old. In order to gather as many cases of offending agents as possible, more than 50 references were collected.**

Results and Conclusion: **We divided BS into as 4 groups; classical baboon syndrome, topical drug-induced baboon syndrome, systemic drug-induced baboon syndrome and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). The pathomechanism of BS is still unknown. A delayed type of hypersensitivity reaction, a recall phenomenon, pharmacologic interaction with immune-receptors and anatomical factors may be involved in the causation of BS.** ***(Asian Pac J Allergy Immunol 2011;29:150-60)***

Key words: *baboon syndrome, allergic contact dermatitis syndrome (ACDS), systemic reactivation of allergic contact dermatitis (SRCD), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), classical baboon syndrome, topical drug-induced baboon syndrome, systemic drug-induced baboon syndrome, recall phenomenon, p-i (pharmacologic interaction with immuno-receptors) concept.*

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Introduction

The term "baboon syndrome"(BS) was introduced in 1984 to describe a mercury-induced characteristic eruption with previous sensitization to mercury[1]. It presents with a diffuse symmetrical erythema, predominantly on major flexural areas, and an inverted triangular or V-shaped erythema on both upper antero-medial thighs[1]. BS was named after the red bottomed baboon[1].

Recently it has been revealed that an eruption which resembles mercury-induced BS was due not only to mercury but also other metals, drugs and natural products, with or without previous sensitization to offending or related drug(s). Despite its characteristic eruptions, the name "baboon syndrome" is not well understood among doctors except for dermatologists. Therefore BS may be wrongly diagnosed as candida intertrigo or diaper dermatitis, which can lead to the wrong treatment. There is also the possibility that doctors, parents or even patients may overlook the symptoms.

Moreover, the definition of BS is not clear. In the present paper we try to establish the definition of BS and to review this syndrome.

History and classification

In 1983, Nakayama *et al.* reported characteristic eruptions induced by mercury[2]. A generalized rash appearing after inhalation of mercury vapor has also been reported[3]. It presented as a diffuse symmetrical erythema predominantly on major flexural areas and an inverted triangular or V-shaped erythema on both upper antero-medial thighs. It mostly appeared after breaking a clinical thermometer or during dental treatment by persons with a history of contact dermatitis to Mercurochrome.

Table 1. Definition of SDRIFE[6]

1. Exposure to a systemically administered drug either following the first or subsequent dose (excluding contact allergens)
2. Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area
3. Involvement of at least one other intertriginous/flexural localization
4. Symmetry of affected areas
5. Absence of systemic symptoms and signs.

Abbreviations: SDRIFE, systemic reactivation of allergic contact dermatitis.

In 1984, the term baboon syndrome(BS) was introduced to describe the characteristic development of diffuse bright red erythema resembling the red bottom of baboons[1]. In this paper, this reaction was noted in 3 patients, previously sensitized by topical contact, upon subsequent systemic exposure to the same substance (mercury, nickel and ampicillin)[1].

The name of BS is very catchy and easy to use. However, the term 'BS' is so widely used that it is difficult to define the real essence of this syndrome. There was confusion over whether other gluteal erythema such as candida intertrigo or diaper dermatitis should be called BS or a BS-like pattern[4]. Therefore, a specific definition of BS was made.

The concept of allergic contact dermatitis syndrome (ACDS) was developed by Lachapello[5] recently. There are four clinical stages of ACDS with a previous cutaneous sensitization comprising: localized ACDS(stage1), regional dissemination of ACDS via lymphatic vessels(stage2), and hematogenous dissemination of ACDS to distance sites (stage 3A) or systemic reactivation of ACDS (stage 3B). Stage 3A of ACDS can be defined as a generalized dissemination of skin lesions from the primary site of application of the allergen via blood vessels; whereas in stage 3B, allergen(s) are introduced by systemic administration (ingestion, inhalation or injection). Patients with stage 3B of ACDS were previously sensitized to the same contact allergen or chemically closely related substance(s) to the contact allergen. Lachapello called stage 3B of ACDS as systemic reactivation of allergic contact dermatitis (SRCD)[5]. The clinical signs observed in stage 3B of ACDS share a similar pattern with skin lesions observed in stage 3A of ACDS. The only difference is that in stage 3B, no current skin contact occurs. Drug-related BS with a previous cutaneous sensitization is a special case of stage 3A or 3B of ACDS.

However, cases of drug-related BS without a previous cutaneous sensitization cannot be categorized as stage 3A or 3B of ACDS. In 2004, Häusermann et al. proposed that systemically induced drug-related BS could occur without previous cutaneous sensitization(symmetrical drug-related intertriginous and flexural exanthema, SDRIFE)[6]. SDRIFE specifically refers to the distinctive clinical pattern of these drug eruptions and the following diagnostic criteria are proposed: 1) exposure to a systemically administrated drug either at the first or repeated dose (excluding contact allergens; 2) sharply demarcated erythema of the gluteal area and/or V-shaped erythema of the inguinal/perigenital area; 3) involvement of at least one other intertriginous/flexural localization; 4) symmetry of affected areas; and 5) absence of systemic symptoms and signs, as listed in Table 1[6]. SDRIFE differs from stage 3A and 3B of ACDS which are associated with previous sensitization.

There are several reasons of why Häusermann *et al.* proposed SDRIFE[6]: first, BS is historically equated with the gluteal erythema induced by systemic absorption of mercury and other agents, often after a previous cutaneous sensitization with the same substance. Second, based on recent results, the previous classification does not reflect the entire range of clinical symptoms and signs of BS. Third, according to various investigators, BS incorporates a spectrum of diseases.

In 2009, Özkaya suggested a subclassification of BS, based on the causative agent and previous sensitization: contact allergen-induced BS(excluding drugs), contact allergenic drug-induced BS and non-contact allergenic drug-induced BS[4]. Non-contact allergenic drug-induced BS is the same as SDRIFE. This classification has merit, but there is still disagreement about how to classify cases of infections or other dermatoses affecting the gluteal region.

