

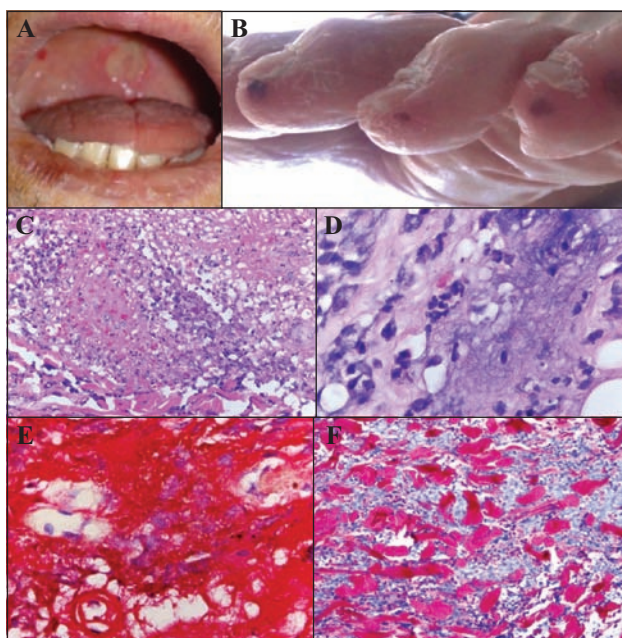


Figure 1. A, B) Physical examination of Case 1 revealed multiple lesions, including haemorrhagic bullae exhibiting prominent acral involvement, as well as ulcerations of the oral mucosa. C) Case 1. The skin biopsy shows a very striking necrotising leukocytoclastic reaction, characterised by mural and luminal fibrin deposition involving capillaries and venules of the superficial and deep dermis. Emanating from the zones of necrotising leukocytoclastic vasculitis are marked extravascular neutrophilic infiltrates assuming a sheet-like pattern within the dermis. The vessel walls are infiltrated by neutrophils with concomitant leukocytoclasia (haematoxylin and eosin; $\times 400$). D) Case 2. The skin biopsy revealed a deep-seated vascular reaction, characterised by vascular thrombosis and accompanied by mural fibrin deposition. An interesting finding was the presence of extravascular neutrophilia although without infiltration of the vessel wall by neutrophils. The neutrophilic foci exhibited a striking pattern of basophilic degeneration (haematoxylin and eosin; $\times 1,000$). E) In both cases, we were able to demonstrate that the basophilic foci of cellular degeneration contained IgG and myeloperoxidase; the double stain showed a definite colocalisation between IgG and myeloperoxidase (Case 2; red chromogen myeloperoxidase/brown chromogen IgG; $\times 1,000$). F) Case 2. The basophilic areas were highlighted by PTAH, indicative of their extracellular DNA content ($\times 400$).

ANCA induces a peculiar form of cell death, named NETosis, characterised by the formation of NETs with decondensed chromatin threads, encrusted with various cytoplasmic proteins including lactoferrin, myeloperoxidase, and proteinase. We believe that the basophilic granular material containing neutrophil remnants, highlighted by a DNA stain (*i.e.* PTAH), along with the intermingling of IgG and myeloperoxidase, is an *in vivo* demonstration of the NET. The so called NETs are held to play a critical role in the induction of ANCA, in part, through their direct *in vivo* effect on enhancing plasmacytoid dendritic cell activity. NETs directly cause endothelial cell injury and promote thrombosis. Indeed, the vessels in the immediate vicinity of the NET showed pauci-inflammatory vascular thrombosis.

Brinkmann's group provided the first evidence that neutrophils release extracellular chromatin upon activation [3]. The extruded DNA also is enmeshed with other intracellular components, especially granular proteases and nuclear constituents, which form a web to trap bacteria. In 2009, Kessenbrock described the importance of NETosis in the evolution of small-vessel vasculitis [4]. In this seminal study, they described the role of ANCA in the induction of NETosis, while NET contribute to externalisation of proteinase 3 and myeloperoxidase. It is held that the DNA web adheres to and damages the endothelium following the interaction of ANCA with either myeloperoxidase or proteinase 3.

