

EBS-gen nDM and EBS-loc.^{2,6,7} In the family presented here, the p.Met272Thr mutation was found in the proband's father and his mother (proband's grandmother) – who both manifested clinical symptoms of EBS-loc. The other mutation, p.Arg471His in KRT5, has not been reported before; however, in one Turkish family the other amino acid substitution of the same residue, p.Arg471Cys, was found.⁶ Arg471 is located within the most conserved helix termination motif in the helical segment of the central rod domain in position 'e' of the superhelix model, indicating its active participation in heterodimer formation. Thus, the Arg471 substitution may distort the α -helical conformation.

The mutation, p.Arg471His, was of maternal origin; the mother had initially claimed to be asymptomatic. However, clinical investigation revealed minor trauma-induced blisters on her feet and, like her mother, who also carried the mutation on one allele, she complained of cracking feet. These data may suggest that p.Arg471His in KRT5 acts in a dominant-negative manner and leads to mild skin fragility when present alone, but in the presence of a mutation in the other keratin it exacerbates the symptoms.

In recent years, more data have indicated that the EBS phenotype is modulated by biallelic mutations. Yasukawa *et al.* showed that the coexistence of two KRT5 mutations, p.Glu170Lys and p.Glu418Lys, in a cellular model leads to increased keratin aggregation by 2.3-fold in comparison with p.Glu170Lys alone.⁸ It has been suggested that other factors also influence disease outcome. Ołdak *et al.* reported homozygous p.Glu170Lys in the KRT5 gene in a proband with EBS-gen nDM, whose heterozygous parents manifested features of EBS-loc while his older heterozygous sister had no symptoms.⁵ The digenic inheritance of EBS has been observed once before. The patient (a 2-year-old boy with EBS-gen nDM) inherited p.Ile183Thr in KRT5 from his mother, who was mildly affected with EBS-loc, and p.Arg388His in KRT14 from his unaffected father. In both affected cases the disease was exacerbated during the summer months; however, no mucosal or nail involvement was observed in either.⁹

In summary, our report strongly supports the idea of fully sequencing KRT5 and KRT14 genes for genetic counselling purposes and for better understanding genotype–phenotype correlations. This observation is also of extreme importance for personalized therapeutic strategies, which are the subject of extensive research.¹⁰

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Effects of omalizumab in a patient with three types of chronic urticaria

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DEAR EDITOR, Chronic urticaria (CU) is a common and debilitating disease affecting approximately 1% of the world's population. When diagnosing CU, it is important to be mindful of its heterogeneity, i.e. its many subtypes, which fall into two groups: spontaneous urticaria (CSU) and inducible urticaria (CIndU, e.g. physical urticarias such as symptomatic dermographism).¹ CSU and CIndU are sometimes present in the same patient, but although they share common features, they are generally considered to be distinct entities with different underlying causes and response to treatment.

For all CU subtypes, second-generation antihistamines are the first-line treatment, and doses should be increased if

Table 1 Patient characteristics

Parameter	Details
Age	37 years
Sex	Female
Weight	60 kg
Total duration of urticarias	16 years
Duration of chronic urticaria before omalizumab	11 years
Normal test results	Haemogram; C-reactive protein; sedimentation rate; TSH; antiperoxidase antibody; IgE-antiperoxidase; antimicrosomal antibody; anti-VDRL antibody; anti-HIV I-II antibody; anti-toxoplasma antibody; anti- <i>Helicobacter pylori</i> antibody; hepatitis A, B and C tests; CH50; C1 esterase inhibitor; C3, C4 complements; hepatic and renal functions; parasitological and urine tests; IgE levels; food-specific IgE; rheumatoid factor; anticardiolipin; anti-Ro and anti-La antibodies; autologous serum skin test; imaging tests (abdominal ultrasound, thoracic and paranasal sinuses X-ray)
Pathological test results	Antinuclear antibody of 1/160 Dermographic and pressure test positive Skin biopsy compatible with chronic urticaria (oedema, sparse infiltrate)

needed. Treatment options for antihistamine-refractory CU patients include montelukast, ciclosporin A and omalizumab.² Omalizumab, anti-immunoglobulin E (IgE), is approved for the treatment of severe allergic asthma and has been reported to be effective in several CU subtypes.^{3–5}

Here, we report the effects of omalizumab in a patient with three subtypes of CU. Our patient, a 37-year-old white woman (Table 1), has had CSU, pressure urticaria and symptomatic dermographism since 1997. Both physical urticarias were confirmed by standardized skin provocation testing performed as recommended.⁶ She had previously received various treatments including homeopathy, orthomolecular medicine, autohaemotherapy and restrictive diets. In addition, she had been treated with antihistamines, up to 5× the standard dose (fexofenadine, desloratadine, ebastine, epinastine, chlorpheniramine, hydroxyzine), all with little or no benefit. She also frequently used short-term glucocorticosteroid treatments (prednisolone 50 mg per day or betamethasone 5–10 mg per week) during exacerbations, which provided temporary relief but failed to induce long-term remission. Furthermore, our patient started to experience side-effects (weight gain, skin atrophy, gastritis, osteoporosis). In 2007, she started treatment with ciclosporin 300 mg per day combined with desloratadine 10 mg per day. This, initially, resulted in control of the disease, but symptoms started to reoccur 2 months later, and she was unable to increase the dose because she developed arterial hypertension. Montelukast (10 mg per day) and rupatadine (20 mg per day) were added, but failed to reduce disease activity.

