Development of angio-oedema after omalizumab injections in a patient with chronic spontaneous urticaria

doi: 10.1111/ced.13616

We report an unusual case of a patient with severe antihistamine resistant chronic spontaneous urticaria (CSU) without concomitant angio-oedema. The CSU showed an excellent response to omalizumab, but the patient developed attacks of angio-oedema after each omalizumab injection.

A 26-year-old woman presented with a 7-month history of severe generalized urticaria without angio-oedema, which was unresponsive to antihistamine treatment (fexofenadine 180 mg) at higher than licensed doses (up to 720 mg/day). The patient's weekly Urticaria Activity Score (UAS-7) was calculated as 32 during the first week of follow-up. Subcutaneous omalizumab 300 mg/month was started as an add-on treatment to fexofenadine 180 mg four times daily. Two days after the first omalizumab administration, the patient reported a dramatic improvement of her CSU, but she also reported an appearance of severe angio-oedema of her lips, face and eyelids for the first time, which disappeared in 3 days. The patient continued fexofenadine 180 mg four times daily for 7 additional days, and then reduced the dose to 180 mg once daily. During the 4 weeks after omalizumab administration, the patient experienced a dramatic improvement of her CSU, corresponding to an UAS-7 of 4–6. Nevertheless, after each subsequent dose of omalizumab she deveoped similar manifestations of angio-oedema on her face and lips, which resolved in 2–3 days. Six months later, the patient discontinued the omalizumab injections, but continued fexofenadine 180 mg twice daily. She had a severe relapse of urticaria, but without angio-oedema. The clinical worsening of her CSU continued during the subsequent 8 weeks of follow-up, even though she continued treatment with fexofenadine 180 mg four times daily (720 mg/day). At this point omalizumab was restarted, and fexofenadine 180 mg four times daily was continued. The day after omalizumab administration, severe angio-oedema developed on the patient's face, lips and eyelids, which resolved in 3 days. Nonetheless, there was a dramatic improvement in the weals and pruritus of CSU.

The patient had normal blood levels of C1-INH, complement factor 4 and tryptase at baseline and during the described episodes of angio-oedema after omalizumab-injections. We considered that the patient had omalizumab related nonhistaminergic angio-oedema. Previously, antifibrinolytic agents have been shown to be an effective treatment in idiopathic nonhistaminergic angio-oedema,[1] so she was given tranexamic acid 1 g three times daily for 7 days after each omalizumab injection. After two subsequent omalizumab injections under tranexamic acid therapy, the angio-oedema did not relapse.

While chronic angio-oedema appears to be histaminergic in most cases, in 14% of patients it has nonhistaminergic features.[2] The pathophysiology of nonhistaminergic AE is mostly speculative, and several biological mediators acting as triggers or enhancers of vascular permeability have been implicated.[3] The ineffectiveness of high-dose antihistamines and the efficacy of tranexamic acid led us to consider that our patient's angio-oedema after omalizumab administration might be mediated by bradykinin.

Another major component of mast cell granules is heparin, which is released following IgE/antigen activation and possibly during anti-IgE therapy.[4] We hypothesize that in our patient, AE may possibly have been mediated by omalizumab-induced mast cell heparin release and heparin-driven Factor XII activation, which triggered the cleavage of high molecular weight kininogen by kallikrein, thus releasing bradykinin.[5]

To our knowledge, this is the first reported case of omalizumab-induced angio-oedema successfully treated with tranexamic acid.

E. Magen[1] and T. Chikovani[2]
[1]*Medicine C Department, Clinical Immunology and Allergy Unit, Ben Gurion University of Negev, Barzilai University Medical Center, Ashkelon, Israel; and* [2]*Department of Immunology, Tbilisi State Medical University, Georgia*
E-mail: allergologycom@gmail.com
Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 9 January 2018

References

1 Cicardi M, Bergamaschini L, Zingale LC *et al.* Idiopathic nonhistaminergic angioedema. *Am J Med* 1999; **106**: 650–4.
2 Zingale LC, Beltrami L, Zanichelli A *et al.* Angioedema without urticaria: a large clinical survey. *CMAJ* 2006; **175**: 1065–70.
3 Cicardi M, Suffritti C, Perego F, Caccia S. Novelties in the diagnosis and treatment of angioedema. *J Investig Allergol Clin Immunol* 2016; **26**: 212–21.
4 Oschatz C, Maas C, Lecher B *et al.* Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. *Immunity* 2011; **34**: 258–68.
5 Maas C, Oschatz C, Renné T. The plasma contact system 2.0. *Semin Thromb Hemost* 2011; **37**: 375–81.