In this article, we paraphrased contact allergen-induced BS (excluding drugs) as classical BS, BS of ACDS stage 3A as topical drug-induced BS, BS of ACDS stage 3B (or SRCD) as systemic drug-induced BS and non-contact allergenic drug-induced BS as SDRIFE. We also propose that eruptions resembling BS induced by generalized infections be describes as infection-induced BS-like pattern and that other dermatoses affecting the gluteal region without generalized infections(candida intertrigo and diaper dermatitis) be described as BS-like pattern. This subclassification is shown in Table 2.

Table 2. Classification of baboon syndrome

Our proposal	classical BS	topical drug-induced BS	systemic drug-induced BS	SDRIFE	infection-induced BS-like pattern	BS-like pattern
Häusermann P et al.[6]		stage 3A of ACDS	stage 3B of ACDS/ SRCD	SDRIFE		
Özkaya E[4]	BS type1:contact allergen-induced BS (excluding drugs)	BS type 2:contact allergenic drug-induced BS		BS type 3:non-contact allergenic drug-induced BS		
previous sensitization	+	+	+	-	-	-
drug induced	-	+	+	+	-	-
generalized infection	-	-	-	-	+	-
other dermatoses affecting the gluteal region	-	-	-	-	+	+
patch tests	+-	+	+	+-	-	-
current skin contact	+-	+	-	-	-	-

Abbreviations: BS, baboon syndrome; ACDS, allergic contact dermatitis syndrome; SRCD, systemic reactivation of allergic contact dermatitis; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

Etiologies

Causative agents of BS have been reported by various investigators (Table 3).

Classical BS

Although there have been many cases of classical BS reported, the number of causative agents are few; mercury, nickel, balsam of Peru[7](very rare) and poison ivy [8] (very rare). BS is historically often equated with a mercury-induced exanthema (eczema rubrum) in patients with previous contact sensitization[6] and the most common offending substance in classical BS is mercury.

Patients with mercury-induced BS have been sensitized to Mercurochrome previously. Mercurochrome has been used for a topical antiseptic for minor cuts and scrapes in children and for umbilical antiseptic at birth in some countries until recently. As mercury exists in liquid form and easily evaporates at room temperature, it is easily inhaled. Mercury-induced BS generally occurs as a result of inhalation of mercury released by breaking a thermometer or by ingestion of dental amalgam during dental filling. However, some atypical cases were also reported: playing with a "mercury maze"[9], ingestion of mercury-containing homeopathic medicine [10] and walking around cinnabar (mercuric sulfide) mines[11].

Patch tests with mercury are sometimes negative, but other mercury compounds sometimes produce positive results [12]. Patients with classical BS are positive for mercury or at least for one mercury compound. There is the question as to whether thimerosal causes classical BS. Thimerosal is an organomercury compound and is a well established antiseptic and antifungal agent. Thimerosal has been used widely for ophthalmologic and contact lens solutions, immunoglobulin, vaccines, cosmetics and toothpastes for preservative worldwide and is still used in some countries. The administration of thimerosal-containing components, especially thimerosal-containing vaccines may account for thimerosal sensitization. Some patients with mercury-induced BS are thimerosal-positive on patch tesing[12]. There are two reported cases of systemic contact dermatitis due to thimerosal in vaccines [13]. These offending vaccines were oral anticatarrhal vaccine (Lantigen B (R) Bruschettini) and nasal antipneumococcal vaccine. However,

Table 3. List of causes of BS

subclass		offending agents
classical BS		
		mercury (vapor [1] and dental [1])
		nickel [1]
		blalsam of Peru [7]
		poison ivy [8]
topical drug-induced BS		
		amipicillin [1]
		5-aminosalicylic acid [16]
		bufexamac[17]
		cinchocaine[17]
systemic drug-induced BS		
		ethlendiamine (intravenous) [18]
		neomycin (oral) [19]
		nystatin (oral) [20]
		erythromycin(oral) [21]
		predonisolene (oral) [22]
		methylprednisolene (oral) [22]
		betamethasone (oral) [22]
		dexamethasone (oral) [22]
		hydrocorotisone (oral) [22]
		cloprednol (oral) [22]
BS-like pattern		
		erysipelas
		intertrigo
		staphylococcal scalded skin syndrome (SSSS)
infection-induced BS-like pattern		
		streptococcus [46]
		parvovirus B19 [47]
		common cold [48]
SDRIFE		
	antibiotics (beta-lactam)	
		amoxicillin [1]
		ampicillin [23]
		amoxicillin/clavulanic acid [24]
		pivampicillin [25]
		penicillin V [26]
		ceftriaxone [24]
		cefuroxime [24]
		cephalexin [24]
	antibiotics (non beta-lactam)	
		clindamycin [28]
		roxithromycin [29]
	corticosteroids	
		deflazacort [33]
	radiocontrast	
		barium sulfate [24]
		iomeprol [31]
		iopromide [31]
	monoclonal antibodies	
		cetuximab [40]
		glembatumumab vedotin (CR011-vcMMAE) [41]
	psychopharmaceuticals	
		risperidone [43]
		loflazepate ethyl [44]
	Other drugs	
		allopurinol [30]
		cimetidine [32]
		hydroxyurea [34]
		heparin (intravenous) [35]
		IVIG (intravenous human immunoglobulins) [36]
		mitomycin C [37]
		naproxene [24]
		oxycodone [24]
		pseudoephedrine [27]
		salsalate [38]
		terbinafin [39]
		valacyclovir [42]

Abbreviations: BS, baboon syndrome; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

no other articles mention BS following the use of vaccines, allergenic extracts, or any other compound containing thimerosal as a preservative. The reason could be that the amount of thimerosal is too small and thimerosal containing vaccines have been reduced in number or removed recently. Many vaccines containing thimerosal are used outside North America, Europe and Japan and in some other countries, nevertheless the World Health Organization has concluded that there is no evidence of toxicity from thimerosal in vaccines and no reason, on safety grounds, to change to more-expensive single-dose administration[14]. A positive patch test to thimerosal does not represent a contraindication to use thimerosal-containing vaccines.