The exact pathogenetic basis by which hydralazine evokes antibodies to myeloperoxidase remains hypothetical. Procainamide and hydralazine are both metabolized by MPO released from activated neutrophils to form reactive intermediate compounds. Such metabolites may act as a hapten for MPO and result in anti-MPO antibody formation. The combination of the ANCA could result in the neutrophil respiratory burst, releasing the histone DNA complexes into the extracellular tissue, contributing to the formation of the NET.

In summary, hydralazine-associated ANCA positive vasculitis is a very distinctive syndromic complex whereby the histopathology, which depicts Netosis, emphasizes the pathogenetic importance of ANCA in the induction of vascular injury through direct endothelial cell injury. ■

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1. Pendergraft WF 3rd, Niles JL. Trojan horses: drug culprits associated with antineutrophil cytoplasmic autoantibody (ANCA) vasculitis. *Curr Opin Rheumatol* 2014; 26: 42-9.
2. Lenert P, Icardi M, Dahmouch L. ANA (+) ANCA (+) systemic vasculitis associated with the use of minocycline: case-based review. *Clin Rheumatol* 2013; 32: 1099-106.
3. Brinkmann V, Reichard U, Goosmann C, *et al.* Neutrophil extracellular traps kill bacteria. *Science* 2004; 303: 1532-5.
4. Kessenbrock K, Krumbholz M, Schönermarck U, *et al.* Netting neutrophils in autoimmune small-vessel vasculitis. *Nat Med* 2009; 15: 623-5.

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Management of immediate hypersensitivity reaction to glatiramer acetate

Glatiramer acetate (GA; Copaxone®), a mixture of four synthetic polypeptides, is used in the form of subcutaneous injection (20 mg/day) for the treatment of multiple sclerosis (MS). Only few systemic reactions suggestive of

Table 1. Patient details following treatment with GA.

Case	Gender	Age (yrs)	Personal atopic background	Time from the beginning of treatment to reaction (months)	Time of appearance of reaction after injection	Clinical symptoms	Emergency treatment required	Positive control results with histamine chlorhydrate, wheal/flare (mm)	PT undiluted 20mg/mL	IDT 2µg/mL	IDT 20µg/mL	IDT 0.2mg/mL	IDT 2mg/mL	IDT undiluted	Positive challenge
1	M	52	asthma	12	Unknown	CSU	None	10/27	Neg	Neg	Doubtful	ND	ND	ND	No
2	F	44	AR	3	2 hours	CSU	None	Unknown	Neg	Neg	11/30	ND	ND	ND	No
3	F	26	No	12	1 hour and a quarter	CSU	None	10/42	Neg	ND	07/36	ND	ND	ND	No
4	F	28	Unknown	6	Unknown	CSU	None	06/25	Neg	Neg	Neg	ND	ND	ND	No
5	F	43	Unknown	4 days	A few hours	AU	None	06/30	Neg	ND	Neg	08/20	ND	ND	No
6	F	35	No	3	A few minutes	IPISR: face erythema, tingling, facial oedema, painful stomach and feeling faint	None	08/30	Neg	ND	Neg	11/35	ND	ND	No
7	M	25	Unknown	1	Immediately	IPISR: chest tightness, feeling faint, dyspnoea, face oedema, palpitations	Emergency consultation, corticosteroid for 4 days	06/30	Neg	ND	Neg	08/20	ND	ND	No
8	F	50	Asthma	8	Immediately	Palm itching and rash and burning sensations of the vagina	None	12/45	Neg	ND	Neg	Neg	12/37	ND	No
9	F	37	Asthma	4	A few minutes	IPISR: swelling of hands, skin erythema with urticaria, heat sensation, dyspnoea, feeling faint	None	03/20	Neg	ND	Neg	Neg	Solitary doubtful, papule	ND	No
10	F	40	No	8	6 hours	AU	None	08/30	Neg	ND	ND	11/40	ND	ND	No
11	F	34	Unknown	21	Immediately	IPISR: heat sensations, nausea, chest tightness, face erythema	Emergency consultation, no treatment	08/46	Neg	ND	Neg	08/21	11/45	ND	Yes, relapse of IPISR
12	F	37	No	18	1 to 2 hours	AU	None	20/60	Neg	ND	Neg	10/20	ND	ND	No
13	M	28	Asthma	9	A few minutes	IPISR: painful stomach, dyspnoea, chest tightness, swelling of lips and face	None	10/40	Neg	ND	12/40	ND	ND	ND	No
14	F	30	Asthma	3	30 minutes	IPISR: feeling faint, facial erythema and swelling	Emergency consultation, no treatment	10/30	ND	10/40	ND	ND	ND	ND	Not performed
15	F	42	No	23	Immediately	IPISR: heat sensations, redness, feeling faint, tachycardia, chest tightness, nausea	None	07/40	Neg	ND	Neg	Neg	ND	ND	No
16	F	43	No	5	Unknown	AU	None	08/35	ND	ND	ND	ND	ND	12/30	No
17	F	31	Unknown	16	Immediately	AU	Emergency consultation with antihistamines and corticosteroid	Unknown	Neg	ND	12/30	ND	ND	ND	No
18	M	44	No	10	Unknown	CSU	None	Unknown	Neg	ND	09/40	ND	ND	ND	No