Pemphigus foliaceus and acquired haemophilia: a rare but important association with life-threatening consequences

doi: 10.1111/ced.13617

A 48-year-old white woman presented with extensive crusted erosions around her eyes and on her neck and trunk, without involvement of mucosal surfaces (Fig. 1a,

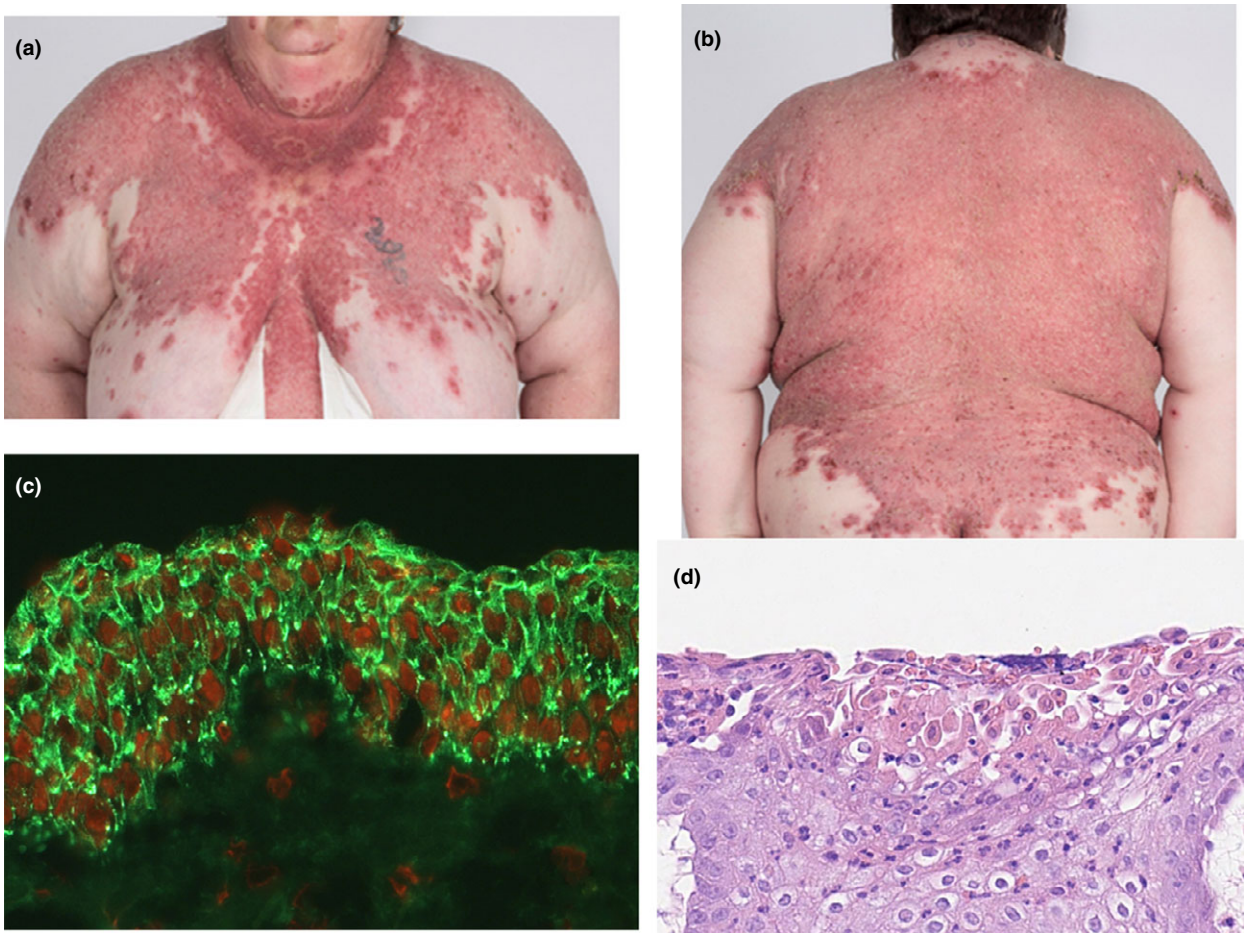

Figure 1 (a) Large areas of superficial erosions involving the chest, neck and shoulders, in keeping with pemphigus foliaceus; (b) widespread confluent erosion across the entire back. (c) Direct immunofluorescence on perilesional skin, demonstrating IgG antibodies at intercellular junctions in the epidermis (original magnification × 40). (d) Affected skin demonstrating loss of stratum corneum, focal acantholysis and spongiosis with subepidermal oedema and occasional neutrophilis, with perivascular inflammation visible in the superficial dermis (haematoxylin and eosin, original magnification × 40). [Colour figure can be viewed at wileyonlinelibrary.com]

b). Pemphigus foliaceus (PF) was suspected and confirmed on investigation.

Histological examination of a skin biopsy revealed absence of the stratum corneum with focal acantholysis (Fig. 1d). Direct immunofluorescence showed intercellular deposition of IgG, IgA and C3 (Fig. 1c), and indirect immunofluorescence confirmed the presence of anti-desmoglein (Dsg)1 antibodies (ELISA titre 149 U/mL) without anti-Dsg3 antibodies.

Following limited response to oral prednisolone 30 mg daily, three pulses of intravenous methylprednisolone 1 g were administered, and mycophenolate mofetil was initiated and titrated to 1 g twice daily. This resulted in 50% improvement after 2 months.

The patient attended a routine follow-up 6 months after diagnosis, looking pale and short of breath, and she reported a new-onset painful swelling of her right leg. She was noted to be tachycardic and tachypnoeic. Her right leg was tender, firm and swollen, with purplish discolouration.

