DEAR EDITOR, In December 2020, a 78-year-old female Caucasian presented to the emergency department of a local hospital with tongue swelling and dysphagia. There was no fever, odynophagia or local pain. She had no urticaria, itching or cardiovascular instability. Symptoms started ~12 h earlier and ~3 h after receiving a second i.v. dose of tocilizumab (TCZ, 8mg/kg body weight) for a recent relapse of GCA. Previously, she has been treated with TCZ without problems. She was on a triple-antihypertensive therapy, including an angiotensin-converting enzyme (ACE) inhibitor. The emergency department physicians suspected angioedema in response to the TCZ infusion in the presence of the risk factor ACE inhibitor and initiated treatment with i.v. methylprednisolone (250mg) and clemastine (2mg). Because of insufficient clinical response, the patient was referred to our university clinic for further evaluation.

Clinical examination revealed primarily left-sided tongue swelling, swelling of the floor of the mouth, the uvula, the base of the tongue and the aryepiglottic fold. Her glottis was free, and there was no stridor. Her temperature was 36.4°C (97.5°F). Bedside neck US showed no fluid collection. Laboratory tests showed leucocytosis (27 × 10⁹/l), with normal CRP (<5 mg/l). Tryptase was not measured. She was intubated to protect the airways.

The ACE inhibitor was withheld. Treatment with methylprednisolone and clemastine was repeated and, in the absence of clinical response, a dose of a C1-esterase inhibitor (20 IU/kg body weight) administered. Over the next 24 h, she developed intense odynophagia. CT scan of the neck revealed extensive abscess formation in the floor of the mouth and left submandibular space, in addition to suspicion of an abscess in the left parapharyngeal space (Fig. 1). Laboratory blood tests showed a further increase of leucocytes (29 × 10⁹/l), a markedly elevated IL-6 (850 ng/l) and a normal CRP. Complement factor C4, C1-esterase inhibitor levels and C1-esterase inhibitor function were normal.

The patient was started on broad-spectrum antibiotics (piperacillin and tazobactam). Surgical incision of the abscess of the floor of the mouth and left submandibular space, an ipsilateral tonsillectomy with parapharyngeal incision, and extraction of tooth 37 were performed. Microbiology from the abscess yielded Streptococcus intermedius (milleri). She could be extubated on postoperative day 5. After cessation of antibiotic therapy, there was no sign of recurrence. IL-6 levels peaked at 1361 pg/ml and normalized to baseline over the following 2 weeks. The residual seroma at the site of the abscess resolved within three months. Other than mild dysphagia owing to the missing tooth and a persistent asymmetry of the soft palate, she recovered fully. A blood sample 4
weeks after the infection showed mild hypogammaglobulinemia (total IgG 6.3 g/l). TCZ was permanently withdrawn, and she remained free of symptoms of GCA for 3 months. Owing to PMR and systemic inflammation, we initiated glucocorticoids and a CS-sparing therapy with MTX.

Infections are among the main complications of TCZ therapy. Even in severe infections, fever and systemic inflammatory parameters (i.e. CRP and ESR) may be absent in patients treated with TCZ owing to the suppressed IL-6 signalling pathway [1, 2]. Moreover, typical symptoms may be masked; consequently, there is a risk of substantially delayed diagnosis, as illustrated in this case. We have reported previously that IL-6 measurements may help to identify underlying bacterial infections in TCZ-treated subjects [3].

In the presented case, the history of TCZ infusion shortly before the symptom onset, the absent fever and acute-phase reaction, and the co-medication with an ACE inhibitor, falsely indicated angioedema [4]. Leucocytosis, the asymmetric swelling, the absent response to therapy of angioedema, and the known suppression of the inflammatory response by TCZ were clinical clues hinting at masked infection. Physicians should be aware that TCZ therapy may mask infections, warranting careful evaluation of acute symptoms in these patients.

**Funding:** No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

**Disclosure statement:** The authors have declared no conflicts of interest.

**Consent:** The patient gave written informed consent for the publication of this article.

**Data availability statement**

Data from the report can be made available upon request.

**References**

1 Berger CT, Recher M, Daikeler T. Interleukin-6 flags infection in tocilizumab-treated giant cell arteritis. Rheumatology (Oxford) 2018;57:196–7.

2 Berman M, Ben-Ami R, Berliner S et al. The effect of tocilizumab on inflammatory markers in patients hospitalized with serious infections. Case series and review of literature. Life (Basel) 2021;11:258.

3 Berger CT, Recher-Menchaca B, Recher M, Manigold T, Daikeler T. Serial IL-6 measurements in patients with tocilizumab-treated large-vessel vasculitis detect infections and may predict early relapses. Ann Rheum Dis 2019;78:1012–4.

4 Busse PJ, Christiansen SC. Hereditary angioedema. N Engl J Med 2020;382:1136–48.