In December 2008, omalizumab treatment (150 mg per month, s.c.) was initiated. After the first injection, in < 24 h, our patient experienced complete remission of her three urticarias. She suspended all other medications and did not develop any symptoms for 30 days. Our patient continued to receive 150 mg omalizumab every month for 2 years, without experiencing any symptoms. She then became pregnant, and during the fourth month of pregnancy, her disease activity increased markedly. After informing the patient of the poten-

tial risks and unknown safety of omalizumab during pregnancy, and after the patient had consented to do so, omalizumab treatment was continued and intervals were shortened to every 15 days, which resulted in complete remission. Our patient had no symptoms or complications before, during or after labour. She gave birth to a healthy child in October 2010 and has remained on omalizumab therapy with dosing intervals of 28 days ever since.

This, to the best of our knowledge, is the first report on the effects of omalizumab treatment on multiple CU subtypes in the same patient. It is also the first description of a patient with CU who used omalizumab during pregnancy and lactation. Our patient showed complete remission of her three distinct CU subtypes after the first day of treatment and continued and increased her use of omalizumab during pregnancy without experiencing adverse effects.

The efficacy of omalizumab has been described in CSU^{3,4} and physical urticarias,⁵ but never for more than one urticaria subtype in one individual patient. The fact that all three subtypes responded with similar kinetics and a complete protection from symptoms strongly argues that omalizumab worked by the same mechanism in all three conditions. Omalizumab is held to act by binding and neutralizing free serum IgE, but sensitizations and allergies to environmental allergens are typically not the cause of CSU or CIndUs. Omalizumab, in the three urticarias of our patient, may work by neutralizing free IgE against autoantigens, so-called autoallergic IgE. Autoallergic IgE has been shown to be expressed by up to 60% of patients with CSU,⁷ and is thought to explain why CIndUs can be transferred to healthy individuals by injection of the serum of some patients. Also, omalizumab has been shown to be effective in patients with CSU with autoallergic IgE.⁸

Omalizumab is not approved for use during pregnancy. Because our patient suffered from three distinct, severe urticarias, and after careful consideration of alternative treatment options and omalizumab's risk–benefit profile, our patient continued to receive omalizumab during her pregnancy and

benefited from this. Our case study demonstrates the efficacy and safety of omalizumab in different types of urticaria and suggests a common mechanism of action in chronic spontaneous and chronic inducible urticarias. The latter should be tested for responses to omalizumab treatment in randomized controlled trials.

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Repeated skin sampling and prolonged incubation period identified cutaneous *Mycobacterium chelonae* infection on the face in an immunocompetent man

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DEAR EDITOR, *Mycobacterium chelonae* is a rapidly growing form of nontuberculous mycobacteria (NTM) that commonly affects

the skin, viscera, soft tissues, bones and joints.^{1,2} Cutaneous *M. chelonae* infection mainly occurs in immunocompromised hosts and presents as multiple disseminated lesions.³ The infection is much less common in immunocompetent hosts, in which it usually develops as a localized cutaneous lesion at the site of trauma, surgery, injection, tattooing or cosmetic procedure.^{3–5} In immunocompetent hosts, facial involvement is extremely rare without these risk factors.⁶ For the diagnosis of *M. chelonae* infection, identification of the pathogen is crucial. To our knowledge, no case has been reported that required more than 8 weeks of incubation to isolate *M. chelonae* from the skin. Here we report a case with cutaneous *M. chelonae* infection presenting as multiple facial lesions in an immunocompetent patient with no specific risk factors and diagnosed by 9-week mycobacterial culture.

A 68-year-old Japanese man presented with an 8-month history of multiple asymptomatic eruptions on the face. The patient had no history of disorders known to cause compromised immunity, such as HIV infection, diabetes mellitus or malignant neoplasm, nor was the patient taking any immunosuppressive medication. On physical examination, more than 20 dark-reddish papules and nodules up to 2 cm in diameter were disseminated on the right side of his face (Fig. 1a) and the right cervical lymph nodes were swollen, but he was otherwise healthy. Blood test showed an elevated white blood cell count ($13\,900\text{ mm}^{-3}$; normal range $3500\text{--}9300$) and elevated C-reactive protein (2.19 mg dL^{-1} ; normal $0\text{--}0.39$). He was negative for HIV antibody. Histology of the reddish nodule on his right eyebrow showed a dense mixed-cell infiltrate of neutrophils, histiocytes, plasma cells and lymphocytes throughout the dermis with neither granuloma nor necrotic foci (Fig. 2a). Multinucleated giant cells were also observed (Fig. 2b). From the clinicopathological findings, fungal or mycobacterial infection was suspected. Lesional skin was sampled for fungal and mycobacterial culture, but both were negative. Neither bacilli nor fungi were observed by Grocott, periodic acid–Schiff or Ziehl–Neelsen staining. Lesional skin was repeatedly sampled for culture thereafter, four times in total, which finally detected acid-fast bacilli (Gaffky scale 1) by smear Ziehl–Neelsen staining in only one sample. Visible colonies were identified after 9 weeks of incubation at $35\text{--}37\text{ }^{\circ}\text{C}$ with the BD Bactec™ Mycobacteria Growth Indicator Tube (MGIT™) 960 system (BD, Franklin Lakes NJ, U.S.A.) and Ogawa medium, and they were subsequently confirmed as *M. chelonae* by DNA–DNA hybridization. Thus, a diagnosis of cutaneous *M. chelonae* infection was finally made. A combination of clarithromycin, rifampicin and ethambutol was orally administered for 6 months. The eruptions disappeared within a month after the start of treatment, with no clinical recurrence at 6-month follow-up (Fig. 1b).

In the present case, cutaneous infection of *M. chelonae* developed on the face, although the patient was not immunocompromised and lacked specific risk events for the infection, such as trauma or iatrogenic procedure. To our knowledge, only a few cases of cutaneous *M. chelonae* infection involving the face have been reported in immunocompetent hosts with