AR: allergic rhinitis; CSU: chronic spontaneous urticaria; AU: acute urticaria; ND: not done; IPISR: immediate post injection systemic reaction; PT: Prick test; IDT: intradermal test.

anaphylaxis have been so far reported [1-10]. Anaphylaxis is estimated to develop in less than 0.1% of treated patients [8]. The most frequent systemic reaction is immediate post-injection systemic reaction (IPISR), which occurs at least once in 10-15% of patients [1]. IPISR is of unknown pathophysiology. It generally presents with flush, dyspnoea, chest tightness, palpitations and anxiety, appears immediately after injection, and invariably disappears spontaneously within a few minutes [1, 3]. This condition may be misdiagnosed as anaphylaxis, which leads to treatment discontinuation.

We retrospectively reviewed all patients with immediate hypersensitivity reactions (IHS) to GA, seen between 2003 and 2015 in our dermatology and allergology department (Tenon Hospital, Paris). We collected data on 18 patients (12 women; median age: 37 years). The treatment had been discontinued in all patients because of a reaction. According to the history and clinical examination, we diagnosed isolated urticaria in 10 patients (five chronic spontaneous urticaria [CSU] and five acute urticaria), IPISR in seven patients, and isolated rash in one patient.

The majority of the reactions disappeared spontaneously within a few minutes to some hours. Only two patients required treatment, but none received epinephrine. All patients had skin testing for GA, an undiluted (20 mg/mL) prick test (PT), followed (if negative) by an intradermal test (IDT) at 1/1,000 (20 µg/mL), 1/100 (200 µg/mL), and for some patients 1/10 (2 mg/mL), and undiluted. In cases of more severe reaction, an IDT was initiated at 1/10,000 (2 µg/mL). The PT was negative for all 16 patients tested, and the IDT was positive for 15/18 patients at different dilutions (2 µg/mL: $n = 1$; 20 µg/mL: $n = 4$; 200 µg/mL: $n = 7$; 2 mg/mL: $n = 2$; undiluted; $n = 1$). Only three patients had negative tests (PT and IDT). Two controls (who had never received GA) had a positive IDT (at 200 µg/mL or 2 mg/mL).

We performed a single, blinded, placebo-controlled challenge test in 17/18 patients even though the allergy tests were positive in 15/18 patients, because the symptoms, history, and clinical examination did not suggest IgE-mediated IHS, the treatment was mandatory, and two controls had positive IDT suggestive of an irritant. The patients received full-dose GA (20 mg) in a hospital setting under close medical supervision by injection of split doses (maximum three subcutaneous injections) *versus* placebo (one subcutaneous injection of normal saline). Only Patient 11 experienced IPISR (table 1). After the challenge, all patients continued the treatment. Patient 14 was not challenged because of the positive IDT at 1/10,000, but clinical manifestations did not suggest an IgE-mediated IHS.

Five patients experienced CSU after GA treatment initiation. To our knowledge, no reports exist of an association between CSU and GA treatment or MS.

Reports of allergic reactions to GA are rare, and sometimes poorly-documented and/or clinically non-convincing [1, 2, 6-10]. Because patients self-administer GA injections at home, neurologists might be reluctant to continue the treatment if they are not fully confident with the diagnosis of the reaction. Allergy tests for GA are not standardised. Our results support previous reports suggesting that a positive IDT for GA at ≥ 200 µg/mL (and probably at 20 µg/mL for some patients) seems to be indicative of an irritant [2, 10]. In contrast to a recent report of positive PT in three patients, none of our patients had positive PT [8].

