Dear Editors,

In 2016, a 25-year-old woman presented to our department with a seven-year history of recurrent swelling of the upper lip. She described the swelling as being continuously present and associated with periodic flares that usually lasted for several days. The patient also reported to occasionally experience palpebral edema and dysphagia. She had various type I sensitizations and a history of migraine.

Clinical examination revealed swelling of the upper lip (Figure 1a, b), the buccal mucosa and the hard palate. The remainder of the physical exam was unremarkable, in particular there was no evidence of a fissured tongue (lingua plicata), facial palsy or Crohn’s disease. Laboratory tests (including inflammatory markers, C3, C4) were within normal limits.

Based on the suspected clinical diagnosis of cheilitis granulomatosa (CG), the patient subsequently underwent a biopsy of the upper lip.

Histology revealed a superficial and deep lymphocytic, spongiotic cheilitis with perivascular accentuation, as well as noncaseating granulomas in the mid and deep dermis (Figure 2). The findings were consistent with CG (with eczematos changes). In the past, several multi-week courses of systemic corticosteroids had resulted in only temporary symptom relief.

As there have been a number of case reports showing dapsone to be beneficial [1–3], we decided to start her on dapsone therapy. While she did experience improvement in the continuous swelling, she subsequently presented multiple times with recurrent – at times severe – angioedema of the upper lip (Figure 1c); the latter was successfully managed with high-dose IV corticosteroids and antihistamines.

Upon further questioning, she stated that she had also developed angioedema a few hours after taking ibuprofen several months earlier. Moreover, she reported that she had noticed wheals in the weeks following her initial presentation to our department; these lesions had persisted for only a few hours. As the autologous serum skin test subsequently showed a distinctly positive reaction, we additionally diagnosed the patient with chronic spontaneous urticaria (CSU) with recurrent angioedema.

**Figure 1** Cheilitis granulomatosa. Initial presentation (a, b). Marked increase in upper lip swelling during a flare of the patient’s CSU-related angioedema (c). Clinical presentation in 2019. Significant improvement on combination therapy with dapsone and omalizumab (d).
In keeping with guideline recommendations, she was initially treated with an H1 antihistamine (desloratadine 5 mg, up to 3 tablets a day) [4]. As she continued to develop severe recurrent angioedema, she was subsequently also started on omalizumab (anti-IgE antibodies) 300 mg every four weeks [4, 5]. On this regimen, she has experienced nearly complete disease control (Figure 1d). She does, however, continue to require dapsone for her CG, given that our attempt at treatment discontinuation resulted in disease recurrence.

To the best of our knowledge, this is the first reported case of a patient with CG coinciding with CSU-related recurrent angioedema.

Cheilitis granulomatosa is clinically characterized by initially recurrent and eventually persistent swelling of either or both lips. Similar to other granulomatous conditions, it may be associated with systematic involvement (Melkersson-Rosenthal syndrome, sarcoidosis, Crohn’s disease, ulcerative colitis).

At present, it is impossible to conclusively comment on whether and to what extent there is a pathogenetic link between CG and CSU. While there have been reports of cinnamon and benzoates as potential triggers for both conditions [6–10], we saw no evidence for that in our patient’s history.

As the pathophysiology of CG is still largely unknown, there is currently no standard treatment [1]. Corticosteroids are frequently used due to their ability to effectively reduce the swelling, but their role in long-term treatment is very limited. Although the exact mode of action of dapsone in the treatment of CG has not been elucidated, various mechanisms have been implicated, including suppression of prostaglandin and leukotriene activity and inhibition of neutrophil recruitment and activation [11]. Another anti-leprosy drug available for off-label treatment is clofazimine [1, 12]. In addition, there has been a report of successful treatment of CG using infliximab in a patient with Crohn’s disease. This may support the proposed notion that CG is associated with increased levels of tumor necrosis factor (TNF) alpha [13].

Chronic spontaneous urticaria is defined as the presence of recurrent wheals for a period of more than six weeks. Angioedema is characterized by submucosal and subcutaneous swelling, especially in the perioral and periorbital region, that develops within minutes to hours and usually subsides within hours or days [4]. In 25–50 % of patients, symptoms are exacerbated by stress, changes in dietary habits or alcohol consumption as well as by nonsteroidal antiinflammatory drugs (NSAIDs) [14, 15]. While an association with thyroid disorders has been established [16], there are as yet no reports of an association with granulomatous conditions.

As a first step, it is recommended to start patients with CSU on a second-generation antihistamine given at the standard dose. Roughly one-quarter of patients will see no clinical improvement with this approach. For these patients, the antihistamine dose may be increased up to four times the standard dose. If the condition persists, patients may be switched to a different antihistamine or to omalizumab. Clinical studies have shown the latter to be associated with complete remission rates of 70 %. If there is still no adequate symptom control, off-label treatment with montelukast or cyclosporine may be considered [17].

In conclusion, the present case highlights the importance of considering the possibility of an additional diagnosis in patients with recalcitrant angioedema. In our patient, combination therapy with omalizumab and dapsone was effective.

Conflict of interest
N. Hunzelmann has received lecture fees from Novartis.

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