

# Trigeminal trophic syndrome, a rare and often overlooked cause of facial ulceration: a case report and literature review

Laura Đorđević Betetto<sup>1</sup>, Vid Bajuk<sup>1</sup> ✉

<sup>1</sup>Department of Dermatovenerology, University Medical Center Ljubljana, Ljubljana, Slovenia.

## Abstract

Trigeminal trophic syndrome (TTS) is an uncommon and relatively unknown cause of facial ulceration that occurs after damage to the trigeminal nerve. It characteristically involves non-healing facial ulceration(s) with accompanying anesthesia, paresthesia, and dysesthesia along the distribution of a trigeminal dermatome. The ulcerations are believed to be self-induced in response to paresthesia. The disease is most common in middle-aged women, manifesting as a unilateral crescent-shaped ulceration on the ala nasi, with sparing of the nasal tip. The diagnosis is clinical and mostly based on exclusion of other possible causes of facial ulcerations, with emphasis on neoplasms, infection-associated vasculitis, and factitial disorders. There are no specific histological or laboratory signs. There is no standard treatment protocol; however, a number of different successful strategies have been reported, including pharmaceutical and surgical interventions, transcutaneous nerve stimulation, and simple occlusion dressings. Due to the self-inflicted nature of this disorder, the cornerstone of management is patient education with behavioral modification. Here, we report a case of TTS following herpes zoster ophthalmicus and review the current literature on this subject.

**Keywords:** trigeminal trophic syndrome, facial ulceration, cutaneous dysesthesia, herpes zoster, behavioral modification

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## Introduction

In patients presenting with facial ulceration, numerous causes should be considered, including malignancy, infection, vasculitis, and factitial dermatitis (1). Trigeminal trophic syndrome (TTS) is an often-overlooked cause of facial ulceration, even though it was first described as early as the beginning of the 20th century (2, 3). Since then, fewer than 200 cases have been reported in the literature (4, 5), with different names being used, all of which point to trigeminal nerve involvement and trophic ulceration, such as *trigeminal neurotrophic ulceration*, *trigeminal neuropathy with nasal ulceration*, and *trophic ulceration of the ala nasi* (6). In recent years, the name TTS has most commonly been used (6). This article presents a case of TTS and reviews the epidemiology, pathogenesis, clinical presentation, diagnosis, differential diagnosis, and current management options of TTS.

## Case presentation

A 90-year-old female patient presented to our clinic in January 2022 with erosions covered with dry crusts on her right forehead, edema, erythema of her right eyelids, and warm erythema of her right cheek. The first lesions had appeared 3 days prior. She thought they were due to an impact to the head that she had sustained a week prior. She was prescribed antibiotic eye drops by a general practitioner, which did not result in any improvement. On the day of the first visit to our clinic, she first noticed swelling of her right lip and left eyelids. She had a fever of 37.7 °C. She denied photophobia, headache, vision loss, and painful neck, but she complained about lack of energy. An ophthalmologic examination showed signs of right ophthalmic herpes zoster. She was prescribed a combination therapy with an antibiotic, corticosteroids, antiviral eyedrops, and artificial tears.

She had a history of arterial hypertension, chronic gastritis,

and type 2 diabetes. She had no allergies, and her family history was negative for dermatological diseases. She was taking pantoprazole, acetylsalicylic acid, lacidipine, gliquidone, and sertraline. She had not been vaccinated against herpes zoster.

A swab of the erosions was positive for varicella-zoster virus, *Staphylococcus aureus*, and *Enterococcus faecalis*. She was prescribed a 1-week course of oral valaciclovir, a 10-day course of oral flucloxacillin, and a topical antibiotic cream.

One month later, she returned to our clinic because her lesions were not improving. She had been taking the antibiotics according to our guidelines. Because the ophthalmologists discovered persistence of herpetic keratitis, the oral antiviral therapy with valaciclovir was prolonged for 1 month. She had no fever, chills, malaise, vomiting, or stiff neck. She had a mild headache. Her family members noticed a new ulceration on her right forehead, and in the last week a similar but smaller ulceration had appeared in the scalp. She stated that the skin changes were very itchy but not painful, and she admitted scratching them occasionally.

On examination, there was extensive erythema extending from the right upper eyelid through almost the entire scalp. Inside the erythema there was a clearly demarcated ulceration 6 × 3 cm in size with no undermined edges. The base on the periphery was covered with yellow fibrin. On the right parietal part of the scalp there was a similar ulceration 7 × 2 cm in size (Fig. 1). There were no pustules, vesicles, or similar lesions on other parts of the skin, except for excoriated papules on her upper back. She had no visual field defects or other clinical signs of visual impairment, and no fever or systemic symptoms.