The patient was transferred to the accident and emergency unit, and admitted under the care of the Haematology department. An acute drop in haemoglobin from 93 g/L to 63 g/L (normal range 127–163 g/L) was attributed to spontaneous bleeding into her leg. A clotting screen revealed a high activated partial thromboplastin time (aPTT) ratio (1.7; normal range 0.8–1.2) and elevated reticulocyte count (280.4×10^9 g/L; normal range 20–100 g/L). The aPTT prolongation was not corrected by 50 : 50 plasma mixing studies, and confirmatory factor assay demonstrated almost complete factor VIII deficiency (1 IU/dL; normal range 50–150 IU/dL). Positive factor VIII antibodies on Bethesda testing confirmed a diagnosis of acquired haemophilia.

Table 1 Characteristics of patients in the literature and the current report.

References	Type of pemphigus	Patient demographics		Time to development of haemophilia	Presentation / Complications	Treatment
		Age, years	Ethnicity			
Ishikawa *et al.*, 1993[2]	PV	45	Japanese	Onset 16 days after diagnosis of PV	Bleeding from skin biopsy site, with haematuria and left arm haematoma	FVIII replacement; plasma exchange and dexamethasone 25mg/day. Good response
Filipczak A *et al.*, 2015[4]	PF	55	Caucasian	Onset at time of diagnosis of PF	Acute pain in left leg and lumbosacral region; 3 abdominal haematomas on CT	Recombinant activated rFVIIa; IV methylprednisolone 500 mg/day for 4 days; oral prednisolone (1 mg/kg/day) and cyclophosphamide 2 mg/kg/day. Good response at 6 weeks
Halbertsma *et al.*, 2015[5]	PV	68	No specified	Known PV at time of diagnosis, but timing not specified	Subcutaneous haematomas on trunk and limbs	Prednisolone 80 mg daily, gradually tapered. Good response
Current report	PF	48	White	Onset 6 months after diagnosis of PF	Shortness of breath, haematoma right leg and abdominal haematoma	FEIBA; combination of oral prednisolone and cyclophosphamide 150 mg daily; rituximab weekly IV infusions for 4 weeks. Good response