Nickel is also a cause of contact allergen-induced BS but is seen less frequently. Loosely-bonded nickel in the interior surface of the metallic eyelet in an intravenous catheter, which is easily removed by the shearing stress of fluid flow, can cause BS in patients with previous nickel contact sensitization[15]. Tetraethlthrum disulfide(Antabuse (R)), which was used for nickel-associated pompholyx, causes an anitial acute increase in the blood nickel concentration, which may evoke BS[1].

Natural components can also induce classical BS, however not very often. The use of suppositories that contained balsam of Peru has induced classical BS[7]. A 30-year-old man with a history of acute contact poison ivy dermatitis developed a widespread bright red eruption with confluence in the groin, buttocks, thighs, palms, soles, and intertriginous areas[8].

Topical drug-induced BS and systemic drug-induced BS (contact allergenic drug-induced BS)

Although many cases of classical BS and SDRIFE have been reported, the number of cases with contact allergenic drug-induced BS is relatively few. One reason may be that many topical drugs are not available for systemic administration (ingestion, inhalation or injection).

There are two types of exposure; topical (topical drug-induced BS) and systemic (systemic drug-induced BS). Examples of systemic absorption due to topical exposure are ampicillin(topical cream)[1], 5-aminosalicylic acid for a foam enema[16], bufexamac[17] and cinchocaine[17]. Except for ampicillin, these drugs were used in the anal area and are thought to be absorbed from mucosal surfaces. Examples of systemic exposure are intravenous ethylenediamine[18], oral neomycin[19], oral

nystatin[20], oral erythromycin[21] and oral corticosteroids[22] (prednisolone, methylprednisolone, betamethasone, cloprednol, deflazacort, dexamethasone and hydrocortisone).

Ethylenediamine was infused with amminophyline for asthma attacks.Patch tests were negative or 20 standard agents but positive for ethylenediamine[18].

All patients with contact allergenic drug-induced BS had positive reactions on patch testing with the offending agent.

SDRIFE

Approximately 50 cases of SDRIFE have been reported to date. According to various investigators, miscellaneous offending substances have been identified. Examples of offending agents are; amoxicillin[1], ampicillin[23], amoxicillin/clavulanic acid[24],pivampicillin[25], penicillin V[26], ceftriaxone[24], cefuroxime[24], cephalexin[24], pseudoephedrine[27], clindamycin[28], roxithromycin[29], allopurinol[30], barium sulfate-containing contrast media[24], iomeprol[31], iopromide[31], cimetidine[32], oral deflazacort[33], hydroxyurea[34], heparin[35], immunoglobline[36], mitomycin C[37], naproxen[24], oxycodone[24], salsalate[38], terbinafine[39], cetuximab[40], glembatumumab vedotin(CR011-vcMMAE)[41], valacyclovir[42], risperidone[43] and loflazepate ethyl[44].

The most common offending drugs are antibiotics, especially beta-lactum antibiotics. Amoxicillin is the leading eliciting agent [6]. In SDRIFE, the causative chemical in amoxicillin and other beta-lactam antibiotics is probably the beta-lactam ring, or less probably the thiazolidine ring, because two penicillins (amoxicillin/ sulbactam and phenoxylpenicillin) that have different side chains have caused SDRIFE in the same patient[45]. Recently, cases of SDRIFE due to psycho-pharmaceuticals (risperidone[43] in 2009 and loflazepate ethyl[44] in 2009) have been reported.

Infection-induced BS-like pattern

Three cases of infection-induced BS-like pattern were reported (*Streptococcus pyogenes*[46], *parvovirus B19*[47] and common cold[48]); one case was described as BS[46] and the other two cases BS-like. This was due to obscurity of the definition of BS. Surprisingly, these infection-related BS like lesions have been reported only in Japan.

BS-like pattern

There is still disagreement as to whether cases of infection or other dermatoses affecting the gluteal region should be termed as a BS-like pattern[4], because these dermatoses have previously been give other names and do not need to be renamed as BS-like pattern. Examples of BS-like pattern are erysipelas, intertrigo, diaper dermatitis and staphylococcal scalded skin syndrome(SSSS).

Epidemiology

More than 120 cases have been reported to date[4]. Patients with SDRIFE tend to be elderly people[6] whereas mercury-induced BS occurs in young people who break thermometers or play with mercury[12]. But there are some exceptions; a 3-year-old boy developed BS after oral treatment with cefadroxil[49] (patch tests were not done), an 8-year-boy after oral treatment of risperidone[43] and an 18-month-old boy developed systemic drug-induced BS after oral treatment with erythromycin[21]. He had previously been treated with erythromycin for eczema.

Females and males of any age seem to be equally affected by mercury-induced BS, whereas there is a predominance of middle-aged male patients (70%) observed in SDRIFE[6].

Whether BS is related to a genetic factor is unknown. In mercury-induced BS there were two familial cases: a mother and her child[2] and among siblings[50]. This may be due to not to a genetic factor but to environmental factors.

