

Systemically induced allergic exanthem from mercury

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Cutaneous reactions to mercury can manifest themselves in different forms. Apart from contact dermatitis, flare-up reactions, disseminated exanthem as well as skin symptoms in previously unaffected skin are known. Regarding systemic allergen application, 2 separate clinical patterns, namely acute generalized exanthematous pustulosis (AGEP) and symmetric flexural exanthem 'baboon syndrome' have been described. Systemic allergic reactions to mercury are most commonly provoked by the inhalation of metallic mercury vapours from a broken thermometer, often after previous sensitization to mercury compounds, e.g. Mercurochrome. Patch testing with mercurials yields positive reactions in approximately 80% of patients. We report 3 patients, 2 with flexural exanthem, and 1 presenting with AGEP, respectively. Positive patch tests to mercury derivatives could be demonstrated in all of them. Furthermore, non-toxic serum mercury levels were detected in 2 of the patients. The present review provides a survey of the literature on systemic allergic exanthem to mercury. However, plausible explanations for the distribution pattern of the skin manifestations in AGEP and flexural exanthem are still lacking.

Key words: AGEP; baboon syndrome; children; mercury; patch test; systemic contact dermatitis.
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Although for the most part banned from modern antiseptic preparations, allergic reactions to mercury can still be a problem today. Depending on the form and the extent of exposure, the derivatives of this heavy metal may cause different types of cutaneous symptoms, for example: allergic contact dermatitis from thimerosal (merthiolate) and other organic as well as inorganic mercurials; lichenoid or granulomatous reactions to mercuric sulphide (cinnabar-vermilion); and nummular dermatitis to amalgam (1–4).

So-called systemically induced allergic contact dermatitis is most commonly provoked by the inhalation of metallic mercury vapours, usually from a broken thermometer, often initiated by previous exposure to organic mercury compounds such as thimerosal and Mercurochrome. For the diffuse and symmetric erythematous maculopapular eruption of the flexural areas, with a V-shaped pattern on the medial thighs and diffuse erythema of the buttocks within a few days of exposure, the term 'baboon syndrome' has been proposed (5). In some cases, pustule formation has been observed as the disease pro-

gressed. Usually, patients do not present systemic symptoms. In contrast to this, acute generalized exanthematous pustulosis (AGEP) is characterized by the sudden formation of numerous small, mostly non-follicular pustules on a widespread oedematous erythema. This particular form of exanthem is most frequently due to aminopenicillins and macrolides but also to mercury. Patients with AGEP present with fever (frequently above 38°C), typical histologic findings and blood neutrophilia (6, 7).

We report 3 patients with acute exanthematous reactions after exposure to mercury derivatives, 2 with typical flexural and V-shaped pattern and 1 with AGEP, respectively. In all 3, a delayed-type hypersensitivity to mercury compounds could be confirmed by patch tests.

Patients and Results

Case no. 1

An 8-year-old boy with a history of atopic diseases presented with an acute itchy exanthem

a few hours after taking a mercury-containing lozenge for a pharyngitis. There was a history of contact allergy to mercurial disinfectants as an infant, but no side effects after vaccinations.

On clinical examination, flexural erythema of the large folds, the genital and gluteal area was present. There were no pustular lesions.

After the application of topical betamethasone valerate and oral terfenadine, there was complete resolution within 7 days.

Case no. 2

After playing with metallic mercury for several hours, a 12-year-old boy developed acute, severely itchy exanthem within a day. There was no history of contact allergy and no side effects after vaccines.

The boy presented with erythroderma with disseminated pustules, particularly of the large folds as well as the trunk and neck, but no mucosal lesions were present.

Temperature was 37.1°C and on clinical examination, there were no neurological symptoms.

A complete blood count revealed elevated leucocytes ($11\,000\,\mu^{-1}$). Initial serum mercury level was $290\,\text{nmol l}^{-1}$ (normal $< 25\,\text{nmol l}^{-1}$). Within 30 days serum level of mercury decreased to $42\,\text{nmol l}^{-1}$ and to $16\,\text{nmol l}^{-1}$ within another 40 days, respectively. However, urine mercury levels increased from $44\,\text{nmol l}^{-1}$ (normal $< 25\,\text{nmol l}^{-1}$) at the beginning of the exanthem [day 7 (D7)] to $84\,\text{nmol l}^{-1}$ after 6 weeks.

Complete resolution with desquamation occurred within 7 days, with initially 20 mg prednisone per day and the application of topical mometasone furoate.

Case no. 3

A 28-year-old woman with a history of atopic diseases presented with an acute burning erythematous rash that started on the upper inner thighs, with later involvement of the lower limbs, chest, hands and back. 2 days

before, she had replaced old leaking batteries from a Geiger counter. There were no new medications and no previous contact allergies.

On clinical examination, the patient showed macular exanthem of the large folds with some small pustules. Temperature was 37.5°C, and no mucosal lesions were present.

