

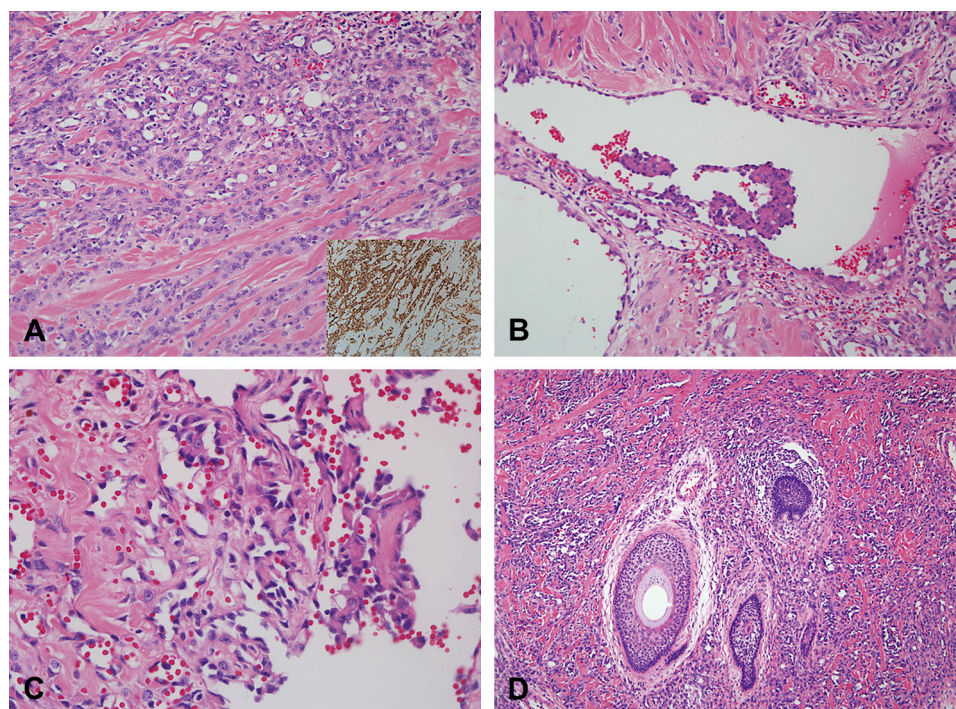


Fig 2. Composite hemangioendothelioma. **A**, Epithelioid hemangioendothelioma-like pattern with cytoplasmic lacunae and red blood cells is predominant component (**inset**: CD31 immunostain). **B**, Dabska tumor-like areas with dilated vascular channels containing intraluminal papillae with hyaline cores and hobnailed endothelial lining. **C**, Irregular branching thin-walled vessels lined by cuboid hyperchromatic endothelial cells reminiscent of retiform hemangioendothelioma. **D**, Low-grade angiosarcomatous areas with dissecting vascular channels between skin adnexal structures. (**A** to **D**, Original magnifications: **A** and **B**, $\times 200$; **C**, $\times 400$; **D**, $\times 100$.)

Department of Dermatology, Chang Gung Memorial Hospital,^c Taipei, Taiwan

Funding sources: None.

Conflicts of interest: None declared.

Correspondence to: Tzu-Lin Hsiao, MD, PhD, Department of Dermatology, National Taiwan University Hospital, College of Medicine, National Taiwan University, 15th Floor, No. 7, Chung Shan S Rd, Zhongzheng District, Taipei City, Taiwan (R.O.C.)

E-mail: tlhsiao@ntu.edu.tw

REFERENCES

1. Nayler SJ, Rubin BP, Calonje E, Chan JK, Fletcher CD. Composite hemangioendothelioma: a complex, low-grade vascular lesion mimicking angiosarcoma. *Am J Surg Pathol* 2000;24:352-61.
2. Tsai JW, Huang HY, Lee JC, Yen YS, Tung CL, Huang CC, et al. Composite hemangioendothelioma: report of four cases with emphasis on atypical clinical presentation. *Pathology* 2011;43:176-80.
3. Fukunaga M, Suzuki K, Saegusa N, Folpe AL. Composite hemangioendothelioma: report of 5 cases including one

with associated Maffucci syndrome. *Am J Surg Pathol* 2007;31:1567-72.

4. Utaş S, Canöz O, Ferahbaş A, Özcan N. Composite cutaneous hemangioendothelioma treated with interferon. *J Eur Acad Dermatol Venereol* 2008;22:503-5.
5. Suchak R, Thway K, Zelger B, Fisher C, Calonje E. Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas. *Am J Surg Pathol* 2011;35:60-9.

<http://dx.doi.org/10.1016/j.jaad.2012.08.044>

Effective treatment of idiopathic chronic cold urticaria with omalizumab: Report of 3 cases

To the Editor: Physical chronic urticaria (CU), including chronic cold urticaria (CCU), is often refractory to conventional treatments like nonsedative antihistamine drugs. Then other therapeutic approaches may be considered, such as omalizumab, a recombinant humanized monoclonal antibody directed against IgE that is approved for the treatment of moderate to severe persistent asthma. The off-label use of this drug in CU is supported by several studies and case reports. However, its efficiency in treating physical

Table I. Overview of patients with chronic cold urticaria treated with omalizumab

