ARCUEIL, 11/28/2022

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published in:
European Journal of Dermatology, 2022, Volume 32, Numéro 5

John Libbey Eurotext

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doi:10.1684/ejd.2022.4322

Successful treatment with omalizumab for cold urticaria in a patient with chronic hepatitis C virus infection

Cold urticaria (ColdU) is primarily (idiopathic) or secondarily due to infections, autoimmune and lymphoproliferative diseases, drugs or food. The diagnosis relies on the patient's history, cold stimulation testing (CST) and a search for associated conditions. The management of ColdU includes cold avoidance, H1-antihistamines (for refractory cases) and off-label administration of omalizumab, an anti-immunoglobulin E antibody used as treatment for severe allergic asthma, chronic spontaneous urticaria and nasal polyps [1, 2].

We report a 65-year-old woman with ColdU and hepatitis C virus (HCV) infection who experienced significant improvement with regards to severity of skin disease and quality of life (QOL) after three months of treatment with omalizumab. The first symptoms and signs occurred at the age of 17 years with recurrent pruritus and rash on the face and other areas after contact with cold objects or water. She described itching of the lips and tongue after consumption of cold foods and drinks. Within a few months, urticaria became generalized with occasional shortness of breath. The diagnosis of ColdU was established on the basis of the clinical history and positive CST using an ice cube, resulting in significant wheals and redness within three minutes following removal [1]. The patient had no family history of ColdU. Treatment using standard doses of H1-antihistamines was administered with satisfactory control of symptoms. She had been infected with HCV after blood transfusion following a road accident at the age of 21 years, and the diagnosis of chronic hepatitis C was established at the age of 44 years. Treatment with interferon and ribavirin led to hepatitis remission until the age of 58 years. Thereafter, concomitant with recrudescence of hepatitis, the patient described progression of skin symptoms, limiting her outdoor activities and food choices, requiring a two-fold increase in the doses of H1-antihistamines. At the age of 59 years, polyclonal cryoglobulins were detected in serum (type III cryoglobulinaemia) based on immunoelectrophoretic analysis. Serum complement levels (C3, C4, CH50) were normal and rheumatoid factor was negative. Treatment with ledipasvir/sofosbuvir at 90 mg/400 mg, once daily, for eight weeks induced remission of hepatitis and disappearance of serum cryoglobulins without improvement of skin symptoms, despite four-fold doses of H1-antihistamines. Because of the severity of ColdU with a score of symptoms on the visual analogue scale [VAS] of 9, and a high negative impact on QOL (Chronic Urticaria-related Quality of Life CU-Q2OL score of 90.22 [3]), treatment with subcutaneous omalizumab, 300 mg every four weeks, was started. Omalizumab was well tolerated with significant improvement of clinical signs (wheals), symptoms (pruritus; VAS 2 score) and QOL (CU-Q2OL score: 9.78), observed after three months of treatment.

The efficacy of omalizumab for ColdU resistant to H1-antihistamines has been demonstrated based on a randomized trial and a recent meta-analysis with similar benefit for 150 mg and 300 mg administered every four weeks. A complete response with negative CST was observed in $\geq$40% of patients at 10 weeks of treatment [4, 5]. Our patient reported significant improvement of symptoms but also of QOL, which has not previously been described in adults. The mechanism of action of omalizumab for ColdU has not yet been identified, even though data suggest that mast cell degranulation in ColdU involves immunoglobulin E and an unknown cutaneous autoallergen that becomes accessible upon cold stimulation [1, 4, 6].

Our patient had a complex history with ColdU and HCV infection and cryoglobulins during active hepatitis. Cryoglobulins were detected in 27% of patients with ColdU, even though their pathogenic role is unknown [7]. Conversely, mixed cryoglobulinaemia is present in 40% of patients with hepatitis C [8], and HCV infection is a major cause of mixed cryoglobulinaemia (95% of cases) [9, 10]. Direct-acting antivirals represent the most effective treatment for HCV-related mixed cryoglobulinaemia [10]. The clinical history of this patient with ColdU, present before HCV infection, the disappearance of serum cryoglobulins after antiviral therapy, and the persistence of severe skin symptoms, despite the effective treatment of hepatitis, suggested to us that the patient suffered from idiopathic ColdU and prompted the initiation of omalizumab treatment, which proved successful. Further research is needed to understand the role of infections or cryoglobulins in ColdU pathogenesis and the mechanism of action of omalizumab. ■

Disclosures. *Financial support: none. Conflicts of interest: none. Informed consent was obtained from the patient.*

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doi:10.1684/ejd.2022.4324

A case of Bazex syndrome with type 2 immune response

Bazex syndrome (acrokeratosis paraneoplastica) is a rare paraneoplastic dermatosis characterized by acral hyperkeratotic lesions, of which the aetiology remains unknown. This study reports the second case of Bazex syndrome with elevated serum thymus and activation-regulated chemokine (TARC) (also known as C-C class chemokine ligand 17 [CCL17]) levels. In addition, infiltration of C-C chemokine receptor 4 (CCR4)-positive cells was observed in this case, suggesting the involvement of type 2 immune responses in the pathophysiology of Bazex syndrome.