With regard to mercury-induced BS, there is a surprising predominance in countries like Spain, Portugal, Belgium, France and Japan[10]. In these countries, especially Japan[3], Mercurochrome and mercury thermometers were commonly used. Recently, however these thermometers have been withdrawn from use in Japan. It is uncertain why almost all cases of mercury-induced BS in Southeast Asia have been reported from Japan. Only one case of mercury-induced BS in China was reported in 2007[51] and few cases in Korea[52,53]. These incidences are surprisingly lower than in Japan. In other Southeast Asia countries, especially Thailand, mercury is commonly used. There is, however, the possibility of wrong diagnosis or oversight in Southeast Asia. Therefore, doctors and health care practitioner should be aware of BS.

Clinical features

BS is a form of benign dermatitis with an acute onset. It is characterized by diffuse erythema of the buttocks and the anogenital area, usually demarcated by sharp well-defined borders, thus showing a bathing trunk distribution on the underpants area[5]. BS sometimes involves other areas; e.g. neck, face

and lips. Bullae between patient's toes and fingers have also been reported[24]. BS is essentially symmetrical, but a 14-year-old boy was diagnosed with classical BS coexisting with vitiligo, due to broken thermometers, presented with erythematous eruptions which were more evident on the vitiliginous side of his trunk[54].

The latency between the drug ingestion and the onset of the eruption ranges from hours to a few days, but there are few exceptions; the shortest latent time is about one hour[42].

Most cases of BS are not accompanied by generalized symptoms. Moreover, patients with SDRIFE have no systemic symptoms and signs by definition. But some cases, especially cases of mercury-induced BS are sometimes accompanied by generalized symptoms, such as fever[2], abdominal pain[53], diarrhea[53], malaise and thirst[2]. Fever is generally mild but may be up to 40 ^{o}C[2]. In mercury-induced BS with abdominal pain and diarrhea, upper gastrointestinal endoscopic and colonoscopic findings were non-specific [53]. Some patients feel an itchy or burning sensation, which is relatively mild. However some reports did not mention any symptoms.

In most cases, blood chemistry and hematology are normal, but some cases, especially mercury-induced BS, have mild eosinophilia or leukocytosis with positive C-reactive pattern and mild proteinuria[2]. In mercury-induced BS, concentrations of mercury in serum, blood and urine are within normal levels and have a decreasing trend[51].

Histopathology

Although BS shows homogeneity for clinical distribution, range of primary cutaneous lesions, latency after systemic absorption and course, heterogeneity is observed histologically and in the results of skin tests and in vitro investigations[6]. Most histopathological examinations reveal non-specific changes. In many cases a predominance of superficial perivascular infiltrates of mononuclear cells[6] is reported and some cases have infiltration with erythrocytes, neutrophils and eosinophils with mild dermal edema and spongiosis[5]. PAS (Periodic acid-Schiff) stains are negative for fungal elements[24].

There have been several immunohistological investigations. One case was SDRIFE induced by intravenous human immunoglobulins[36]. Immunohistological investigation revealed granular deposits of C1q along the dermo-epidermal junction and perivascular infiltration with CD4+ lymphocytes. An expression of CD62P (P-selection) was observed on keratinocytes along the dermo-epidermal junction. Another case with SDRIFE, due to radiocontrast media, revealed that the lymphocytes were predominantly CD3 and CD4 positive, with only a few scattered CD8-, CD20- and CD56- positive cells[31]. These two immunohistological investigations are overall compatible with T-cell-mediated hypersensitivity.

Pathogenesis

The precise mechanism of BS pathogenesis is still unknown.

A 14-year-old boy with segmental vitiligo on the right thoracolumbar region presented with BS due to a broken thermometer[54]. Interestingly, the erythematous eruptions were more evident on the vitiligous side of the trunk. This indicates that BS is due to immunological reactions as the pathogenesis of vitiligo is thought to be due both cellular and humerally mediated immunity.

There is strong evidence for the role of a T-cell mediated delayed type hypersensitivity reactions in the pathogenesis of BS, supported by positive patch tests, by a positive delayed skin test [55], by an immunohistochemical evidence for CD4+ T-cell infiltration[31,36] and by lymphocyte transformation tests (LTT)[21].

Häusermann *et al.* believed that SDRIFE was presumably elicited by an immunological type IV mechanism[6]. Özkaya reported that the pathomechanism of BS involvs with type IVa (reaction with Th1 cells and macrophages) and IVc (reaction with cytotoxic CD8 T cells) reactions [4].

However, there was a case where a patient developed SDRIFE only one hour after taking valacyclovir[42], which could not be explained only by a T-cell mediated delayed type hypersensitivity reaction. Moreover, patients with drug eruptions may have had previous contact with the offending agent or a related drug. This cannot explain why patients represent SDRIFE without previous sensitization to a specific drug.

Daito et al.[42] and Wolf et al.[24] referred the recall phenomenon as the cause of BS. The concept of the recall phenomenon has been extended to include drug- or contact-induced reactivation of tissue toxicity initially evoked by sun exposure, previous allergen injections or mechanical injuries[42]. Most cases of BS may represent a recall of any form of dermatitis that has occurred in the past in the same area after exposure to a new drug. Previous dermatitis may have been severe diaper rash in

infancy, contact dermatitis to any allergen or irritant, or other forms of typical intertrigo. If this is the case, the agent causing BS is generally different and unrelated to the agent that has caused the dermatitis in the past, even though it might in specific cases be the same[24].

Recently, a novel pathological mechanism, the p-i concept (pharmacologic interaction with immunoreceptors) was suggested to be involved in direct recognition of some chemically inert molecules[4]. According to this new concept, certain drugs are able to bind directly and noncovalently to a fitting T-cell receptor without first being presented by MHC (major histocompatibility complex) molecules and without prior metabolism [4]. The p-i concept may explain several aspects of drug reactions including: the ability of an inert substance to induce an immune response, the preferential localization of drug reactions in the skin and reactions occurring on first exposure to a drug and the fact that high drug doses are more often associated with systemic allergic dermatitis [4]. Moreover, suggesting that certain drugs are capable of inducing primary sensitization to T cells by direct systemic exposure, the p-i concept might be a reasonable explanation for the absence of previous cutaneous sensitization in the majority of drug-induced BS cases[4].