CT, computed tomography; FEIBA, Factor VIII inhibitor bypassing agent; FVIII, Factor VIII; IV, intravenous; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

The patient was treated with blood products and inhibitor bypassing agents. Mycophenolate was switched to cyclophosphamide 150 mg daily with oral prednisolone 30 mg daily to treat both conditions. Magnetic resonance imaging showed a thick-walled collection in the posterior thigh muscles, which required surgical drainage. Computed tomography did not show any evidence of internal malignancy, but demonstrated a large abdominal haematoma. With no recovery of her Factor VIII levels, the patient was treated with weekly IV doses of 375 mg/m^2 rituximab for 4 weeks. Following this, the patient's PF completely resolved and her factor VIII levels gradually improved. She remained in remission at 6 months after treatment discontinuation.

This case demonstrates a rare association between acquired haemophilia developing on the background of underlying refractory PF. Acquired haemophilia is a life-threatening disorder characterized by IgG antibodies produced against endogenous clotting factors, and 50% of cases are associated with an underlying condition.[1] Causes can be subdivided into autoimmune disorders (12%) as in our patient, malignancy, infections (mycoplasma, acute hepatitis B and C), medications and pregnancy. Treatment is aimed at achieving haemostasis and eradicating inhibitors.

An association with autoimmune bullous dermatoses has been described in bullous pemphigoid, pemphigus vulgaris and linear IgA disease,[2–5] but only one previous report of PF co-existing with acquired haemophilia has been described.[6] The features of reports associated with pemphigus subtypes are demonstrated in (Table 1). This may occur due to crossreactions between certain skin antibodies and Factor VIII.[6]

Physicians should be aware of this potential association and be alerted by any sudden drop in haemoglobin or any evidence of spontaneous bleeding. Documented mortality rates range from 8 to 42%.[1] Early detection and treatment is therefore essential.[1] Our case also demonstrates that an excellent response to refractory PF can be seen with a combination of oral prednisolone, cyclophosphamide and rituximab.

A. G. Wernham[1], C. Peng[1], B. Bailiff[2] and A. Ilchyshyn[1]
Departments of [1]Dermatology, and [2]Haematology, University Hospitals Coventry and Warwickshire NHS Foundation TrustCoventry, Clifford Bridge Road, CV2 2DX, UK
E-mail: aaron.wernham@nhs.net
Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 30 January 2018

References

1 Collins PW, Chalmers E, Hart D, Jennings I. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol* 2013; **162**: 758–73.
2 Chen C, Chen Y, Ho J *et al.* Bullous pemphigoid associated with acquired haemophilia. *DSI* 2010; **28**: 173–6.
3 Ishikawa O, Tamura A, Ohnishi K, Miyachi Y. Pemphigus vulgaris associated with acquired hemophilia A due to factor VIII inhibitor. *Acta Derm Venereol* 1993; **73**: 229–30.

4 Ly A, Roth B, Causeret AS. Anti-laminin 5 pemphigoid and acquired haemophilia. *Br J Dermatol* 2002; **146**: 1104–5.
5 Halbertsma FJ, van der Linden PW, Mauser-Bunschoten EP. A patient with acquired haemophilia A and pemphigus. *Neth J Med* 1998; **52**: 190–2.
6 Filipczak A, Michaelska-Jakubus M, Górska-Kosicka M *et al.* Coexistence of pemphigus foliaceus and acquired hemophilia A: a case report. *J Dermatol* 2015; **42**: 638–41.

Unilateral periorbital swelling: a diagnostic dilemma

doi: 10.1111/ced.13618

A 50-year-old man presented with a 6-month history of unilateral periorbital swelling and an erythematous plaque with adherent crust on the left upper eyelid (Fig. 1) following an insect bite. The plaques were nontender on palpation. The patient had been prescribed intermittent antihistamines and oral steroids, but the symptoms had continued to worsen.

