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A case of severe immediate type reaction to macrogol and polysorbate 60 after intravaginal drug application

Polyethylene glycols (PEG; pharmacologically called macrogols [C₂nH₄n+2O_n+1]) are water-soluble polymers used in pharmacy and cosmetics as carriers. PEG may be occult and an underestimated inducer of immediate type reactions [1, 2]. We report a 26-year-old non-atopic woman who presented with generalized urticaria, pruritus, and dyspnoea which developed 15 minutes after using a vaginal suppository containing lactic acid, macrogol 1500/6000, and sodium lactate (Vagisan® Zäpfchen) as well as a vaginal cream containing benzyl alcohol, cetearyl alcohol, cetyl palmitate, lactic acid, octyldodecanol, polysorbate 60, sodium lactate, and sorbitan stearate (Vagisan® Feuchcreme). She recovered under adrenaline intramuscular and intravenous antihistamines. In the past, she had suffered from multiple immediate type reactions after the use of different cosmetics (*i.e.* tooth pastes, hair conditioner, and body lotion).

Total IgE was 53.7 kU (normal <114), serum tryptase 7.2 µg/L (normal <11.0), and specific IgE was negative for frequent pneumallergens. Skin prick test (SPT) with vaginal suppository and cream as well as with polysorbates and macrogols was positive for both drugs as well as for macrogol 1500 and 4000 (*table 1*). Shortly after having applied prednicarbat ointment (Dermatop®, containing polysorbate 60) for treatment of itchy wheals during SPT, she developed contact urticaria. The basophil activation test was positive for polysorbate 80 and macrogol 4000 (each at 500 mg/mL). Single-blind placebo-controlled oral provocation testing (OPT) with macrogol 400 was well tolerated, while OPT with polysorbate 20 induced generalized urticaria.

We diagnosed immediate type hypersensitivity to different concentrations and sizes of PEG. History indicated sensitization to macrogol 1500 and/or 6000, while allergy tests were also positive for polysorbate 80. Polysorbates are frequently used as surface-active or emulsifying agents in cosmetics, drugs, and food (*e.g.* additives E432-436) and contain PEG as side chains which may lead to cross reactions with macrogols [2, 4, 6]. Thus, in this case, concomitant sensitization to polysorbate 60 or cross reactivity between polysorbate 60 and macrogol 1500 (and/or macrogol 6000 which was not tested) was possible. As the patient denied further testing, she was told to avoid contact with PEG with the exception of macrogol 400 that had been well tolerated and she received PEG-free emergency drugs.

Macrogols of lower size (*i.e.* 400) have been more rarely reported to be inducers of immediate type reactions than those of larger size (*i.e.* 3000-4000). Several patients with PEG hypersensitivity were reported to have positive skin tests to macrogols of different sizes [3-5]. An IgE-mediated mechanism has been postulated, and recently IgE antibodies to macrogol 400, 4000 and 6000 were shown by dot-blot assay [6]. However, non-IgE-mediated hypersensitivity mechanisms have also been suggested [7].

A recent report listed 37 cases of PEG hypersensitivity to different drugs, and the authors suggested individual reactivity thresholds and the potential of cross-reactivity between structurally related polymers and PEG [8]. Also, in the perioperative setting, hypersensitivity to PEG should be taken into account [2, 5]. Recently, polysorbate 20 in omalizumab, a drug approved for IgE-mediated asthma and urticaria, was suggested to induce anaphylaxis [9]. The frequent use of PEG as a laxative was reported to lead to sensitization and anaphylaxis, especially when there is damage to mucosal integrity at the gastrointestinal membrane [10]. In conclusion, PEG should be considered as a rare potential cause of local or systemic hypersensitivity, especially in patients with reactions to multiple drugs and/or cosmetics. To the best of our knowledge, this is the first report of anaphylaxis due to intravaginal drug application.

Table 1. Results of diagnostic tests in our patient: skin prick test (wheal/erythema) and basophil activation test (macrogol and polysorbate at 500 mg/mL; manufactured by Fagron GmbH & Co. KG, Germany).

Substance	Size	Concentration	SPT	BAT	History/Provocation
Histamine		1%	7/>20	-	-
NaCl		0.09%	negative	-	-
Vagisan® ZäpfchenMG 1500/6000		Pure	5/10	-	Anaphylaxis (mucosal)
Vagisan® Feuchtcreme PS 60		Pure	4/0	-	Anaphylaxis (mucosal)
Dermatop® cream PS 60		Pure	-	-	Contact urticaria (dermal)
Macrocol	300	0.5g/mL	negative	-	-
	400	0.5g/mL	negative	negative	Negative (oral)
	1500	0.5g/mL	7/>20	-	-
	4000	0.5g/m	11/>20	positive	-
	6000	not tested	-	-	-
Polysorbate	20	0.1g/mL	3/10	-	-
		0.2g/mL	4/16	-	-
		0.3g/mL	4/15	-	-
		0.5g/mL	5/20	negative	Urticaria (oral)*
	40	0.1g/mL	-	-	-
		0.2g/mL	-	-	-
		0.3g/mL	-	-	-
		0.5g/mL	Negative	negative	Negative (oral)
	60	0.1g/ml	2/5	-	-
		0.2g/mL	3/10	-	-
		0.3g/mL	5/20	-	-
		0.5g/mL	5/>20	Positive	-
	80	0.1g/ml	2/5	-	-
		0.2g/mL	3/10	-	-
		0.3g/mL	5/20	-	-
		0,5g/mL	5/>20	-	-

MG: magrogol; PS: polysorbate; SPT: skin prick test; BAT: basophil activation test. Testing of macrogols at different sizes was chosen according to availability of products. Positive results are marked in bold. *maximum single dose of 0.35g, cumulative dose of 0.95g; **maximum single dose of 0.5g, cumulative dose of 1.1g.