Häusermann et al.[6] also referred to anatomic structures, e.g. the density of apocrine or eccrine glands, temperature, and humidity at relevant factors. As for sweat glands, some reports suggest a relationship between the eccrine glands and chemotherapy-induced intertriginous eruptions[6,42].

Diagnosis

BS is often an obvious diagnosis i.e. diffuse symmetrical erythema predominantly on major flexural areas. An inverted triangular or V-shaped erythema on both upper antero-medial thighs is a common feature[2], but a diagnostic criteria that would be applicable to all types of BS is still lacking.

Questions about previous drug and/or metal allergy, recent medicine and whether the patient came in contact with a broken thermometer may help to make a diagnosis and may reveal previous BS[22].

On the other hand, offending agents cannot be identified by simple history taking, since there are still mercury counting substances in use and thus occupational and/or behavioral oriented questions are needed. For example, cases of mercury-induced BS due to mercury-containing homeopathic medicine[10], "mercury maze"[9] and cinnabar (mercuric sulfide) mines [11] are reported. BS by loosely-bonded nickel in the interior surface of the metallic eyelet in an intravenous catheter could be wrongly diagnosed as drug related BS, when in fact it is due to the substance infused by the catheter[15]. A tetraethlthrum disulfide (Antabuse (R)) which was used for nickel-associated pompholyx leads to an initial acute increase in the blood nickel concentration, which evokes BS[1]. Therefore, specific history taking including medical history, social history and occupational history may be required for a clear diagnosis.

Eruptions of classical BS tend to first appear in the flexures[2]. A symmetrical diffuse erythematous or erythemato-papular rash spreads rapidly within a few days. The main clinical findings include a sharp demarcation of V-shaped erythema in inguinal/genital and gluteal/perianal areas and, in most cases, additional involvement of at least one other flexural or intertriginous fold[6].

Although patch testing is essential for diagnosis of BS, the rate of positive tests is not high. The positive rate of metallic mercury in mercury-induced BS, contact allergenic drug-induced BS and SDRIFE is about 82%[12], 100%[6] and 52%[6] respectively. Patients with BS are sometimes positive to patch tests with substances that resemble who are negative on the metallic mercury patch test are sometimes positive with other mercury components[12]. As for *in vitro* tests, there is a report that lymphocyte transformation tests (LTT) which indicates a T-cell mediated delayed type hypersensitivity was positive in a patient with systemic drug-induced BS[21].

Systemic symptoms, laboratory data and specimens from biopsy are not specific nor diagnostic. In mercury-induced BS, concentrations of mercury in serum, blood and urine are within normal levels and yet had a descending trend [51].

An oral provocation test is recommended for a precise diagnosis. A patient with BS to oral prednisolone and methylprednisolone had a positive oral provocation tests with polyvalent corticosteroids (betamethasone, cloprednol, deflazacort, dexamethasone and hydrocortisone)[22].

Differential diagnosis

It is very important to draw attention to clinical presentations of any drug eruption because these cases might be easily overlooked or misdiagnosed.

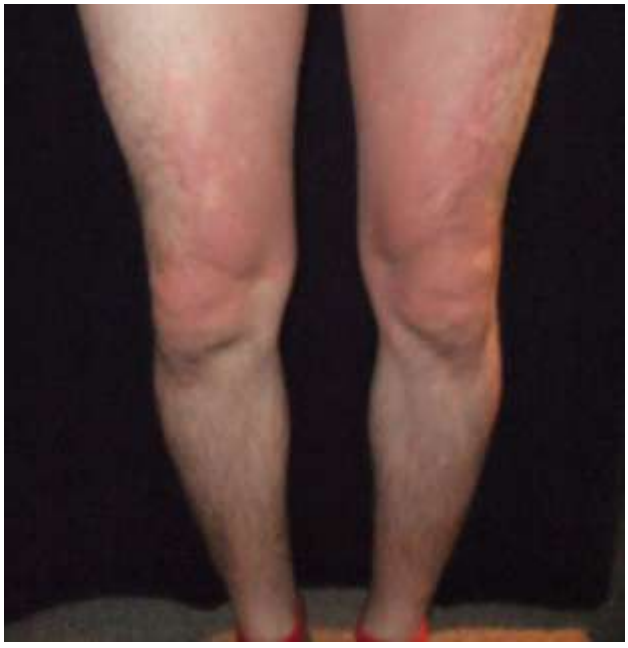

Figure1. A case of probable topical drug-induced BS

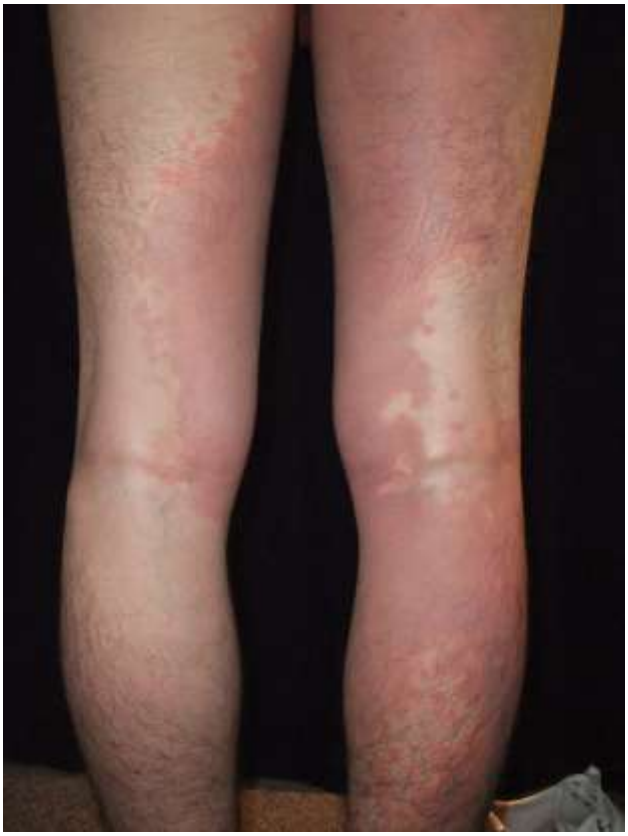

Figure3 . A case of probable topical drug-induced BS: A 30-year old man had pruritus of his thighs and used an ointment containing bufexamac. He presented erythema with scaling on the upper antero-medial thighs, knees, bottom, back and upper arms after one or two days.