Laboratory data showed an elevated eosinophil count of 9.3% and bacteriologic examination revealed sterile pustules. Skin histology showed focal spongiform pustules containing mainly neutrophils, but also eosinophils as well as dermal perivascular lymphocytic infiltration and oedema. Serum mercury levels decreased from $29\,\text{nmol l}^{-1}$ to $10\,\text{nmol l}^{-1}$ within 16 days, while urine mercury levels were elevated ($32\,\text{nmol l}^{-1}$) 17 days after the exanthem started.

Complete remission was observed with 40 mg prednisone per day and daily topical hydrocortisone butyrate application for 7 days.

After complete resolution, all 3 patients were patch tested with an extended European standard series and metals. Reactions were evaluated at D2 and D3 according to ICDRG guidelines. The results are summarized in Table 1.

Discussion

Systemic allergic contact dermatitis may present with different cutaneous symptoms. First, flare-up reactions at the primary site of dermatitis or previously positive patch test sites are a specific sign. Secondly, there are also skin symptoms in previously unaffected skin, e.g. vesicular hand eczema, maculopapular rash and vasculitis-like lesions (8).

Apart from external allergen exposure, systemic allergen application may also produce cutaneous symptoms in previously sensitized patients.

AGEP is characterized by extensive formation of non-follicular sterile pustules on a widespread erythema, fever and peripheral blood leucocytosis. In contrast to this, patients with symmetric flexural

Table 1. Patch test results

		Patient number 1	Patient number 2	Patient number 3
Patch test allergens	Concentrated/Vehicle	D2/D3	D2/D3	D2/D3
Phenylmercuric acetate	0.05% petrolatum (pet.)	NT	+/+	+/+
Phenylmercuric borate	0.05% pet.	++/+++	NT	NT
Mercury ammonium chloride	1% pet.	+++ / +++	-/-	+++ / ++
Thimerosal	0.1% pet.	++ / +++	-/-	-/-
Metallic mercury	0.5% pet.	+++ / +++	-/+	+++ / ++
Amalgam	1% pet.	NT	-/-	+/+

maculopapular eruption or so-called baboon syndrome usually do not present with systemic symptoms (9, 10).

AGEP is most frequently due to penicillins, macrolides and mercury and flexural exanthema to antibiotics, particularly aminopenicillins, and mercury, respectively. In the literature, more than 50 patients who clinically presented with AGEP or a symmetric flexural eruption, mainly after exposure to broken thermometers, have been reported (Table 2). Most of them were previously sensitized to mercury compounds, usually by exposure to topical disinfectants, but also to ophthalmologic preparations (11) and antiparasitic powders (12). Patch tests with metals, including ammoniated mercury, phenylmercuric nitrate/acetate, metallic mercury, mercury chloride and thimerosal, were done in most of the patients. However, serum and urine mercury levels were measured in 4 patients only (13–16), 1 showing an elevated urine mercury level of 65 µg/l (normal value 5 µg/l) on D5 (13).

While patch testing in AGEP patients shows positive, sometimes strong and even pustular reactions more often than in other drug eruptions (7), even extensive patch testing sometimes fails to confirm the diagnosis of systemic contact dermatitis in patients with flexural exanthem (8). Nevertheless, delayed-type hypersensitivity to metallic mercury and thimerosal and mercury chloride was shown in 80% of the cases of a larger Japanese series of systemic contact dermatitis from mercurials (17).

In our 3 patients, positive patch tests to various mercury derivatives could be demonstrated. In addition, elevated non-toxic levels of mercury were detected in patients 2 and 3, indicating exposure and absorption.

While histopathology of flare-up lesions of previous patch test sites is similar to that of other eczematous skin lesions, flexural exanthem histologically differs from this pattern. Apart from spongiosis, early lesions show some necrosis and infiltration with leucocytes. The dermal perivascular infiltrate consists of lymphocytes, erythrocytes, and a variable number of neutrophils. Nuclear dust is occasionally seen (8).

Histopathologic examination was performed in approximately 1/4 of the patients of our survey. Thereby, the common features were neutrophilic pustules (13, 14, 18), spongiosis (10, 16, 19), subepidermal blisters (15) and dermal lymphocytic infiltrates with exocytosis (16, 17, 19), respectively. In patients with AGEP, the main histopathological findings were subcorneal pustules, papillary oedema and a subepidermal lympho-

histiocytic perivascular infiltrate with some polymorphonuclear neutrophils (PMNs) and eosinophils. Furthermore, the hyperplastic epidermis showed hydropic degeneration of some keratinocytes. Immunohistochemically, keratinocytes are killed mainly by CD8⁺ cytotoxic antigen-specific T cells (10, 20). Pichler et al. suggest that AGEP as a drug-induced and T-cell-regulated disease might represent a model for T-cell-PMN interaction, which is thought to be important in various other pustular diseases (20, 21). AGEP as well as pustule formation in severe cases of symmetric flexural exanthem was described as far back as 20 years ago (9, 22). This, together with the fact that 'baboon syndrome' shares the same aetiologies and likewise represents a systemic hypersensitivity reaction raises the question as to whether AGEP and flexural exanthem should not be regarded as variants of a continuous spectrum of possible clinical manifestations (2, 15, 23).