A man in his 60 s, with a history of alcohol intake and smoking for 50 pack-years, and no history of allergic diseases including atopic dermatitis, presented to the dermatology department with a two-week history of enlarging lesions on his palms, forearms, lower limbs, and soles (*figure 1A*). Physical examination revealed bilateral thickening of the skin of the palms and soles, and scaly pink patches on both forearms and legs. Laboratory studies revealed macrocytic anaemia (haemoglobin: 12.5 g/dL, reference range: 13.7-16.8; mean corpuscular volume: 108.7 fL, reference range: 83.6–98.2), and elevated C-reactive protein (0.68 mg/dL, reference range: 0.00–0.14), TARC (3,928 pg/mL, reference range: <450), and soluble interleukin 2 receptor (1,969 U/mL, reference range: 122–496) levels. White blood cell count, differential count, and immunoglobulin E levels were normal.

Histological analysis of a biopsy specimen from the skin of his left palm revealed hyperkeratosis, parakeratosis, acanthosis, spongiosis, and dyskeratotic keratinocytes, with lymphocytic infiltrates (*figure 1B*). The upper dermis showed perivascular infiltrates comprising lymphocytes and eosinophils (*figure 1C*). Furthermore, immunological staining using mouse anti-human CCR4 monoclonal antibody (Poteligeo Test IHC; Minaris Medical Co., Ltd., Tokyo) revealed that CCR4 was expressed within these infiltrating cells (*figure 1D*).

An underlying malignancy was suspected, and after imaging and pathological work-up, the patient was diagnosed with cStage II (cT1bN0M0) oesophageal cancer. The patient stopped smoking after the diagnosis. Neoadjuvant chemotherapy was initiated, and surgical treatment was performed six months after the initial presentation. The skin lesions resolved after the surgery, however, a new pruritic eczematous eruption of unknown cause developed on his trunk and extremities six months after the surgery, accompanied by serum TARC elevation to 18,330 pg/mL. The new skin eruption gradually resolved with topical steroids, and serum TARC levels declined to 6,019 pg/mL at 12 months post-surgery. Finally, both the palmoplantar lesions and pruritic dermatitis resolved completely (*figure 1E*), and serum TARC levels declined to 744 pg/mL at 15 months post-surgery. The patient exhibited no signs of cancer for 19 months post-treatment.

Bazex syndrome is a paraneoplastic dermatosis characterized by symmetric psoriasiform lesions on the extremities, nose, and ears, which clinically resembles psoriasis [1]. However, the unique pathological findings of Bazex syndrome include spongiosis and dyskeratosis, which are observed in the eczematous immune response, including atopic dermatitis, while acanthosis, hyperkeratosis, and parakeratosis are common in both psoriasis and Bazex syndrome [1, 2].

The pathophysiology of Bazex syndrome remains unclear, although several hypotheses have been proposed [1]. TARC is a CCR4 ligand involved in type 2 immune responses by selectively recruiting CCR4-positive type 2 helper T (Th2) cells. CCR4 is predominantly expressed by Th2 cells, cutaneous lymphocyte antigen-positive skin-homing T cells, and regulatory T cells [3]. Strong infiltration of CCR4-positive cells is observed in atopic dermatitis, whereas this is weak in psoriasis [4]. Serum TARC levels accurately reflect the disease activity of atopic dermatitis, which is characterized by Th2 cell proliferation during the acute phase.

To the best of our knowledge, this is the second case of Bazex syndrome in which serum TARC levels are reported. A previous case also reported prolonged high serum TARC levels (3,984 pg/mL and 4,277 pg/mL two weeks and six months after removing the underlying tumour, respectively). However, baseline TARC levels prior to the development of any skin lesions were not provided for either the previous case [5] or our own case. Spongiosis and dyskeratosis, histological hallmarks of Th2 immune deviation [2], have also been observed in cases of Bazex syndrome, including the present case. Furthermore, strong infiltration of CCR4-positive cells in a lesion of Bazex syndrome was reported for the first time in the present case. These findings