Skin biopsies revealed superficial perivascular infiltrates of many lymphocytes and few eosinophils in dermis. Blood congestion was observed in small vessels. The epidermis was scattered with mild spongiosis. These findings were compatible with contact dermatitis. Patch tests ware not performed.

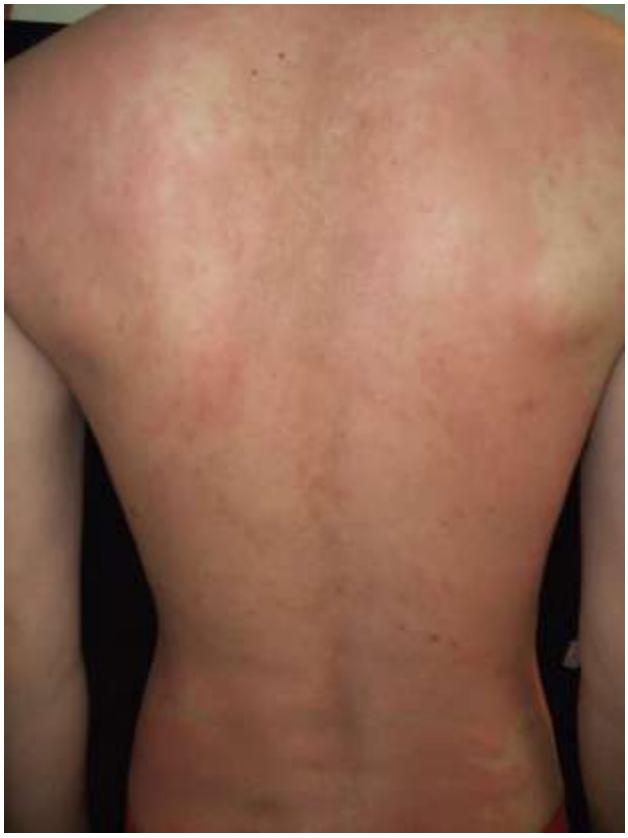

Figure2. A case of probable topical drug-induced BS

As there are many diseases that evoke eruptions in intertriginous and flexural areas, physicians may diagnose BS as another disease such as candida intertrigo[24]. In that case, topical antifungal agents are not effective. On the other hand, in children, it is an important entity to take into account in the differential diagnosis of viral exanthem. Because of exanthem on face[49] and lips[21] in addition to intertriginous and flexural areas, BS in childhood may be misdiagnosed as Staphylococcal scalded skin syndrome (SSSS), therefore physicians should check children who have intertriginous and flexural exanthem to see whether eye discharge and Nikolsky sign are present.

Other drug eruptions also need to be considered. A classification of SDRIFE as a separate entity

within the spectrum of drug eruptions requires a separation from FDE (fixed drug eruption), AGEP (acute generalized exanthematous pustulosis), TEN (toxic epidermal necrolysis) and DRESS (drug rash with eosinophilia and systemic symptoms)[6].

Treatment

BS is generally benign. Eruptions usually tend to resolve spontaneously with desquamation after discontinuing the offending drugs within 1-2 weeks. None of the cases reported have residual hyperpigmentation. Although in rare cases eruptions may spread despite the discontinuation of the offending drug, they resolved spontaneously without any pigmentation in the end[24].

Topical corticosteroids and systemic antihistamines result in symptomatic relief. In severe cases a short course of systemic corticosteroids may be helpful. In severe cases of mercury-induced BS, it may be advisable to screen for toxic mercury levels in the blood and urine.

If the eruption does not resolve after the discontinuation of the offending drug, other dermatoses affecting the gluteal region such as candidiasis should be considered.

Conclusions

BS is a drug eruption that appears as a diffuse symmetrical erythema, predominantly on major flexural areas and an inverted triangular or V-shaped erythema on both upper antero-medial thighs[1]. BS was named after the red bottomed baboon[1]. Regarding the cause and the role of previous sensitization, generally there are three types of BS: contact allergen-induced BS (excluding drugs), contact allergenic drug-induced BS and non-contact allergenic drug-induced BS. In this article, we try to reclassify contact allergen-induced BS (excluding drugs) as classical BS, BS of ACDS stage 3A as topical drug-induced BS, BS of ACDS stage 3B (or SRCD) as systemic drug-induced BS and non-contact allergenic drug-induced BS as SDRIFE.

Classical BS is generally due to mercury vapour from broken thermometers with previous mercury sensitization. Sensitization to mercury occurs by the use of topical antiseptic for minor cuts and scrapes in children and umbilical antiseptic at birth. An introduction by systemic administration (generally inhalation from a broken thermometer) can cause BS. Although some Southeast Asian countries are still using mercury, it is unclear why cases of classical BS have not been reported, except for Japan, Korea and China, which could mean that physicians, patients and parents may have overlooked BS.