She was hospitalized for further diagnostic workup and treatment. Routine laboratory tests showed mildly lowered renal function (urea 9.3 mmol/l, creatinine 110 μmol/l, glomerular filtration 38 ml/min) and raised erythrocyte sedimentation rate (ESR, 72 mm/h). Follow-up laboratory tests showed no clinically important changes. A bacterial swab of the ulceration was again positive for

✉ Corresponding author: vid.bajuk@kclj.si

*S. aureus*, sensitive to all antibiotics tested. Swabs of the ulceration on the forehead and papules on the back were negative for herpes viruses. Blood cultures were negative. The consultant ophthalmologist reported worsening of the herpetic keratitis and advised prolonged treatment with oral valaciclovir and combination topical therapy with eyedrops. We initiated treatment with regular cleaning of the ulcerations and dressings with polyurethane foam. In a week, we observed partial healing of all ulcerations, and regression of the erythema and edema. No new lesions appeared. We decided not to vaccinate her against herpes zoster.

The clinical diagnosis of TTS following herpes zoster ophthalmicus was made based on exclusion of similarly presenting diseases and rapid clinical improvement. On discharge there was only a 4 mm erosion on her forehead, and the one in the scalp was completely epithelized. There was mild edema of the right upper eyelid and mild erythema of the right forehead and scalp. She was discharged with strict instructions not to scratch or manipulate the lesions in any way and instructions on preventative measures (protective dressings).

At a dermatological follow-up examination in May 2022, the patient reported further improvement, and she had noticed no new lesions. The only complaints were paroxysms of stabbing pain in the right forehead and persistence of herpetic keratitis, which was

under ophthalmological observation. It was decided to continue a prophylactic dose of oral valaciclovir. For the first time, she reported occasional watery discharge from her right nostril, which had started 2 months prior. She had not hit her head again after the trauma she sustained a few weeks prior to her first visit to our clinic.

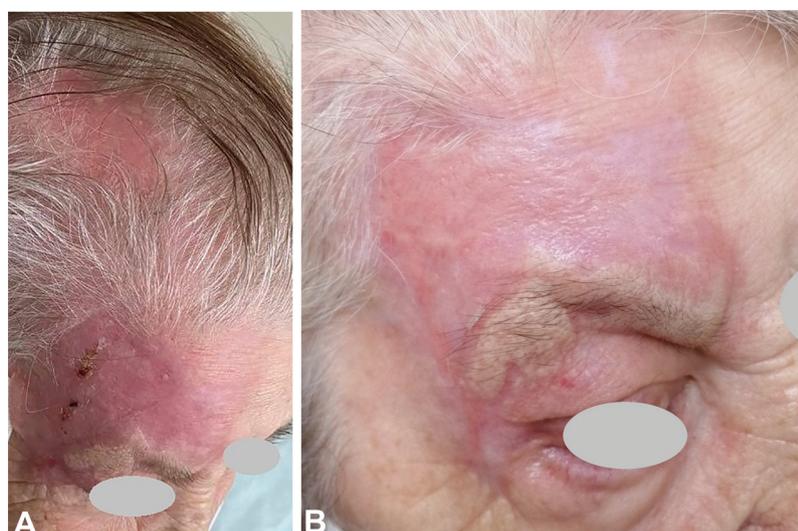
We observed total healing of all ulcerations and almost complete regression of the erythema. The previous ulcerations evolved into pink scars with no signs of inflammation or new ulcerations. Slight edema of the right upper eyelid persisted (Fig. 2). She was advised to continue with protective measures and was referred to an otorhinolaryngologist, who excluded a cerebrospinal fluid fistula with additional tests (beta-trace protein test and computerized tomography scan of the sinuses).

### Discussion and literature review

TTS is a rare but important cause of facial ulceration that consists of the classic clinical triad of trigeminal anesthesia, facial paresthesias, and crescent-shaped nasal ulceration (1, 6). The exact incidence of the disease is still unknown (6), with 75% of TTS cases occurring after Gasserian ganglion ablation (6, 7). The age of presentation varies, with a mean age of 57 years and a slight female



**Figure 1** | Ulcers on the right side of the face (A) and scalp (B) at the time of presentation: clearly demarcated crescent-shaped ulcers, 6 × 3 and 7 × 2 cm in size, with surrounding erythema and no pustules or vesicles.



**Figure 2** | Patient at first (A) and last (B) follow-up examination: partial regression of the erythema and epithelization of both ulcers with formation of secondary pink scars.

predilection (6). This corresponds to the female predominance for trigeminal neuralgia (7).