Patient	Sex/age, y	Duration of urticaria, y	Previous medications for urticaria	Atopy	Total IgE (kU/L) at baseline (N < 91)	UAS (/6) before/after 4 initial injections	DLQI (/30) before/after 4 initial injections	Relapse after 4 initial injections	Total no. of injections	Current status
1	F/66	6	Hydroxyzine,* ketotifen,* [†] desloratadine,* [‡] levocetirizine,* ebastine,* [‡] mizolastine,* [§] montelukast, ^{//} colchicine (1 mg/d), dapsone (100 mg/d), [¶] methotrexate (15 mg/wk), hydroxychloroquine (400 mg/d)	No	89	6/0	18/0	No	4	Free of symptoms after 16 mo of F/U after fourth injection
2	F/42	3	Ketotifen,* [†] desloratadine,* [‡] levocetirizine,* montelukast, ^{//} colchicine (1 mg/d), hydroxychloroquine (400 mg/d), cyclosporin (2.5 mg/kg/d)	Yes (asthma)	493	6/0	7/0	Yes; onset of relapses: respectively, 4 and 5 mo after fourth and fifth injection	6	Free of symptoms after 1 mo of F/U after sixth injection
3	F/21	8	Desloratadine,* [‡] levocetirizine,* ebastine,* mizolastine,* [§] rupatadine,* bilastine,* montelukast, ^{//} colchicine (1 mg/d)	Yes (asthma)	1772	6/0	17/0	Yes; onset of relapse: 1 mo after fourth injection	5	Free of symptoms after 2 mo of F/U after fifth injection

All patients received 4 initial subcutaneous injections of 300 mg of omalizumab every 2 wk.

DLQI, Dermatology Life Quality Index; F, female; F/U, follow-up; UAS, Urticaria Activity Score.

*Standard dose.

[†]Sedative H1 antihistamines.

[‡]High dose (4-fold increase).

[§]Nonsedative H1 antihistamines.

^{//}In combination with nonsedative H1-antihistamine.

[¶]Disrupted because of anemia.

[#]Disrupted because not tolerated at high dose.

urticaria, and in particular CCU, is less documented. We report 3 patients with refractory CCU who experienced significant and rapid improvement with omalizumab.

Our patients had long-lasting CCU with severe symptoms, as confirmed by the Urticaria Activity Score¹ and the Dermatology Life Quality Index (Table I). The ice cube provocation test revealed positive results within less than 5 minutes for all patients. Two patients had a personal history of atopy (asthma) that was associated with an increased serum level of total IgE at baseline. The clinical examinations and laboratory investigations eliminated an underlying disease for all patients. These patients had previously received numerous treatments that were taken over at least 6 weeks but without sufficient effects on symptoms (Table I). We opted to treat these patients with omalizumab after obtaining the patients' written consent regarding the off-label use of this drug. All other treatments, including H1-antihistamines, were discontinued when omalizumab was started. We initially planned 4 subcutaneous injections with 300 mg of omalizumab every 2 weeks. No side effects were observed except for a slight erythema at the site of the injection for the second and third patients. All patients reported significant improvement after the first injection and complete control of symptoms after the second injection. Indeed, after the second injection, the Urticaria Activity Score and Dermatology Life Quality Index Score were measured as 0, and the ice cube provocation test produced negative findings. The first patient received 4 injections, and her symptoms remained controlled after a follow-up of 16 months without further treatment. The second patient experienced a relapse 4 months after the fourth injection; a fifth omalizumab dose (300 mg) was administered and was accompanied by rapid and complete remission, maintained for 5 months after this fifth injection without further treatment. Currently, she has experienced a mild relapse (Urticaria Activity Score 3/6) rapidly controlled by a sixth omalizumab dose (300 mg). The third patient achieved complete remission after 4 injections. After 1 month of treatment disruption without any symptoms, the urticaria reappeared and we prescribed a fifth omalizumab dose (300 mg). We rapidly observed a complete remission maintained 2 months after the fifth dose.

The impact of omalizumab on physical CU has been reported in very few case reports. To our knowledge, there are only 2 published case reports of CCU treated by omalizumab.^{2,3}

The mechanisms of therapeutic efficiency of omalizumab in CU remain unclear.

As in asthma, some authors correlated the clinical improvement induced by omalizumab in spontaneous or physical CU with the reduction in free IgE levels. However, numerous patients with CU successfully treated with omalizumab in published case reports or studies exhibited neither increased total IgE levels nor IgE specific to allergens, as in our first patient who remained asymptomatic after 16 months of follow-up.

Because the efficiency of omalizumab appeared not to be strictly correlated with the serum IgE levels, we did not base the dosage choice on patients' baseline serum IgE levels and weights, as recommended in asthma. Instead, after analyzing the published controlled studies,⁴ we arbitrarily chose a 300-mg dose given every 2 weeks, for a total of 4 injections. A supplementary dose was given in case of relapse. There are few data in the literature concerning the rate and onset of relapse after omalizumab discontinuation. Large clinical trials will be necessary to determine the best protocol and duration for drug administration in CU.

Amandine Le Moing,^a Céline Bécourt,^a Emeline Pape, MD,^{a,b} Yves Dejobert, MD,^a Emmanuel Delaporte, MD,^{a,b} and Delphine Staumont-Sallé, MD, PhD^{a,b}

Department of Dermatology, University Hospital of Lille, Hôpital Claude-Huriez,^a and Faculty of Medicine Henri Warembourg, University Lille 2,^b France

Funding sources: None.

Conflicts of interest: None declared.

Correspondence to: Delphine Staumont-Sallé, MD, PhD, Department of Dermatology, University Hospital of Lille, Hôpital Claude-Huriez, Rue Michel Polonovski, 59037 Lille cedex, France

E-mail: delphine.salle@chru-lille.fr

REFERENCES

1. Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;63:777-80.
2. Metz M, Altrichter S, Ardelean E, Kessler B, Krause K, Magerl M, et al. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol* 2011;154:177-80.
3. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol* 2006;117:1415-8.
4. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;128:567-73.