In accordance with the data of a multinational epidemiological case-control study on severe cutaneous adverse reactions and AGEP, respectively (7, 10), the review of 56 cases indicates that males and females of any age seem to be equally affected by systemic contact dermatitis due to mercury derivatives (Table 2 and references therein).

Type IV sensitization can be induced by local application of (organic) mercury compounds. Thereby, probably due to a single or few contacts on a limited surface, only mild cutaneous signs are seen. Systemic rechallenge leads to an activation of preformed memory T cells. However, systemic exposure to mercury might not only induce the classical antigen-presenting cell-T-cell activation pathway but also enhance the proliferation of lymphocytes through a direct mitogenic stimulus (32). Moreover, the excretion of mercury by sweat glands (33, 34) could explain attraction and localized accumulation of activated and proliferating T cells in the flexural areas.

In summary, today only sparse information on the correlation of HLA-types and predisposition to systemic allergic reactions exist (35–37). Moreover, apart from the type of exposure and the chemical form, e.g. of mercury derivatives, explanations for the distribution pattern of the skin lesions in AGEP and flexural exanthem or allergic contact dermatitis are lacking. Thus, other individual factors, e.g. HLA-type, metabolism or sweat gland quantity and distribution, might be important. Therefore, further investigations are needed to elucidate additional factors contributing to the mechanism of these uncommon hypersensitivity reactions.

Table 2. Cases of systemically induced exanthem from mercury exposure

Number assigned to reported patient	Authors (reference number)	Year	Age (years)	Sex	Clinical manifestation	Previous mercury exposure	Eliciting mercury source	Latency	Positive patch test
1-11	Nakayama (9)	1983	9-48	4 male/ 7 female	AGEP/baboon	Topical	Thermometer	1-2D	See text
12	Andersen (5)	1984	52	Male	Baboon	Topical	Thermometer	3-4D	D
13	Bartolo (24)	1988	32	Female	Baboon	Mercurochrome	Thermometer	1D	A
14	Delavierre (13)	1988	27	Male	AGEP	Hg cream	nm	36h	C
15	Delavierre (13)	1988	37	Male	AGEP	Topical	Thermometer	3D	nd
16-19	Roujeau (10)	1991			AGEP	Unknown	Topical/thermometer	24-48h	nd
20	Faria (25)	1992	40	Female	Baboon	Topical	Thermometer	3D	A B D E MB
21	Faria (25)	1992	40	Female	Baboon	Topical	Thermometer	2D	A D G MB
22	Bolzinger (14)	1993	11	Male	AGEP	Topical	Patch test/thermometer	48h	G
23-31	Vena (12)	1994	19-57	Male	Baboon	Antiparasitic powder	nm	8-10D	A D G
32	Fernandez (26)	1995	3	Female	Baboon	Topical	Thermometer	24h	C D MC
33	Jelen (2)	1995	22	Female	Baboon	Unknown	Thermometer	5D	D G
34	Jelen (2)	1995	39	Male	Baboon	Unknown	Thermometer	2 weeks	B D G
35	Jelen (2)	1995	68	Male	Baboon	Mercurochrome	Thermometer	1D	nd
36	Koch (27)	1996	5	Male	Baboon	Topical	Plastic boots	24h	A C E F G
37	Le Coz (28)	1996	25	Male	Baboon	Skill game	Skill game	nm	A C D G MC
38	Descamps (18)	1997	13	Male	Baboon	Mercurochrome	Metallic Hg vapor at school	18 h	D E G MC
39	Descamps (18)	1997	30	Female	Pustular exanth.	Unknown	Thermometer	1D	nd
40	Galindo (29)	1997	32	Male	Exanthema	Unknown	Thermometer	1D	nd
41-45	Nakada (4)	1997	25-27	Female	Baboon	Unknown	nm	nm	D E
46	Zimmer (15)	1997	68	Male	Baboon	Unknown	Thermometer	12h	nd
47	Zimmer (15)	1997	32	Female	Baboon	Unknown	Thermometer	12h	D
48	Barrazza (11)	1998	27	Male	Pustular exanth.	Ophthal. Hg cream	nm	2D	D
49	Alegre (19)	2000	7	Male	Baboon	Unknown	Drop of Hg	1D	A D
50	Bartolome (16)	2000	15	Male	Baboon	Topical	Thermometer/cinnabar	4D	A B C D E MC
51	Suzuki (17)	2000	26	Female	AGEP	Unknown	mines	48h	A D E G
52	Suzuki (17)	2000	26	Female	Baboon	Unknown	Sphygmomanometer	24h	A D E G
53	Audicana (30)	2001	5	Female	Baboon	Topical	Hg tablet	24h	D G
54	Lozé (23)	2001	45	Female	Baboon	Unknown	Thermometer	48h	nd
55	Lozé (23)	2001	30	Female	Baboon	Unknown	Thermometer	72h	nd
56	Diego (31)	2002	13	Female	Baboon	Topical	Thermometer	1D	C D E H MB

A = ammoniated mercury; B = phenylmercuric nitrate; C = phenylmercuric acetate; D = metallic Hg; E = mercury chloride; F = amalgam; G = thimerosal; H = Hg oxide; MB = merbromin; MC = mercurochrome; nd = not done; nm = not mentioned.

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