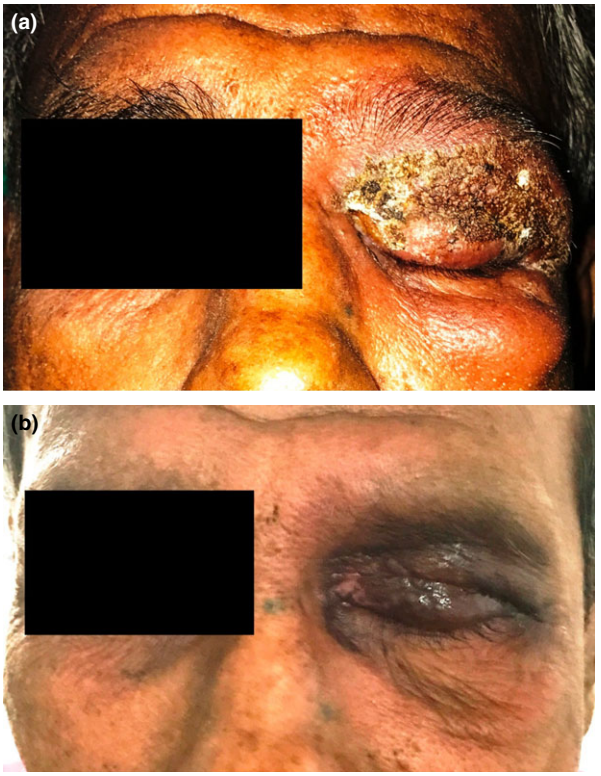

Figure 1 (a) Unilateral periorbital swelling along with erythematous plaque with adherent crust on the left eyelid; (b) after treatment with application of liposomal amphotericin B gel the crust was removed.

Dermoscopy under polarized light revealed a few yellow tears and a white starburst pattern (Fig. 2a).

Histological examination of a skin biopsy revealed dense infiltrate of lymphocytes, histiocytes, plasma cells and epitheloid cells with round to oval basophilic bodies in macrophages (Fig. 2b).

The patient was diagnosed with cutaneous leishmaniasis (CL). He was treated for 4 weeks with oral miltefosine 50 mg twice daily, which produced partial improvement, but the adherent crusts were still persistent. Topical

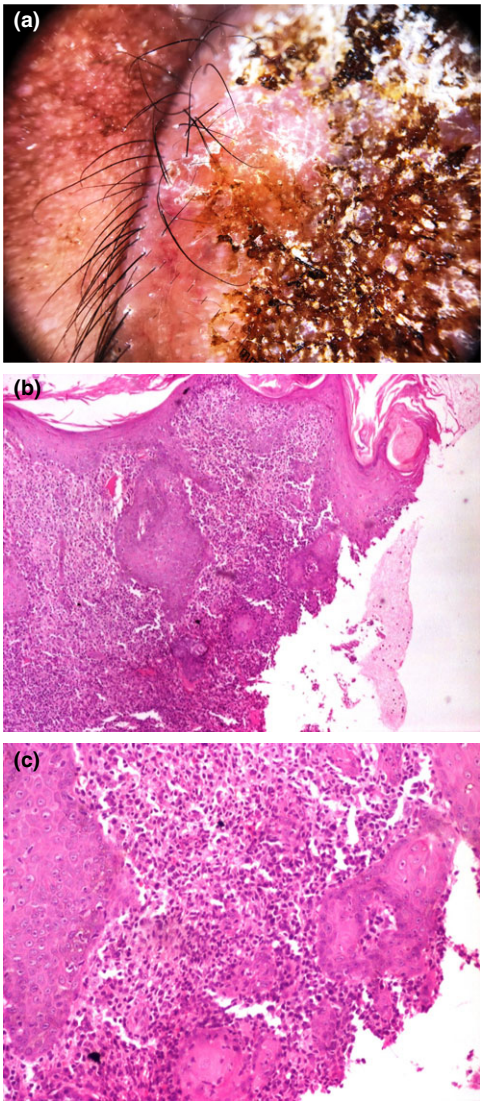

Figure 2 (a) Dermoscopy under polarized light showing yellow tears and white starburst pattern (original magnification × 10). (b,c) Histopathology revealed dense infiltrates of (b) lymphocytes, histiocytes, plasma cells and epitheloid cells; and (c) lymphocytes, histiocytes, plasma cells and epitheloid cells with a few round to oval basophilic bodies in macrophages. Haematoxylin and eosin, original magnification (b) × 10; (c) × 40.