With our challenge, the split doses cannot be considered to have led to desensitization.

To date, this is the largest study with skin tests to investigate suspected GA-related IHS. In such cases, the history and clinical examination may exclude non-IgE-mediated IHS (such as CSU or IPISR); for others reactions, a challenge under close medical supervision may be proposed if the treatment is mandatory and the reaction is not life-threatening, as skin tests with GA at ≥ 20 µg/mL appear to indicate an irritant. A desensitization protocol may be reserved for severe cases with a history suggesting IgE-mediated IHS. Patients should not be deprived of one of the most effective treatments for MS due to a wrong diagnosis of allergy. Further prospective studies are needed to clearly determine the value of GA skin tests. ■

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1. Bayerl C, Bohland P, Jung EG. Systemic reaction to glatiramer acetate. *Contact Dermatitis* 2000; 43: 62-3.
2. Sánchez-López J, Rodríguez del Río P, Cases-Ortega B, Martínez-Cocera C, Fernandez-Rivas M. Allergy workup in immediate-type local reactions to glatiramer acetate. *J Invest Allergol Clin Immunol* 2010; 20: 521-3.
3. Koller S, Kranke B. Nicolau syndrome following subcutaneous glatiramer-acetate injection. *J Am Acad Dermatol* 2011; 64: e16-7.
4. Kluger N, Thouvenot E, Camu W, Guillot B. Cutaneous adverse events related to glatiramer acetate injection (copolymer-1, Copaxone). *J Eur Acad Dermatol Venereol* 2009; 23: 1332-7.
5. Ball NJ, Cowan BJ, Moore G, Hashimoto SA. Lobular panniculitis at the site of glatiramer acetate injections for the treatment of relapsing-remitting multiple sclerosis. A report of two cases. *J Cutan Pathol* 2008; 35: 407-10.
6. Rauschka H, Farina C, Gudek S, Breier F, Schmidbauer M. Severe anaphylactic reaction to glatiramer acetate with specific IgE. *Neurology* 2005; 64: 1481-2.
7. Baumgartner A, Stich O, Rauer S. Anaphylactic reaction after injection of glatiramer acetate (copaxone) in patients with relapsing-remitting multiple sclerosis. *Eur Neurol* 2011; 66: 368-70.
8. Corominas M, Postigo I, Cardona V, Lleónart R, Romero-Pinel L, Martínez J. IgE-mediated allergic reactions after the first administration of glatiramer acetate in patients with multiple sclerosis. *Int Arch Allergy Immunol* 2014; 165: 244-6.
9. Soriano Gomis V, Perez Sempere A, Gonzalez Delgado P, Sempere J, Niveiro Hernandez E, Marco F. Glatiramer acetate

Bullous pemphigoid in infancy with spontaneous remission

A boy, aged three months and nine days, was noted to have small papules on his limbs seven days before receiving bacillus Calmette-Guérin vaccine, which was followed, nine days later, by diphtheria-pertussis-tetanus (DPT) vaccine. Two days later, abdominal erythema appeared. About three weeks after the DPT shot (at the age of four months and 15 days), tense blisters emerged on the face and extremities, and spread to the body. His mother had faced no similar symptoms during pregnancy. The patient was hospitalised 1.5 months after the onset of skin lesions. He had tense blisters mainly on the face and extremities and multiple annular, oedematous, erythematous lesions on the trunk. Histopathology revealed liquefaction degeneration, eosinophil infiltration into the epidermis, and lymphocyte and eosinophil infiltration into the dermis (figure 1A). Direct immunofluorescence (IF) revealed IgG and C3 deposition on the basal membrane zone (BMZ) (figure 1B), and indirect IF revealed circulating anti-BMZ IgG autoantibodies (titre: 1:80). The serum anti-bullous pemphigoid (BP) 180 antibody titre, by enzyme-linked immunosorbent assay, was reported with an index value of 1,000 (normal: <9). A diagnosis of BP was made. The attending physician presented several therapeutic options, including topical and systemic corticosteroids. However, the parents had a fear of corticosteroids and denied such treatments; they desired observation with only moisturizing agents. The annular erythema regressed marginally, but blistering and erosions persisted. The anti-BP180 antibody titre dropped to 844.8 by 10 days after the first visit. The patient was admitted to our hospital for a second opinion two months after onset. He still had tense blisters, erosions, and annular erythematous lesions on the face, extremities, and trunk (figure 1C). There was no mucosal involvement. The white blood cell count was 32,700/ μL , with 43% eosinophils (14,100/ μL). The parents continued to refuse steroid treatment, thus only topical Vaseline was administered. The number of new blisters gradually decreased, and the erosions re-epithelialised. Two weeks after admission, the eosinophil count had dropped to 6,400/ μL , and the anti-BP180 titre decreased to 440. The eruptions on the trunk regressed substantially, and the patient was discharged on the fifteenth hospital day. Three weeks later (four months from onset), the eruptions had almost disappeared and the anti-BP180 antibody titre was 80.3. Fourteen months from onset, antibody titres were negative. The patient received his second and third DPT vaccinations at 21 and 23 months after onset of BP, respectively. However, there was no BP relapse. He subsequently received vaccines for pandemic influenza