The exact pathogenesis of TTS remains unknown (5), but it is known that it occurs after central or peripheral damage to the trigeminal nerve (6). The underlying causes are myriad, ranging from various surgical procedures for treating trigeminal neuralgia (such as nerve ablation or transection of the Gasserian ganglion), vascular insufficiencies (vertebrobasilar insufficiency) and strokes (specifically Wallenberg syndrome), tumors (acoustic neuroma, meningioma, and astrocytoma), trauma, craniotomy, infections (postencephalitis, herpes zoster, herpes simplex, leprosy, and syphilis), syringobulbia, and amyloid deposits in the central nervous system and trigeminal nerve (5–8). Trigeminal injury causes paresthesia and dysesthesia, which trigger unconscious self-mutilation and in the long run traumatic ulcer formation (6, 9). Patients describe paresthesias as burning, itching, crawling, or tingling, and often admit to picking or rubbing the area (6). Added anesthesia from trigeminal nerve damage leads to persistent ulcers due to repetitive painless manipulation. It also causes a sensation of nasal blockage or drainage in the nasopharynx (5). However, it is important to note that not all patients suffering from trigeminal damage and only the minority of those experiencing paresthesia develop TTS. In addition, the time between nerve damage and ulceration formation varies from weeks to decades, with a median of 1 year (6). Consequently, other factors that currently remain unknown are probably involved in the etiology of TTS. For example, TTS occurrence is thought to be more likely in patients prone to skin picking (6, 7). It has even been reported that TTS can be provoked by Alzheimer's disease after a long latent period by disinhibiting compulsive habitual picking behavior (10).

To this day, it also remains unknown why ulcers tend to develop at particular limited sites—namely, the ala nasi—despite the large dermatome covered by each trigeminal branch. It has been postulated that this is due to only partial damage to the affected nerve or ganglia. The location of the ulcer may consequently correspond to the destroyed part of the ganglia. TTS most often affects the second (maxillary) branch of the trigeminal nerve, and ulcers most frequently arise at the ala nasi and nostrils (6). Thirteen percent of lesions involve locations other than the nose, such as the forehead, scalp, cheek, jaw, ear, and lip (6, 7). Most ulcerations follow the infraorbital nerve distribution (5).

The ulcers characteristically start as a small crust that enlarges into a crescent-shaped ulcer on the ala nasi and may extend to involve the cheek and upper lip, while sparing the nasal tip, which receives sensory innervation from the anterior ethmoidal branch of the nasociliary nerve. The ala nasi lesion may result in a punched-out appearance, corresponding to the area of the nose lacking cartilage (6). Extension of the ulceration to the cheek and lip with soft tissue scarring can draw the upper lip into a characteristic sneer (5, 6). The ulcers may be single or multiple, or focal or extensive, and they are reported more often on the right side of the face (4, 6). They are typically unilateral, with only one bilateral case recently reported (1). The location and overall gross appearance of the ulcers tend to be characteristically uniform and, once ulcers appear, they are extremely persistent (5, 6). These characteristics should aid in the clinical diagnosis of TTS. Eye lesions are not rare, often resulting in eyelid involvement and even canthal and corneal lesions (4).

TTS is a diagnosis of exclusion, often made by clinical observation and exclusion of other main causes of facial non-healing ulcers (5, 6). To date, there is no diagnostic algorithm for TTS (5).

Frequently patients report a preceding condition causing trigeminal nerve damage such as stroke, trigeminal neuralgia, herpes zoster, meningioma, acoustic neuroma, encephalitis, syphilis, or surgical procedures affecting the nerve (1, 5). In cases where there is a high clinical suspicion of TTS and patients fail to report any preceding conditions, magnetic resonance imaging (MRI) may demonstrate trigeminal nerve injury or distortion and should therefore always be acquired in order to ensure that underlying causes of TTS are not overlooked (11). Functioning of the trigeminal nerve can also be evaluated using neurophysiological studies such as electromyography. It has been reported that MRI can show mild chronic inflammation of facial sinuses in TTS patients (1). Laboratory workup in TTS is normal and nonspecific (5). Histology is also non-diagnostic and nonspecific because it only shows chronic ulceration with adjacent lichenification and epidermal and dermal scarring with mild mixed inflammatory cell infiltrate and no giant cells, granulomas, or vasculitic lesions (1, 5, 6, 12). However, a thorough histological examination is crucial for excluding other causes of facial ulceration, especially in ruling out malignancy, vasculitis, and certain infections (12).