SDRIFE is systemically induced drug-related BS without previous cutaneous sensitization. Although the most common causative agents are beta-latum antibiotics, especially amoxicillin, some other medications can also cause BS. Recently, cases of SDRIFE due to psychopharmaceuticals (risperidone[43] in 2009 and loflazepate ethyl[44] in 2009) have been reported. There is a predominance of middle-aged male patients (70%) observed in drug-induced BS[6], but some cases in children have also been reported.

A careful examination, history taking and patch tests are important in diagnosing BS, since it may be diagnosed wrongly as candida intertrigo or diaper dermatitis and therefore treated wrongly.

The pathogenesis of BS is still unknown but there is strong evidence for the role of a T-cell mediated delayed type hypersensitivity reaction in the pathogenesis of BS. However, other mechanisms such as recall the phenomenon, the p-i concept (pharmacologic interaction with immunoreceptors) and anatomical factors must be considered.

BS is generally benign. The eruption usually tends to resolve spontaneously with desquamation after discontinuing the offending drug within 1-2 weeks. None of the cases have residual hyperpigmentation.

Our new subclassification of BS is clinically-oriented and useful; however a more precise, detailed and easily applied subclassification of BS is needed.

References

1. Andersen KE, Hjorth N, Menne T. The baboon syndrome: systemically-induced allergic contact dermatitis. Contact Dermatitis. 1984; 10: 97-100.
2. Nakayama H, Niki F, Shono M, Hada S. Mercury exanthem. Contact Dermatitis. 1983; 9: 411-417.
3. Matsumoto J, Natsuaki M. [Three Cases of Mercury Allergy (in Japanese)] Skin Resarch [Hifu]. 1997; 39: 48-52.
4. Özkaya E. Current understanding of Baboon syndrome Expert Review of Dermatology. 2009; 4: 163-175.
5. Lachapelle J-M. The Spectrum of Diseases for Which Patch Testing is Recommended. In: Lachapelle J-M, Maibach HI, editors. Patch Testing and Prick Testing: A Practical Guide Official Publication of the ICDRG, 2nd edition. Berlin: Springer-Verlag; 2009. p. 7-31.
6. Häusermann P, Harr T, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis. 2004; 51: 297-310.

7. Veien N, Menné T. Systemic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, editors. Contact Dermatitis ,4th edition. Berlin: Springer; 2009. p. 295-307.
8. Young A. baboon_syndrome_12_050523: Dermatology Image Atlas. Johns Hopkins Medical Institutions. 2005 May [cited 2010 Nov 1];[about 1p.]. Available from: http://dermatlas.med.jhmi.edu/derm/display.cfm?ImageID=-1844504124
9. Le Coz CJ, Boos V, Cribier BJ, Grosshans EM, Heid E. An unusual case of mercurial baboon syndrome. Contact Dermatitis. 1996; 35: 112.
10. Audicana M, Bernedo N, Gonzalez I, Munoz D, Fernandez E, Gastaminza G. An unusual case of baboon syndrome due to mercury present in a homeopathic medicine. Contact Dermatitis. 2001; 45: 185.
11. Bartolome B, Cordoba S, Sanchez-Perez J, Fernandez-Herrera J, Garcia-Diez A. Baboon syndrome of unusual origin. Contact Dermatitis. 2000; 43: 113.
12. Moreno-Ramírez D, García-Bravo B, Pichardo AR, Rubio FP, Martínez FC. Baboon syndrome in childhood: easy to avoid, easy to diagnose, but the problem continues. Pediatr Dermatol. 2004; 21: 250-253.
13. Zenarola P, Gimma A, Lomuto M. Systemic contact dermatitis from thimerosal. Contact Dermatitis. 1995; 32: 107-108.
14. World Health Organization. Thiomersal and vaccines: Global Advisory Committee on Vaccine Safety. 2006 Jul [cited 2010 Nov 1];[about1p.]. Available from: http://www.who.int/vaccine_safety /topics/thiomersal/ en/index.html
15. Bircher AJ, Schmidli F, Strub C, Muller B, Scherer K. Systemic allergic dermatitis reaction to nickel released from an eyelet in an intravenous catheter. Contact Dermatitis. 2009; 61: 180-182.
16. Gallo R, Parodi A. Baboon syndrome from 5-aminosalicylic acid. Contact Dermatitis. 2002; 46: 110.
17. Proske S, Uter W, Schnuch A, Hartschuh W. [Severe allergic contact dermatitis with generalized spread due to bufexamac presenting as the "baboon" syndrome (in German)] Dtsch Med Wochenschr. 2003; 128: 545-547.
18. Guin JD, Fields P, Thomas KL. Baboon syndrome from i.v. aminophylline in a patient allergic to ethylenediamine. Contact Dermatitis. 1999; 40: 170-171.
19. Menné T, Weismann K. [Hematogenous contact eczema following oral administration of neomycin. (in German)] Hautarzt. 1984; 35: 319-320.
20. Lechner T, Grytzmann B, Bäurle G. [Hematogenous allergic contact dermatitis after oral administration of nystatin. (in German)] Mykosen. 1987; 30: 143-146.
21. Goossens C, Sass U, Song M. Baboon syndrome. Dermatology. 1997; 194: 421-422.
22. Treudler R, Simon JC. Symmetric, drug-related, intertriginous, and flexural exanthema in a patient with polyvalent intolerance to corticosteroids. J Allergy Clin Immunol. 2006; 118: 965-967.
23. Schultz ES, Diepgen TL. [Clinical characteristics and the cause of the baboon syndrome. (in German)] Derm Beruf Umwelt. 1996; 44: 266-269.
24. Wolf R, Orion E, Matz H. The baboon syndrome or intertriginous drug eruption: a report of eleven cases and a second look at its pathomechanism. Dermatol Online J. 2003; 9: 2.
25. Rasmussen LP, Menné T. [Systemic contact eczema--the baboon syndrome--in ampicillin allergy. (in Danish)] Ugeskr Laeger. 1985; 147: 1341-1342.
26. Panhans-Gross A, Gall H, Peter RU. Baboon syndrome after oral penicillin. Contact Dermatitis. 1999; 41: 352-353.
27. Sanchez TS, Sanchez Perez J, Aragues M, Garcia Diaz A. Flare-up reaction of pseudoephedrine baboon syndrome after positive patch test. Contact Dermatitis. 2000; 42: 312-313.
28. Wolf R, Elman M, Brenner S. Drug-induced "intertrigo". Int J Dermatol. 1993; 32: 515-516.
29. Amichai B, Grunwald MH. Baboon syndrome following oral roxithromycin. Clin Exp Dermatol. 2002; 27: 523.
30. Montag G, Weber L, Gall H. Baboon-syndrom auf Allopurinol. Akt Dermatol. 1996; 22: 311-313.
31. Arnold AW, Hausermann P, Bach S, Bircher AJ. Recurrent flexural exanthema (SDRIFE or baboon syndrome) after administration of two different iodinated radio contrast media. Dermatology. 2007; 214: 89-93.
32. Helmbold P, Hegemann B, Dickert C, Marsch WC. Symmetric ptychotropic and nonpigmenting fixed drug eruption due to cimetidine (so-called baboon syndrome) Dermatology. 1998; 197: 402-403.
33. Garcia Bravo B, Repiso JB, Camacho F. Systemic contact dermatitis due to deflazacort. Contact Dermatitis. 2000; 43: 359-360.
34. Chowdhury MM, Patel GK, Inaloz HS, Holt PJ. Hydroxyurea-induced skin disease mimicking the baboon syndrome. Clin Exp Dermatol. 1999; 24: 336-337.
35. Pfeiff B, Pullmann H. Baboon-artiges arzneiexanthem auf heparin. Deutsch Dermatologe. 1991; 39: 559-560.
36. Barbaud A, Tréchot P, Granel F, Lonchamp P, Faure G, Schmutz JL, *et al.* A baboon syndrome induced by intravenous human immunoglobulins: report of a case and immunological analysis. Dermatology. 1999; 199: 258-260.
37. de Groot AC, Conemans JM. Systemic allergic contact dermatitis from intravesical instillation of the antitumor antibiotic mitomycin C. Contact Dermatitis. 1991; 24: 201-209.
38. Gordon E. Baboon syndrome caused by Salasate. J Drugs Dermatol. 2002; 1: 66.
39. Weiss JM, Mockenhaupt M, Schopf E, Simon JC. [Reproducible drug exanthema to terbinafine with characteristic distribution of baboon syndrome. (in German)] Hautarzt. 2001; 52: 1104-1106.
40. Sans V, Jouary T, Hubiche T, Smith D, Milpied B, Taieb A. Baboon syndrome induced by cetuximab. Arch Dermatol. 2008; 144: 272-274.