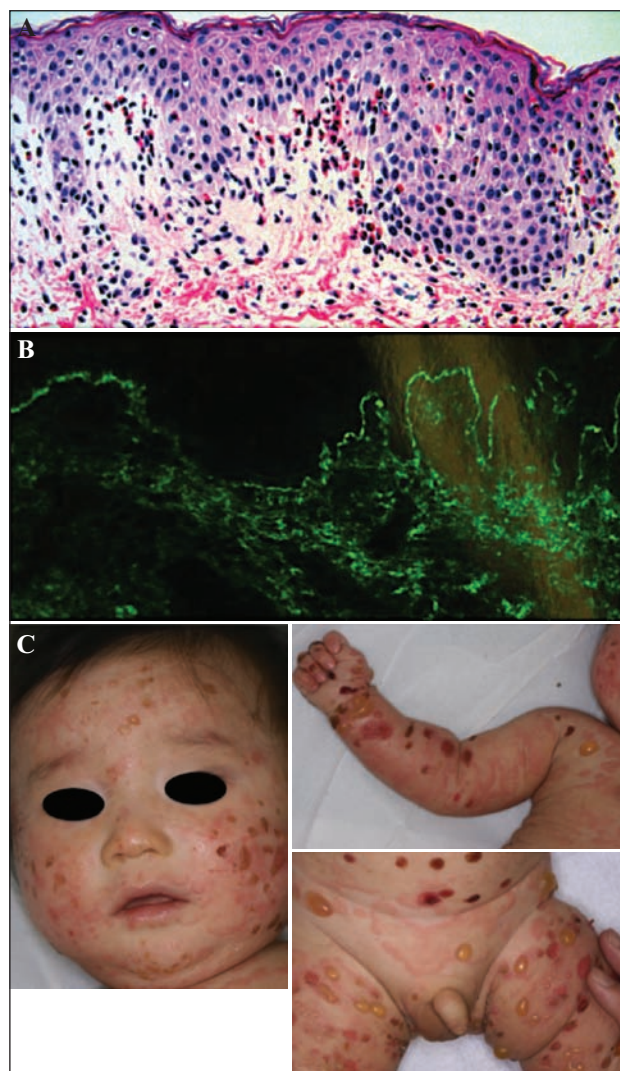


Figure 1. A) Histopathology of the lesion shows liquefaction degeneration of the epidermis, eosinophilic infiltration of the epidermis, and inflammatory cell infiltration, including lymphocytes and eosinophils, in the upper dermis. B) Direct immunofluorescence analysis; immunoglobulin G deposition on the basement membrane zone. C) Clinical manifestation upon admission included multiple tense blisters, erosions, and oedematous annular erythema on the face, extremities, and trunk.

virus, polyomavirus, and measles-rubella (MR), which did not cause recurrence. He remains disease-free seven years after remission.

Infantile or childhood BP is relatively rare with only just over 100 published cases [1], most occurring before 12 months of age [2, 3]. Medical intervention is usually required to achieve remission. Response to therapy ranges from several days to months [3]. To our knowledge, this is the first detailed report of spontaneous remission. Because our patient was three or four months old at onset, it is unlikely that pathogenic anti-BP180 antibodies had been passively transferred from the mother [4]. Because he had skin papules before his vaccinations, we cannot prove that his BP was associated with the vaccinations. However, since the typical BP blisters emerged after immunisation,