The differential diagnosis of TTS is broad and includes other causes of facial ulcerations such as skin neoplasms (basal cell carcinoma, squamous cell carcinoma, sarcoma, and lymphoma), infections (herpes, syphilis, mycobacteria, leishmaniasis, and dimorphic fungi), systemic vasculitis (granulomatosis with polyangiitis [GPA] and giant cell arteritis), pyoderma gangrenosum (PG), granulomatous diseases, and factitial dermatitis (dermatitis artefacta [DA] and delusions of parasitosis [DP] (5, 6, 8, 13–16). Clinically, with features of erythema, crusting, and easy bleeding, ulcers of TTS may resemble neoplastic lesions. Biopsy is an important first step in exclusion of such lesions in cases of high suspicion (5, 6). In immunocompromised patients with vesicles preceding painful ulcerations, a diagnosis of herpetic reactivation is more probable, but it can also manifest as a non-healing ulcer similar to that of TTS (6). Tzanck smear and biopsy showing an absence of multinucleated giant cells or a negative herpes virus DNA detection by PCR will rule out this diagnosis (5, 6). TTS can also mimic vasculitic pathologies, especially GPA. In contrast to TTS, laboratory workup in GPA shows positive antinuclear and antineutrophil cytoplasmic antibodies as well as elevated ESR and C-reactive protein. In addition, there are usually systemic signs and symptoms of GPA, especially pulmonary and renal involvement. Finally, biopsy shows typical signs of vasculitis (5, 17). Similarly, PG usually presents with systemic signs and symptoms of an underlying disease. PG ulcers are also painful, have typical features such as surrounding erythema and clearly evident undermined violaceous borders, and rarely develop on the face (15, 18). Finally, patients with TTS are often misdiagnosed with factitial dermatitis, especially DA. Intractable facial sensations, a sense of intense relief on skin picking described by the patient, and confession of voluntary picking, combined with the characteristic distribution of the lesions and a history of neurological deficit, should suggest a diagnosis of TTS (1, 19). Similarly, DP also occurs without an organic cause, and delusions of infestation are not limited to specific dermatomes (on the face) (5).

Treatment of TTS is challenging and often requires a multidisciplinary approach (involving dermatology, neurology, psychiatry, and surgery) to successfully manage this condition (1, 5). There are no large controlled studies on TTS treatment and no standardized treatment algorithm exists; consequently, management strategies mostly originate from individual case reports (5, 6). A

number of different approaches have been reported with varying degrees of success, including pain management for control of paresthesia, psychological counseling for behavioral modification, pharmaceutical treatment, installation of a protector, and surgical repair (8). Therapies are aimed at the underlying cause of the disease (namely, trigeminal neuropathy, which causes the anesthesia and/or paresthesia that drives self-mutilation) and at prevention of ulceration through behavioral modifications (5). The most commonly administered medications are gabapentin and carbamazepine (19–21); other medications reported being used in case reports are olanzapine, amitriptyline, diazepam, vitamin B supplementation, chlorpromazine, and pimozide (22–24). Carbamazepine seems to be most effective because it influences both paresthesias and behavioral factors in TTS (21, 25). Surgical interventions can be successful, especially if the underlying neuropathy and self-manipulation are addressed. Well-innervated and well-vascularized rotational flaps from outside the affected dermatome or contralateral side of the face should be considered (8, 26, 27). Other treatments tried with good results in individual case reports have been cervical sympathectomy, transcutaneous nerve stimulation, negative pressure therapy, simple occlusion (hydrocolloid) dressings, local antibiotic therapy, thermoplastic face masks, and autologous epidermal cell transplant (6, 8, 22, 26, 28–32). Topical corticosteroids have not been reported to be helpful and can even delay healing (13).

However, to this day, patient education to create awareness about the self-inflicted nature of the disease and behavioral modi-

fication with reversal of the destructive scratching habits are the most important treatment strategies (5, 6, 29, 33). Patients that are aware of the nature of their condition have fewer recurrences (34) as well as fewer secondary bacterial infections, such as cellulitis (8). Prevention with occlusive dressings, wearing gloves at night, trimming the nails, and limiting hand movements with night arm splinting may be helpful (1, 12, 13, 24). In our patient, complete healing of all the ulcers was achieved only by simple occlusive dressings and stopping the scratching. The role of oral valaciclovir in healing the ulcers seems less likely because the PCR swabs for herpes viruses on admission to the hospital were negative.

Recurrences are common because the underlying trigeminal neuropathy persists. Long-term follow-up is recommended, even if the ulceration heals completely (4). Because TTS often affects the eyes in the forms of iritis, neurotrophic keratitis, corneal ulcerations, and opacifications, periodic ophthalmologic consultations are also crucial (35).

## Conclusions

We present a case of TTS following herpes zoster ophthalmicus to increase awareness of this rare but important differential diagnosis in cases of persistent unilateral facial ulceration(s). Because this distinct disorder results from injury to the trigeminal nerve that causes sensory loss–induced self-inflicted ulcerations, it requires special management with emphasis on patient education and prevention of manipulation.

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