41. Elmariah SB, Cheung W, Wang N, Kamino H, Pomeranz MK. Systemic drug-related intertriginous and flexural exanthema (SDRIFE). Dermatol Online J. 2009; 15: 3.
42. Daito J, Hanada K, Katoh N, Katoh S, Sakamoto K, Asai J, *et al*. Symmetrical drug-related intertriginous and flexural exanthema caused by valacyclovir. Dermatology. 2009; 218: 60-62.
43. Akay BN, Sanli H. Symmetrical drug-related intertriginous and flexural exanthem due to oral risperidone. Pediatr Dermatol. 2009; 26: 214-216.
44. Watanabe T, Yamada N, Yoshida Y, Yamamoto O. A case of symmetrical drug-related intertriginous and flexural exanthema induced by loflazepate ethyl. J Eur Acad Dermatol Venereol. 2010; 24: 357-358.
45. Handisurya A, Stingl G, Wohrl S. SDRIFE (baboon syndrome) induced by penicillin. Clin Exp Dermatol. 2009; 34: 355-357.
46. Ichimiya M, Hamamoto Y, Muto M. A case of baboon syndrome associated with group a streptococcal infection. J Dermatol. 2003; 30: 69-71.
47. Yamada Y, Iwasa A, Kuroki M, Yoshida M, Itoh M. Human parvovirus B19 infection showing follicular purpuric papules with a baboon syndrome-like distribution. Br J Dermatol. 2004; 150: 788-789.
48. Hanada K, Kinoshita H, Kato N, Kishimoto S. [Repeatedly appeared baboon syndrome like eruption associated with common cold (in Japanese)] (kanbouni tomonai kurikaeshi syutugenshita baboon syndrome youhishin) Hifu no kagaku. 2006; 4: 327.
49. Dhingra B, Grover C. Baboon syndrome. Indian Pediatr. 2007; 44: 937.
50. Garcia Menaya JM, Cordobes Duran C, Bobadilla P, Lamilla A, Moreno I. Baboon syndrome: 2 simultaneous cases in the same family. Contact Dermatitis. 2008; 58: 108-109.
51. Wen L, Yin J, Ma DL, Lanier B. Baboon syndrome induced by mercury - first case report in China. Contact Dermatitis. 2007; 56: 356-357.
52. Hong JH, Hong SH, Moon KC. A case of baboon synrome due to mercury smoke of an amulet. Korean J Biochem. 1993; 31: 607-611.
53. Oh CK, Jo JH, Jang HS, Kim MB, Kwon YW, Kwon KS. An unusual case of mercurial baboon syndrome from metallic mercury in a broken industrial barometer. Contact Dermatitis. 2003; 49: 309-10.
54. Utaş S, Ferahbaş A. Baboon syndrome and segmental vitiligo coexistence. Turk J Pediatr. 2009; 51: 392-394.
55. Kick G, Przybilla B. Delayed prick test reaction identifies amoxicillin as elicitor of baboon syndrome. Contact Dermatitis. 2000; 43: 366-367.