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Sarcoidosis mimicking malar rash: a case of lupus pernio

Cutaneous sarcoidosis is known as “the great imitator” [1] and exhibits a variety of macroscopic presentations such as maculopapular lesions, subcutaneous nodules, plaques, and lupus pernio, which is one of the most characteristic features. We describe a case of lupus pernio on both cheeks that mimicked a butterfly rash.

A 43-year-old Japanese man noticed subcutaneous nodules on his upper limbs five years ago. The nodules were suspected to be sarcoidal granulomas based on skin biopsy at another hospital, but regressed spontaneously within a few years. Two years later, the patient noticed reddish swelling on his cheek and subcutaneous nodules on the upper limbs, and was referred to us. Physical examination revealed diffuse erythema with induration on the bridge of the nose and both cheeks (*figure 1A*). There were several subcutaneous nodules of 1-2 cm in size on both upper limbs. He had no extracutaneous manifestations and was afebrile.

Skin biopsy of the right cheek revealed multiple non-caseating granulomas with a few Langhans-type giant cells throughout the whole dermis and subcutis with fibrosis (*figure 1B-C*). Some granulomas were surrounded by lymphocytes and eosinophils. Neither interface dermatitis nor atypical lymphoid cells were present. Laboratory test results were as follows: normal blood cell count, calcium at 9.4 mg/dL (normal range: 8.7-10.3), complement component 3 at 113 mg/dL (86-160), anti-nuclear antibody (homogenous pattern) at 1:40 (<1:40), soluble IL-2 receptor at 1,466 U/mL (135-421), and angiotensin converting enzyme at 24.0 U/L (8.3-21.4). Chest computed tomography revealed lymph node enlargement in the mediastinum and small nodules in both lungs. Bronchoalveolar lavage fluid contained an infiltrate predominantly made of macrophages and lymphocytes (62.4% and 34.1%, respectively), with an increased CD4/CD8 ratio (6.28; normal <3.5). Needle biopsy of a subcarinal lymph node obtained during bronchoscopy also revealed granulomatous changes. Normal sinus rhythm without signs of cardiac ischaemia was found on the electrocardiogram. Ophthalmological examination showed bilateral uveitis. Based on these find-

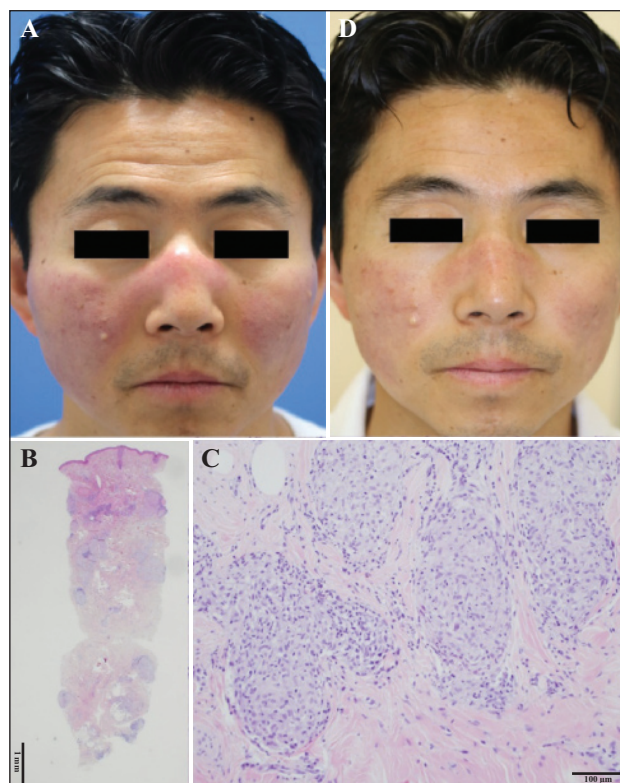


Figure 1. A). Clinical features on the first visit, including indurated erythema on the bridge of the nose and both cheeks. B) Histopathological features of the right cheek; high-power magnification shows non-caseating granulomas with inflammatory cell infiltrates and fibrosis in the dermis and subcutis (haematoxylin-eosin staining; $\times 20$). C) Low-power magnification showing non-caseating granulomas, some of which are surrounded by lymphocytes and eosinophils (haematoxylin-eosin staining; $\times 200$). D) Improvement of indurated erythema on the nose bridge and bilateral cheeks is seen after treatment with oral prednisolone (30 mg/d).

ings, the patient was diagnosed with sarcoidosis. To prevent systemic involvement, he was treated with 30 mg/d of oral prednisolone (PSL). After a month of treatment, the erythematous induration started regressing gradually without deformity (*figure 1D*), the subcutaneous nodules on the upper limbs began decreasing and the soluble IL-2 receptor level normalised (256 U/mL). PSL was tapered to 5 mg/day over six months, and the disease is being controlled.

Lupus pernio has been reported in 2-6% of all cases of cutaneous sarcoidosis [1-3]. In this type, the deep tissues are commonly affected, which may lead to deformities and/or functional impairment [1]. To avoid these complications, therapeutic intervention before disease progression may be needed, and oral PSL is the first-line treatment [3]. The present case was successfully treated by a moderate dose of PSL.

Malar rash is a characteristic skin manifestation of systemic lupus erythematosus, but occurs in several other conditions, including rosacea, seborrheic dermatitis, dermatomyositis, pellagra, erysipelas, Lyme disease, photosensitivity, and Bloom syndrome [4]. The macroscopic features of lupus pernio generally include violaceous or erythematous